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Pathways linking regional hyperintensities in the brain and slower gait

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ABSTRACT

Importance: Cerebral white matter hyperintensities (WMHs) are involved in the evolution of impaired mobility and executive functions. Executive functions and mobility are also associated. Thus, WMHs may impair mobility directly, by disrupting mobility-related circuits, or indirectly, by disrupting circuits responsible for executive functions. Understanding the mechanisms underlying impaired mobility in late life will increase our capacity to develop effective interventions.
Objective: To identify regional WMHs most related to slower gait and to examine whether these regional WMHs directly impact mobility, or indirectly by executive functions.
Design: Cross-sectional study. Twenty-one WMH variables (i.e., total WMH volume and WMHs in 20 tracts), gait speed, global cognition (Modified Mini-Mental State Examination; 3MS), and executive functions and processing speed (Digit-Symbol Substitution Test; DSST) were assessed. An L1–L2 regularized regression (i.e., Elastic Net model) identified the WMH variables most related to slower gait. Multivariable linear regression models quantified the association between these WMH variables and gait speed. Formal tests of mediation were also conducted.
Setting: Community-based sample.
Participants: Two hundred fifty-three adults (mean age: 83 years, 58% women, 41% black).
Main Outcome Measure: Gait speed.
Results: In older adults with an average gait speed of 0.91 m/sec, total WMH volume, WMHs located in the right anterior thalamic radiation (ATRR) and frontal corpus callosum (CCF) were most associated with slower gait. There was a >10% slower gait for each standard deviation of WMH in CCF, ATRR or total brain (standardized beta in m/sec [p value]: −0.11 [$p = 0.046$], −0.15 [$p = 0.007$] and −0.14 [$p = 0.010$], respectively). These associations were substantially and significantly attenuated after adjustment for DSST. This effect was stronger for WMH in CCF than for ATRR or total WMH (standardized beta in m/sec [p value]: −0.07 [$p = 0.190$], −0.12 [$p = 0.024$] and −0.10 [$p = 0.049$], respectively). Adjustment for 3MS did not change these associations. The mediation analyses also found that DSST significantly mediated the associations between WMHs and gait speed. Our models were adjusted for age, sex, BMI, quadriceps strength, years of education, standing height, and prevalent hypertension.
Conclusion: The impact, direct or indirect, of WMHs on gait speed depended on their location and was mediated by executive function. Thus, multi-faceted interventions targeting executive control functions as well as motor functions, such as balance and strength training, are candidates to the maintenance of mobility across the lifespan.

Introduction

Impaired mobility in older adults is a significant public health concern. The prevalence of impaired mobility is 35% for community-dwelling older adults aged 70 years and older (Odenheimer et al., 1994). Reducing both the incidence and progression of impaired mobility could preserve functional independence, reduce health-care resource utilization, and sustain health-related quality of life in older adults. However, we must first gain a better understanding of the mechanisms underlying physical disability in late life to increase our capacity to develop valid screening strategies and effective interventions.

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Neuroepidemiological studies highlight white matter hyperintensities (WMHs) in the evolution of impaired mobility in older adults (Annweiler and Montero-Odasso, 2012; Rosano et al., 2010; Wakefield et al., 2010; Zheng et al., 2011). White matter hyperintensities are common magnetic resonance imaging (MRI) findings among otherwise healthy older adults (Bolandzadeh et al., 2012; Breteler et al., 1994; Gunning-Dixon and Raz, 2000; Lindgren et al., 1994). These abnormalities are due to damage to the brain parenchyma (Kuo and Lipsitz, 2004), ranging from demyelination to complete axonal disruptions (Frisoni et al., 2007; Galluzzi et al., 2008). Both regional and total WMH volume are independently associated with impaired mobility, specifically, gait speed (Rosano et al., 2010; Wakefield et al., 2010).

White matter hyperintensities are also associated with impaired cognitive function, in particular, executive functions. Specifically, the prefrontal subcortical networks contain neural circuits responsible for executive functions. These circuits are located in the watershed areas and are vulnerable to lower perfusion, and are thus at high risk for WMH formation. Therefore, WMHs in prefrontal subcortical regions may further affect the tracts important for executive functions. Executive functions include the ability to concentrate, to attend selectively, and to plan and to strategize.

Of particular relevance to our current study, lower executive functions are associated with impaired mobility. It is now widely recognized that gait depends on both higher-level cognitive function (i.e., executive functions) as well as sensorimotor processes (Malouin et al., 2003; Woollacott and Shumway-Cook, 2002; Yogev-Seligmann et al., 2008). For example, Rosano et al. (2005a) demonstrated that both global cognitive function, as measured by the Modified Mini-Mental State Examination (3MS), and executive functions and information processing speed, as measured by Digit Symbol Substitution Test (DSST), are associated with impaired gait in otherwise healthy older adults.

Given the established association between WMHs, mobility, and executive functions, we hypothesize that WMHs negatively impact mobility through two central pathways: 1) directly, by disrupting mobility-related circuits (Filley, 1998; Whitman et al., 2001; Zheng et al., 2012) (i.e., direct pathway; Fig. 1); and 2) indirectly, by disrupting circuits responsible for executive functions (Guttmann et al., 2000; Starr et al., 2003) (i.e., indirect pathway; Fig. 1). It is also possible that WMH in the sensorimotor cortex is related to the executive functions performance. Therefore, we are exploring the mediating effects of cognition on both pathways.

If we demonstrate that the negative impact of WMHs in EF circuits on gait speed is mediated by cognitive function, then interventions targeting these networks, such as cognitive and aerobic and resistance training, should be key components in the management of older adults with impaired mobility. Both cognitive and aerobic and resistance training have been shown to be effective in promoting executive functions among older adults (Ball et al., 2002; Colcombe and Kramer, 2003; Liu-Ambrose et al., 2010; Nagamatsu et al., 2012; Verghese et al., 2010; Willis et al., 2006).

Thus, in this cross-sectional study, we examined whether WMHs directly impact mobility, or indirectly by executive functions (Fig. 1). Specifically, we seek to extend our current understanding of the relationship between WMHs and mobility by: a) identifying specific tracts in which WMH volumes are most strongly associated with gait speed, using an automated state of the art statistical method (Zou, 2005); and b) examining whether the association between WMHs and gait speed in the selected tracts is mediated by DSST or 3MS. Moreover, due to a possible effect of age, sex, body mass index (BMI), quadriceps strength, chronic pain, and hypertension on the association between WMH, cognitive function and gait speed, we are adjusting our models for these covariates. Identifying mechanisms underlying the association between WMHs and mobility will refine the focus in future research. This, in turn, will increase our capacity to identify and develop effective interventions to combat impaired mobility in older adults.

Methods

The Healthy Brain Project and participants

Our study participants were enrolled in the Healthy Brain Project (HBP). The HBP is an ancillary study on Health Aging and Body Composition (Health ABC) cohort to examine the association of structural white matter and gray matter abnormalities with age-related mobility impairment.

Among the 803 Health ABC participants alive in 2006 to 2008, 339 were eligible for inclusion in the HBP study: they walked without an assistive device, had completed the 6-meter walking test, and were eligible for MRI scanning. Three hundred nineteen Health ABC participants were ineligible for inclusion in the HBP and 145 refused to participate. Among the 339 eligible for the HBP study, 13 changed their mind after consent, 1 person died prior to scanning, and 10 were not eligible for 3 Tesla (T) scanning (i.e., 315 were included and assessed). After removal of missing data across all variables of interest, the final sample size was 253.

Independent variables: total and focal WMH volume

Brain MRIs were acquired at the MRI Research Center, University of Pittsburgh Medical Center, with a 3 T scanner. Two sequences of T1-MPRAGE and T2-FLAIR were captured. An Automated Labeling Pathway (ALP) (Wu et al., 2006) was used to quantify volumes and localization of focal WMHs. The ALP method adapts a fuzzy connected algorithm to automatically segment the WMHs. Using Johns Hopkins University White Matter Atlas that includes 20 white matter tracts (Hua et al., 2008; Wakana et al., 2007), ALP then employs a demons-based image registration technique to automate the anatomical localization of the hyperintensities. The 21 anatomical WMH variables for this study are presented in Appendix 1. The total and focal WMHs are adjusted for total brain volumes.

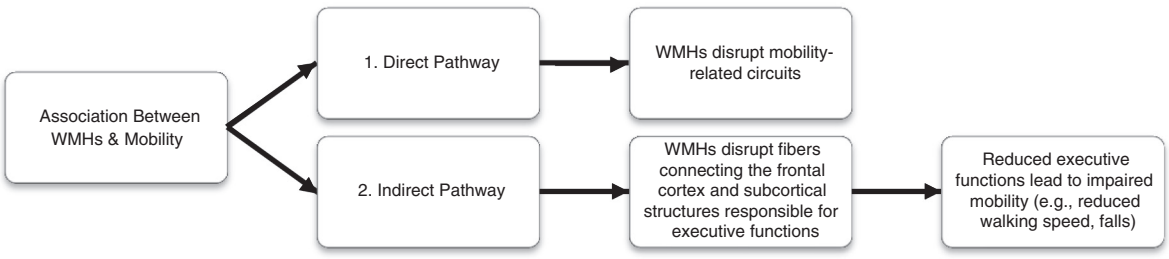

Fig. 1. Two hypothesized pathways for the negative impact of WMHs on mobility: 1. Direct pathway—WMHs impair mobility by directly disrupting mobility-related circuits; 2. Indirect pathway—WMHs disrupt circuits responsible for cognitive function leading to impaired mobility.

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