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

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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.

Keywords

White matter hyperintensities; Mobility; Cognitive function; Executive function; Gait speed; Mediation

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.

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.

Dependent variable: gait speed

Gait speed is a reliable biomarker of overall health and functional status in older adults (Abellan van Kan et al., 2009). Slower gait in older adults is a significant predictor of disability and mortality (Abellan van Kan et al., 2009; Studenski et al., 2011).

The GaitMat II velocity (EQ Inc., Chalfonte, PA) measured baseline gait speed. The GaitMat II is a 4-meter long walkway with embedded pressure sensors that facilitate gait analysis. In case of missing data from GaitMat II, gait speed was obtained from walking over 3, 4 or 6 meters.

Mediators: cognitive function

We assessed global cognitive function, executive functions, and information processing speed. Global cognitive function was assessed using the 3MS (Teng and Chui, 1987). This test comprehensively evaluates cognitive domains of orientation, attention, calculation, language and short-term memory. Scores for the 3MS range from 0 to 100. Compared with the Mini-Mental State Examination, the 3MS assesses a broader range of cognitive processes.

Executive functions and information processing speed were indexed using the Digit Symbol Substitution Test (DSST) (Lezak, 1995). For this task, participants were first presented with a series of numbers (1 to 9) and their corresponding symbols. They were then asked to draw the correct symbol for any digit – placed randomly in pre-defined series – in 90 seconds. A higher number of correct answers in this time period indicated a better executive functions and processing speed.

Covariates: age, body mass index, quadriceps strength, years of education, standing height, prevalent hypertension, chronic pain

Age measured in years, sex, BMI calculated as kg/m^2, years of education, and standing height in mm were added to our models. Quadriceps strength modifies the association between WMHs and gait speed (Rosano et al., 2005b, 2010). Thus, quadriceps strength was measured by the Kin-Com isometric dynamometer (Kin-Com Chattanooga, TN). We evaluated the average torque generated by the quadriceps (i.e., knee extensors) at 60 degrees per second. The mean of three trials and was used in our analysis.

Moreover, Rosano and colleagues (Buckalew et al., 2013) have shown that chronic pain might be a contributor in the association between white matter hyperintensities and disability. Therefore, chronic pain in knee, back, or leg was documented as a binary variable and added to the models as a covariate.

Prevalent hypertension for participants with average sitting systolic blood pressure 140 mm Hg or diastolic blood pressure 90 mm Hg concurrently or before the year of MRI, was also documented as a binary variable, and was added to the models as a covariate. This variable has been shown to be associated with both WMHs and gait speed in older adults (Rosano et al., 2011).

Statistical analysis

Our statistical analyses consisted of three phases: 1) data reduction to identify WMH tracts most associated with gait speed; 2) multivariable regression models to quantify the association between the variables of interests; and 3) formal tests of mediation analysis. The multivariable regressions as well as the mediation models were adjusted for age, BMI, and quadriceps strength.

For data reduction, we used Elastic Net (Zou, 2005) to identify which of the 21 WMH variables were most associated (i.e., minimal regularized regression error using cross-validation) with gait speed. Elastic Net is an automated shrinkage and penalized statistical method. It is a preferred alternative to conventional variable selection methods, such as

stepwise regression, that have been criticized for their bias, over-fitting, and exaggerated *p* values (Walter and Tiemeier, 2009). In Elastic Net, both L1 (i.e., the positive weighting parameter which promotes shrinkage in the regularized regression coefficients) and L2 (i.e., the weighting parameter which promotes stability on regularization) regularizations are introduced into the standard multiple linear regression model to shrink the coefficients to zero. For a given lambda (i.e., the L1 parameter) and an alpha between 0 and 1 (i.e., the L2 parameter), Elastic Net minimizes the error as presented below.

$$\text{Min} \frac{1}{2N} \left[\|Y - \beta_0 - X\beta\|^2 + \lambda\|\beta_1\| + \frac{(1-\alpha)}{2}\lambda\|\beta_2\|^2 \right].$$

Here, *Y* represents gait speed for our 253 participants, and *X* is a 253*21 matrix of WMH volumes for 21 WMH variables. λ was set to the default value of 100, and α was set to 0.5. This analysis was performed in Matlab (R2011b, Natick, Massachusetts, The Mathworks Inc.). The process of variable selection using the Elastic Net method is illustrated in Fig. 2a and explained in greater detail in Appendix 2.

For the second phase, multivariable linear regression models adjusted for age, sex, BMI, quadriceps strength, chronic pain, and prevalent hypertension were built with gait speed as the dependent variable and WMHs from specific tracts identified in phase one as independent variables. Each WMH tract was entered in a separate linear regression model, with and without adjustment for the putative mediators (e.g., DSST and MMSE).

For the third phase, mediation analyses were performed using PROCESS (Hayes, 2012), a computational macro developed for SPSS. For each WMH variable selected in phase one (i.e., data reduction) we constructed two mediation models—one for each cognitive mediating variable (i.e., 3MS and DSST). Each selected WMH variable was entered as the independent variable and gait speed as the dependent variable, while adjusting for age, BMI, and quadriceps strength. The general mediation model is illustrated in Fig. 2b.

We calculated the direct effect, indirect effect and total effect for each mediation model. The direct effect refers to the change in gait speed when WMH variable changes while the cognitive function mediators are maintained fixed (Fig. 2b: path coefficient *A*; the association between WMHs and gait speed adjusted for covariates and all cognitive function variables). The indirect effect refers to the change in gait speed when the independent WMH variable is maintained fixed and the cognitive mediator changes to the level it would have attained if the independent gait speed variable increased by one unit (Fig. 2b: product of path coefficients *B* and *C*). We used bootstrapping (*n* = 10,000) to obtain a 95% confidence interval for the indirect effect. The total effect in our linear system is the sum of direct and indirect effects of WMH volume on gait speed (i.e., the association of WMHs and gait speed adjusted for covariates; A + BC).

For each standardized model, we reported percentages of direct and indirect effect out of the total effect (i.e., direct effect * 100/total effect and indirect effect * 100/total effect), to compare the size of direct and indirect effects in each mediation model. A larger percentage

for the direct or the indirect effect indicates a greater effect of the independent or the mediator variable on gait speed, respectively.

Results

Data reduction

Elastic Net selected three WMH variables that were most associated with gait speed. In addition to total WMH volume, WMHs located in right anterior thalamic radiation (ATRR) and frontal corpus callosum (CCF) were selected. Table 1 provides the descriptive statistics for all the variables of interest.

Multivariable regression analyses

The effects of total, ATRR and CCF WMHs on gait speed were −0.146, −0.152, and 0.114 in models adjusted for age, sex, BMI, quadriceps strength, education, and standing height (Table 2, Model 1). Since prevalent hypertension and chronic pain were also associated with slower gait (−0.240 and −0.244, $p < 0.001$ respectively) models were further adjusted for these variables (Table 2, Model 2). The association between WMHs and gait speed remained similar, and did not significantly modify previous results (change $< 10\%$).

By contrast, the association between WMHs and gait speed substantially decreased when 3MS or DSST were added to the models (Table 2, Model 3 and 4; 15% and 25% for Total WMHs, 6% and 19% for ATR WMHs, and 21% and 35% for CCF WMHs). Results remained similar in men compared to women.

Mediation analyses

We constructed six mediation models in total; two per selected WMH variable. Overall, executive functions and information processing speed, as measured by DSST, mediated the association between WMH volume and gait speed, after adjusting for age, sex, BMI, quadriceps strength, years of education, standing height, and prevalent hypertension. Global cognitive function, as measured by 3MS, was not a significant mediator (Table 3).

Table 3 provides the total, direct and indirect (both unstandardized and standardized beta) effects for each of the three WMH variables on gait speed, adjusted for age, sex, BMI, quadriceps strength, education, height, and prevalent hypertension. The total effect of WMH volume on gait speed was significant and negative for all three WMH variables of total brain, ATRR and CCF (standardized beta in m/sec [p value]: −0.15, −0.16, −0.11 [$p < 0.05$], respectively). The direct effect of WMH volume on gait speed was significant and negative for total brain and ATRR (standardized beta in m/sec [p value]: −0.10 and −0.12 [$p < 0.05$], respectively), but not significant for CCF (standardized beta in m/sec [p value]: −0.06 [$p = 0.16$]). The indirect effect of WMH volume on gait speed through executive functions and information processing speed was significant and negative for all the three WMH variables of total brain, ATRR and CCF (standardized beta in m/sec [significant based on 95% CI]: −0.02, −0.02, −0.03, respectively). Moreover, for total WMH volume, the direct effect was 72% of its total effect and the indirect effect was 19% of its total effect. For ATRR, the

direct effect was 78% of its total effect and the indirect effect was 14% of its total effect. For CCF, the direct effect was not significant and the indirect effect was 27% of its total effect.

Discussion

In this cohort of community-dwelling old adults free from overt neurological conditions, total WMHs, as well as WMHs in CCF and ATRR, were most strongly associated with slower gait speed. While previous studies have consistently found an association between total WMH volume and slower gait, few studies to date have looked at focal WMHs in selected tracts. These associations were robust and independent of age, sex, body mass index, quadriceps strength, education, height, prevalent hypertension, and chronic pain.

Compared to previous studies examining the effect of focal WMHs on physical function, our current study had several new aspects; our subjects had higher average age (de Laat et al., 2011; Srikanth et al., 2010; Zheng et al., 2012), and our statistical analysis were adjusted for relevant covariates (Srikanth et al., 2010). Our study applied imaging with a high level of spatial resolution to quantify WMHs in individual white matter tracts. Other studies applied lower resolution methods and limited their analyses to overall volumes of lobar WMHs (Zheng et al., 2012) or distributed in deep versus periventricular WMHs (de Laat et al., 2011; Soumare et al., 2009; Srikanth et al., 2010). Importantly, our study provides novel insight into potential mechanistic pathways by which WMHs impact gait speed in older adults. Our results concur with previous studies that suggest WMHs in cortical regions containing projection fibers (e.g. anterior thalamic radiation) (Buckalew et al., 2013; Guttmann et al., 2000), commissural fibers (e.g. corpus callosum) (de Laat et al., 2011; Srikanth et al., 2010; Zheng et al., 2012) and association fibers (e.g. superior longitudinal fasciculus) (Zheng et al., 2012) play an important role in mobility.

Lower DSST performance, an indicator of executive dysfunction and impaired processing speed, but not global cognitive function, was a significant mediator of associations between WMH volumes and gait speed, after accounting for age, BMI, and quadriceps strength, education, and height. However, the degree by which DSST mediated the association between WMHs and gait speed depended on WMH location. Specifically, it was strongest for CCF than for ATRR or total brain WMH.

The corpus callosum is the largest white matter tract and plays a primary role in cognitive function. The CCF, or corpus callosum genu and rostrum, connects the prefrontal cortex between the two hemispheres of the brain and hence, plays a role in executive functions (Jokinen et al., 2012). Of particular relevance to DSST performance, Jokinen et al. (2007) demonstrated that overall corpus callosum atrophy was associated with impaired processing speed, and that anterior corpus callosum (genu and rostrum) atrophy was associated with impaired attention and executive functions in community-dwelling older adults with WMHs. Therefore, WMHs localized in this portion of the corpus callosum may impair mobility indirectly, because they impair executive control function.

While the association between CCF WMHs and gait was not significant after adjustment for DSST (i.e., the direct effect was not significant), the association between WMHs in the

ATRR and slower gait was significant and independent of DSST (i.e., the direct effect was significant). In fact, it had a large significant direct effect (i.e., 78%) on gait speed. This finding concurs with the neuroanatomy of the ATRR. The ATRR contains fibers from superior fronto-occipital fasciculus that connects pre-motor areas with the parietal lobe (Srikanth et al., 2010). Thus, any disruption of these fibers may impair the somatosensory feedback required for gait (Srikanth et al., 2010) and thus, directly impair gait. We also found a significant indirect effect (i.e., 14%) of ATRR WMHs on gait speed through DSST performance. Duering et al. (2011) previously found that WMHs in the ATR were independently associated with executive functions and processing speed. Therefore, WMHs in ATRR may negatively impact mobility through two central pathways: 1) directly, by disrupting mobility-related circuits (Filley, 1998; Whitman et al., 2001; Zheng et al., 2012); and 2) indirectly, by impairing circuits responsible for executive functions and subsequently impairing motor control (Guttmann et al., 2000; Starr et al., 2003).

Overall, our findings highlight the importance of a multisystem assessment of slowing gait, which should include both executive functions and processing speed as well as motor pathways (Rosano et al., 2005a, 2010; Yogev-Seligmann et al., 2008) and the negative impact of WMHs on these processes. Interventions targeting these networks, for example cognitive interventions and aerobic and resistance training, may be particularly effective in promoting mobility among older adults (Ball et al., 2002; Colcombe and Kramer, 2003; Verghese et al., 2010; Willis et al., 2006). Future studies should also examine whether interventions aimed at reducing vascular risk factors (e.g., hypertension, diabetes type II, hypercholesterolemia, etc.) also improve mobility and the underlying CNS mechanisms. Although we found an association between cardiovascular factors and gait, this association did not seem to modify the relationship between WMHs and gait speed. It is possible that cardiovascular factors may impact mobility through pathways that do not include WMHs.

We highlight two key strengths of our study. First, we applied automated WMH segmentation and volume quantification method in order to localize WMHs; majority of studies only examine total WMH volume. Specifically, our WMH localization method enabled us to identify WMHs located in different white matter tracts and hence, allowed us to investigate the impact of WMH location on gait speed. Second, we applied state-of-the-art reliable statistical methods for both data reduction and mediation analysis to extend our current understanding of how WMHs impact gait speed in older adults.

We recognize the limitations of our study. The cross-sectional design limits our understanding of the temporal relationship between WMHs and slowing gait. Our study sample consisted exclusively of independent community-dwelling older adults who were without significant physical and cognitive impairments. Thus, the results of our study may not generalize beyond this population and we may have underestimated both the direct and indirect effects of WMHs on gait speed. Furthermore, we did not use diffusion tensor imaging which is more sensitive to white matter abnormalities than T2-FLAIR MRI (Zheng et al., 2012). However, we did apply a DTI-based white matter atlas to register on our MRI data and segment the WMHs in different tracts. Finally, we used a very limited neuropsychological testing battery and thus, did not have a comprehensive assessment of cognitive function. Therefore, future studies should include a broader battery to advance our

understanding of which cognitive processes are most impacted by WMHs and are most relevant to mobility impairments in older adults.

Conclusion

Our current study suggests that executive functions and processing speed significantly mediate the impact of WMHs on gait speed. Current evidence suggests that both aerobic and resistance training has specific benefits for executive functions in older adults. Thus, our findings lend further support that exercise is an essential component in the maintenance of mobility across the lifespan – by improving physical function, such as balance and strength – but also cognitive function. Exercise may also have the potential to minimize the progression of WMHs and there are ongoing research exploring this possibility (Cyarto et al., 2012). Our results also suggest that mobility screening in older adults should have far greater attention to the assessment of cognitive processes of executive functions and processing speed.

Acknowledgments

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Appendix 1. The 21 anatomical WMH variables for this study

1. Total volume of WMHs

2. Anterior thalamic radiation, left

3. Anterior thalamic radiation, right

4. Corpus callosum, frontal

5. Corpus callosum, occipital

6. Corticospinal tract, left

7. Corticospinal tract, right

8. Cingulate, lower part left

9. Cingulate, lower part right

10. Cingulate, upper part left

11. Cingulate, upper part right

12. Inferior fronto-occipital fasciculus, left

13. Inferior fronto-occipital fasciculus, right

14. Inferior longitudinal fasciculus, left

15. Inferior longitudinal fasciculus, right

16. Entire superior longitudinal fasciculus, left

17. Entire superior longitudinal fasciculus, right

18. Superior longitudinal fasciculus, the branch to the temporal lobe, left

19. Superior longitudinal fasciculus, the branch to the temporal lobe, right

20. Uncinate fasciculus, left

21. Uncinate fasciculus, right

Appendix 2. Data reduction procedure

With Jackknifing resampling technique (Steps 2 to 4; Fig. 2a), the complete process was repeated for each participant in the X matrix separately (i.e., 253 times). On each run, one participant was assigned to the testing set, and the rest was assigned to the training set (Step 2; Fig. 2a). Then a Leave-One-Out Cross-Validation (LOOCV) Elastic Net was performed within the training set to minimize the mean squared error (Step 3; Fig. 2.a). The resulting optimal coefficients on training sets were tested on their independent test sets (Step 4; Fig. 2a).
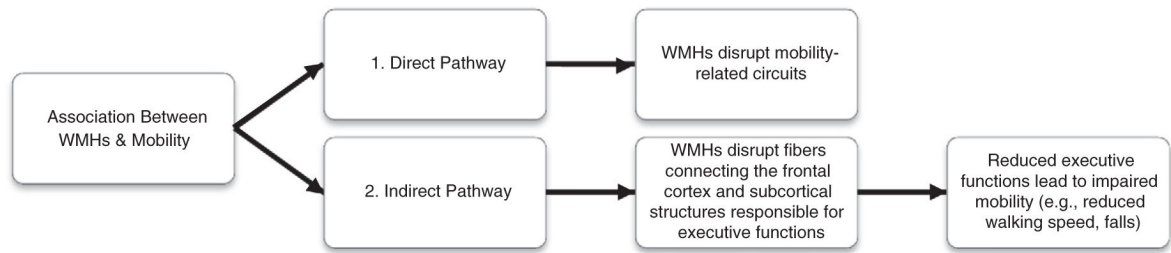
Fig. 1.
Two hypothesized pathways for the negative impact of WMHs on mobility: 1. Direct pathway—WMHs impair mobility by directly disrupting mobility-related circuits; 2. Indirect pathway—WMHs disrupt circuits responsible for cognitive function leading to impaired mobility.
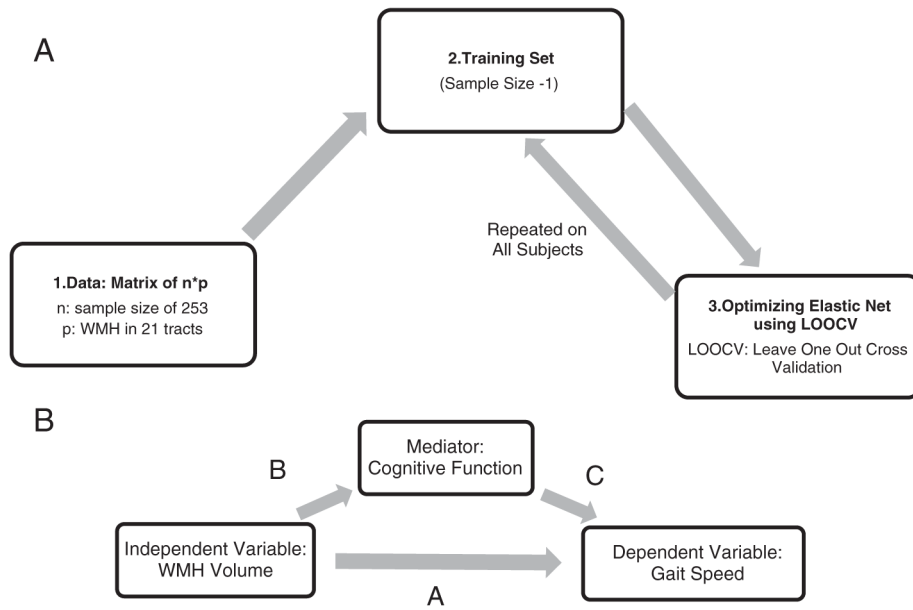
Fig. 2.
A) Variable selection using Elastic Net: Step 1 shows the $n * p$ data where n is the sample size and p is the size of the independent variables. Step 2 employs jackknifing technique to assign one participant to the test set and the rest to the training set. This loop is required to prevent from overfitting. In Step 3, the optimized model (i.e., minimal error using cross validation) is estimated for the training set using Elastic Net. The whole process is repeated over for all the participants to avoid any bias. B) The mediation model of cognitive function for the impact of WMH volume on gait speed. The path coefficient A represents the direct effect of WMH volume on gait speed, adjusted for age, BMI, and quadriceps strength. The product of path coefficients B and C represents the indirect effect of WMH volume on gait speed through cognitive function. The total effect is the sum of the direct effect and the indirect effect $(A + B * C)$.

Table 1

Descriptive statistics for covariates of age, BMI and quadriceps strength, education, height, independent WMH variables, dependent gait speed variable, and cognitive mediators.

Variables	Number	Minimum	Maximum	Mean	Standard deviation
Age	253	78	90	82.74	2.68
% Women	58%				
BMI	253	16.88	39.10	27.25	4.43
Quadriceps strength (newton meters)	253	18	140	64.53	23.98
Education (years)	313	1	3	2.37	0.71
Standing height (mm)	309	1390.50	1853.50	1621.62	95.34
% With chronic pain	53%				
% With hypertension	67%				
Total WMH volume[a]	253	$1.1 * 10^{-5}$	$2.69 * 10^{-2}$	$3.34 * 10^{-3}$	$4.11 * 10^{-3}$
ATRR WMH volume[a]	253	$Exp -8$	$4.31 * 10^{-3}$	$8.18 * 10^{-4}$	$7.54 * 10^{-4}$
CCF WMH volume[a]	253	$Exp -8$	$6.12 * 10^{-3}$	$5.20 * 10^{-4}$	$7.42 * 10^{-4}$
DSST	253	0	68	37.10	13.06
3MS	253	61	100	92.98	6.83
Gait Speed (m/s)	253	0.37	1.50	0.91	0.18

Abbreviations: BMI: body mass index, WMH: white matter hyperintensity, ATRR: anterior thalamic radiation right, CCF: corpus callosum right, 3MS: Modified Mini-Mental State Examination, DSST: Digit Symbol Substitution Test.

[a]WMH volumes are adjusted for total brain volume.

Table 2

The results of multivariable regression analysis for the effect of three selected WMH measures on gait speed.

WMH variables of interest:	Standardized beta [Model 1]	Standardized beta [Model 2]	Standardized beta [Model 3]	Standardized beta [Model 4]
Total WMHs	−0.146[*] [−0.257, −0.035]	−0.135[*] [−0.249, −0.023]	−0.1244[*] [−0.233, −0.015]	−0.109 [−0.218, 0.000]
ATRR WMHs	−0.152[**] [−0.262, −0.042]	−0.159[***] [−0.273, −0.048]	−0.130[*] [−0.238, −0.021]	−0.123[*] [−0.230, −0.016]
CCF WMHs	−0.114[*] [−0.225, −0.002]	−0.115[*] [−0.227, −0.003]	−0.090 [−0.200, 0.020]	−0.073 [−0.183, 0.037]

Model 1: Linear regression model for the effect of WMHs on gait speed, controlling for age, sex, BMI, quadriceps strength, education, and height.

Model 2: Linear regression model for the effect of WMHs on gait speed, controlling for age, sex, BMI, quadriceps strength, education, height, chronic pain, and prevalent hypertension.

Model 3: 3MS added to Linear regression Model 1 with the addition of 3MS as an independent variable.

Model 4: DSST added to Linear regression Model 1 with the addition of DSST as an independent variable.

Abbreviations: 3MS: Modified Mini-Mental State Examination, DSST: Digit-Symbol Substitution Test, WMHs: white matter hyperintensities, ATRR: anterior thalamic radiation right, CCF: corpus callosum frontal.

[*]
$p < 0.05$.

[**]
$p < 0.01$.

[***]
$p < 0.005$.

Table 3

The total, direct, and indirect effects for WMH volumes of total brain, ATRR and CCF, on gait speed are presented.

Variables of interest: WMH volumes	Total effect		Direct effect		Indirect effect through 3MS		Indirect effect through DSST	
	Unstandardized *B* (95% CI)	Standardized beta (95% CI)	Unstandardized *B* (95% CI)	Standardized beta (% of total)	Unstandardized *B* (95% CI)	Standardized beta (% of total)	Unstandardized *B* (95% CI)	Standardized beta (% of total)
Model 1: Total brain	−6.90** [−11.93, −1.88]	−0.15** [−0.25, −0.04]	−4.96* [−9.87, −0.06]	−0.10* (72%)	−0.60 [−2.02, 0.04]		−1.33[a] [−3.18, −0.35]	−0.02[a] (19%)
Model 2: ATRR	−41.31** [−68.49, −14.13]	−0.16** [−0.27, −0.05]	−32.13* [−58.57, −5.68]	−0.12* (78%)	−3.34 [−11.71, 0.23]		−5.84[a] [−14.93, −0.42]	−0.02[a] (14%)
Model 3:CCF	−29.42* [−57.49, −1.34]	−0.11* [−0.22, −0.005]	−17.59 [−45.04, 9.84]	−0.06 (60%)	−3.60 [−12.22, 0.00]		−8.21[a] [−19.79, −1.95]	−0.03[a] (27%)

All three models are adjusted for age, sex, body mass index, quadriceps strength, education, height, and prevalent hypertension.

The direct effect represents the association of WMH volume on gait speed adjusted for age, sex, BMI, quadriceps strength, and prevalent hypertension, when the effect of both cognitive tests on gait speed are taken into consideration. The indirect effect represents the effect of WMH volume on gait speed through cognitive function. The total effect is the sum of the direct effect and the indirect effect.

Abbreviations: WMH: white matter hyperintensity, ATRR: anterior thalamic radiation right, CCF: corpus callosum frontal, 3MS: Modified Mini-Mental State Examination, DSST: Digit-Symbol Substitution Test.

*
p < 0.05.

**
p < 0.01.

[a]
Statistically Significant based on 95% confidence interval.