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Associations between mobility, cognition and callosal integrity in people with parkinsonism

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ABSTRACT

Falls in people with parkinsonism are likely related to both motor and cognitive impairments. In addition to idiopathic Parkinson's disease (PD), some older adults have lower body parkinsonism (a frontal gait disorder), characterized by impaired lower extremity balance and gait as well as cognition, but without tremor or rigidity. Neuroimaging during virtual gait suggests that interhemispheric, prefrontal cortex communication may be involved in locomotion, but contributions of neuroanatomy connecting these regions to objective measures of gait in people with parkinsonism remains unknown. Our objectives were to compare the integrity of fiber tracts connecting prefrontal and sensorimotor cortical regions via the corpus callosum in people with two types of parkinsonism and an age-matched control group and to relate integrity of these callosal fibers with clinical and objective measures of mobility and cognition. We recruited 10 patients with frontal gait disorders, 10 patients with idiopathic PD and 10 age-matched healthy control participants. Participants underwent cognitive and mobility testing as well as diffusion weighted magnetic resonance imaging to quantify white matter microstructural integrity of interhemispheric fiber tracts. People with frontal gait disorders displayed poorer cognitive performance and a slower, wider-based gait compared to subjects with PD and age-matched control subjects. Despite a widespread network of reduced white matter integrity in people with frontal gait disorders, gait and cognitive deficits were solely related to interhemispheric circuitry employing the genu of the corpus callosum. Current results highlight the importance of prefrontal interhemispheric communication for lower extremity control in neurological patients with cognitive dysfunction.

1. Introduction

Parkinsonian gait disorders greatly increase the risk of cognitive decline, institutionalization and death in the elderly (Verghese et al., 2006; Srikanth et al., 2009). Falls in people with parkinsonism are likely related to both their balance and gait impairments as well as their cognitive impairments; however, the relationships between mobility disability and abnormal prefrontal lobe function are unclear (Segev-Jacubovski et al., 2011). In addition to idiopathic Parkinson's disease (PD), a large number of older adults with gait unsteadiness have 'higher level gait disorders', often termed frontal gait disorders (FGD) (Masdeu et al., 1989; Verghese et al., 2002; Verghese et al., 2006). FGD is sometimes referred to as vascular or lower body parkinsonism because it clinically resembles some motor aspects of PD, namely short, shuffling steps, postural instability, difficulty with gait initiation, and freezing of gait (Giladi et al., 2007). However, unlike the well-characterized balance and gait deficits in PD, objective measures of mobility and brain/motor behavior relationships in people with FGD are currently limited. While only anecdotal to date, stride width appears to provide a clear, distinguishing gait characteristic between PD (narrow) and FGD (wide). In addition, people with FGD may show less improvement with levodopa, less tremor or rigidity, and more severe cognitive impairments, compared to patients with PD (FitzGerald and Jankovic, 1989; Yamanouchi and Nagura, 1997).

Reduced white matter microstructural integrity within a diffuse subcortical network including the genu and anterior limbs of the internal capsule are the principal neuropathological changes seen in FGD (Yamanouchi and Nagura, 1997; Demirkiran et al., 2001; Zijlmans et al., 2004). Unlike fibers in the body of the corpus callosum interhemispherically connecting the sensorimotor cortices, the functionality of interhemispheric communication via the genu remains poorly understood. Recent gerontological research reveals that white matter abnormalities in the genu detected by MRI are most strongly associated with slower gait speed (Bolandzadeh et al., 2014), suggesting that disruption of interhemispheric, prefrontal cortex communication has a substantial impact on locomotive performance. Further, Wang

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et al. (2012) found that reduced fiber tract integrity through the genu of the corpus callosum and the anterior limbs of the internal capsule were associated with poorer clinical measures of postural instability and slowed gait in this population. While interesting, previous work has yet to compare such neuroimaging measures between people with FGD and those with idiopathic PD.

Poorer white matter integrity within frontal and prefrontal cortices has also been described in people with PD (Gattellaro et al., 2009), however the relationship between interhemispheric fiber tracts connecting these regions with balance, gait and cognitive impairment in PD has yet to be studied. The aims of this project were to compare the integrity of fiber tracts connecting prefrontal and sensorimotor cortical regions via the corpus callosum in people with FGD and PD. Further, we aimed to evaluate the relationship between integrity of these callosal fibers with clinical and objective measures of mobility (stride width and gait speed) and cognition in people with parkinsonism. Since both idiopathic PD and FGD are characterized by relatively similar mobility deficits, we hypothesized that both groups would show similar deficits in interhemispheric sensorimotor circuitry compared to age-matched healthy controls (HC). Conversely, due to the enhanced cognitive decline experience by those with FGD, we hypothesized that microstructural integrity of fibers in the anterior regions of the callosum (genu) in people with FGD would be: 1) poorer than their PD and HC counterparts and 2) positively related with their mobility performance.

2. Materials and methods

2.1. Subjects

This cross-sectional study recruited 10 patients with FGD, 10 patients with a clinical diagnosis of idiopathic PD from the Parkinson's Center of Oregon at Oregon Health & Science University, Portland, Oregon and 10 age-matched healthy control (HC) participants. All patients or their next of kin gave informed, written consent to a protocol approved by the Institutional Review Board of Oregon Health and Science University. People with FGD all complained of gait and balance difficulties as the initial symptom of their movement disorder. Clinical features necessary for inclusion were a slow, shuffling, wide-based gait and a predominance of bradykinesia in the lower extremities only. Freezing of gait and a history of vascular risk factors were optional, supportive features for inclusion. A senior clinician with expertise in gait disorders (J.G.N.) reviewed patient videos and medical records to confirm appropriateness of inclusion in the FGD group. We elected to use clinical gait characteristics, rather than radiographic white matter lesion burden, as criteria for inclusion, however all subjects had brain imaging to exclude large strokes, masses, cerebellar and brainstem atrophy or ventricular dilation not related to cortical atrophy (Vizcarra et al., 2015). We excluded subjects with a diagnosis of progressive supranuclear palsy, multiple system atrophy, corticobasal syndrome, Lewy Body dementia, cerebellar ataxia, and normal pressure hydrocephalus post-shunting. Individuals with large, space-occupying lesions on previous imaging or significant pyramidal weakness on exam were also excluded. Other exclusionary criteria were as follows: severe tremor, peripheral neuropathy with proprioceptive deficits, severe peripheral vascular disease, uncorrected vision or vestibular problems, joint disease significantly limiting gait, and inability to tolerate an MRI due to claustrophobia or other medical contraindications. For all people with FGD and PD, a clinician with expertise in movement disorders performed the MDS-UPDRS III, and we also extracted scores for the sub-components (items #29–33) that comprise postural instability and gait disorder (PIGD) measures.

Cognitive, mobility and neuroimaging collection were performed over the course of two days, separated by less than one week. All participants refrained from taking any morning antiparkinsonian medications and thus were tested in the OFF state following at least 12 h of withdrawal from dopaminergic medication.

2.2. Cognitive assessments

Cognitive functioning was assessed using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) and the SCales for Outcomes in PArkinson's disease-COGnition (SCOPA-COG). Both paper-and-pencil tests were administered and scored by trained researchers. The MoCA is a cognitive screening tool for mild cognitive impairments. Five domains were examined, including attention, verbal learning and memory, executive functions/language, and orientation. A maximum score of 30 can be obtained, higher scores indicating better performance. The SCOPA-COG consists of 10 items that tap into four cognitive domains that have been associated with Parkinson's disease: memory, attention, executive function and visuospatial function (Marinus et al., 2003; Verbaan et al., 2007). Higher scores indicate better cognitive performance, with 43 as the maximum score. Both the MoCA and SCOPA-COG have been validated in Parkinson's disease (Marinus et al., 2003; Verbaan et al., 2007; Gill et al., 2008) and produced equally high sensitivity and specificity to detect dementia and mild cognitive impairment (Dalrymple-Alford et al., 2010).

2.3. Mobility assessments

Participants walked three times over an 8-meter long instrumented walkway with an active area of 6 meter × 0.6 meter sampling at a frequency of 60 Hz (GAITRite®, CIR System, Havertown, USA). Participants also wore inertial sensors on their shoes and the lumbar spine using Velcro straps, sampling at a frequency of 128 Hz Opals (APDM Inc. Portland, OR USA). Step width was determined using the instrumented walkway whereas gait speed (average stride velocity) was derived from the inertial sensor data using Mobility Lab Software (APDM Inc.; Mancini et al., 2011). Measures of mobility and cognitive performance were compared between groups via independent sample *t*-tests, with UPDRS-III included as a covariate.

2.4. Image acquisition

Participants were scanned on a 3.0T Siemens Magnetom Tim Trio scanner with a 12-channel head coil at Oregon Health and Science University's Advanced Imaging Research Center. One high-resolution T1-weighted MP-RAGE sequence (orientation = sagittal, echo time = 3.58 ms, repetition time = 2300 ms, 256 × 256 matrix, resolution: 1.0 × 1.0 × 1.1 mm, total scan time = 9 min 14 s) was acquired. High angular resolution diffusion images (HARDI) were also collected using a 72-gradient direction, whole-brain echo-planar imaging sequence (TR = 7100 ms, TE = 112 ms, field of view = 230 × 230 mm^2, b value = 3000 s/mm^2, isotropic voxel dimensions = 2.5 mm^3) and ten images in which the b value was equal to zero. A static magnetic field map was also acquired using the same parameters as the diffusion weighted sequence.

2.5. Diffusion tensor imaging analysis

Diffusion data were processed using the tools implemented in FSL (Version 5.0; www.fmrib.ox.ac.uk/fslwww.fmrib.ox.ac.uk/fsl). Diffusion date were first corrected for eddy current distortions and motion artifacts, then averaged to improve signal-to-noise ratio (Eickhoff et al., 2010) and subsequently skull-stripped (using FSL's brain extraction tool). Non-diffusion weighted images (B0) were also utilized for field map correction to reduce geometric distortions. For each individual, the fractional anisotropy images were normalized into Montreal Neurological Institute (MNI) space by using a linear (affine) registration and Fourier interpolation through the FMRIB linear image registration tool.

2.6. Tract based spatial statistics

We performed whole-brain, voxelwise analysis of fractional anisotropy (FA) using tract-based spatial statistics within the FSL environment. Tract-based spatial statistics (TBSS) is a relatively new method where analysis is restricted to those white matter voxels that constitute the skeleton (core) of the brain's connectional architecture and this skeleton can be matched more accurately (compared with whole-brain normalization) across subjects (Smith et al., 2006). The FA images were used as input for TBSS by registering all subjects' FA images to a common space (FMRIB_58 FA MNI template) via a nonlinear transform and then an affine transform to MNI152 space. The two transformations were combined before being applied, to avoid having to resample images twice. The above results in a standard-space version of each subject's FA image, from which average group FA maps were created and skeletonized, thresholding the skeleton at FA > 0.25. The resulting alignment-invariant representation of the central trajectory of white matter pathways was used for voxelwise statistical analysis (randomize, 10,000 permutations). The contrasts FGD < PD and FGD > PD were examined using threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009), with correction for multiple comparisons at $\alpha < 0.05$.

2.7. Interhemispheric callosal tractography

We performed probabilistic fiber tractography to assess quantity and quality of interhemispheric structural connectivity for the genu and body of the corpus callosum. Due to limited knowledge regarding the specific cortical areas connected via the genu we used a broad, well-defined geometric segmentation (Witelson, 1989; Hofer and Frahm, 2006; Fling et al., 2011b) and combined the genu and rostrum into one ROI using the Johns Hopkins University white matter labels, provided by FSL. We utilized a multiple ROI approach to more specifically identify fiber tracts connecting the well-studied primary and secondary sensorimotor areas. The Human Motor Area Template (Mayka et al., 2006), transformed from its original Talairach space, was co-registered to each individual's MNI-normalized FA image and subsequently used as a mask for cortical regions (Fling et al., 2013a). The HMAT is the result of a meta-analysis examining cortical activity assessed by functional MRI; strict inclusion criteria were used to identify six sensorimotor regions: dorsal and ventral premotor cortices (PMd and PMv, respectively), supplementary and pre-supplementary motor areas (SMA and preSMA, respectively), primary motor (M1) and the primary somatosensory (S1) cortices. In addition, for each interhemispheric sensorimotor fiber tract we utilized a 'waypoint' ROI within the corresponding region of the body of the corpus callosum as identified by our previous work (Fig. 1A; Fling et al., 2013a).

Interhemispheric fiber tracts passing through the genu of the callosum were identified with probabilistic fiber tracking (using FDT 1.0; see Behrens et al., 2003) initiated from every voxel within the binarized callosal seed ROI in each participant's native diffusion space (Fig. 1A). For all interhemispheric sensorimotor tracts, probabilistic fiber tracking was initiated from every voxel within the binarized cortical seed HMAT ROI in each participant's native diffusion space, was required to pass through the corresponding callosal ROI waypoint, and terminated in the contralateral hemisphere's homologous regions ROI. Due to the difficulty in delineating differences between the interhemispheric connections between the ventral and dorsal premotor cortices (Fling et al., 2013a), we choose to omit these ROIs from the current analysis. Thus we identified five interhemispheric fiber tracts, those connecting the: 1) prefrontal cortices (genu), 2) preSMA, 3) SMA, 4) M1, and 5) S1, respectively.

The principal diffusion direction was estimated for each voxel as a probability density function, using Bayes' rules in order to account for noise and uncertainty in the measured data. As described elsewhere (Behrens et al., 2003), the implicit modeling of noise in a probabilistic model enables a fiber tracking procedure without externally added constraints such as fractional anisotropy threshold or fiber angle. Thus, fiber-tracking in or near cortical areas becomes more sensitive. The use of a 2-fiber model (Behrens et al., 2007) also improves the modeling of crossing fibers. For all tractography, streamline samples (25,000) were sent out from each voxel, with a step length of 0.5 mm and a curvature threshold of 0.2. For group analyses, the probabilistic connectivity distribution maps from individual participants were thresholded at 50% (thus selecting all connections where >12,500 of 25,000 samples passed; a very conservative level in comparison to previous work using a threshold of 5% (Gschwind et al., 2012; Fling et al., 2013b)). Tracts were then binarized and affine-transferred with tri-linear interpolation into MNI space and summed across participants to obtain the connectivity probability maps of the group. Tract volume, mean diffusivity (MD) and fractional anisotropy (FA) were calculated for all tracts identified within the five interhemispheric pathways of interest, and diffusion derived metrics were compared via a repeated measures analysis of variance (RMANOVA: 3 groups × 5 tracts). Larger FA and lower MD values are indicative of greater directional diffusivity, which is typically interpreted as better white matter microstructure, e.g. denser axonal packing and higher levels of myelination (Behrens et al., 2003; Behrens et al., 2007). Significant main effects were further assessed via post-hoc comparisons. Due to the small cohort, linear regression analyses were solely performed between FA (not MD or tract volume) of the five fiber tracts and performance on clinical (UPDRS-III, PIGD), cognitive (MOCA, SCOPA-COG) and mobility (stride width, gait velocity) assessments and were Bonferroni-corrected for multiple comparisons. In addition, we complement these findings with a whole-brain

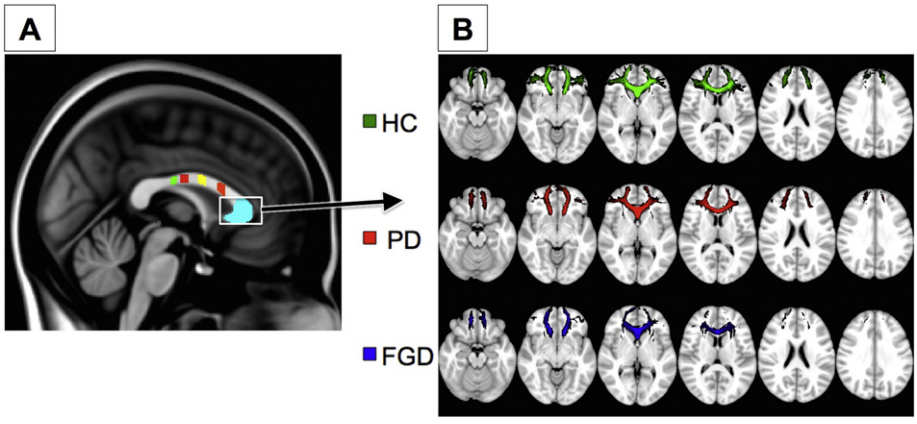

Fig. 1. A) Callosal ROIs used to identify specific interhemispheric fiber tracts from one representative participant with FGD displayed on a mid-sagittal slice of the MNI_152_1mm template. B) Binarized interhemispheric tracts for each group traversing the genu.

TBSS approach that lends support to the specificity of the results of our a priori ROI-based analyses.

3. Results

3.1. Clinical characteristics, cognitive and motor performance

People with FGD had lower overall scores on the MDS-UPRDS-III, although average composite scores were not significantly different (Table 1). Despite less overall motor impairment, people with FGD had slightly worse scores on measures of postural instability and gait (PIGD – items #29–33) and higher Hoehn & Yahr scores (due to poor postural stability). People with FGD also performed poorer on the MOCA ($P = 0.002$) and SCOPA-COG compared to HC ($P = 0.006$) and were also significantly worse on the SCOPA-COG ($P = 0.038$) compared to people with PD, with deficits noted in attention and executive function. People with FGD also had significantly wider stride width and slower gait speed than HC and those with PD ($P < 0.01$ for both gait measures). Finally, individuals with PD had significantly reduced gait velocity compared to HC ($P = 0.001$).

3.2. Diffusion imaging results

People with FGD had widespread reduced white matter microstructural integrity observed throughout the TBSS skeleton compared to those with PD, demonstrating more pronounced effects in anterior brain regions (Fig. 2). No areas were found to be significantly greater when performing the FGD > PD contrast - i.e. there were no regions in the brain where white matter integrity was worse for the PD cohort compared to the FGD cohort at the group level.

3.3. Callosal tractography

See Table 2 for measures of fiber tract microstructural integrity. In brief, a significant main effect of group ($F_{2,24} = 4.8$, $P = 0.18$) and tract ($F_{4,96} = 8.6$, $P < 0.001$) was evident for FA as well as a group × tract interaction ($F_{8,96} = 5.2$, $P < 0.01$). Post-hoc tests showed that for callosal tracts connecting homologous interhemispheric regions, people with FGD had reduced fiber tract quality (i.e. lower FA) within the genu ($P < 0.001$), M1 ($P = 0.04$) and S1 ($P = 0.001$) compared to HC. Compared to those with PD, people with FGD solely had reduced integrity of fiber tracts traversing the genu ($P = 0.04$). Finally, those with idiopathic PD had significantly reduced FA of interhemispheric S1 fiber tracts ($P = 0.006$) compared to HC. For measures of mean diffusivity (MD) we report a significant main effect of group ($F_{2,25} = 38.2$, $P < 0.001$) and tract ($F_{4,100} = 32.1$, $P < 0.001$) as well as a significant group × tract interaction ($F_{8,100} = 21.6$, $P < 0.001$). Post hoc analysis revealed that MD of fiber tracts through the genu was significantly reduced in those with FGD compared to both HC ($P = 0.019$) and people with PD ($P = 0.027$). Further, MD of all interhemispheric sensorimotor fiber tracts of the callosum was significantly higher for people with either FGD or PD compared to HC (Table 2). Further, those with FGD had higher MD of tracts through the genu and PreSMA compared to people with PD. No other group differences were noted in FA or MD of sensorimotor callosal fiber tracts of those with FGD compared to people with PD ($P > 0.5$ for all comparisons).

In addition to the observed differences in fiber tract "quality", substantial differences in fiber tract volume (quantity) were also found (Figs. 1B, 3A). A significant main effect of group ($F_{2,21} = 6.99$; $P = 0.005$), tract ($F_{4,84} = 157.9$; $P < 0.001$), and a group × tract interaction ($F_{8,84} = 6.82$; $P < 0.001$) were found for tract volume. Group differences were most pronounced in anterior regions of the callosum; post hoc tests showed those with FGD had significantly lower tract volume within the genu compared to both HC ($P = 0.002$) and those with PD ($P = 0.001$). No differences in white matter volume were noted for the remaining interhemispheric sensorimotor fiber tracts in people with FGD, and no difference between HC and people with PD were found.

3.4. Associations between interhemispheric fiber tracts and clinical, cognitive, and mobility measures

Results from all regression analyses can be viewed in Table 3. Consistent with our hypothesis, better integrity of fibers passing through the genu was significantly related to better clinical (PIGD: $r = -0.69$; $P = 0.013$), cognitive (SCOPA-COG: $r = 0.62$; $P = 0.027$), and mobility performance (reduced stride width: $r = -0.67$; $P = 0.017$) within the FGD group. Contrary to our hypothesis, while we observed a positive relationship between genu fiber tract integrity and cognitive performance within people with PD and HC, none of these associations were statistically significant (Table 3). In people with PD, better tract microstructure of fibers connecting M1 and S1 was associated with faster gait velocity (M1: $r = 0.59$, $P = 0.049$; S1: $r = 0.60$. $P = 0.043$), but did not maintain significance when adjusting for multiple comparisons. Thus, no significant relationships were observed between microstructural integrity of the sensorimotor fiber tracts and performance on any of the clinical, cognitive, or mobility measures.

We supplemented our hypothesis-driven approach with an analogous, whole-brain TBSS skeleton regression analyses to search for converging evidence regarding the principal distinguishing gait characteristic between these populations, stride width. Stride width was first demeaned across the entire sample and then regressed against FA using randomize within the FSL environment (10,000 permutations). The results of this analysis (Fig. 3B) show a strong relationship between lower FA of the genu and wider stride width only in people with FGD (significant voxels survived correction for multiple comparisons using TFCE, $\alpha < 0.05$). This result provides a strong accordance with the correlation reported from our a priori ROI analysis, with significant voxels clearly overlapping with the tractography-derived network through the genu of the callosum.

Table 1
Demographic and disease characteristics along with cognitive performance and measures of mobility. All assessments were performed in the OFF state. Values are mean (±SD). Main group effects are highlighted in bold.

	HC N = 10	PD N = 10	FGD N = 10	*P*-value
Age	75 (62–84)	70.1 (63–84)	74.6 (67–84)	0.23
M/F	4/6	8/2	7/3	–
MDS-UPDRS III	N/A	46.6 (18.26)	33.1 (16.8)	0.13
PIGD	N/A	7.6 (5.6)	9.2 (3.5)	0.46
Hoehn & Yahr	N/A	2.8 (0.83)	3.4 (1.01)	0.15
MoCA	26.6 (2.07)	24.6 (4.3)	**21.1 (4.11)**	<**0.01**
SCOPA-COG total	31.2 (2.82)	26.4 (5.97)	**19.3 (7.73)**	<**0.01**
Stride width (cm)	11.2 (2.42)	11.2 (2.27)	**18.9 (4.19)**	<**0.001**
Gait velocity (m/s)	1.2 (0.11)	**0.93 (0.20)**	**0.59 (0.29)**	<**0.01**

4. Discussion

Despite better overall motor performance, as assessed by clinical Parkinson's scales, people with FGD had slower gait velocities and larger stride widths, likely to maintain postural stability during locomotion, compared to those with idiopathic PD. When investigating our principal hypothesis comparing the integrity of callosal fiber tracts connecting prefrontal and sensorimotor cortical regions, we found that people with FGD had reduced quality and quantity of callosal tracts traversing the genu compared to age-matched controls and people with PD. While both Parkinsonian groups had reduced fiber tract quality and quantity of sensorimotor fiber tracts compared to their healthy cohort, it is interesting to note that people with FGD did not show reduced microstructural integrity of fiber tracts connecting primary and secondary sensorimotor cortices compared to those with PD. In addition, gait and

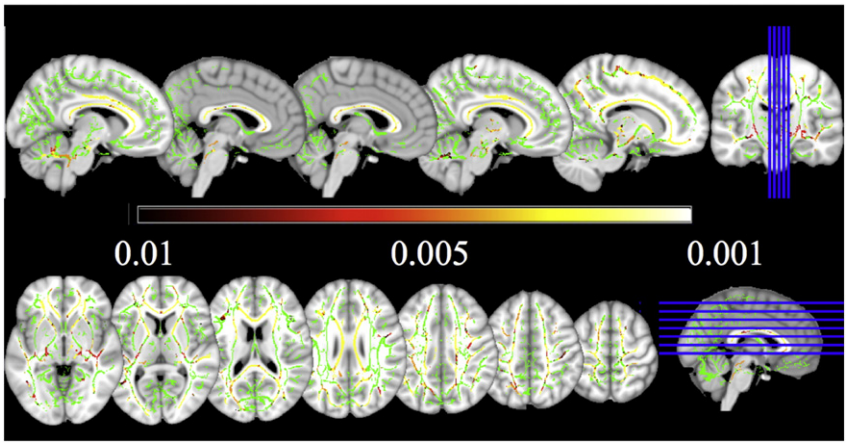

Fig. 2. TBSS whole-brain group differences (PD > FGD) in fractional anisotropy. No areas were significantly greater in the FGD group.

cognitive deficits in people with FGD, but not PD, were related to circuitry employing the genu. This result was further strengthened by whole-brain voxelwise linear regression demonstrating a strong association between genu microstructure and stride width in those with FGD. These findings support the notion that frontal lobe cognitive processes coordinated across the brain's hemispheres play a more important role in the balance and gait impairments of people with FGD, than in people with PD.

As hypothesized, one of the defining characteristics of FGD is a slow, wide-based, shuffling gait (FitzGerald and Jankovic, 1989). In the current study, despite better overall motor performance, assessed by the UPDRS-III, people with FGD had several mobility deficits including higher PIGD scores, slower gait velocities and larger stride widths compared to people with PD. This echoes recent clinical comparisons of idiopathic PD to those with vascular parkinsonism (Wang et al., 2012). While the UPDRS is the classical scale to assess clinical severity in PD, the test contains many components related to tremor, rigidity and manual upper extremity bradykinesia, symptoms not traditionally associated with FGD (FitzGerald and Jankovic, 1989; Yamanouchi and Nagura, 1997). Conversely, sub-scores specific to postural stability and gait (the PIGD postural alignment, sit to stand, gait and pull test of balance responses) were noticeably worse in people with FGD.

Interhemispheric transfer via the corpus callosum plays a key role in the production of coherently integrated behavior and undergoes significant degeneration with age both in terms of white matter quantity and quality (Sullivan et al., 2010; Fling et al., 2011b). Even with healthy aging, older adults rely more on bilateral activation of the frontal and prefrontal cortices during motor performance, reflecting the importance of commissural fibers with advancing age (Seidler et al., 2010). This increased reliance on bilateral frontal cortex has been attributed to a reduction in callosal fiber tract integrity, resulting in unintentional overflow (i.e. "miscommunication") between the brain's hemispheres (Fling et al., 2011a). In the current study we found that people with FGD had reduced quality and quantity of fiber tracts traversing the genu. Genu tract integrity was positively correlated with cognitive performance assessed with the SCOPA-COG for those with FGD. And, although not significant, both HC and PD groups had strong positive correlations between genu integrity and scores on the MoCA and SCOPA-COG assessments (Table 3). As hypothesized, FA of genu fiber tracts was also correlated with mobility performance in people with FGD. The common relationship of genu fiber integrity with both gait and cognitive function suggests that some gait disorders are related to higher level (i.e. cognitive), rather than sensorimotor, control of gait. For example, the frontal cortex may be critical for coupling control of postural weight shifting with the locomotor pattern, consistent with the wide base and difficulty coordinating postural adjustments with gait initiation seen in those with FGD.

The genu contains fibers connecting the bilateral prefrontal cortices (Chao et al., 2009) that receive information from virtually all sensory systems and have preferential connections with motor processing structures. As such, the genu has been proposed to play a central role in the cognitive control of motor performance (Miller and Cohen, 2001). de Laat et al. (2011) were among the first to demonstrate that the loss of fibers interconnecting the bilateral prefrontal cortices involved in the cognitive control of motor performance were involved in gait disturbances in people with small vessel disease (i.e. FGD). Specifically, the authors reported that shorter stride length was related to microstructural integrity of the genu in a large cohort of patients with small vessel disease (N = 429). Similar to the current study, they report that this relationship was independent of the integrity of other callosal segments (de Laat et al., 2011). Additionally, a recent study found a strong correlation between FA of fibers interhemispherically linking the prefrontal cortex (genu) and along the cortico-striatal pathway (anterior limb of the internal capsule) with the clinical severity of gait, balance, and falls in people with vascular parkinsonism (Wang et al., 2012). Reinforcing the work of Wang et al. (2012), we report strong associations between the PIGD metric derived from the MDS-UPDRS III and tract integrity of fibers within the genu for people with FGD. Although

Table 2
Group comparisons of callosal fiber tract integrity. Significantly lower fiber tract integrity compared to HC is highlighted in bold. Data are presented as mean (±SD).

	Fractional anisotropy (FA)			Mean diffusivity (10^{-3} mm^2/s)		
	HC	PD	FGD	HC	PD	FGD
Genu	0.42 (0.03)	0.41 (0.05)	**0.35*** (0.04)**	0.667 (0.05)	0.694 (0.03)	**0.770* (0.09)**
PreSMA	0.41 (0.07)	0.36 (0.08)	0.33 (0.07)	0.63 (0.05)	**0.843*** (0.12)**	**0.921*** (0.15)**
SMA	0.45 (0.08)	0.41 (0.09)	0.40 (0.14)	0.614 (0.05)	**0.804*** (0.14)**	**0.826*** (0.13)**
M1	0.49 (0.05)	0.43 (0.08)	**0.41* (0.07)**	0.605 (0.05)	**0.795*** (0.12)**	**0.822*** (0.16)**
S1	0.47 (0.05)	**0.36** (0.08)**	**0.35*** (0.08)**	0.607 (0.04)	**0.90*** (0.14)**	**0.930*** (0.13)**

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

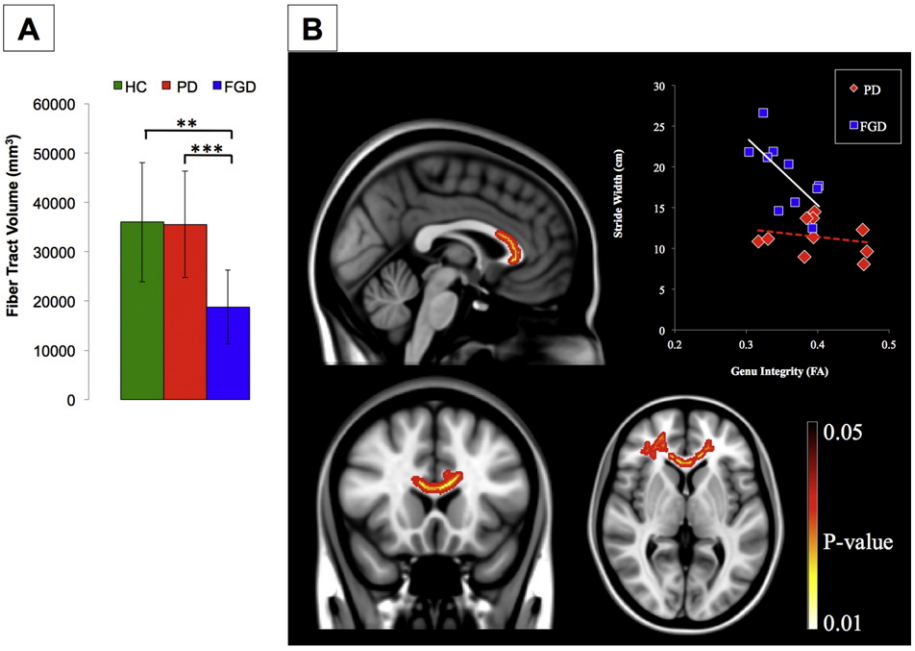

Fig. 3. A) Those with FGD had significantly lower tract volume compared to their HC (**$P < 0.01$) and PD counterparts (***$P < 0.001$). B) Whole-brain, TBSS regression analysis identifying white matter associated with stride width in participants with FGD. $P < 0.05$, TFCE-corrected (X,Y,Z = 0,19,3). Significant correlation between genu fiber tract microstructural integrity (FA) and stride width in people with FGD ($r = -0.67$; $P = 0.017$), but not people with PD ($r = -0.24$), nor for HC ($r = -0.05$).

not significant, a similar relationship was evident in people with PD as well. Further, reduced quality of fibers connecting the prefrontal cortices was strongly related to a wider stride width in those with FGD, potentially in an effort to increase stability. Perhaps surprisingly, no relationships were observed between measures of mobility and integrity of callosal fiber tracts connecting sensorimotor cortical regions.

In agreement with the typically described anterior gradient of white matter decline in FGD (Yamanouchi and Nagura, 1997; Demirkiran et al., 2001; Zijlmans et al., 2004), no significant group differences were observed in the more posterior sensorimotor callosal fiber tracts comprising the body of the callosum (assessed by FA). In people with PD and their healthy counterparts, there were positive associations (though not significant) between FA values of fiber tracts connecting the bilateral M1 and S1 cortical regions and gait velocity. This finding compliments a recent positron emission tomography study using [^{18}F]-fluoro-deoxy-glucose ([^{18}F]-FDG) that demonstrates strong cortical activity in medial leg sensorimotor representations in the pre- and post-central gyri that is communicated interhemispherically via these callosal pathways (la Fougère et al., 2010). In addition to primary sensorimotor cortical regions, supraspinal locomotor circuitry has principally been described as signals originating in the SMAs that are transmitted through the basal ganglia via disinhibition of the subthalamic and mesencephalic locomotor region where they converge with cerebellar signals from the cerebellar locomotor region (Jahn et al., 2008). A limited number of case studies demonstrate that agenesis of callosal white matter tracts connecting the bilateral SMAs, or lesions within the SMA itself, can result in gait apraxia or freezing of gait issues (Della Sala et al., 2002; Nadeau, 2007). This suggests that at least some interhemispheric communication between the right and left SMA - the higher order, motor planning region of the motor system, is required for effective locomotion. However, based on the current results, communication between the two SMAs does not appear to constitute principal neural circuitry underlying gait speed or postural stability during gait (stance width).

Notable limitations of the current manuscript include the size of the Parkinsonism cohort. Additional work is necessary to strengthen the translation and generalizability of the current findings, in accord with the work of Wang and colleagues (Wang et al., 2012). Further, the current diffusion imaging approach to assess the relationship between white matter fiber tracts and mobility in people with FGD and PD principally employed an a priori tract-based analysis and not a white matter hyperintensity burden analysis. Within people with FGD, white matter lesions and lacunar infarcts are widely accepted signs of cerebral small vessel disease; however, white matter hyperintensity burden resulting from these lesions has previously been shown not to correlate with PIGD scores in people with PD (Herman et al., 2013). Further, in a very large cohort of patients with small vessel disease, the majority of white matter integrity related to gait disturbances were localized to regions where the white matter lesion probability was low, or even absent, highlighting the importance of microstructural integrity of fibers

Table 3
Associations between callosal tract microstructural integrity (FA) and clinical, cognitive and mobility measures. Significant associations are highlighted in bold.

Fiber tracts	MDS – UPDRS III			PIGD			MoCA			SCOPA-COG			Stride width			Gait velocity		
	HC	PD	FGD	HC	PD	FGD	HC	PD	FGD	HC	PD	FGD	HC	PD	FGD	HC	PD	FGD
Genu	N/A	−0.38	−0.12	N/A	−0.49	**−0.69***	0.58	0.36	0.11	0.58	0.37	**0.62***	−0.05	−0.24	**−0.67***	0.07	0.33	0.49
PreSMA	N/A	0.16	−0.02	N/A	−0.26	−0.60	0.13	0.30	0.06	−0.19	0.42	0.32	−0.15	−0.51	−0.51	−0.19	0.28	0.49
SMA	N/A	0.23	−0.50	N/A	−0.17	−0.36	0.36	0.17	−0.11	0.37	0.29	0.46	−0.35	−0.39	−0.13	0.15	0.28	0.05
M1	N/A	−0.12	−0.15	N/A	−0.40	−0.51	−0.13	0.30	−0.03	−0.18	0.48	0.47	−0.27	0.02	−0.32	0.32	0.59	0.37
S1	N/A	−0.35	0.01	N/A	−0.39	−0.55	−0.35	0.20	−0.13	−0.19	0.40	0.51	−0.05	0.37	−0.36	0.45	0.60	0.35

* $P < 0.05$.

in normal-appearing white matter in gait disorders (de Laat et al., 2011).

5. Conclusions

Recent research has demonstrated the important relationships between balance/gait/falls and cognitive function (Jacobs and Horak, 2007; Yogev-Seligmann et al., 2008). The limited success of rehabilitation treatment for mobility problems in parkinsonism may be partly due to the fact that current treatment rarely addresses issues with (pre)frontal cortical control of balance and gait. Executive functions affected by parkinsonism include task-planning, conflict-resolution (inhibition), set-switching, sensory integration, and flexibility of attention (Chong et al., 2000; Frank et al., 2007). These cognitive components are required for safe navigation and functional mobility in complex, everyday environments (Yogev-Seligmann et al., 2008). Taken together with the current work, this growing line of study supports the notion that gait and cognition are connected, perhaps because gait relies upon specific cortical-subcortical networks critical for executive control of balance and gait (mobility). Thus, interventions targeted at increasing cognitive performance (cf. Anguera and Gazzeley, 2015) may have substantial ancillary mobility benefits for the ever-growing aging population with FGD.

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Conflict of interest statement

The Oregon Health & Science University and Dr. Horak have a significant financial interest in APDM, a company that may have a commercial interest in the results of this research and technology. This potential institutional and individual conflict has been reviewed and managed by OHSU.

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