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Supplementary motor area connectivity and dual-task walking variability in multiple sclerosis

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ABSTRACT

Background: Despite the prevalence of dual-task (e.g., walking while talking) deficits in people with multiple sclerosis (MS), no neuroimaging studies to date have examined neuronal networks used for dual-task processing or specific brain areas related to dual-task performance in this population. A better understanding of the relationship among underlying brain areas and dual-task performance may improve targeted rehabilitation programs. The objective of this study was to examine relationships between neuroimaging measures and clinical measures of dual-task performance, and reported falls in persons with MS.

Materials and methods: All participants completed measures of dual-task performance, a fall history, and neuroimaging on a 3 T MRI scanner. Spearman correlations were used to examine relationships among dual-task performance, falls and neuroimaging measures.

Results: Eighteen females with relapsing-remitting MS [mean age = 45.5 ± 8.2 SD; mean symptom duration = 12.3 ± 6.7 years; Expanded Disability Status Scale median 2.25 (range 1.5–4)] participated in this study. Structural imaging measures of supplementary motor area (SMA) interhemispheric connectivity were significantly related to dual-task walking variability.

Conclusions: The SMA interhemispheric tract may play a role in dual-task performance. Structural neuroimaging may be a useful adjunct to clinical measures to predict performance and provide information about recovery patterns in MS. Functional recovery can be challenging to objectively report in MS; diffusion tensor imaging could show microstructural improvements and suggest improved connectivity.

1. Introduction

Individuals with Multiple Sclerosis (MS), a debilitating neurodegenerative disease, experience declines in walking ability [1] and cognitive function [2]. Up to 60% [3] of individuals with relapsing remitting MS (RRMS) report cognitive impairments. Divided attention, the ability to respond to multiple stimuli simultaneously, is one of the most common domains affected [4]. Difficulty dividing attention during gait motor-cognitive (i.e. a motor task paired with a simultaneous cognitive task) dual-tasks [5] has been linked with falls in MS [6].

A better understanding of the underlying neural network responsible for successful dual-task performance may provide insight into the etiology of falls in the MS population. This is particularly important given a large body of evidence suggesting that dual-task practice in rehabilitation results in improvements in function [7,8]. Prior work has utilized fMRI to examine neuronal networks. Among healthy adults, the supplementary motor area (SMA) which is located just anterior to the primary motor cortex and traditionally associated with planning and initiation of bimanual and sequential movements [9], has been linked with dual-tasking [10,11], task switching [12], and interlimb coordination [13]. Similarly, dual-tasks are associated with activation of SMA [14] and other prefrontal regions [14,15] in elderly adults. Dual-task walking is associated with greater functional connectivity in the SMA and prefrontal regions compared to single-task walking in elderly adults on resting state fMRI [16]. Structural neuroimaging has not been explored in the context of dual-task performance. Diffusion tensor imaging (DTI) quantifies the diffusion of water within tissues to provide an in vivo model of white matter integrity and microstructural damage [17]. The primary outcomes of DTI are fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD);

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higher FA and lower MD, AD and RD values indicate a greater degree of white matter integrity. Damage to white matter tracts affecting neuronal networks in the SMA could be related to dual-task deficits in people with MS.

Despite the prevalence of dual-task deficits in people with MS, no structural neuroimaging studies to date have examined the relationship among specific brain areas and dual-task processing. Therefore, the objectives of this study were to a) determine brain activation patterns in the SMA with fMRI and connectivity between interhemispheric SMA with DTI; and b) examine relationships between neuroimaging (i.e., structural and functional) measures, and clinical measures of dual-task performance, as well as reported falls. We hypothesized that greater activation during a motor task and/or axonal integrity of the SMA would be related to better dual-task performance and fewer reported falls in individuals with MS.

2. Materials and methods

Participants were recruited from a parent study exploring training effects of video-game exercise. The inclusion criteria were dictated by the parent study, and all data analyzed for this study was assessed at baseline in a single laboratory session. Inclusion criteria included 30–59 years of age, a diagnosis of RRMS using the 2010 McDonald criteria [18], physically inactive (no > 30 min of structured exercise weekly), and an Expanded Disability Status Scale (EDSS) score between 1.0 and 5.5. Participants were excluded if they were unable to receive an MRI or reported an orthopedic, neurologic or cognitive impairment that would limit participation in study assessments. All eligible individuals with MS participated in a single testing session that included a mobility assessment and a multi-modal 3 T MRI. This study was approved by the Institutional Review Board at The Ohio State University. All participants signed consent forms prior to participation. Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at The Ohio State University [19].

2.1. Clinical measures of dual-task performance

2.1.1. GaitRite

Gait parameters were acquired with the GAITRite electronic walkway (V3.9, MAP/CIR Inc.; Franklin, NJ), which records spatio-temporal measures of gait and is reliable and valid for use in individuals with MS [20]. Individuals ambulated across the GAITRite for three trials of each of two conditions: forward at their self-selected comfortable pace (FW) and forward with a cognitive task of serial 3 subtraction starting at 97 (FWC). Trials for each condition were averaged and coefficients of variability (CV) were calculated (where CV = mean/standard deviation). We a priori chose to examine a minimal number of spatial and temporal measures (i.e. stride length, stance time, double support % and their CVs) as well as velocity. These measures were chosen because stride length, stance time, and double support have been shown to relate to balance measures in older adults [21], individuals with MS [22], and other neurodegenerative disorders [23].

2.1.2. Walking While Talking Test (WWTT)

Walking While Talking Test (WWTT) is a reliable and valid test to identify older individuals at high risk for falls [24]. The test is performed and timed under three conditions: 1) walk 40 ft with a 180° turn at the midpoint; 2) condition 1 + recite the alphabet aloud (WWTT-Simple); 3) condition 1 + recite alternate letters of the alphabet aloud (WWTT-Complex) [24]. Poor performance on the WWTT-Complex (> 33 s) accurately predicts elderly fallers [24] and is related to falls in other neurodegenerative conditions [25].

2.1.3. Timed Up and Go (TUG)

Timed Up and Go (TUG) requires the participant to stand from a chair, walk 10 ft, turn, walk back and sit down [26]. The TUG is reliable in MS [27]. The TUG-Cognitive requires performance of the TUG with a simultaneous serial-3 subtraction task; this modification of the TUG measures dual-task performance. A time of > 15 s to complete the TUG-Cognitive accurately predicts fallers in MS with a sensitivity of 73% [28].

2.2. Fall history

All participants self-reported the number of falls in the past week, past 2 months, and past 6 months.

2.3. MRI acquisition

All participants with MS were scanned on the same Siemens 3 T Magnetom Trio scanner. High resolution structural images were collected using a 3D magnetization prepared rapid gradient echo imaging (MPRAGE) protocol (160 contiguous axial slices; TE/TR/TI 4.68/2000/950 ms; 256 mm FOV; 1.0 × 1.0mm^2 in-plane resolution). To identify white matter lesions, a T2-weighted fluid attenuated inversion recovery (FLAIR) (60 axial slices; TE/TR 7.3/14000 ms; 256 mm FOV; 0.8 × 0.8mm^2 in-plane resolution) was acquired. Diffusion tensor images were acquired in the axial plane (TE/TR 85/8300 ms; 288 mm FOV; voxel sizes 2.0 × 2.0mm^2; b-values 0 and 800 s/mm^2) with diffusion gradients in 64 directions.

Functional images (34 slices, TE/TR 28/2000 ms; 220 mm FOV; voxel size 3.4 × 3.4mm^2) were collected in a block design with 40 s epochs of active ankle movement, alternating with rest. During each active epoch, the participants dorsi- or plantar-flexed their right ankle in response to arrows pointing up or down, separated by a rest cue, presented at 1 Hz. Ankle dorsiflexion fMRI paradigms have been previously utilized in individuals with MS [29] and stroke [30]. We a priori chose to examine only the SMA, rather than all motor areas, with functional imaging.

2.4. Imaging analysis

2.4.1. Lesion load analysis

T2 FLAIR images were processed to localize white matter hyperintensities (Jim 6.0, Xinapse Systems, Essex, UK). Lesions were identified manually to create a ROI mask, which was applied to a fuzzy connectivity algorithm [31] to extend the manually identified regions into a 3D representation of lesions based on fuzzy affinity between adjacent voxels. The fuzzy connectedness threshold was set to 0.62 with an associated probability weighting set at 0.25. The fuzzy connectedness value measures each manually selected region of interest's location and size to an MS lesion template created by the Xinapse research team, while affinity, or probability weighting between pixels, takes into account the degree of adjacency among voxels as well as the similarity of their intensity values.

2.4.2. Functional magnetic resonance imaging analysis

Motion correction [32], non-brain removal [33], and spatial smoothing were applied to allow for measurement of the functional activation in each of our participants in response to the ankle-motor task (fMRIB, Oxford, UK) [34]. Functional images from each participant were spatially co-registered with their high resolution image and a standard MNI152 brain using the affine transform tool [35] to create subject-specific stereotaxic templates and reduce registration bias due to individual differences in brain structure.

First level analysis of functional scans was carried out with Z > 2.33 and a corrected cluster significance threshold of $p = .01$. EDSS was entered as a covariate, but did not significantly contribute to the group analysis. ROI analysis of the SMA was calculated using FSL's Featquery and predefined masks from the Harvard Oxford Cortical Probability Atlas (MNI152 space with FLIRT normalization). Mean (i.e., mean activation of all voxels) and peak z-statistics (i.e., voxel with peak

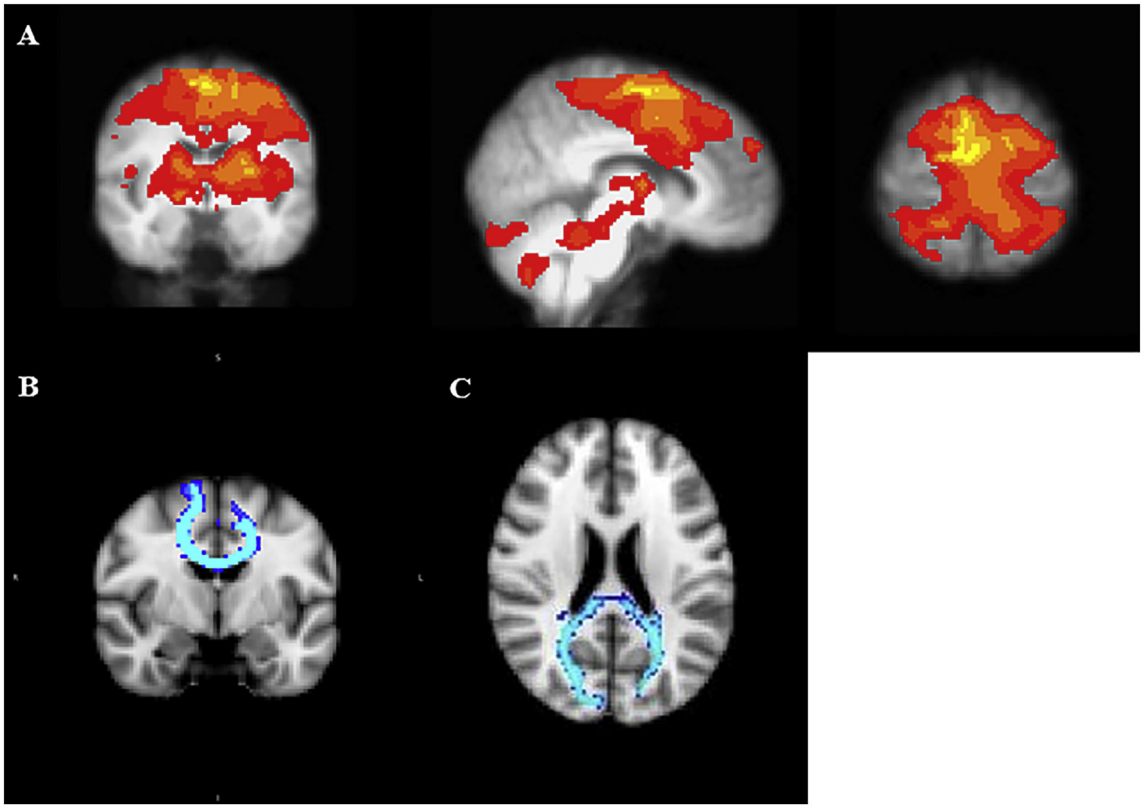

Fig. 1. fMRI data from individuals with MS showing A) group peak activation in the SMA (X = 41, Y = 60, Z = 67) between the active (ankle dorsiflexion) and rest conditions in coronal, sagittal and axial planes. Region of interest analyses performed in FSL Featquery with a 5 mm spherical region of interest mask of the SMA formed around the SMA peak activation voxel. Tractography models in representative participants demonstrating successful modeling of the B) interhemispheric SMA (coronal view) and C) interhemispheric V4 (axial view) connectivity. Supplementary Motor Area (SMA).

activation) were calculated; peak z statistic was considered to represent the underlying neural activity [36].

2.4.3. Diffusion tractography reconstruction

Images were corrected for head movement and eddy current distortion. The tensor model was then fitted to the preprocessed diffusion images to generate FA and eigenvector images (fMRIB Diffusion Toolbox). SMA activity during the fMRI was used to localize the SMA region of interest along with the Harvard-Oxford Cortical Probability Atlas for tractography. Masks were created to standardize tractography across participants. Seed and target masks were created in the sagittal plane to track from the left SMA to the right SMA. Eighty-eight voxel seed and target masks were placed 8 mm from the midline in the juxtapositional lobule cortex (Harvard-Oxford Cortical Probability Atlas). Both a 119-voxel mask corresponding to the middle one-third of the corpus callosum and the subject's individual white matter mask were used as waypoint masks. An axial/frontal exclusion mask was applied below the level of the corpus callosum to improve the sensitivity of the tractography. Finally, a termination mask was applied 2 mm lateral to the target mask, and probabilistic tractography was used to model the SMA interhemispheric tract.

To determine specificity of the SMA tract's relationship to dual-task walking, we chose another interhemispheric tract to serve as a control tract that would be unlikely to be involved in dual-tasking but crosses at the corpus callosum. The Harvard-Oxford Cortical Probability Atlas was used to localize V4, part of the visual system important for recognizing shapes. Forty voxel seed and target masks were created in the sagittal plane in the occipital fusiform gyrus to track from left V4 to right V4. A 120-voxel mask corresponding to the posterior one-third of the corpus callosum and the participant's individual white matter mask were used as waypoints. An axial exclusion mask placed below the supratentorium at the level of the superior cerebellum was applied. Finally, a termination mask was applied 2 mm lateral to the target mask, and probabilistic tractography was used to model the V4 interhemispheric tract.

2.5. Statistical analyses

Statistical analyses were performed using SPSS version 25. Descriptive statistics were used to examine dual-task performance and neuroimaging measures. Normality of the data were assessed using Shapiro-Wilk tests. To examine relationships among clinical measures of dual-task performance, falls, and acquired neuroimaging measures Spearman correlations were used, with values of $p < .05$ considered significant; post-hoc analyses were not completed for this exploratory study, but bootstrapping analysis was performed to calculate 95% confidence intervals.

3. Results

Eighteen females with RRMS [mean age = 45.5 ± 8.2 SD (range 32–57); mean symptom duration = 12.3 ± 6.7 years (2–29); EDSS median 2.25 (1.5–4), 5 African-American, 13 Caucasian; and 17/18 on disease modifying therapies] participated in this study.

3.1. Lesion load analysis

The total number of lesions per participant in all regions was 25.7 ± 19.0 (1–75). The lesions were found predominantly in juxtacortical regions 12.2 ± 12.0 (0–45) and periventricular regions 12.4 ± 10.5 (1–49). Total lesion area (2594.0 ± 1733.5 mm^2) and volume (9.36 ± 6.21 ml) did not correlate with clinical measures of dual-task nor were they related to EDSS score.

3.2. Functional MRI

The mean group effect of ankle dorsiflexion vs. rest indicated that participants had significant peak activation in only the SMA (X = 41, Y = 60, Z = 67) for this single motor task. The SMA demonstrated a positive signal change between active and rest phases, with an average signal change of mean (SD) 4.06(1.51)% and a peak signal of 6.73(2.32)% (Fig. 1A). The group average maximum z-scores across the SMA region of interest well exceeded the preset 2.33 z-score for $p < .01$ significance.

3.3. Structural MRI

Tractography was successful in all participants; diffusion measures in the interhemispheric SMA (Fig. 1B) for this MS cohort were FA mean (SD): 0.346 (0.029); AD: 1.44 (0.113) 10^{-3} mm^2/s; RD: 0.911 (0.116) 10^{-3} mm^2/s and MD: 1.09 (0.114) 10^{-3} mm^2/s.

3.4. Relationships among fMRI measures and clinical performance

Both lower mean and peak z-score of the SMA demonstrated moderate correlation with slower TUG-Cognitive times ($r = -0.461$; $p = .063$; 95%CI: -0.833 to 0.081; and $r = -0.456$; $p = .076$; 95%CI: -0.802 to 0.096), but were unrelated to FWC, WWTT, or reports of falls at any time point.

3.5. Relationships among structural MRI measures and clinical performance

DTI measures demonstrated robust relationships with FWC variability. AD was associated with FWC step length CV ($r = 0.490$; $p = .039$; 95%CI: -0.022 to 0.834), FWC stance time CV ($r = 0.559$; $p = .016$; 95%CI: 0.032 to 0.897), and FWC double support time CV ($r = 0.501$; $p = .034$; 95%CI: 0.004 to 0.817), with higher variability associated with higher AD values. Similarly, RD was significantly related to FWC stance time CV ($r = 0.579$; $p = .012$; 95%CI: 0.033 to 0.873) while MD was significantly related to both FWC stance time CV ($r = 0.593$; $p = .009$; 95%CI: 0.086 to 0.872) and FWC double support time CV (r = 0.501; p = .034; 95%CI: -0.029 to 0.781) (Fig. 2). FA was not related to FWC measures; and interestingly, no DTI measures were related to spatiotemporal (i.e., stance time, step length or double support time) measures of walking, or reports of falls at any time point. However, clinical dual-task performance was related to falls, with higher BWC stride length and velocity significantly related to fewer reports of falls at 6 months ($r = -0.678$; $p = .003$ and $r = -0.483$; $p = .050$, respectively).

To examine the specificity of the interhemispheric SMA tract diffusion measures, we modeled the V4 interhemispheric tract (Fig. 1C), which crosses in the splenium [37], and found no significant or trending correlations between any of the tract-specific diffusivity measures and the clinical measures of dual-task.

4. Discussion

As hypothesized, we found that structural and functional neuroimaging measures correlated with dual-task measures. Significant activation of the SMA region was demonstrated during the performance of an ankle dorsiflexion task (albeit not a dual-task) with fMRI. Some data has suggested that activation in the SMA in persons with MS may be a result of maladaptive plasticity, with increased activation linked to poorer performance. One study found increased activation in the SMA on a hand flexion/extension task compared to healthy adults [38]. Our data demonstrated only moderate, non-significant correlations among lower mean and peak z-stat for SMA and poor dual-task performance on one clinical measure (TUG-Cognitive) which is in line with newer work demonstrating reduced activation of the SMA was indicative of poorer performance and worse fatigue [39]. Structural imaging results showed

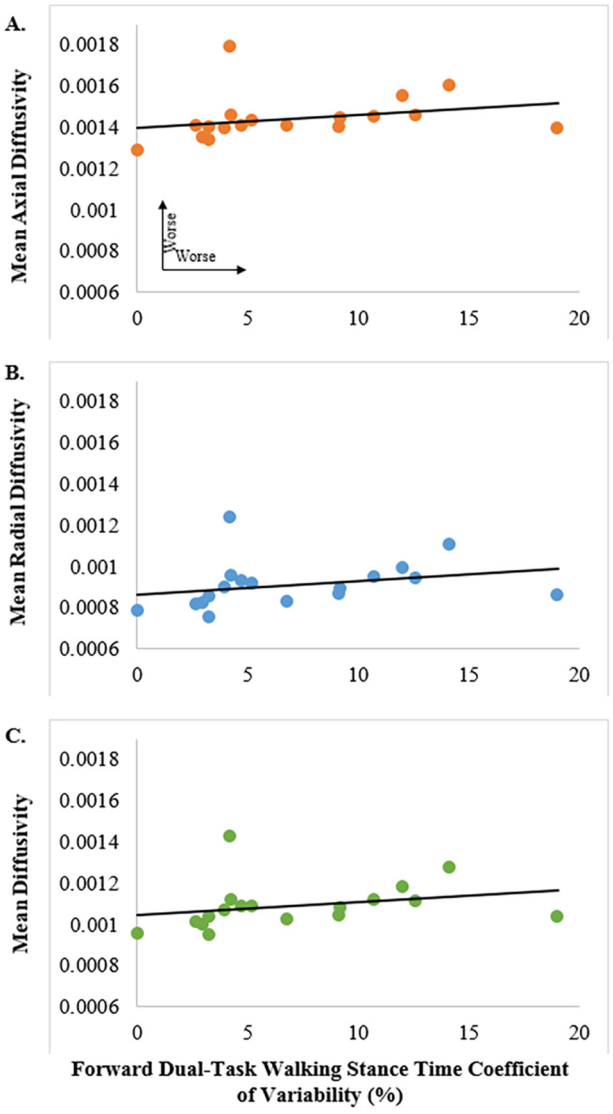

Fig. 2. Dual-task walking variability is significantly related to structural measures of supplementary motor area connectivity. Greater coefficients of variability of stance time during forward dual-task walking were significantly correlated with A) greater axial diffusivity ($r = 0.559$; $p = .016$; 95%CI: 0.032 to 0.897); B) greater radial diffusivity ($r = 0.579$; $p = .012$; 95%CI: 0.033 to 0.873); and C) greater mean diffusivity ($r = 0.593$; $p = .009$; 95%CI: 0.086 to 0.872).

that participants who demonstrated greater variability in spatiotemporal parameters during FWC had higher interhemispheric SMA AD, RD and MD values, indicating lower white matter integrity. This relationship was not observed in the V4 interhemispheric tract, suggesting that the SMA tract may be specifically related to dual-task walking in individuals with MS, rather than a function of a damaged corpus callosum. These results support animal work suggesting that AD and RD may demonstrate more specific relationships to white matter pathology than FA [40], with RD modulated by myelin and AD specific to axonal degeneration [41,42]. Among persons with MS, AD has been strongly linked to axonal degeneration; indeed, corpus callosum AD correlates strongly with EDSS [43].

Gait variability has been shown to differentiate between both individuals with MS and healthy controls and MS fallers and non-fallers [44], as well as being linked to disability level, fatigue, and attention in persons with MS [45]. Therefore, the association between SMA DTI measures with gait variability (CVs) is particularly relevant, and represents a novel finding among persons with MS. A recent imaging

study demonstrated relationships among increased gait variability and lower hippocampal and putamen volumes in MS fallers, but no DTI measures or tract-specific imaging was performed [46]. The relationship between higher gait variability and poorer SMA tract integrity and not with gait speed and spatiotemporal measures builds upon work by Hausdorff et al., who reported that gait variability (also referred to as unsteadiness or inconsistency and arrhythmicity of stepping) was closely associated with risk of falls in the elderly and in people with Parkinson's disease, whereas measures of gait speed and average gait cycle timing did not discriminate future fallers from non-fallers [47,48]. They proposed that there may be different neural mechanisms for control of gait variability than for control of speed and average gait cycle timing [47]. Although we did not demonstrate a relationship between SMA tract integrity and falls in our cohort, this may be due to retrospective fall reporting rather than the prospective fall reporting used by Hausdorff et al. [47,48]. Our findings suggest that SMA tract might have important contributions to maintenance of both spatial and temporal variability during dual task walking in individuals with MS.

Interestingly, although structural integrity of the SMA as measured by DTI was linked to gait variability, the SMA neuroimaging measures were not related to numbers of reported falls. This is surprising, as poor dual-task performance has been linked to falls in persons with MS [6]. One possible reason is that in addition to dual-task ability, many different factors, such as motor control, sensory function and vision contribute to fall-risk [49]. Further, because of the retrospective nature of falls recall, we do not know the circumstances surrounding the reported falls, or whether any of these falls occurred while participants were dual-tasking. It is also possible that people with MS are aware of their dual-task deficits and compensate for them by slowing down, utilizing assistive devices to prevent falls, or avoiding dual-task situations.

There is limited work demonstrating relationships among imaging markers and dual-task performance in persons with MS. Our findings extend work demonstrating relationships among greater postural stability and lower corpus callosum RD [50], as well as lower AD and RD of the superior and middle cerebellar peduncles [51]. Better integrity of the pyramidal tract on DTI has been linked with lower disability in MS [52] and relationships among SMA and dual-task performance on the WWTT in elderly adults have been reported [14]. These results indicate the potential for white matter tractography to predict functional performance and provide important information about recovery patterns in MS.

In addition to a small sample size, lesion load analysis demonstrated a high variability between the number and size of lesions across participants that was unrelated to functional performance. While this may be related to the inherent variability of MS lesions, it is also likely that many of our participants had lesions in their spinal cord, which were not evaluated in this study and may impact performance on outcome assessments. Further, it has been established that 1.5 T and 3 T have relatively low sensitivity in identifying MS lesions [53,54]. There is a likelihood that smaller lesions might have gone undetected; however, all lesions were identified by one independent rater. Another limitation of this study is that a single motor task was utilized for the fMRI portion of the study. Future work should examine the relationship of dual-tasks in the scanner to clinical measures of dual-task and fall reports.

5. Conclusions

This study correlated structural and functional imaging measures with clinical measures to gain a better understanding of the neural circuitry that underlies dual-task performance in MS. Our results suggest that the SMA interhemispheric tract plays a role in dual-task performance. Given improvements possible with dual-task training [7,8], DTI may be a useful adjunct to clinical measures to predict performance and provide information about recovery patterns in MS [50–52; 55–59]. Functional recovery is challenging to objectively report in MS; structural imaging could show microstructural improvements. Future work in this area should include a larger sample size, addition of matched controls, and use of a dual-task requiring both cognition and motor components during the fMRI to better define areas related to dual-task and improve the focus for connectivity studies.

Conflicts of interest and source of funding

All authors declare no conflicts of interest.

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