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Higher step length variability indicates lower gray matter integrity of selected regions in older adults

Andrea L. Rosso [a,*], Megan J. Olson Hunt [b], Mei Yang [a], Jennifer S. Brach [c], Tamara B. Harris [d], Anne B. Newman [a], Suzanne Satterfield [e], Stephanie A. Studenski [f], Kristine Yaffe [g], Howard J. Aizenstein [h], Caterina Rosano [a] for the Health ABC study

[a] Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, USA
[b] Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, USA
[c] Department of Physical Therapy, School of Health and Rehabilitation Sciences, University of Pittsburgh, Pittsburgh, USA
[d] Laboratory of Epidemiology, Demography, and Biometry, Intramural Research Program, National Institute on Aging, Bethesda, USA
[e] Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, USA
[f] Division of Geriatric Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, USA
[g] Department of Psychiatry, University of California, San Francisco, USA
[h] Department of Psychiatry, University of Pittsburgh, USA

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ABSTRACT

Step length variability (SLV) increases with age in those without overt neurologic disease, is higher in neurologic patients, is associated with falls, and predicts dementia. Whether higher SLV in older adults without neurologic disease indicates presence of neurologic abnormalities is unknown. Our objective was to identify whether SLV in older adults without overt disease is associated with findings from multimodal neuroimaging. A well-characterized cohort of 265 adults (79–90 years) was concurrently assessed by gait mat, magnetic resonance imaging with diffusion tensor, and neurological exam. Linear regression models adjusted for gait speed, demographic, health, and functional covariates assessed associations of MRI measures (gray matter volume, white matter hyperintensity volume, mean diffusivity, fractional anisotropy) with SLV. Regional distribution of associations was assessed by sparse partial least squares analyses. Higher SLV (mean: 8.4, SD: 3.3) was significantly associated with older age, slower gait speed, and poorer executive function and also with lower gray matter integrity measured by mean diffusivity (standardized beta = 0.16; $p = 0.02$). Associations between SLV and gray matter integrity were strongest for the hippocampus and anterior cingulate gyrus (both $\beta = 0.18$) as compared to other regions. Associations of SLV with other neuroimaging markers were not significant. Lower integrity of normal-appearing gray matter may underlie higher SLV in older adults. Our results highlighted the hippocampus and anterior cingulate gyrus, regions involved in memory and executive function. These findings support previous research indicating a role for cognitive function in motor control. Higher SLV may indicate focal neuropathology in those without diagnosed neurologic disease.

1. Introduction

Higher step length variability is present in those with neurologic diseases and may precede dementia onset [1]. Variability in step length has been related to gait instability, loss of postural control, and increased fall risk [2]. Step length at preferred speeds is quite constant in healthy adults, but higher step length variability can be present in older adults without overt neurologic disease [3]. Previous research has demonstrated that the range of values observed for step length variability is greater in older age, indicating that variability can be particularly high in a subset of older adults [4]. Slower gait is common in older adults and is associated with higher gait variability, but age-related increases in variability are independent of gait slowing [5].

Step control is a multifactorial process with involvement from the musculoskeletal system, peripheral nervous system, and central nervous system (CNS). A healthy neural system is needed to minimize stride-to-stride fluctuations in walking [2]. Declines in automatic motor control may lead to greater cortical involvement

* Corresponding author at: 130 N Bellefield Avenue, Suite 400, Pittsburgh, PA 15213, USA. Tel.: +1 412 383 1066; fax: +1 412 383 1956.
E-mail address: alr143@pitt.edu (A.L. Rosso).

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in walking and increased step variability. However, the neural contributors to higher step length variability in the older population without overt neurologic disease are unknown. An emerging understanding of disease-related pathologies in the brain has revealed that subclinical pathology, both neurodegenerative and cerebrovascular, is quite common in older adults without conventionally defined neurologic diseases. Furthermore, these pathologies can adversely affect motor function and gait in older adults [6].

Recent implementation of advanced neuroimaging techniques in gait studies has revealed that lower total brain volume and lower integrity of the white matter are associated with higher step length variability [7]. However, there is limited evidence regarding the regional distribution of CNS abnormalities related to step length variability in older adults without overt neurologic disease. Initial results have demonstrated associations for three general regions: the basal ganglia [8], the hippocampus [9,10], and motor areas [10]. In addition, executive function and attention may be related to step length variability [11,12].

Determining the neuroanatomical correlates of step length variability in older adults is important to developing appropriate and effective interventions to improve gait and prevent falls. Gait variability is amenable to pharmacologic intervention and behavioral training in PD and stroke patients [13,14], but evidence is lacking for older adults without overt disease. Part of the barrier to development of interventions in those without overt disease is the lack of evidence for the pathophysiology or regional distribution of brain abnormalities underlying gait variability in this population. Mean diffusivity (MD) measured from magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI) may indicate abnormalities of the brain parenchyma that precede measurable changes to gray matter macrostructure [15] and may provide evidence for the early brain changes associated with step variability.

We explored the regional distribution of differences in neuroanatomy related to step length variability as determined by DTI in a cohort of community-dwelling older adults free from neurologic disease. Gray matter regions related to memory, executive function, and motor function were selected based on previous research indicating associations between gait and these neurologic domains [16,17]. We hypothesized that lower integrity of these regions, indicated by higher mean diffusivity, would be associated with higher step length variability.

2. Methods

2.1. Study subjects

Participants were from the Healthy Brain Project ancillary to the Health, Aging, and Body Composition (Health ABC) study. Health ABC is a cohort of 3075 well-functioning, white and black, men and women, aged 70–79 years from Pittsburgh, PA and Memphis, TN enrolled 1997–1998. In 2006–2007, 314 of the eligible 652 Health ABC participants at the Pittsburgh site were interested and eligible for MRI of the brain and were able to walk 20 meters. Medical histories were reviewed to rule out endocrinal, neurological and psychological illnesses. Participants in the Healthy Brain Project were similar to the Pittsburgh cohort of the Health ABC study as previously reported [18]. All subjects provided written informed consent and the protocol was approved by the University of Pittsburgh institutional review board.

2.2. Image acquisition

Details of the image acquisition protocol have been previously published [19]. Images were obtained with a Siemens 12-channel head coil and 3T Siemens Tim Trio MR scanner at the Magnetic Resonance Research Center, University of Pittsburgh. T1-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted images were collected. Diffusion-weighted images were acquired using a single short spin-echo sequence (TR = 5300 ms, TE = 88 ms, TI = 2500 ms, 90° flip angle, 256 mm × 256 mm FOV, two diffusion values of $b = 0$ and 1000 s/mm, 12 diffusion directions, four repeats, 40 slices, 3 mm thick, 128 × 128 matrix size, 2 mm × 2 mm × 3 mm voxel size, and GRAPPA = 2). A neuroradiologist examined each MRI for neurologic abnormalities.

2.3. Image processing

Macro-structural measures (gray matter (GM) volume and white matter hyperintensity (WMH) volume) and micro-structural measures (MD and fractional anisotropy (FA)) were obtained using previously published methods [19], briefly described below.

Volumes for GM, white matter (WM), and cerebrospinal fluid (CSF), were calculated by segmenting the skull-stripped T1-weighted image in native anatomical space. Volumes were estimated in cubic millimeters by summing tissue-specific voxels. Intracranial volume was contained within the inner skull. Atrophy was calculated as 1-GM volume/intracranial volume. WMH volume was obtained from T2-weighted FLAIR image and was normalized to brain volume.

DTI estimates the microstructural integrity of brain tissues using the molecular diffusion of water which is influenced by the characteristics of the surrounding tissue [15]. MD estimates an average magnitude of water diffusion and in gray matter likely represents the density of the molecular structure. Greater structural density results in greater restriction of water diffusion and a lower MD value. FA is an index of white matter tract integrity with higher values indicating greater integrity [15]. The diffusion-weighted images were pre-processed to remove eddy current distortions and the tensor were computed and diagonalized to compute the FA and MD maps. Mean FA and MD were calculated for normal-appearing WM and GM only. Due to poor segmentation between WM and CSF, two individuals were excluded from analyses of WM.

2.4. Gait analysis

Gait measures were obtained from GaitMat™ II, an instrumented, computerized eight meter walkway. The first and last two meters were inactive for acceleration and deceleration. Participants were asked to walk at their usual pace and made at least four passes. Only passes with at least four valid steps were included. Gait speed was distance divided by time in seconds. Step length was defined as the distance between the heel of one footprint and the heel of the next footprint from the opposite foot. Step length variability was calculated from both left and right steps as the coefficient of variation (CoV) using the formula (standard deviation/mean) × 100 [8]. Results using the standard deviation were qualitatively similar to those using CoV; only results with CoV are reported here. The coefficient of variation was based on no fewer than 16 steps made over 16 m of walking. Reliability of this measure over similar distances has been previously reported [20].

2.5. Covariates

Variables known to be associated with brain health and gait were included as covariates. Age, gender, and race were self-reported. Body mass index (BMI) was calculated by the standard formula (weight in kilograms)/(height in meters) [2] and obesity was defined as ≥30. Diabetes was determined by self-report, use of hypoglycemia medication, a fasting glucose of ≥126 mg/dL, or a