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Compromised prefrontal structure and function are associated with slower walking in older adults

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ABSTRACT

Our previous work demonstrates that reduced activation of the executive network is associated with slow walking speed in a cohort of older adults from the MOBILIZE Boston Study. However, the influence of underlying white matter integrity on the activation of this network and walking speed is unknown. Thus, we used diffusion-weighted imaging and fMRI during an n-back task to assess associations between executive network structure, function, and walking speed. Whole-brain tract-based spatial statistics (TBSS) were used to identify regions of white matter microstructural integrity that were associated with walking speed. The integrity of these regions was then entered into multiple regression models to predict task performance and executive network activation during the n-back task. Among the significant associations of FA with walking speed, we observed the anterior thalamic radiation and superior longitudinal fasciculus were further associated with both n-back response speed and executive network activation. These findings suggest that subtle damage to frontal white matter may contribute to altered executive network activation and slower walking in older adults.

1. Introduction

Walking speed has long been established as a predictor of poor outcomes in older adults. Specifically, slow walking is one of Fried's defining criteria for frailty and is predictive of falls, morbidity, and mortality (Afilalo et al., 2010; Fried et al., 2001; Studenski et al., 2011). Slow walking has also been associated with poor cognitive outcomes, including impaired processing and psychomotor speed, poor global cognition, and dementia (Welmer et al., 2014; Soumaré et al., 2009; Atkinson et al., 2007; Dumurgier et al., 2016). With older age and associated changes in locomotor function, walking loses some of its automaticity and becomes increasingly dependent on several additional neural systems and cognitive processes (Yogev-Seligmann et al., 2008; Takakusaki, 2013; Woollacott and Shumway-Cook, 2002). One critical system is the executive (i.e., fronto-parietal) neural network, which underlies attention, working memory, multi-tasking, and awareness (Naghavi and Nyberg, 2005).

Previously, in a cohort of older adults from the Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston Study (MOBILIZE Boston Study), we found that increased activation of the executive network during an executive (working memory) task, as measured by functional magnetic resonance imaging (fMRI), was associated with both better task performance and faster walking speed (Jor'dan et al., 2017; Sorond et al., 2011). We further demonstrated that executive network activation mediated the relationship between the ability to deliver cerebral blood flow to frontal regions, as measured by transcranial Doppler ultrasonography (TCD), and walking speed.

The recruitment of neural networks, however, also relies upon the integrity of underlying white matter structure. Studies have shown that with age and disease, white matter tracts projecting from frontal executive control regions are susceptible to both damage and degeneration (Grambaite et al., 2011; Salat et al., 2005; Grieve et al., 2007). Ischemic damage, for example, as evident by frontal subcortical and periventricular white matter hyperintensities on T2 MRI scans, has been

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associated with slower walking speed and falls (Wakefield et al., 2010; Holtzer et al., 2014). Although this may represent irreversible damage, the observed relationships are variable – some older adults with white matter hyperintensities walk normally, while others without these macrostructural changes experience slow gait and falls (Sorond et al., 2011). For these individuals, micro-structural integrity, not detected in traditional MRI scans but rather with diffusion-weighted imaging, likely influences walking speed. For example, the micro-structural integrity of the genu of the corpus callosum, which connects the frontal lobes and promotes interhemispheric communication, has been associated with both cognitive and walking outcomes (van der Knaap and van der Ham, 2011; Bhadelia et al., 2009). This is likely because intact axonal integrity is required for neural signaling and communication between task-relevant regions and networks that are necessary for optimal gait and executive functioning (Bennett and Rypma, 2013). We propose that micro-structural integrity, particularly in executive network hubs in the frontal lobes, will influence both the ability to activate the executive network as well as maintain fast walking speed.

Thus, in the current study, we utilized diffusion tensor imaging to determine how the integrity of normal-appearing white matter is associated with walking speed and the ability to activate executive regions in the brains of older adults. We hypothesized that the micro-structural integrity of frontal regions underlying executive network hubs would be associated with walking speed. Further, we hypothesized that this same frontal white matter would also be associated with executive network activation, suggesting a neurocognitive mechanism by which white matter alterations may impact gait.

2. Material and methods

2.1. Participants

Sixty-eight older adults were recruited from the MOBILIZE Boston Study to undergo a walking assessment and MRI protocol. The original 2005–2008 cohort included Boston-area residents 70+ years of age (or > 65 if living with an already-enrolled participant) able to walk 20 ft without personal assistance. They had no history of neurological or mental illness, at least a 12th grade education, and considered themselves to be generally healthy. Mini-Mental State Exam (MMSE) scores ranged from 24 to 30 at the time of enrollment. A full description of the MOBILIZE Boston Study is provided elsewhere (Leveille et al., 2008). To qualify for the current study, individuals had to be able to complete the full protocol, which included a walking assessment and a 90-min MRI session. Participants with an updated medical history of Parkinson's disease or stroke, or reported difficulty while walking were also excluded from participation. The Hebrew SeniorLife and VA Boston Healthcare System IRBs approved this protocol and written consent was acquired from all participants.

2.2. Study design

During the first visit at the Hebrew SeniorLife Clinical Research Laboratory, participants completed a gait assessment where they quietly walked at a preferred speed. This condition had two trials consisting of three separate passes over a 16-ft GAITRite mat (CIR Systems Inc., Havertown, PA), starting from a standing position. Walking speed (m/s) was computed by dividing distance by time, which was quantified from each full step that occurred over the mat within each trial. This measure was then averaged across the six passes.

Participants then returned for a second visit (11 ± 13 days later) for an MRI at the VA Boston Healthcare System. During this protocol, a T2-weighted fluid-attenuated inversion recovery (FLAIR) scan (TR = 6000 ms, TE = 279 ms, 1.0 mm isotropic res, 256 × 256 mm, TI 1: 2100 ms, 160 slices/slab) was collected to assess macrostructural white matter integrity. Diffusion data were collected to assess micro-structural white matter integrity (Acquisition Type 2D, 60 diffusion directions, b value = 700, FA 90°, TR = 10,000 ms, TE = 103 ms, 2.0 mm isotropic resolution, 128 × 128 mm). A T1-weighted MPRAGE was collected for whole-brain high-resolution anatomy (TR = 2530 ms, TE = 3.35 ms, 1.0 mm isotropic res, 256 × 256 mm, 176 slices). Finally, participants performed a modified *n*-back task during a gradient-echo echo-planar sequence scan (TR = 2000 ms, TE = 30 ms, flip angle = 90°, 3.75 mm slice thickness, 3.0 × 3.0 mm in-plane resolution, 38 slices). These neuroimaging sessions were performed across two 3 T Siemens MRI scanners (TIM Trio and Prisma Fit) with a 12- and 20-channel head coil. To consider inter-scanner differences, scanner was included as a covariate in statistical analyses.

2.3. MRI data pre-processing

2.3.1. T2-weighted FLAIR

To assess the extent of macrostructural damage, white matter hyperintensity (WMH) maps were generated using the widely-used Lesion Growth Algorithm (LGA) (Schmidt et al., 2012) as implemented in the Lesion Segmentation Toolbox (v1.2.3) for SPM8. This program was chosen as an automated method to reduce human error in the absence of a trained radiologist, while quantifying WMH volume as burden for our analyses. Although a recent study has found automated lesion segmentation tools can have difficulty differentiating confluent areas and thus underestimate white matter lesion load (García-Lorenzo et al., 2013), LGA is a time- and cost-effective alternative to manual raters and has a strong correlation with manual lesion segmentation (Egger et al., 2017). The algorithm calculated lesion probability maps from co-registered T2 FLAIR and T1 images, which were then visually inspected and manually edited for minor false-positives. The volume of WMH lesions was then normalized as a percentage of brain parenchyma volume ($WMH_{\%PBV}$).

2.3.2. Diffusion-weighted imaging

Standard pre-processing for diffusion-weighted data was performed using the FSL (v5.0.9; University of Oxford, UK) and AFNI (v17.2.10) softwares (Smith et al., 2004; Cox, 1996). Data were corrected for head movement and eddy currents, skull-stripped, masked, and fit for diffusion tensors. Voxel-wise maps of scalars were thresholded to exclude FA of tissue < 0.2, normalized to the MNI152 template, and skeletonized for group-level Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006). Global measures of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were then calculated by averaging across these skeletonized tracts.

2.3.3. Functional MRI (fMRI)

Described more fully in our previous work (Jor'dan et al., 2017), functional data were collected during a modified *n*-back task with Identify-X (IdX; i.e., control) and 2-back (i.e., working memory) conditions. During this 6-min task, there were four 1.5-min blocks, two of the control (IdX) and two of 2-back condition. During the IdX, participants were asked to press one button on a response box to target letter "X" (22% of trials), and another button for all other letters. During the 2-back, participants were asked to press one button to any letter repeated two positions back, and another button for all other letters. *N*-back performance was evaluated with percent accurate target detections (% correct of 8 appearances) per condition. Response time was also reported but should be interpreted with caution since accuracy was emphasized in the instructions given to participants, and their response window was long (3 s stimulus duration +2 s inter-trial interval).

Following acquisition, functional data were registered to the third volume, aligned to T1 anatomy, normalized into the Talairach standard space, smoothed with a 8-mm kernel, and scaled to a percentage of the voxel mean. A general linear model was then performed to generate a 2-back > IdX contrast, while removing the effects of 6-degrees of motion, cerebral spinal fluid, white matter, and global signal. Individuals with > 30% of time points with > 0.5 mm in sudden movement were removed from the analysis ($n = 8$). This resulted in voxel-wise

activation maps for the 2-back > IdX contrasts, which were then averaged across regions belonging to Network 6 (fronto-parietal/executive control network) of the 7-network Yeo 2011 parcellation (Yeo et al., 2011). This atlas of functional networks, derived from the resting-state fMRI of 1000 healthy adults, allowed reliable and unbiased localization of regions involved in the fronto-parietal/executive control network.

2.4. Statistical methods

To determine the best clinical predictors of walking speed, the following factors were entered into a mixed step-wise regression model with minimum BIC stopping rule: age, sex, BMI, MMSE, and self-reported medical history (e.g., hypertension, diabetes, cardiovascular disease) status. The selected covariates were then entered into subsequent multiple linear regression models to assess relationships between measures of white matter integrity and walking speed and/or fMRI activation. These analyses were performed using the JMP software (Pro 11; SAS Institute, Cary, NC).

To assess regional white matter, walking speed was entered as a predictor into voxel-wise TBSS models of skeletonized tracts. The Randomise tool was used to carry out 5000 permutations of Threshold-Free Cluster Enhancement (TFCE), which yielded maps of significance adjusted for covariates and corrected for multiple comparisons and family-wise error. These maps were then parsed according to Johns Hopkins (JHU) ICBM DTI-based white matter tract probability atlas and regional averages of significant voxels in each tract were used to predict *n*-back activation. For all analyses, statistical significance was set at $p < .05$.

3. Results

3.1. Participant results

Table 1 summarizes the demographic and clinical characteristics, and *n*-back task performance for participants enrolled in the study. The final sample consisted of 68 elderly older adults (84.3 ± 4.4 years; 23 males) with a wide range of comorbidities. WMH burden was not reported for six participants missing T2 FLAIR scans.

Table 1
Population demographic, clinical, and cognitive performance characteristics.

	DTI	DTI + fMRI
N	68	49
Female (%)	66	72
Age (years)	84.3 ± 4.4	83.9 ± 4.2
BMI	25.6 ± 4.9	25.3 ± 5.1
CVD (%)	10	12
Atrial Fibrillation (%)	21	16
Hypertension (%)	56	49
High Cholesterol (%)	54	53
Diabetes (%)	4	6
Osteoarthritis (%)	43	37
Rheumatoid Arthritis (%)	16	18
Any Arthritis (%)	51	47
Mini-Mental State Exam (MMSE)	26 ± 2	26 ± 2
Gait assessment		
Speed during quiet walk (m/s)	1.1 ± 0.3 (0.4, 1.9)	1.2 ± 0.3 (0.4, 1.9)
Global measures of WM integrity		
WMH volume (%PBV)	0.8 ± 0.7	0.9 ± 0.8
Global FA	0.4 ± 0.04	0.4 ± 0.03
N-back performance		
IdX correct target rate (%)		97 ± 7
IdX mean RT (s)		0.8 ± 0.2
2-back correct target rate (%)		81 ± 24
2-back mean RT (s)		1.2 ± 0.3

Note: Data = mean ± SD or percentage. DTI = diffusion tensor imaging; fMRI = functional magnetic resonance imaging; BMI = body mass index; CVD = cardiovascular disease; WMH = white matter hyperintensity; PBV = brain parenchyma volume; FA = fractional anisotropy; IdX = Identify X condition; RT = response time.

Of the 68 participants, 49 were included in the secondary fMRI analyses. The nineteen excluded exhibited excessive movement during the scan ($n = 8$), did not comply with *n*-back task instructions ($n = 4$), had missing performance due to response keypad failure or computer error ($n = 4$), or did not have fMRI during their scanning session ($n = 3$). When we compared these participants to the fMRI-included dataset ($n = 49$), those excluded had lower MMSE scores ($\chi^2 = 4.25$, $p = .039$) and tended to walk slower ($\chi^2 = 3.04$, $p = .08$) than the rest of the cohort. This indicates that our fMRI subset was a higher functioning group, though the groups did not otherwise differ.

3.2. Clinical associations with walking speed

To consider the clinical characteristics that were most strongly associated with walking speed, we ran a step-wise regression procedure (see Methods). The final model revealed that age, sex, BMI, and arthritis best explained variance for quiet walking ($F(4,63) = 13.34$, $p < .0001$, $R^2 = 0.46$, $R^2_{Adj} = 0.42$), such that increased age ($\beta = -0.41$, $t = -4.37$, $p < .0001$), female sex ($\beta = -0.31$, $t = -3.33$, $p = .00015$), increased BMI ($\beta = -0.33$, $t = -3.55$, $p = .0007$), and arthritis ($\beta = 0.23$, $t = 2.46$, $p = .0165$) predicted slower walking. Of note, although MMSE was found to be independently associated with walking speed ($\beta = 0.32$, $t = 2.79$, $p = .007$), it was not selected by the step-wise procedure.

3.3. Global WM associations with walking speed

Associations with white matter integrity were then investigated at the global level. Higher overall FA was associated with faster walking speed in the cohort ($\beta = 0.27$, $t = 2.32$, $p = .024$). This association ($\beta = 0.24$, $t = 2.06$, $p = .04$) remained after adjusting for the above confounders (i.e., age, sex, BMI, arthritis) and scanner ($F(6,61) = 7.99$, $p < .0001$, $R^2 = 0.44$, $R^2_{Adj} = 0.39$). The degree of WMH burden (i.e., $WMH_{\%PBV}$) was not associated with walking speed ($p > .4$), neither was it associated with global FA ($p > .4$).

3.4. Regional WM associations with walking speed and N-back activation

At the voxel-wise level, TBSS linear regression models revealed extensive white matter associations with walking speed (Figs. 1, 2A), such that as FA increased and AD/RD/MD decreased, walking speed increased. These associations survived correction for age, sex, BMI, arthritis, and scanner.

When these voxels were broken into the 20 JHU template tracts (Fig. 2B, Table 2), the gait-specific regional FA was then treated as the main predictor in a multiple regression with task-related activation in the executive control network as the dependent measure (see Methods) in the participants with fMRI ($n = 49$). Regions associated with executive network activation and surviving full covariate correction included the left ($\beta = 0.29$, $t = 2.28$, $p = .028$) and right ($\beta = 0.34$, $t = 2.41$, $p = .021$) anterior thalamic radiation, and the left ($\beta = 0.32$, $t = 2.44$, $p = .019$) and right ($\beta = 0.41$, $t = 2.87$, $p = .0064$) superior longitudinal fasciculus (Figs. 2C, 3). Similar to our previous reports (Jor'dan et al., 2017), decreased activation of the executive network for this contrast was associated with slower walking speed ($r_s = 0.32$, $p = .027$).

3.5. Associations with n-back performance

Although exploratory, we then examined the relationship between n-back task performance and walking speed, gait-related FA regions, and executive network activation. Specifically, we examined the mean

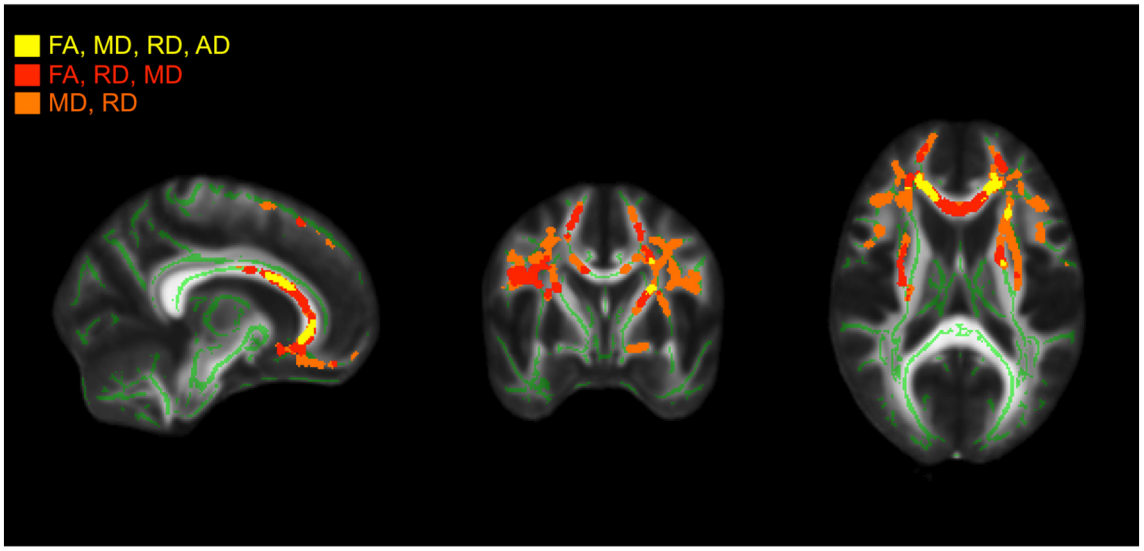

Fig. 1. Regions of white matter showing a significant relationship (corrected $p < .05$) between walking speed and diffusion parameters, such that participants exhibiting greater white matter integrity (i.e., higher FA, lower AD, RD, and MD) walked faster. (Left = Right).

response time during the IdX and 2-back conditions, as well as accuracy for the 2-back condition (% targets detected; see Methods). We did not examine accuracy on the IdX condition, since all but nine participants were at ceiling.

Slower mean RT during the IdX condition was associated with slower walking ($\beta = -0.28$, $p = .012$) and decreased FA in the right anterior thalamic radiation ($\beta = -0.33$, $p = .024$). Slower mean RT during the 2-back condition was associated with decreased FA in the right superior longitudinal fasciculus ($\beta = -0.35$, $p = .015$). These relationships are corrected for scanner, age, and sex. There were no

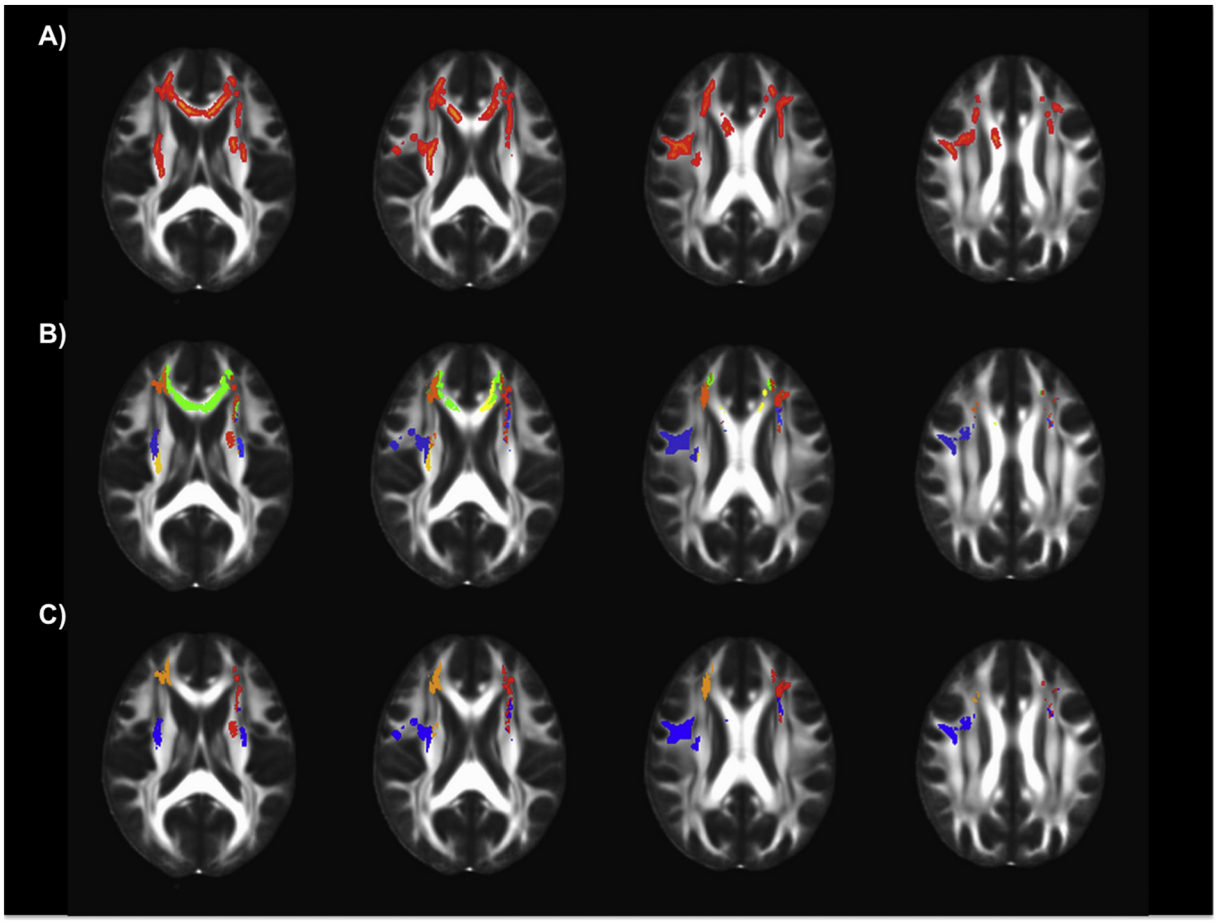

Fig. 2. Regional FA associations with walking speed (A) adjusted for all covariates and corrected to $p < 0.05$, (B) broken into JHU tracts (ref. Table 2), and (C) found to be significantly associated with activation after adjusting for scanner, age, and sex. Voxels surviving adjustment were located in the left and right anterior thalamic radiation (red/yellow), and the right superior longitudinal fasciculus (blues). (Left = Right).

Table 2
Complete list of associations between regional FA and walking speed, after adjusting for all covariates, according to the Johns Hopkins' white-matter tractography atlas.

JHU Tract #	JHU Atlas Label	Surviving Voxels
1	Anterior thalamic radiation (L)	674
2	Anterior thalamic radiation (R)	684
3	Corticospinal tract (L)	< 20
4	Corticospinal tract (R)	260
5	Cingulum (cingulate gyrus) (L)	133
6	Cingulum (cingulate gyrus) (R)	25
7	Cingulum (hippocampus) (L)	0
8	Cingulum (hippocampus) (R)	0
9	Forceps major	0
10	Forceps minor (extended corpus callosum)	2750
11	Inferior fronto-occipital fasciculus (L)	60
12	Inferior fronto-occipital fasciculus (R)	283
13	Inferior longitudinal fasciculus (L)	0
14	Inferior longitudinal fasciculus (R)	0
15	Superior longitudinal fasciculus (L)	194
16	Superior longitudinal fasciculus (R)	1294
17	Uncinate fasciculus (L)	40
18	Uncinate fasciculus (R)	189
19	Superior longitudinal fasciculus (temporal) (L)	< 20
20	Superior longitudinal fasciculus (temporal) (R)	< 20

significant behavioral associations with activation, nor any associations with 2-back accuracy. In sum, slowing of response time during the task was associated with slower walking speed and decreased FA in frontal regions.

4. Discussion

In the current study, we demonstrate that white matter integrity underlying frontal regions, as measured by diffusion-weighted imaging, is associated with walking speed in a cohort of very elderly older adults from the MOBILIZE Boston Study. Though others have also observed the association between white matter integrity and walking speed (Holtzer et al., 2014), we are the first to report associations within normal-appearing tracts underlying the prefrontal cortex. Further, we observed that decreased frontal white matter integrity was associated with weaker executive network activation, as well as slower performance during an executive function (working memory) task. Taken together, these findings support the importance of frontal lobe microstructural integrity in executive network function and mobility, and suggest that the decline in walking speed observed in advanced age may be due in part to white matter degeneration and demyelination in brain regions responsible for executive control and gait.

Using diffusion-weighted imaging, we found several associations between gait speed and the integrity of normal-appearing white matter. Among these regions (see Table 2), we report walking associations with the anterior thalamic radiation and superior longitudinal fasciculus underlying the prefrontal cortex. Lower FA in these areas was significantly associated with a reduction in executive network activation and prolonged response times during the *n*-back task, which were independently associated with slower walking speed. These findings support previous literature suggesting that functional and structural abnormalities in the dorsolateral prefrontal cortex (DLPFC), an executive network hub, contributes to both slower processing speed (Hillary et al., 2010) and walking speed (Rosano et al., 2008). It further explains why other populations with executive impairments (Hajjar et al., 2011; Hajjar et al., 2009; Kuo and Lipsitz, 2004; Pugh and Lipsitz, 2002; Killane et al., 2014) and compromised executive network integrity (Yuan et al., 2015; Lo et al., 2017) may also exhibit declines in mobility.

We additionally observed that the integrity (as measured by FA) and myelination of crossing fibers (as measured by RD) within the forceps minor, which connects the lateral and medial frontal lobes through the genu of the corpus callosum, was associated with walking speed ability. This finding is consistent with previous studies reporting the genu as being associated with gait (Bhadelia et al., 2009; Moretti et al., 2005). Surprisingly, the integrity of this structure was not related to executive network activation in our cohort, though lower FA was associated with increased response time to the control task ($\beta = -0.33$, $p = .029$) and has been separately associated with mental slowing (Jokinen et al., 2007). This may be due to insufficient power of our study to detect a significant relationship between forceps minor structure and executive network activation, or a role of the forceps minor in gait, other than through the executive network. Nevertheless, our frontal associations provide potential mechanisms for recent studies using intrinsic functional connectivity, as measured by resting-state fMRI (rs-fMRI), that demonstrate an involvement of the executive network, as well as attentional (Lo et al., 2017), sensorimotor, visual, and limbic networks (Yuan et al., 2015) in normal walking and walking-while-talking paradigms.

While we did not find that accuracy on the n-back task was associated with gait and gait-related FA, we did find that speed on the task, most notably the control (Identify-X) condition, was associated with both measures. On the one hand this suggests that while executive network activation due to the working memory demands of a 2-back task are sensitive to gait and gait-related FA, the task itself is not necessarily sensitive to the executive functioning consequences of reduced

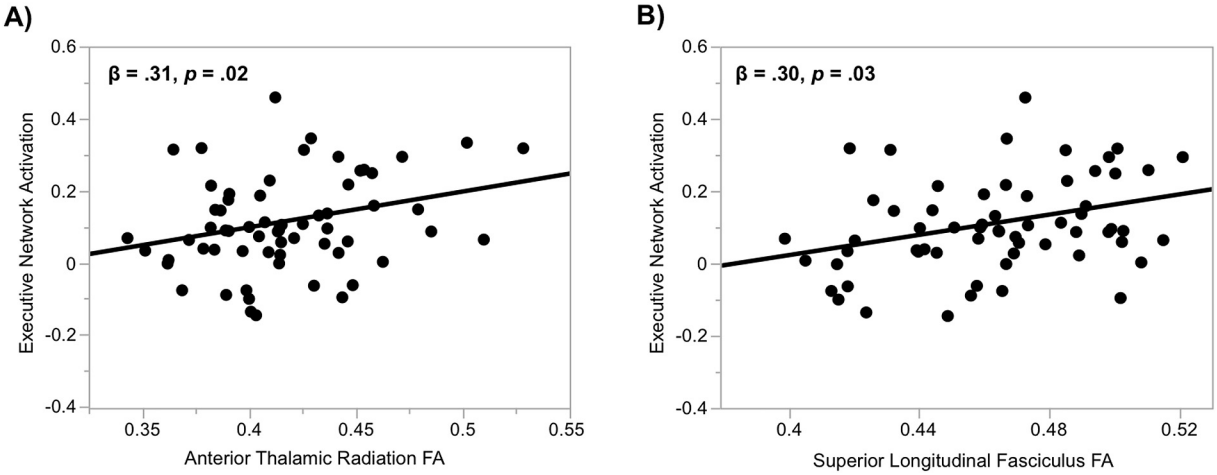

Fig. 3. Scatter plot with line of best fit illustrating positive associations between *n*-back executive network activation and bilateral gait-associated FA in the (A) anterior thalamic radiation and (B) superior longitudinal fasciculus.

activation and white matter integrity. Namely, we speculate according to neural compensation models (Bennett and Rypma, 2013) that reduced executive functioning co-occurs with the loss of white matter, executive activation, and slower gait. On the other hand, it is interesting that slowing on the control task, which can be characterized as a task of sustained attention, was sensitive to gait and gait-related FA. This suggests that more basic cognitive functions, like attention, may also contribute to loss of mobility and be impacted by frontal white matter loss, as attention relies on overlapping neural resources as executive function, and may underlie and modulate performance on executive tasks (Maguire et al., 2018; O'Halloran et al., 2014; Fortenbaugh et al., 2015; Fortenbaugh et al., 2017). This was further supported by observed relationships between MMSE scores and walking speed, suggesting broader cognitive dysfunction in slow walking. Future studies with a more comprehensive neuropsychological battery would be needed to further clarify the cognitive specificity of these white matter and gait relationships.

The presence of macrostructural damage, as measured by the volume of WMH, was neither associated with walking speed, nor global normal-appearing white matter microstructure. This was not expected, as several other studies have found compromised mobility with WM pathology, especially in frontal areas (Whitman et al., 2001; Rosano et al., 2010). We suspect these null findings were due to a lower burden of WMH in our population than in the slow walkers reported in previous studies (Sorond et al., 2011). Nevertheless, in this population of older adults, we found regional associations between walking speed and WM microstructure, such that as the FA in frontal regions decreased, individuals tended to walk slower. Since decreased FA probably precedes the development of WMH seen on T2-weighted FLAIR MRI scans (Maillard et al., 2013), DTI may be more sensitive to early microstructural neurodegenerative changes that impair gait in older adults.

4.1. Limitations

Because of the limitations of subject inclusion unique to MRI research, the generalizability of our current sample is limited to very elderly adults with intact mobility who qualify for MRI scans. We also note this group represents elderly adults with relatively low white matter burden and “fast” walking speed, compared to Sorond and colleagues, which found high degrees of white matter burden to be associated with walking speed (Sorond et al., 2011). Nevertheless, our sample provides evidence that decreased executive network activation and lower frontal structural integrity are associated with slower walking in this relatively high functioning cohort. However, it should be noted that the current study does not fully characterize the role of all white matter tracts in walking speed, but only those that are independent of confounders (e.g., age). As our findings reflect regions found to be independent of age, other WM matter regions tied to age (and close correlates such as cognition, neurodegeneration, and physical conditions) deserve further attention. Nevertheless, our approach represents a conservative approach that isolates neural contributors to gait vs. more generalized age-related factors. The current study is also limited by the fMRI task used. Though robust and challenging (note in Table 1 the difference in accuracy moving from IdX to 2-back for most individuals), the *n*-back task did not allow a great distribution of performance. Thus, we will consider more sensitive cognitive measures of working memory and attention, especially in populations with a range of cognitive function as indicated by the reported MMSE scores, in future studies. A final limitation is that we were unable to account for the role of pain in walking speed. Chronic pain is very common in the older adult population, impairs walking speed, and has been associated with changes in cognition (van der Leeuw et al., 2018), white matter (Cruz-Almeida et al., 2017), and DLPFC structure (Apkarian et al., 2004). Although pain measures were not collected in the present study, we do believe that interference was minimized in the current cohort due to study design – those with severe pain or physical restrictions would not be able to comfortably complete the demanding protocol.

4.2. Conclusions

Results of this study indicate that the neural structure of frontal brain regions is associated with both executive network activation and the walking speed of older adults. These findings were regionally specific and independent of WM lesions as detected by traditional MRI. These findings suggest that interventions that can prevent frontal white matter damage, enhance frontal lobe activation, or exploit the reserve capacity of other brain regions should be explored to maintain or enhance the mobility of older adults.

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