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Compensatory striatal–cerebellar connectivity in mild–moderate Parkinson's disease

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ABSTRACT

Dopamine depletion in the putamen is associated with altered motor network functional connectivity in people with Parkinson's disease (PD), but the functional significance of these changes remains unclear, attributed to either pathological or compensatory mechanisms in different studies. Here, we examined the effects of PD on dorsal caudal putamen functional connectivity, off and on dopamine replacement therapy (DRT), using resting state fMRI. Motor performance was assessed with the Purdue pegboard task. Twenty-one patients with mild–moderate Parkinson's disease were studied twice, once after an overnight DRT washout and once after the administration of a standard dose of levodopa (Sinemet), and compared to 20 demographically-matched healthy control participants. PD patients off DRT showed increased putamen functional connectivity with both the cerebellum (lobule V) and primary motor cortex (M1), relative to healthy controls. Greater putamen–cerebellar functional connectivity was significantly correlated with better motor performance, whereas greater putamen–M1 functional connectivity was predictive of poorer motor performance. The administration of levodopa improved motor performance in the PD group, as expected, and reduced putamen–cerebellar connectivity to levels comparable to the healthy control group. The strength of putamen–cerebellar functional connectivity continued to predict motor performance in the PD group while on levodopa. These findings argue that increased putamen–M1 functional connectivity reflects a pathological change, deleterious to motor performance. In contrast, increased putamen–cerebellar connectivity reflects a compensatory mechanism.

1. Introduction

Parkinson's disease (PD) is associated with a progressive decline in motor control. Motor performance in PD is thought to reflect a balance between dysfunction of motor circuits, mainly due to dopamine denervation in the dorsal caudal putamen (Kordower et al., 2013), and compensatory processes, reflecting spontaneous adaptive adjustments in the interacting neural circuits that contribute to motor control (Lee et al., 2000; Nandhagopal et al., 2008; Palmer et al., 2009). Both dysfunction and compensation may be modulated by dopamine replacement therapy (DRT), the mainstay of PD treatment. The mechanisms underlying compensatory changes in PD remain unclear. It has been shown that patients may accomplish more difficult motor tasks by activating the same motor networks engaged in healthy controls, but to a greater degree and at easier stages of the task. Alternatively, or in addition, they may recruit other networks not typically recruited by healthy controls under the same conditions (Haslinger, 2001; Palmer et al., 2009; Samuel et al., 1997).

To date, investigations into the neural substrates of motor impairment in PD have mainly focused on alterations in cortico-striatal circuitry, detected with functional MRI or H_2O15-PET during the performance of motor tasks. Contralateral caudal putamen and bilateral supplementary motor area (SMA) typically show diminished activation in PD patients off DRT, relative to healthy controls, during the performance of motor tasks (Wächter, 2013). This is widely considered a reflection of PD pathology and is explained by the model of basal ganglia dysfunction in PD in which dopamine deficiency in the putamen leads to excessive firing of the subthalamic nucleus and globus pallidus internal segment, resulting in decreased cortical excitation, and in turn, bradykinesia.

In contrast, several studies have found that activity is enhanced in primary motor cortex (M1) (Haslinger, 2001; Lewis et al., 2011; Sabatini et al., 2000; Wu et al., 2015; Yu et al., 2007) and cerebellum (Cerasa et al., 2006; Lewis et al., 2011; Palmer et al., 2009; Wu and Hallett, 2005; Yu et al., 2007) in PD patients off DRT during the performance of motor tasks. The relationship of these increased activations to motor performance remains unclear, in part because of variability in both task demands and PD patient performance across studies.

The role of enhanced task-related activity in cerebellum also remains unclear. Although the cerebellum is known to play a role in motor control, it has only recently been recognized as potentially important in

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motor function in PD in particular (Bell et al., 2015; Festini et al., 2015; Martinu and Monchi, 2013; Wu and Hallett, 2013). Recent anatomical work in non-human primates has found bidirectional, disynaptic subcortical communication between the basal ganglia and cerebellum: motor regions of the dentate nucleus project via the thalamus to the sensorimotor putamen, and motor regions of the subthalamic nucleus project via the pons to cerebellar cortex, region HVIIB (Bostan and Strick, 2010; Hoshi et al., 2005). These findings emphasize the need to better understand striatal–cerebellar interactions in PD, in addition to the more thoroughly studied cortico-striatal circuits.

Resting state fMRI offers a different perspective on neural network changes in PD, avoiding the confounds related to differential task performance that can arise when comparing clinical and healthy populations (Fox, 2010; Zhang and Raichle, 2010). This method has proved useful in better understanding cognitive function in PD (Baggio et al., 2015; Putcha et al., 2015). Here, we use this approach to study network changes in relation to motor function in PD, both off and on DRT.

Studies show the putamen and M1, and the putamen and cerebellum are functionally connected at rest in healthy adults (Bernard et al., 2013; Di Martino et al., 2008; Kelly et al., 2009). To date, the effects of PD on these resting state networks remain unclear. A consensus has yet to emerge likely because of differences in disease severity or medication status across studies, and because of the small number of studies to date. For instance, putamen–cerebellum functional connectivity has been reported as decreased (Hacker et al., 2012) or not different from healthy controls (Helmich et al., 2010). Likewise, putamen–M1 functional connectivity has been reported as decreased (Helmich et al., 2010), increased (Hacker et al., 2012) or not different from healthy controls (Kwak et al., 2010). Furthermore, the functional significance of alterations to these networks remains unknown: while DRT has been shown to relatively normalize (Wu et al., 2009a), fully normalize (Bell et al., 2015), or lead to differences in motor network functional connectivity in PD compared to controls (Festini et al., 2015), it is unclear how these DRT-induced changes in motor network connectivity in PD relate to motor performance. Moreover, changes in functional connectivity may be viewed as deleterious (disease related) or compensatory, depending on their relationship to motor performance.

Here, we aimed to address key questions about the functional significance of the effects of mild–moderate PD on motor network functional connectivity measured with resting state fMRI in a group of patients tested off and on DRT. Given the putamen's core role in motor networks, and that it is the site of the most severe dopamine depletion in PD, we focused on dorsal caudal putamen functional connectivity.

First, we investigated the relationships between the strength of putamen's functional connectivity with M1 and cerebellum, and motor performance, assessed outside the scanner with the Purdue pegboard task in PD patients off DRT, compared to healthy controls. Second, we examined how DRT, in the form of a standard dose of levodopa, affected the strength of functional connectivity between these regions, and, how it affected the relationships between connectivity and motor performance. We confirmed the specificity of the findings by carrying out the same analyses in a control region also affected in PD, the dorsal caudate.

2. Materials and methods

2.1. Participants

Twenty-one patients with mild–moderate idiopathic Parkinson's disease (mean age 67, S.D. 8.9) and 20 demographically matched healthy control subjects (mean age 65, S.D. 6.7) participated in this study. Patients were recruited from the McGill University Health Centre Movement Disorders clinic. Experienced movement disorder neurologists identified patients with idiopathic PD without dementia, based on the UK brain bank criteria (Hughes et al., 1992). All patients scored ≥24/30 on the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), a screening test for cognitive impairment. Patients with other neurological diagnoses that might affect cognition, or overt clinical depression, were excluded. Healthy controls were recruited from the local community. Controls were excluded if they had a history of neurologic or psychiatric disease, head injury, or were taking psychoactive medication. The local research ethics committee approved the study.

2.2. Study procedure

All participants underwent two MRI scans in a single morning session. PD patients were scanned after an overnight (minimum 18 h) washout of their DRT (off DRT state) and again 45 min after receiving a single standard dose of Sinemet (100 mg L-dopa; 25 mg carbidopa) (on DRT state), timed to coincide with peak plasma concentrations (Olanow and Obeso, 2000). Patients continued all other medications as usual in the washout condition. Controls were not administered DRT but underwent two resting state fMRI scans, with procedures exactly the same as for the patients. The control group's first scan was compared to the PD group's first scan (off DRT), and the control group's second scan was compared to the PD group's second scan (on DRT).

2.3. Behavioral testing: motor performance

Patients completed the Purdue pegboard task (Lafayette Instruments, Lafayette, IN) immediately before both scans, in their DRT 'off' and 'on' states. The task requires using one hand to place as many pins as possible into the holes of a pegboard in 30 s. The score is the number of pins successfully placed. Two trials were performed with each hand (scores were averaged across trials for each hand). Higher scores signify better motor performance.

2.4. Image acquisition

Imaging was carried out with a 3 T Siemens Trio scanner equipped with a standard 12-channel head coil. Foam pads were used to fix the subject's head within the coil to minimize head motion. A high-resolution T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) structural volume was acquired for registration purposes (TE = 2.98 ms, TR = 2300 ms, inversion time = 900 ms, flip angle = 9°, field of view = 256, voxel dimension = 1 mm isotropic). For the two resting state fMRI scans, participants were instructed to lie still with their eyes open, to think of nothing in particular and to not fall asleep. Whole-brain functional imaging was performed using a gradient echo echoplanar imaging sequence (176 volumes, TE = 30 ms, TR = 2160 ms, field of view = 256 mm, flip angle = 90°, matrix = 64 × 64, voxel dimension 4 mm isotropic, acquisition time = 6 min 22 s).

2.5. Image preprocessing

Images were preprocessed and analyzed using tools from the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Preprocessing included: slice time correction, motion correction (3D volume registration using least squares alignment of 3 translational and 3 rotational parameters), non-brain removal, spatial smoothing with a Gaussian 5 mm FWHM kernel, high-pass temporal filtering at 100 s and reslicing to 2 mm isotropic. Registration of high resolution structural images to the MNI152 (Montreal Neurological Institute) template was performed using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002). Transformation to MNI152 standard space was then further refined using FNIRT nonlinear registration (Andersson et al., 2007).

The time series of eight nuisance variables were identified for inclusion: white matter, cerebrospinal fluid and six variable head motion parameters. To extract the covariate time series for white matter and cerebrospinal fluid, each individual's high-resolution structural image was segmented using FSL's FAST segmentation program. Segmented