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Special Article

Aging, the Central Nervous System, and Mobility

Andrea L. Rosso,[1] Stephanie A. Studenski,[2] Wen G. Chen,[3] Howard J. Aizenstein,[4] Neil B. Alexander,[5] David A. Bennett,[6] Sandra E. Black,[7] Richard Camicioli,[8] Michelle C. Carlson,[9] Luigi Ferrucci,[10] Jack M. Guralnik,[11] Jeffrey M. Hausdorff,[12,13] Jeff Kaye,[14] Lenore J. Launer,[15] Lewis A. Lipsitz,[16,17,18] Joe Verghese,[19] and Caterina Rosano[1]

[1]Department of Epidemiology, Graduate School of Public Health and
[2]Division of Geriatric Medicine, School of Medicine, University of Pittsburgh, Pennsylvania.
[3]Division of Neuroscience, National Institute on Aging, Bethesda, Maryland.
[4]Department of Psychiatry, University of Pittsburgh, Pennsylvania.
[5]Department of Internal Medicine, University of Michigan, Ann Arbor.
[6]Department of Neurological Sciences, Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois.
[7]Department of Medicine, Division of Neurology, Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada.
[8]Department of Medicine, Division of Neurology, University of Alberta, Edmonton, Canada.
[9]Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland.
[10]Clinical Research Branch, National Institute on Aging, National Institutes of Health, Baltimore, Maryland.
[11]Department of Epidemiology and Public Health, School of Medicine, University of Maryland, College Park.
[12]Department of Medicine, Harvard Medical School, Boston, Massachusetts.
[13]Department of Neurology, Tel-Aviv Sourasky Medical Center, Israel.
[14]Department of Neurology, Oregon Health and Science University, Portland.
[15]Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda, Maryland.
[16]Division of Gerontology, Beth Israel Deaconess Medical Center, Boston, Massachusetts.
[17]Institute for Aging Research, Hebrew Senior Life, Boston, Massachusetts.
[18]Harvard Medical School, Boston, Massachusetts.
[19]Department of Neurology, Albert Einstein College of Medicine, Yeshiva University, New York.

Address correspondence to Caterina Rosano, MD, MPH, Center for Aging and Population Health, Graduate School of Public Health, 130 North Bellefield Street, Room 507, Pittsburgh, PA 15213. Email: rosanoc@edc.pitt.edu

Background. Mobility limitations are common and hazardous in community-dwelling older adults but are largely understudied, particularly regarding the role of the central nervous system (CNS). This has limited development of clearly defined pathophysiology, clinical terminology, and effective treatments. Understanding how changes in the CNS contribute to mobility limitations has the potential to inform future intervention studies.

Methods. A conference series was launched at the 2012 conference of the Gerontological Society of America in collaboration with the National Institute on Aging and the University of Pittsburgh. The overarching goal of the conference series is to facilitate the translation of research results into interventions that improve mobility for older adults.

Results. Evidence from basic, clinical, and epidemiological studies supports the CNS as an important contributor to mobility limitations in older adults without overt neurologic disease. Three main goals for future work that emerged were as follows: (a) develop models of mobility limitations in older adults that differentiate aging from disease-related processes and that fully integrate CNS with musculoskeletal contributors; (b) quantify the contribution of the CNS to mobility loss in older adults in the absence of overt neurologic diseases; (c) promote cross-disciplinary collaboration to generate new ideas and address current methodological issues and barriers, including real-world mobility measures and life-course approaches.

Conclusions. In addition to greater cross-disciplinary research, there is a need for new approaches to training clinicians and investigators, which integrate concepts and methodologies from individual disciplines, focus on emerging methodologies, and prepare investigators to assess complex, multisystem associations.

Key Words: Motor control—Central nervous system—Mobility.

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Introduction

Approximately, 35% of adults over age 70 years and the majority of adults over age 85 years have clinically diagnosable gait abnormalities (1). Gait abnormalities can lead to mobility limitations, which are associated with loss of independence, substantially reduced quality of life, increased fall risk, hospitalization, and premature death (2–5). Despite the public health importance of gait abnormalities and mobility limitations in our rapidly growing older population, we have neither a full understanding of the underlying mechanisms nor adequate evidence-based interventions.

Walking has traditionally been considered a relatively simple function, primarily affected by peripheral systems or by the severe neuropathology of overt disease. As a consequence, research on age-associated gait abnormalities has focused on either peripheral contributors or on patients with neurologic diseases. In fact, mobility is a very complex construct with a multitude of determinants. Emerging evidence highlights the importance of studying brain processes and substrates in relation to gait abnormalities beyond disease-based models. For instance, control of mobility and of cognition, traditionally assessed as independent functions, is intimately related in community-dwelling older adults free of neurologic disease (6–8). Initial studies have demonstrated that older adults with no evidence of specific neurological diagnoses may have neurologic changes that are associated with alterations in gait (9–11).

Although this initial work suggests that age-related brain changes can impair motor control even in older adults without neurologic disease, there remain a number of factors limiting advancement in this field. The traditional disease-based models, which have predominantly been used, assume that pathology is fairly localized, specific and rapidly manifest, while in aging, it is more typical to observe an accumulation of nonspecific abnormalities distributed across the central nervous system (CNS) possibly over a long period of time. Also, prior research on the CNS, aging, and mobility has largely overlooked peripheral systems, which may affect the plasticity and adaptability of the CNS to other predisposing factors (5,12,13). Further, much of the research to date in this field has focused specifically on gait, one aspect of mobility, and the commonly used measures of gait were not developed to assess the role of the CNS and may not capture the most relevant aspects of performance. Finally, research on the determinants of gait abnormalities in older adults has developed across multiple fields with diverse terminologies and conceptual frameworks.

The conference series "Aging, the CNS, and Mobility" co-ordinated by the Gerontological Society of America, the National Institute on Aging, and the University of Pittsburgh is uniquely focused on a multidisciplinary approach to further our understanding of age-associated changes in mobility. The three workshops are inter-related but distinct and focus on (a) best evidence for a relationship between CNS and mobility, (b) causes and mechanisms underlying mobility limitations in older adults, and (c) potential treatment and prevention strategies. This article provides a summary of the first workshop, including a review of the evidence presented and the gaps and barriers to progress that were identified. We aim to encourage further research and cross-disciplinary approaches in this field with the ultimate goal of enhancing prevention and intervention for mobility limitations in older adults.

Box 1. Definitions of Mobility-Related Terms

Term	Definition
Mobility	Ability of an individual to move about the environment
Mobility limitation	Restriction in mobility
Gait	The pattern of movement of the body during locomotion
Gait impairment	Abnormalities in gait
Motor control	The biomechanical and nervous control of motor functions

We acknowledge there are a multitude of mobility definitions, but given its wide acceptance, we follow the terminology of the World Health Organization International Classification of Functioning, Disability and Health (14) (see Box 1 for definitions). Throughout, we will refer to mobility limitations when speaking generally and gait when referring to specific research findings which assessed gait.

Approach

The workshops, both individually and as a whole, aim to move beyond discipline-specific and disease-based approaches to facilitate further research on CNS-related mechanisms of mobility limitations and to identify successful prevention and intervention strategies. To increase dialogue across disciplines that may not traditionally interact, these workshops bring together experts from basic, clinical, and epidemiological perspectives in the fields of geriatrics, gerontology, movement science, neurology, neuropsychology, neurosciences, and rehabilitation. Seventy-five scientists representing these diverse fields participated in the first workshop hosted at the Gerontological Society of America conference in November 2012.

At the first workshop, existing evidence on the relation between the CNS and mobility in the absence of overt neurologic disease and in the context of other contributors was explored. Talks focused on current evidence from animal and human studies of both aging and disease at the individual and population level. Emphasis was given to methodological challenges related to assessment of mobility, its central and peripheral determinants, and to cutting edge measurements and analysis. In addition, ample time was devoted to discussions and exchange of ideas to identify knowledge gaps, barriers to progress, strategies to move forward, and prospects for future inquiry. Groups discussed the definition of mobility and potential models that integrate CNS with other contributors to mobility. To enhance

integrative discussion, groups were designed to include individuals from various disciplines and both junior and senior scientists.

Evidence Presented

Evidence establishing the CNS as an important contributor to mobility limitations in older adults free from overt neurologic disease is briefly presented here (see http://www.geron.org/annual-meeting/2012-annual-scientific-meeting/aging-the-cns-and-mobility for more information).

Mobility limitations in older adults may be due to a specific disease or event such as stroke or hip fracture, but more often have multifactorial causes connected to age-related changes in the cardiopulmonary, musculoskeletal, and central and peripheral nervous systems (15). Evidence from studies of patients with neurological diseases consistently demonstrates that the CNS is an important contributor to gait and motor function. However, the association between subclinical CNS abnormalities and gait is less well established. Three main areas were reviewed.

First, indirect evidence for the relation between CNS and mobility comes from studies of gait and cognition in older adults. The correlation of measures of gait speed, pace, rhythm and variability, with global cognitive ability, executive function, verbal fluency and memory in non-demented older adults has been known (6–8,16–19). Stronger associations have been detected for information processing and executive functions, which are important for rapid and efficient planning and co-ordination of a sequence of actions. Changes in gait precede and predict cognitive decline (16,19–21), Alzheimer's disease (21,22), vascular dementia (3,21), and stroke (23) and may be an early manifestation of underlying neurologic abnormalities. Cognitive changes also adversely affect gait (16,19–21), and cognitive deficits paired with slowed gait in those without dementia may represent a distinct clinical syndrome (24). Difficulties with dual tasking may also occur, resulting in the classic "stop walking while talking" phenomenon or increased gait variability, and are particularly apparent for those with impairments in executive function (25–28). Further, there is evidence that motor and cognitive functions share genetic determinants (29,30). Overall, these associations indicate a sharing of neural networks between cognitive and motor control (31). Abnormalities in these shared neural networks can explain the decline in the automaticity of walking with age (32,33).

Second, CNS abnormalities, including generalized brain atrophy, small vessel disease and cerebral infarcts, Lewy bodies, neuritic plaques, neurofibrillary tangles and white matter hyperintensities, are very common in older adults who do not have clinical neurologic disease (34–36), and each of these, individually or in combination, may adversely affect motor function and gait (37–41). However, these abnormalities are not specific for mobility limitations, and much of the evidence to date has been cross-sectional (see Annweiler and Montero-Odasso (10), Rosano and Camicioli (11), and Zheng and colleagues (9) for reviews). Recently, more advanced neuroimaging modalities have assessed the spatial distribution of abnormalities and changes in connectivity in relation to gait. These studies indicate that lower integrity of prefronto-subcortical networks, including prefrontal cortex, basal ganglia, and medial temporal lobe are related to slower gait (9–11). Functional magnetic resonance imaging studies of mobility are scarce but have demonstrated significant associations for basal ganglia and prefrontal motor regions in relation to gait (11). Functional near-infrared spectroscopy, which allows assessment of cortical regions during walking tasks, has also demonstrated the importance of the prefrontal cortex during dual-task walking in older adults (42). These networks are traditionally known to be associated with mobility from animal- and disease-based models but are now known to be related to gait in older adults without overt neurologic disease (10,11). Importantly, these networks are also involved in information processing and memory (9) and are known to be more vulnerable than other areas to changes in blood flow and oxygenation because of their localization within watershed areas (43). Thus, current evidence suggests that abnormalities accumulating throughout the CNS in specific networks as we age could lead to mobility decline.

Finally, emerging evidence from intervention studies demonstrates the important role of the CNS in gait. Animal studies indicate that exercise can reverse the age-related synaptic changes in the neuromuscular junction, the related loss of motor neurons, and turnover of muscle fibers (44). These results may have implications for synaptic integrity in the CNS. Intervention studies in humans have shown that physical activity interventions can improve cognitive function and enhance brain structures (45,46) and that cognitive training can improve gait speed, under both normal and dual-task conditions (47). These initial studies indicate that the CNS can positively respond to behavioral modifications and retain a level of plasticity or reserve even late in life. Exercise and environmental stimulation can activate brain plasticity and lead to remodeling of the neuronal circuitry in the brain (12). Brain plasticity or reserve may play an important role in maintenance of mobility in the presence of physiologic impairments and may act to delay or reverse the effects of aging on brain pathology.

Results of the Workshop

Discussions throughout the workshop led to identification of gaps in knowledge and barriers that have limited development of clearly defined pathophysiology, clinical terminology, and effective treatment strategies.

Gaps in Knowledge

The current gaps in knowledge are outlined in Figure 1 and fall into four broad categories.

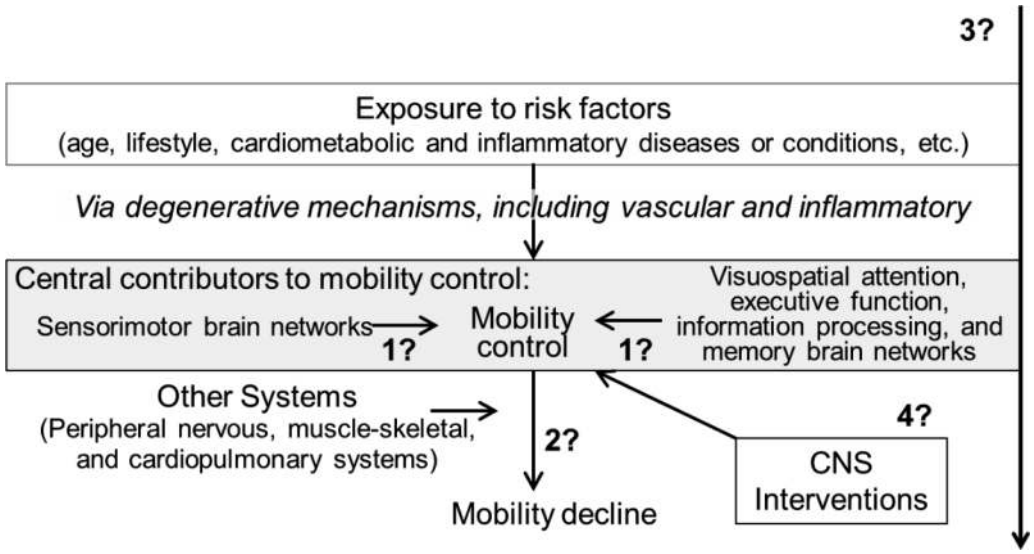

Figure 1. Model of current gaps in knowledge of central nervous system (CNS) involvement in mobility of older adults: 1) what is the CNS contribution to mobility; 2) what are the mechanisms of brain reserve in mobility; 3) when do neurologic changes related to mobility decline occur; and 4) what aspects of CNS are modifiable and amenable to interventions?

First, precise estimates of the contribution of CNS to gait impairments are lacking. This is compounded by a paucity of data on prevalence of CNS-related gait disturbances among those without overt neurologic disease.

Second, the underlying mechanisms leading from neuropathology to gait impairments are not entirely understood. For example, some older adults may tolerate CNS damage better than others, maintaining high levels of function in the presence of neuropathology. The physiologic meaning and underlying biology of this resilience are still unclear (48), and we do not yet understand how brain reserve may compensate for neuropathology or peripheral impairments to maintain mobility.

Finally, much of the research to date on the impact of CNS on mobility in older adults is based on measures collected very late in life. To improve prevention efforts and when interventions should be initiated, a life-span perspective is needed. We do not yet know what the incubation period is from neuropathology onset to mobility limitations and whether early stages of CNS dysfunction emerge only during late life or are present earlier. Assessment of associations between the CNS and mobility earlier in life may also allow for a clearer understanding of these relations before progression of potentially confounding factors has occurred.

An important consequence of these gaps in knowledge is that CNS-targeted interventions to improve mobility are only in the initial stages. Further development and testing of evidence-based interventions are needed.

Barriers and Proposed Strategies

Clearly, not all gait abnormalities in older adults may be explained by CNS abnormalities, and many known risk factors for impaired motor function, such as psychological and social processes or exposure to specific environments, do not leave a pathological footprint as we currently measure them. Indeed, the relationship between CNS and mobility is but one part of a complex of multidirectional interactions between physiologic systems, lifestyle, and the environment. Overall consensus was reached that the previously mentioned gaps in knowledge result from the complexity of the CNS, mobility, and their relation to one another. As a consequence, improvements are needed to the methodologies and models used to study these associations. Strategies, both short and long term, were proposed to move the field forward (Table 1).

The CNS is a very complicated system, yet studies of CNS integrity are largely confined to whole brain analyses, while the spinal cord, cerebellum, and regional specializations within the brain are rarely considered. The CNS has primarily been studied using imaging techniques oriented to the study of cognition and have focused on markers of structural integrity. Although CNS assessment tools have rapidly evolved in the past decade, the current technology is limited in its ability to assess function during mobility activities. Specialists in geriatric and neurologic disciplines should work closely with engineers to promote technological upgrades of CNS measures and with neuroscientists with expertise in central control of mobility to identify focused a priori hypotheses of CNS networks that regulate mobility.

Mobility in the real world is also a complex construct, requiring the ability to navigate, address environmental obstacles, and adapt to changing ambient conditions (50). Yet, current measurements of mobility in studies of aging have mainly focused on steady-state walking under

Table 1. Barriers to Advancement of Research and Clinical Practice Regarding the Role of the CNS in Mobility of Older Adults and Strategies to Address These Barriers as Identified by Workshop Participants (November 2012)

Barriers	Strategies
Complex multidirectional interplay of CNS with other systems, environment, and lifestyle	*Short term*: Assess CNS in relation to multiple systems and environment Apply complex systems analyses (fractals, entropy, and neural networks) to quantify the dynamics of gait, balance, brain networks, metabolic pathways, and genetic regulatory pathways Apply statistical methods for handling multisystem data *Long term*: Education across fields on the emerging technologies/methods (multimodality neuroimaging, genomics, proteomics, metabolomics, epigenomics, muscular physiological assessments, cerebral blood flow regulation, computational approaches to measure variability, real-time mobility measures [eg, cell phone-based accelerometers, body-fixed sensors, global positioning system, low-cost balance plates such as Wii boards])
Current research approaches seldom apply measures of real-world mobility concurrent with CNS	*Short term*: Establish working groups to develop standardized ecologically valid measures of real-world mobility (eg, dual task) *Long term*: Expand use of mobility measures with public health relevance, such as life space
Disciplines studying mobility limitations often operate in silos and use multiple conceptual frameworks and terminologies	*Short term*: Include core measures of mobility (eg, National Institutes of Health toolbox [49]) in studies of aging CNS and vice versa Increase access to data, harmonize existing measures across studies, create database of existing studies with neuroimaging and motor measures Develop unifying framework Adopt definitions of mobility that can be translated/interpreted across disciplines *Long term*: Establish new training programs to address the complexities of this research field Parallel animal and human studies for translational research Replicate findings across disciplines

Note: CNS = central nervous system.

relatively sterile conditions. Although gait is a meaningful and easily assessed measure of mobility, it is not designed to capture these complexities. Moreover, gait itself can be operationalized in a number of ways including speed, variability, dynamics, and asymmetry with each measure capturing distinct aspects of gait (37,51,52), making comparison across studies difficult. To date, research has largely tried to integrate the models of gait and cognition without considering which aspects are most relevant to capture the role of the CNS. Indeed, studies have mainly applied gait measures that capture kinematic and biomechanical components better suited to assess the role of peripheral systems. The multifactorial nature of mobility requires a multidisciplinary approach with experts in biomechanics to develop standardized measures that capture the complexities of real-world mobility. In this regard, dual-task paradigms may be useful assessments that can be measured in the laboratory (25). Measures that capture achieved mobility, such as the life-space assessment (53) and remote sensors (54,55), should also be considered.

In addition to their individual complexities, both the CNS and mobility are affected by a number of physiologic systems and operate within an environmental context (56). There are a large number of risk factors, both intrinsic and extrinsic, that may influence the CNS and mobility. We are only beginning to understand the role that many of these factors may play in determining mobility. Due to these inherent complexities, development of multidisciplinary collaborative models is needed. Several frameworks were developed during the workshop sessions and consensus was that any effective framework must consider complex lifestyle and environmental risk factors, recognize that mobility is a continuum, account for the interactions of the CNS with peripheral physiologic systems, and incorporate feedback between the CNS and mobility itself (Figure 2).

Advancements in understanding the role of the CNS in mobility have occurred in basic, animal, clinical, and epidemiological studies. However, discoveries have generally occurred independently in each field. For example, the terminology used to describe mobility has largely been discipline specific and reflects the expertise of diverse fields. Terms such as walking, ambulation, functional mobility, mobility capacity, mobility impairment, mobility limitation, mobility disability, and navigation may have overlapping meanings but distinct definitions within fields. These can reflect a spectrum of mobility from the micro level, representing individual steps, to the macro level, encompassing participation in the community and can range in the extent

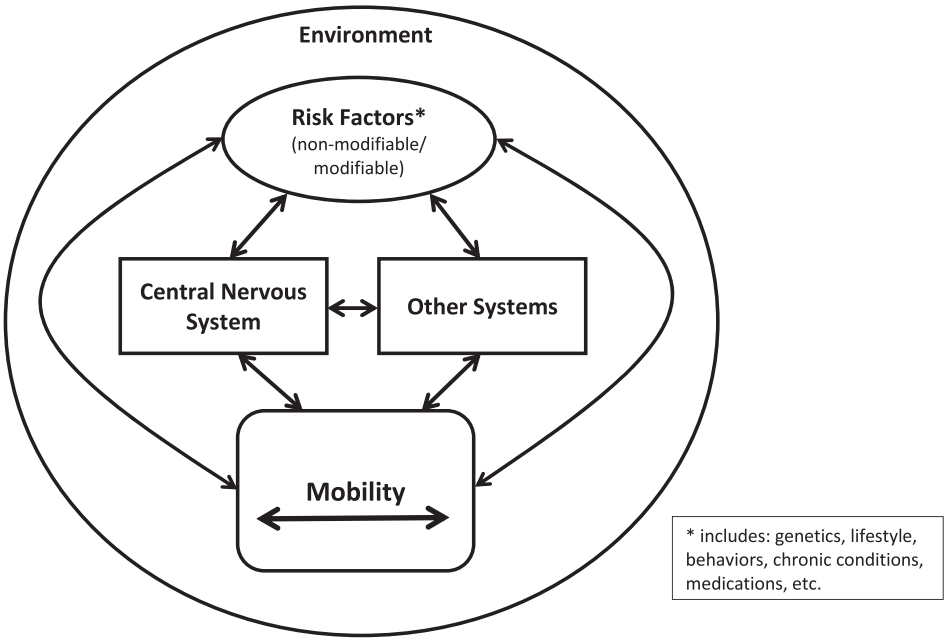

Figure 2. Model of central nervous system involvement in mobility of older adults. Summary model from those developed by workshop participants (November 2012).

to which the CNS is involved in their execution. Much of the mobility terminology has been developed within the disability frameworks (14,57), and these definitions can easily be incorporated into the fields assessing CNS and mobility. Collaboration and improved translation between fields should be fostered in order to speed advancements toward interventions.

Future Directions

Future studies of age-associated mobility declines will require teams of investigators who have a basic understanding of cutting edge neuroimaging techniques that assess morphology, structure and function, sophisticated measures of gait and mobility, and the range of risk factors that impact gait and mobility. It is not possible to address such a complex problem with single-discipline approaches. Multidisciplinary training programs and models of cross-field collaborations need to be implemented to move the field forward. Longitudinal, population-based studies that include a wide spectrum of mobility measures and can evaluate predictive models of gait disorders are needed. Subsequently, experimental designs to test pharmacological and nonpharmacological intervention strategies can be developed. Such intervention studies will require investigators with expertise in sophisticated techniques to measure change in gait, cognition, and brain structure and function. The critical evaluation and application of new technologies in the study of the brain (magnetic resonance imaging, functional near-infrared spectroscopy, and positron emission tomography), muscle function (biopsy and nuclear magnetic resonance), and joint function and pathology (magnetic resonance imaging) can provide major advances in prevention and treatment of mobility limitations and consequent disability in older adults.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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