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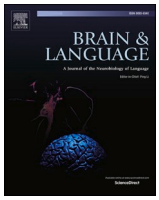

Short communication

Microstructural white matter changes underlying speech deficits in Parkinson's disease

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ABSTRACT

Speech impairments are one of the common symptoms of individuals with Parkinson's disease (PD). However, little is known about the underlying neuroanatomical structural deficits specifically in the basal ganglia-thalamocortical (BGTC) loop in the speech deficits of PD. Here we investigated white matter differences in PD using probabilistic tractography. Diffusion tensor imaging data were downloaded from the Parkinson's Progression Markers Initiative database. We included three groups of participants: 20 PD individuals with speech deficits, 20 PD individuals without speech deficits, and 20 age- and gender-matched control participants. Overall, PD individuals with speech deficits had higher mean diffusivity in the BGTC pathway in the left hemisphere compared with PD individuals without speech deficits. The present study exhibits that there may be a distinct pathophysiological profile of white matter for speech deficits in PD.

1. Introduction

Parkinson's disease (PD) is a common and complex neurodegenerative condition with estimated prevalence of approximately 3% of the population worldwide (Pringsheim et al., 2014). One of the most common symptoms of PD is speech deficits with 90% of individuals with PD being diagnosed with hypokinetic dysarthria, a motor speech disorder associated with basal ganglia impairment. Hypokinetic dysarthria symptoms mainly include difficulties with prosody, phonation, and articulation during speech production (Duffy, 2019). Characteristics of speech production difficulties of hypokinetic dysarthria are associated with the core symptoms, particularly rigidity and bradykinesia (Walsh & Smith, 2012).

Speech production and perception is a highly complex sensorimotor process that requires the coordination of multiple levels of mechanisms including serial ordering of discrete learned phonological units into larger meaningful words and sentences. At the level of speech production, the coordination of laryngeal and articulatory systems and the integration of multiple sensory information including auditory, tactile, and proprioceptive by the brain are required to produce fluent speech without any delay. Several neural models of speech production have been proposed to outline the neural network of speech production. The Direction into Velocities of Articulators (DIVA, Guenther, 2016) and the State Feedback Control model of speech (Houde & Nagarajan, 2011) both hypothesize a role of feedforward and feedback control in speech and their associated neural processes. Feedback and feedforward control mechanisms are both impaired in PD (Chen et al., 2013; Mollaei et al., 2013, 2016). By use of sensorimotor compensation paradigms that probe the control mechanisms of speech production through manipulation of auditory feedback, it has been reported that individuals with PD, respond with higher magnitude to pitch and lower magnitude to first formant frequencies compared to the control group (Mollaei et al., 2016). The feedforward control system, which relies on already learned motor commands, has also been found to be impaired using sensorimotor adaptation paradigms that require the learning of new auditory to motor correspondences (Abur et al., 2018; Mollaei et al., 2013). The neural network supporting feedback and feedforward mechanisms includes several cortical and subcortical structures. Specifically, the feedforward control system involves the left premotor cortex and inferior frontal gyrus, and feedback control system includes superior temporal gyrus (STG) and somatosensory cortex, with both of these control systems connected with the basal ganglia, and notably with the putamen (Tourville & Guenther, 2011). This subcortical structure not only monitors the smooth initiation and sequencing of speech sounds by use

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of feedback control processes, but also updates previously learned motor commands based on auditory information within the feedforward control system (Brown et al., 2009; Hacker et al., 2012; Tourville & Guenther, 2011).

Notably, the basal ganglia-thalamocortical (BGTC) loop has been proposed to be involved in the generation of motor commands within the feedforward control system. The subcortical structure of putamen within the basal ganglia and the globus pallidus, another subcortical structure within the basal ganglia, have been integrated within the DIVA model, with their role in initiation of speech movements and updating of motor commands through reciprocal connections with the supplementary motor area (Bohland & Guenther, 2006; Tourville & Guenther, 2011). Specifically, the putamen which is the primary input nucleus of the basal ganglia for motor processing has connections with cortical structures of premotor, motor, and somatosensory areas for planning and execution of motor movements and is thought to be involved in monitoring motor commands for the smooth initiation of speech (Chang & Guenther, 2020). Reduced connections between the left putamen, left sensorimotor cortex and STG have also been reported in PD (Manes et al., 2018). Based on this evidence, it appears that the putamen not only has a role in the feedforward control of speech through its connections with motor cortices but also in the feedback control mechanisms through its connections with the STG. Hence, it is reasonable to hypothesize that impairment of the putamen can give rise to deficient feedback and feedforward mechanisms that is observed in PD.

Several studies have investigated the neural underpinning of speech deficits of PD using MRI to establish neural regions and networks involved in speech in PD (Manes et al., 2018; Liotti et al., 2003; Pinto et al., 2004; Rektorová et al., 2007, 2012). Functional MRI (fMRI) have been used to assess the functional changes within the neural network of speech in PD. Rektorová et al. (2012) evaluated connectivity between periaqueductal grey matter, a core structure associated with human vocalization, and other brain regions. They found greater functional connectivity in individuals with PD compared to healthy controls (HC) in the right basal ganglia, posterior STG, supramarginal gyrus, fusiform gyrus, and inferior parietal lobe. They argued that this is due to functional plastic changes within the BGTC loop and areas involved in auditory and somatosensory control of speech in PD. However, it is not clear whether these changes are attributable to dopaminergic treatment or compensatory mechanisms since participants were tested on medication. In addition, Manes et al. (2018) reported reduced functional connectivity between left putamen and left STG and increased connectivity between left internal globus pallidus (GPi) and left dorsal laryngeal motor cortex in individuals with PD with speech motor deficits compared to the individuals with PD who did not show any speech impairments. Similarly, Chen et al. (2020) found severity of hypokinetic dysarthria to be significantly correlated with morphological changes in the brain in right precentral cortex and right fusiform gyrus. Surprisingly, they did not find any significant correlations between hypokinetic dysarthria severity and subcortical structures and their white matter connections. Another study by New et al. (2015) investigated resting-state functional connectivity for voice network in PD. They found reduced network connectivity from left thalamus and bilateral putamen to cortical areas like superior temporal gyrus, and rolandic operculum. They interpreted these findings could be related to the reduced dopamine levels in PD.

Structural MRI connectivity measures provides information regarding the underlying nature of fMRI findings and may partly underlie the functional differences found in speech deficits of PD. Structural MRI studies of speech exploring neuroanatomical deficits have used diffusion tensor imaging (DTI) and deterministic tract-based spatial statistics (TBSS) and probabilistic tractography analyses to identify white matter regions involved in speech production (Brabenec et al., 2023; Chang et al., 2015; Watkins et al., 2008). DTI is a non-invasive technique used to explore integrity of white matter and thus ascertain relationships between breakdowns in certain neural networks and presenting impairments, as well as neural responses to treatment (Rodriguez-Porcel et al., 2021). The most common parameter of DTI is fractional anisotropy (FA), a diffusion parameter which measures directionality of water molecules within tissue and a lower value suggests abnormality within white matter, which may reflect reduced density of axons and/or demyelination (Mollaei et al., 2021). In addition, there are other DTI measures including mean, axial, and radial diffusivities (MD, AD, and RD) that can be extracted to give a better account of microstructural properties of the underlying tissue. For example, MD provides an estimation of the overall tissue density and is most sensitive to group effects in small samples (De Santis et al., 2014; Pierpaoli & Basser, 1996). AD and RD provide a more direct measure in the main and perpendicular direction of the diffusion. While deterministic voxel-based methods such as TBSS have been widely used in reporting structural brain profile, probabilistic tractography analysis is better suited to investigate the changes in the BGTC loop compared to TBSS and is capable of following the direction of multiple pathways along this loop based on the tract reconstruction in individuals' native space, and hence it is less prone to inter-subject variability errors compared to the voxel-based methods especially in clinical populations (Behrens et al., 2007; Ben-Shachar et al., 2007).

In the current study, we aimed to investigate structural white matter differences as measured by DTI in order to assess the integrity of the BGTC loop in relation to speech deficits in individuals with PD and neurotypical healthy controls mainly putamen and laryngeal motor area (LMA) as the main structures with the BGTC loop. The selection of LMA is based on the most common PD speech symptoms that include prosodic insufficiencies (Duffy, 2019) and is involved in implementing the previously learned motor commands via the feedforward control system (Tourville & Guenther, 2011). Our main hypothesis is that speech deficits seen in PD are related to impaired microstructural changes within BGTC loop. Specifically, we hypothesize to observe altered white matter metrices within pathways connecting putamen with laryngeal motor area. To test our hypothesis, we measured and extracted FA, MD, AD, and RD from the BGTC loop using probabilistic tractography analysis and compared these parameters within three groups of participants: 2 groups with PD with and without speech deficits and one healthy control group. We have investigated these pathways in two reciprocal directions, one from putamen to LMA and the other from LMA to putamen. To our knowledge, this is the first study to examine and compare the properties of the BGTC loop in PD with and without speech deficits.

2. Methods

2.1. Participants

Data used in the preparation of this article were obtained from the Parkinson's Progressive Markers Initiative database (PPMI; https://www.ppmi-info.org/access-data-specimens/download-data; Marek et al., 2011; RRID: SCR_006431). PPMI's data usage agreement was electronically signed. 40 participants with PD and 20 age- and gender-matched HC were included from PPMI database.

We included two PD groups: 20 PD participants with speech deficit (PDS) and 20 PD participants without speech deficit (PDN). PD participants were allocated to PDS or PDN dependent on their Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (Motor Examination) speech scores (Goetz, 2009), with PDN participants score of 0 and PDS participants score ≥ 2 out of 4 (0 = no speech deficit, 4 = most speech is difficult to understand/unintelligible) to ensure that their speech deficits can be observed. Score of 1 (slight speech deficits) were not included in the participants groups. All HC participants completed their scan at Baseline. Most of the individuals with PD included here were also scanned at Baseline and hence were not on any PD medications, except for 1 in the PDN (scanned at Year 1) group and 2 in the PDS group (both scanned at Year 1). These three individuals were on L-Dopa medication at the time of scanning. Since

dopaminergic medications have provided inconsistent and sometimes no effect on the speech and voice profiles of individuals with PD (Pinto et al., 2004; Tykalova et al., 2022), we have included these three participants in our study. We don't believe that this would change the pattern of the responses found.

Our exclusion criteria included participants in PD groups who had undergone DBS, were left-handed, and participants with cognitive deficits. All participants were right-handed and had no cognitive impairments, as indicated by a score of $\geq$ 26 on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). The sample size was chosen based on the availability of DTI data and the number of participants that scored $\geq$ 2 in Part III (speech item) of MDS-UPDRS found in the PPMI database, which limited this investigation to 20 participants in each group. Table 1 details subject demographic and assessment information.

3. MRI/DTI acquisition

According to the MRI technical operations manual, accessible via https://www.ppmi-info.org, PPMI used an MRI scanner with a 3-Tesla magnetic field strength to acquire participants' data. MRI scans took approximately 7 min to complete. The sequence used, to ensure accuracy of quantitative measurements, was a high-resolution T1-weighted, 3D volumetric sequence, such as MP-RAGE (192 sagittal slices of 1.0 mm thickness; voxel size: 1.0*1.0; matrix 256x256). DTI scans took approximately 8 min to complete. Data were acquired using a 2D diffusion-weighted echo-planar sequence (~80 axial slices of 2.0 mm thickness; voxel size: 2.0*2.0; matrix 128x128; repetition time ~ 10,000 ms; echo time ~ 80 ms; flip angle 90 degrees; 64 diffusion-sensitive gradient directions at B-value 0 and 1000 s/mm^2).

4. Probabilistic tractography analysis

Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (BEDPOSTX) function was applied to estimate fiber orientation in each voxel. The PROBTRACKX2 (Behrens et al., 2003, 2007) command of FMRIB's Diffusion Toolbox (FDT) was then used to calculate the connectivity of seed and target regions similar to the process that was explained in Mollaei et al. (2021) for the tract reconstruction of BGTC loop. The regions of the putamen and the thalamus were extracted based on automatically generated parcellation maps from FreeSurfer (Fischl, 2012). We then manually edited each of these thalamus and the putamen regions within each subject to be localized to the mouth motor area based on previous studies (Mollaei et al., 2021; Nambu, 2011). For the putamen, the mask was localized to its lower medial portion (ventro-medial putamen, VMP) and for the thalamus, it was localized to the ventral lateral nucleus of the thalamus (VLT). The cortical mask of laryngeal motor area (LMA) was manually localized to the ventral portion of pre-central cortex which is found to be involved in vocalization and modulations of vocal folds by intrinsic laryngeal muscles (Eichert et al., 2020). In each hemisphere, we tracked the connectivity pattern from the putamen (seed mask) to the LMA (target mask; Direction 1) and from LMA (seed mask) to the putamen (target mask; Direction 2) through the thalamus (waypoint mask). The FA, MD, RD, and AD values within the BGTC loop for each participant in each group were then extracted.

Analysis of covariance (ANCOVA), with a between-subjects factor of group (HC, PDN, PDS) and within-subjects factors of hemisphere (left vs. right) and connectivity directions (2 directions: Direction 1 (putamen to LMA) and Direction 2 (LMA to putamen) for FA, MD, RD, and AD parameters were applied. We included gender and age as covariates in the analysis between the three groups. Additionally, as motor severity (MDS-UPDRS Total score) was not an appropriate covariate with the HC group, we conducted a two-group ANCOVA between PDN vs. PDS within the three-group ANCOVA with motor severity, age, and gender as covariates. The results did not differ from PDN vs. PDS comparisons in the three-group ANCOVA. Factor and simple effect sizes were quantified using partial η_p^2 (Witte & Witte, 2010) and Cohen's d (Cohen, 1992). Post-hoc testing with Bonferroni-adjusted alpha level was used whenever required. The normality assumption was tested using Shapiro-Wilk tests, the equality of variances with the Levene test, and sphericity assumption with the Mauchly test, and p-value of < 0.05 was set for significance unless otherwise stated.

5. Results

We investigated probabilistic tractography in the BGTC loop to determine the network properties of white matter structural connectivity underlying speech deficits in individuals with PD. Fig. 1 shows the binary images of the thresholded probabilistic maps of BGTC loop for the HC, PDN, and PDS. For FA metric, there were no significant main effects of group [$F(2,55) = 1.127$; $p = 0.331$], hemisphere [$F(1,55) = 0.427$; $p = 0.516$], or connectivity direction [$F(1,55) = 0.008$; $p = 0.928$]. The connectivity direction by group interaction [$F(2,55) = 3.392$; $p = 0.041$; $\eta_p^2 = 0.068$. The hemisphere by connectivity direction and the hemisphere by group were not also significant ($F(1,55) = 0.142$; $p = 0.708$]; $F(2,55) = 1.084$; $p = 0.345$]). None of the post-hoc analysis survived the adjusted alpha level for multiple comparison using Bonferroni correction. For MD, there was a main effect of group [$F(2,55) = 3.353$; $p = 0.044$; $\eta_p^2 = 0.101$], and direction [$F(1,55) = 251.645$; $p < 0.001$; $\eta_p^2 = 0.823$] with higher MD in Direction 1 compared to Direction 2. The main effect of hemisphere was not significant [$F(1,55) = 2.120$; $p = 0.167$]. The group by hemisphere interaction was significant [$F(2,55) = 3.205$; $p = 0.048$]. However, the group by connectivity direction [$F(2,55) = 2.233$; $p = 0.117$], and the hemisphere by direction interaction [$F(1,55) = 0.140$; $p = 0.710$] were not significant. Post-hoc analysis with

Table 1
Demographic and Assessment Information of Study Population.

Variable	HC	PDN	PDS	p-value (PDN vs. PDS)	p-value (HC vs. PDN)	p-value (HC vs. PDS)
Number of participants	20	20	20			
Gender (M:F)	10:10	11:09	14:06	0.093	0.759	0.206
Mean age (SD)	62.39 (10.04)	61.50 (7.15)	66.38 (7.25)	0.07	0.79	0.2
Mean NHY score (SD)	0 (0)	2.11 (0.41)	2.44 (0.72)	0.14	< 0.01	< 0.01
Mean MoCA score (SD)	30 (0)	28.80 (1.32)	28.06 (1.34)	0.09	< 0.01	< 0.01
Mean Speech Score (SD)	N/A	0 (0)	2.44 (0.63)	< 0.01	N/A	N/A
MDS-UPDRS Part I Total score (SD)	N/A	6.25 (1.84)	7.06 (4.26)	0.81	N/A	N/A
MDS-UPDRS Part II Total score (SD)	N/A	6.12 (3.38)	7.12 (5.13)	0.52	N/A	N/A
MDS-UPDRS Part III Total score (SD)	N/A	20.75 (9.7)	27.5 (12.4)	0.09	N/A	N/A
MDS-UPDRS Part IV Total score (SD)	N/A	20.75 (9.7)	27.5 (12.4)	0.09	N/A	N/A
MDS-UPDRS Total score (SD)	N/A	34.43 (10.72)	41.75 (16.60)	0.14	N/A	N/A

NHY = Hoehn & Yahr stage (Hoehn & Yahr, 1998).
MoCA = Montreal Cognitive Assessment (Nasreddine et al., 2005).
Speech Score = Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (motor assessment) Speech Score (Goetz, 2009).
Note: SD = Standard Deviation; PDS = PD group with speech deficits; PDN = PD group without speech deficits; HC = Healthy control group.

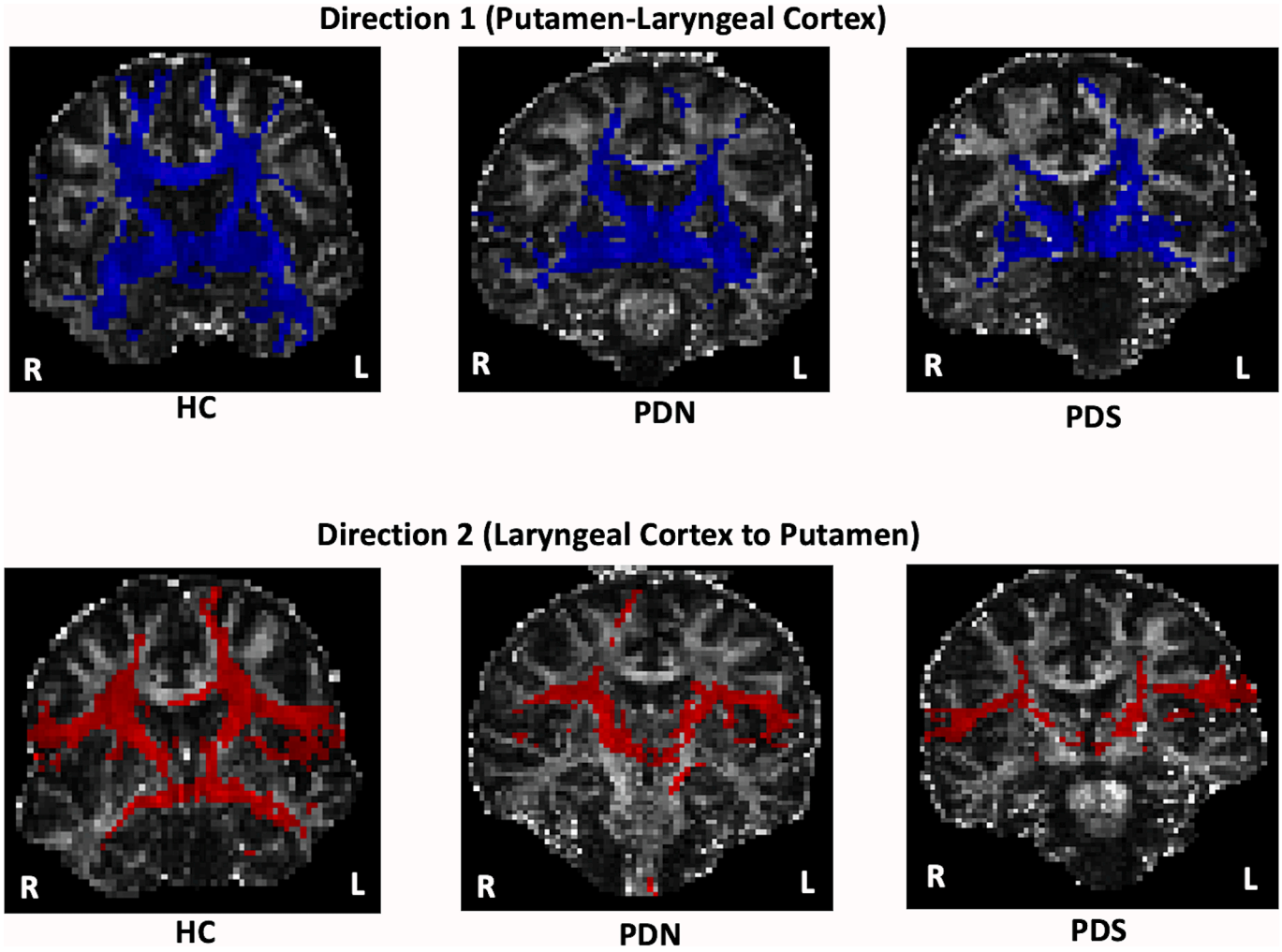

Fig. 1. Basal ganglia-thalamocortical (BGTC) pathway results: The reconstructed binary images of 1% of probabilistic tracts for laryngeal pathway connectivity in Direction 1 (top row) and Direction 2 (bottom row) in HC (left column), PDN (middle column), and PDS (right column) overlaid on the diffusion map of single participant DTI image (coronal view).

Bonferroni adjusted alpha value for multiple comparisons showed significantly increased MD in laryngeal pathway of left hemisphere in Direction 2 [$t(38) = -2.975$; $p = 0.008$; Cohen's $d = 0.665$] in PDS compared to PDN (Fig. 2 and Table 2). However, same laryngeal pathway in Direction 1 did not survive corrections for multiple comparisons [$t(38) = -2.241$; $p = 0.037$].

The analysis of RD did not yield any significant main effects for group [$F(2, 55) = 1.921$; $p = 0.156$], hemisphere [$F(1,55) = 0.154$; $p = 0.696$], or direction [$F(1,55) = 0.703$; $p = 0.405$]. None of the interaction effects were significant (direction by group: [$F(2,55) = 2.725$; $p = 0.074$]; hemisphere by group: [$F(2,55) = 2.637$; $p = 0.081$]; direction by hemisphere: [$F(1,55) = 0.650$; $p = 0.423$). Additionally, for AD, there was no main effect of direction [$F(1,55) = 1.172$; $p = 0.284$], hemisphere [$F(1,55) = 0.209$; $p = 0.649$] or group [$F(2,55) = 1.590$; $p = 0.213$]. The interaction effects were not significant for direction by group: [$F(2,55) = 1.629$; $p = 0.205$] and hemisphere by group: [$F(2,55) = 2.563$; $p = 0.086$]. However, the direction by hemisphere interaction was significant: [$F(1,55) = 9.2787$; $p = 0.004$]).

6. Discussion

This study examined structural changes in white matter metrices of speech deficits in PD. We employed probabilistic tractography to examine differences in the region-to-region connectivity in FA, MD, RD, and AD parameters within the BGTC loop in individuals with PD with and without speech deficits. Our main finding was increased MD in the left hemisphere compared to the right hemisphere that was observed in the direction of laryngeal motor area to the putamen in PDS compared to PDN.

The results of the two connectivity directions point to higher MD from the laryngeal motor area (LMA) to putamen through the thalamus (Direction 2) in the left hemisphere in the PDS group compared to the PDN group. Increased MD has been suggested to be linked to less directional diffusion and thicker than normal fibers in the BGTC loop (Mollaei et al., 2021). These results are consistent with previous investigations targeting the impact of PD on functional connectivity related to speech deficits. In a study by Manes et al. (2018), they found reduced functional connectivity in PDS compared to PDN in the left hemisphere putamen to left STG using functional connectivity analysis. However, they found increased resting-state functional connectivity between GPi and left dorsal laryngeal motor cortex. They hypothesized that this increase in connectivity might be an indicative of compensatory reorganization of these basal ganglia and cortical connections in PD to overcome the disease related progressive changes in voice production. While our results are not directedly comparable to Manes et al. (2018), one possible reason for these contradictory findings might be that Manes et al. (2018) investigated dorsal portion in the pre-central gyrus of laryngeal motor cortex and its connections to subcortical regions, whereas the present study investigated connections from relatively ventral portion of pre-central gyrus of laryngeal motor area (LMA). Both

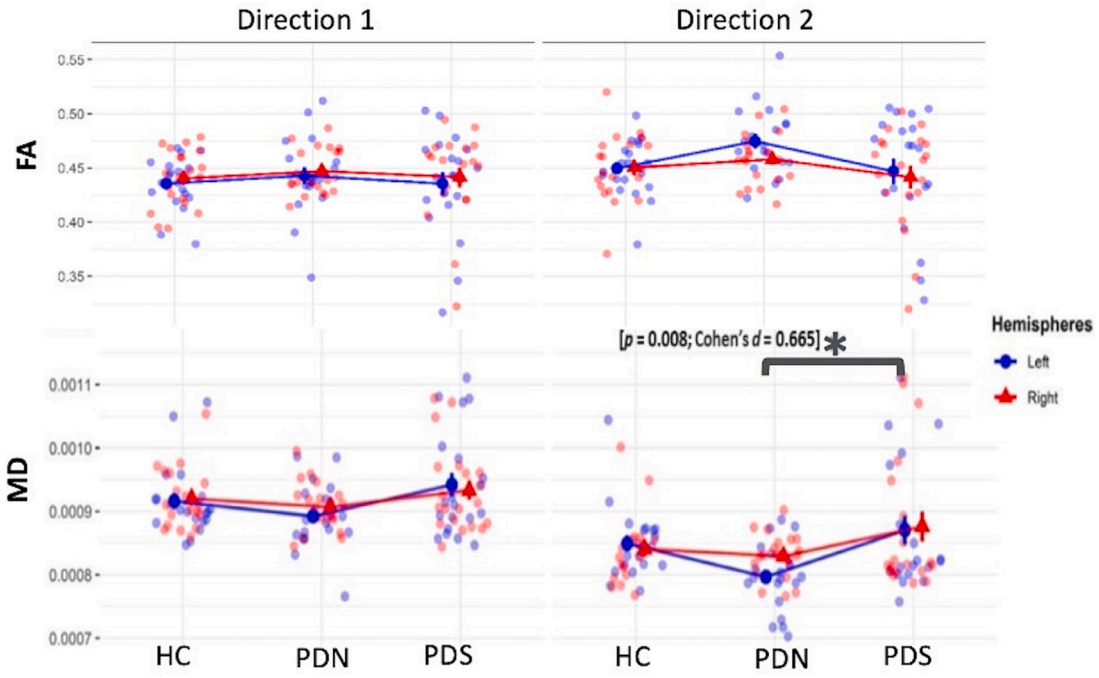

Fig. 2. FA and MD for the basal ganglia-thalamocortical (BGTC) pathway in two connectivity directions. Direction 1: lower medial putamen (seed mask) to laryngeal motor area (target mask) through thalamus (waypoint mask); Direction 2: laryngeal motor area (seed mask) to lower medial putamen (target mask) for the three groups (HC, PDS, and PDS) and the two hemispheres (blue: left hemisphere, red: right hemisphere). Only significant results that survived the Bonferroni-adjusted *p* value for multiple comparisons are shown with an (* < 0.05). HC = healthy controls, PDS = PD with speech deficits, PDN = PD without speech deficits.

Table 2
DTI measure differences between groups.

DTI measures	Direction	Hemisphere	HC	PDN	PDS	p-value (PDN vs. PDS)	p-value (HC vs. PDN)	p-value (HC vs. PDS)
Mean FA (SD)	1	Left	0.435 (0.023)	0.442 (0.035)	0.435 (0.0469)	0.866	0.959	1.000
Mean FA (SD)	1	Right	0.440 (0.026)	0.447 (0.021)	0.441 (0.041)	0.794	0.981	0.897
Mean FA (SD)	2	Left	0.449 (0.026)	0.474 (0.030)	0.446 (0.054)	0.083	0.137	1.000
Mean FA (SD)	2	Right	0.450 (0.031)	0.458 (0.023)	0.441 (0.046)	0.427	0.871	0.898
Mean MD (SD)	1	Left	0.916 (0.056)	0.892 (0.051)	0.941 (0.084)	0.065	0.779	0.667
Mean MD (SD)	1	Right	0.920 (0.047)	0.906 (0.037)	0.933 (0.067)	0.355	1.000	1.000
Mean MD (SD)	2	Left	0.849 (0.057)	0.796 (0.052)	0.870 (0.010)	**0.008***	0.085	1.000
Mean MD (SD)	2	Right	0.840 (0.054)	0.829 (0.035)	0.876 (0.010)	0.136	1.000	0.380

FA = Fractional Anisotropy; MD = Mean Diffusivity; SD = Standard Deviation; PDS = PD group with speech deficits; PDN = PD group without speech deficits; HC = Healthy control group; MD = MD x 10^{-3}.
Direction 1: putamen to laryngeal motor area; Direction 2: laryngeal motor area to putamen.
*p < 0.01.

dorsal and ventral laryngeal motor areas have distinct roles in laryngeal functioning with dorsal being involved in controlling the extrinsic muscles for vertical movements of the larynx and pitch modulation, whereas ventral laryngeal motor area is involved in the control of intrinsic muscles for movement/vibrations of the vocal folds for vocalization (Eichert et al., 2020). In addition, the difference in basal ganglia mask in our investigation, lower median putamen, compared to GPi in Manes et al. (2018) should also be taken into account for these seemingly discrepant results. Additionally, Arnold et al. (2014) found reduced effective connectivity between the prefrontal cortices of the inferior frontal gyrus, dorsolateral prefrontal cortex, supplementary motor area, and the caudate head in PD participants with hypokinetic dysarthria in the left hemisphere compared to HC which is consistent with our current findings.

In addition, it could be that the directionality may play a role in the differences found between Manes et al. (2018) and our results. While our results are not directedly comparable to Manes et al. (2018), functional connectivity versus our investigating structural connectivity, this connectivity partially forms the functional coupling between different neural populations (Hagmann et al., 2008). The directionality along multiple fiber tracts observed at the level of structural white matter can impact these functional neural dynamics (Petkoski et al., 2016). One possible explanation could be that the differences observed at the functional level (L GPi to LMA) may not expand from putamen to LMA at the structural white matter level. It should also be noted that this interpretation needs to be further investigated, as probabilistic tractography does not provide a direct measure of directionality and number of axon projections between the connected regions. Furthermore, the smaller sample size included in our study compared to Manes et al. may give rise to these differences, as there was a trend toward significance in MD in the direction from putamen to LMA direction in our study.

Another possible explanation could relate to the way that feedback and feedforward control mechanisms are affected in the speech sensorimotor control of speech in PD. The changes found in the direction of LMA to putamen in MD may point to the impaired feedforward control of speech, which relies on relying of sensory information for the updating of the future motor commands. Based on the proposed role of neural regions from the DIVA model (Tourville & Guenther, 2011), the LMA and motor regions are more involved with executing the learned motor commands. This area in the left hemisphere is proposed to be one

of the locations of the speech sound map, as part of the DIVA model (Guenther et al., 2006). Structural connectivity deficits in this direction may then result in an inadequate readout of the motor programs for updating the motor commands through feedforward control. The reduced connectivity from left putamen to STG found in Manes et al. (2018) points to the impairment in the feedback control of speech through error detection and correction. The increased connectivity from L GPi to LMA reported in Manes et al. (2018), as they speculated, could be due to overreliance on external cues to compensate for deficient internal cueing (feedforward control). In future studies, it would be of interest to investigate the reciprocal connections of auditory and somatosensory regions to basal ganglia structures, notably the putamen, to be able to tease apart the involvement of each control system in the speech deficits of PD. The input from the putamen to the LMA through the VLT direction is part of the motor circuit within the BGTC loop. As proposed by the GODIVA framework (Bohland et al., 2010), this motor circuit monitors the initiation and production of speech. We speculate that this may be under the control of feedback mechanisms as opposed to the feedforward control system. However, more information regarding the somatosensory and auditory regions, such as the STG, is required in order to integrate this with the current findings and thereby make a firmer claim regarding the effect of PD speech deficits on feedback and feedforward control mechanisms.

Additionally, it is also important to highlight that FA was not significantly different among groups. One possible reason for this could be due to the small sample size to detect differences among groups for the FA measure. It is noteworthy to mention that MD is more sensitive to detect changes in a small sample size (De Santis et al., 2014), and therefore increasing the sample size might show difference in the FA parameter as there seemed to be a non-significant pattern towards lower FA in the PDS compared to PDN. Another possible explanation could be that MD might be a more appropriate measure to discern these microstructural differences of the underlying brain tissue of the BGTC loop compared to FA. In addition, overall, the MD profiles for HC and PDN were more similar, and mean MD was higher across the two directions and the two hemispheres for PDS (mean = 0.905^{-3}) compared to HC (mean = 0.881^{-3}) and PDN (mean = 0.855^{-3}). There was a trend towards significance in MD between the HC and the PDS group in the direction of putamen to LMA (Direction 1) and between HC and PDN group in the direction of LMA to putamen (Direction 2). Combining the two PD groups together might mask the significance of these differences. We believe that increasing the sample size in each group may show the differences between the HC vs. PDN and PDS groups.

Furthermore, the MDS-UPDRS Part III Speech Item score from the PPMI database was used to identify individuals with PD with speech impairment. This measurement is not sensitive to identifying all aspects of the individual speech impairments, for example whether hypokinetic dysarthria and/or stuttering behaviours were present. It would be of interest in future studies to gather a comprehensive demographic data regarding the speech profiles of participants with PD such as perceptual dysarthria assessment, acoustic assessment, and neurogenic stuttering rating (Duffy, 2019; Reif & Goberman, 2021).

7. Limitations

Although this study provides new insights regarding deficits of white matter underlying speech impairments in PD, there are limitations to be considered. Due to the stringent exclusion criteria used and the availability of DTI images in the database, the final sample size gathered for each participant group was relatively small (N = 20). This may have resulted in insufficient power for detecting more subtle reductions in FA that may have been present in a group within each comparison. We also note that the age range and Hoehn & Yahr stage for PDN and PDS were slightly different between PDN and PDS, however, these differences were not statistically significant (see Table 1).

The speech deficits of PD range from the control of movements of the tongue and lips to changes in linguistics features (e.g., loudness, pitch; Duffy, 2019), hence, we were interested in understanding the structural deficits of the BGTC loop, in the motor control of speech in PD at the cortical level of LMA. However, similar to Manes et al. (2018), it would also be of interest to include sensory areas including auditory (e.g., STG) and somatosensory regions in addition to the motor areas (i.e., LMA) as well as gathering perceptual and acoustics measures of speech in the investigation of structural changes in the BGTC loop. This would provide a more complete picture of the feedback and feedforward control systems in the speech deficits of PD.

8. Conclusion

Disrupted structural integrity within the basal ganglia-thalamocortical loop found in increased MD in the left hemisphere for speech production may contribute to the speech impairments found in PD. Considering previous findings of reduced basal ganglia functional connectivity within a vocalization network in participants with PD (Arnold et al., 2014; Manes et al., 2018), this study may exhibit structural changes underlying these functional connectivity abnormalities and a potential distinct white matter pathophysiology of speech impairments in PD. However, due to the limitations discussed, this study must be considered preliminary.

CRediT authorship contribution statement

Fatemeh Mollaei: Supervision, Conceptualization, Methodology, Visualization, Writing – review & editing, Funding acquisition. **Mohammed Asif Basha Chinoor:** Formal analysis, Investigation, Visualization, Data curation, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Secondary data generated from analyses of Parkinson's Progression Markers Initiative (PPMI) database will be submitted to PPMI database upon the request of the PPMI study leadership.

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