Neural Mechanisms of Mobility Impairments:
Summary of the Pre-conference Workshop on Aging, Central Nervous System, and Mobility in Older Adults

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

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Partnership with the Gerontological Society of America, L K. Harootyan

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Background

• Mobility limitations are common and dangerous among older adults, often leading to falls and loss of independent function.
• Associated with multiple pathological conditions, medications, and environmental hazards.
• The role of the brain in mobility disorders is established for diseases such as Parkinson’s disease and stroke.
• However, the role of the brain in mobility disorders is otherwise poorly understood and understudied, especially among older adults living in the community.
• Knowledge of the neural mechanisms underlying mobility disorders is essential for effective treatment strategies.
Background 2

• The 2012 U13 Workshop, which focused on best evidence, concluded that the CNS is an important contributor to mobility limitations in older adults without overt neurological disease.

• The current, 2013 Workshop focused on neural mechanisms underlying mobility limitations in older adults.
Conceptual Model

Exposure to risk factors (age, lifestyle, cardiometabolic and inflammatory diseases or conditions)

Via degenerative mechanisms, including vascular and inflammatory

Central contributors to mobility control:
Sensorimotor brain networks → Mobility control ← Visuospatial attention, information processing, and memory brain networks

Peripheral contributors to mobility control (Peripheral nervous, muscle-skeletal, and cardiopulmonary systems)

Mobility decline

Workshop 1
Workshop 2
Workshop 3
Goals of the conference series

Bring together experts from interrelated disciplines in basic science, epidemiology, and clinical research to better understand the link between the CNS and mobility. This is to be accomplished by:

1) Examining existing evidence from basic science, epidemiological, and clinical perspectives;
2) Linking evidence from animal studies to human investigations of normal aging and disease at individual and population levels;
3) Promoting collaborations between basic, epidemiological, and clinical scientists of interrelated disciplines who might not otherwise have an opportunity to work together; and
4) Identifying knowledge gaps, barriers to progress, alternative strategies, and prospects for future inquiry through discussions of emerging research findings.
Workshop #2 Goals

• To identify neural mechanisms of mobility disability that may serve as targets for future preventive and therapeutic interventions.

• To review previous research on ischemia; inflammation; abnormal protein deposition; metabolic, hormonal, and neurotrophic processes; genetic factors; and other pathological processes that disrupt neural networks responsible for gait and balance.

• To identify the compensatory role of the CNS in maintaining mobility despite pathology in other systems.

• To identify gaps in knowledge and stimulate future multidisciplinary research.
Workshop #2 Methods

- Brief Presentations of current knowledge in the following areas:
  - Neurovascular Mechanisms
  - Inflammation and Misfolded Protein Deposition
  - Genetic and Metabolic Mechanisms
  - Neuromotor Control and Networks
- Summaries of Key Findings and Knowledge Gaps
- Roundtable Discussions and Group Presentations of Future Research Questions and Opportunities
- Junior Faculty and Fellow Poster Session
- Future Publication of Recommendations in JoG.
An example that motivates our research
The importance of external influences.
Neurovascular Mechanisms: What We Learned

• Micro- (WMH) and macro-vascular damage in certain brain regions is associated with impaired mobility.
• Angiogenic response to VEGF is impaired with aging.
• Vascular risk factors affect numerous cerebrovascular regulatory processes, including (Csiszar, Sorond):
  – Cerebral autoregulation
  – Neurovascular Coupling
  – Inflammation
• WMH are also associated with venous outflow abnormalities (Stenosis, collagenosis, edema) (Black)
Faraco, Hypertension 2013
Inflammation: What We Learned

• In Multiple Sclerosis, an age-related transition from adaptive to innate immune activation may change the course to neurodegeneration (DeJager).

• Chronic inflammation may be important for CNS and mobility impairments, especially in the frailty syndrome (Leng).
Acute versus chronic inflammation

Acute Inflammatory Reaction

Chronic Inflammation

Age-related Pro-Inflammatory State

CRP

IL-6

Response

Healing/resolution

Stress/Infection
Genetic Mechanisms:
What We Learned

- Gene polymorphisms that activate the Renin Angiotensin System are associated with impaired cerebrovascular reactivity. RAS inhibition may improve mobility. (Hajjar)
- The BDNF Met allele impairs neural plasticity, motor driving, and stroke recovery (Kleim).
- CADASIL is a small-vessel disease of the brain due to Notch 3 gene mutations, which profoundly impacts executive and physical function. (Viswanathan)
- Reduced PGC-1α activity due to polymorphisms, Parkin gene, telomere shortening, or physical inactivity results in dopamine neuron death and Parkinson’s. (Scherzer)
Neuromotor Control and Networks: What We Learned

• Impairments in neuromuscular activation precede functional decline and can be improved with power training. (Clark)

• Multiple aspects of natural walking are linked to cortical functions and can account for link between cognition and mobility. (McIlroy)

• The brain is an integrated system rather than individual brain regions acting alone. This can now be discerned with resting state fMRI. (Laurienti)
Recommendations for Future Research

• Longitudinal studies of *mechanistic connections* between inflammation, ischemia, genetic polymorphisms, gene expression, neuropathology and other biological processes in the brain and the *development* of mobility impairments in animals and humans across the lifespan.

• Studies that *stress* or *manipulate* components of genetic, molecular, structural, and/or social networks to determine their effects on specific measures of mobility in animals and humans.
Recommendations for Future Research

• Studies that employ unique gerontologic approaches to explore the effects of biological aging (in the absence of disease) on the CNS and mobility, such as parabiosis, caloric restriction, longevity molecules (e.g., resveratrol, rapamycin, etc.), and use of knock-in or knock-out animal models.

• Studies of the molecular mechanisms that impede responsiveness to various stimuli in old age (VEGF).

• Studies of compensatory mechanisms that explain intra-individual variability and enable some people to adapt to pathologies, including how genetic polymorphisms modify the effect of CNS changes on mobility (e.g. BDNF).
Necessary Resources and Tools

• Standardized measures and nomenclature to facilitate cross-institutional animal and human studies:
  – Specific mobility domains and their measures
  – Standard imaging protocols and techniques
• Data repositories of common blood, tissue, and mobility measures that are made publicly available.
• Dynamic measures, analytic tools, and bioinformatic techniques to quantify temporal and spatial changes in complex biologic and physiologic processes.
• An animal model of WMH that mimics human disease.
• Interdisciplinary education & collaboration.
Next Steps

• Written report of Workshop #2 conclusions and recommendations will be submitted to JGMS.
• See Workshop Program Book and recommendations at www.geron.org/cns
• JGMS Special Issue, Aging, CNS and Mobility Papers
• Workshop #3, November 4-5, 2014:
  
  **Interventions**
  
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