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Alterations in striato-pallidal intrinsic functional connectivity as a prodrome of Parkinson's disease

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Abstract:

Although the diagnosis of Parkinson's disease (PD) remains anchored around the cardinal motor symptoms of bradykinesia, rest tremor, rigidity and postural instability, it is becoming increasingly clear that the clinical phase of the disease is preceded by a long period of neurodegeneration, which is not readily evident in terms of motor dysfunction. The neurobiological mechanisms that underpin this prodromal phase of PD remain poorly understood. Based on converging evidence of basal ganglia (BG) dysfunction in early PD, we set out to establish whether the prodromal phase of the disease is characterized by alterations in functional communication within the input and output structures of the BG. We analyzed resting-state functional MRI data collected from patients with REM sleep behavior disorder (RBD) and/or hyposmia, two of the strongest markers of prodromal PD, in comparison to age-matched controls. Relative to controls, subjects in the prodromal group showed reduced interhemispheric functional connectivity in each of the tested BG nuclei (putamen, caudate, pallidum) as well as reduced striato-pallidal inter- and intrahemshpric connectivity. The data suggest that local interactions between input and output BG structures may be disrupted already in the prodromal phase of PD.

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Introduction

While advances in our understanding of Parkinson's disease (PD) keep accumulating, its diagnosis remains centered around the presentence of cardinal motor symptoms, including bradykinesia, rest tremor, rigidity and postural instability (Mahlknecht et al., 2015; Postuma and Berg, 2016). Nevertheless, it is by now clear that these symptoms are preceded by a long period in which neurodegeneration spreads throughout the nervous system (Postuma and Berg, 2016). Markers for this presympotmatic phase, often referred to as the *prodromal* phase of PD are still under investigation. Studies have suggested that a polysomnography-based diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD) is among the strongest markers (Berg et al., 2015; Mahlknecht et al., 2015; Postuma et al., 2015), since up to 80% of patients with RBD will eventually develop a neurodegenerative disease, primarily PD (Postuma and Berg, 2016). Other markers commonly cited in the literature include hyposmia, and a range of autonomic dysfunctions (Mahlknecht et al., 2015; Postuma et al., 2015).

Little is known to date about the neurobiological mechanisms that characterize the prodromal phase of PD. An influential staging scheme for PD postulated that α-synuclein pathology first begins in the caudal brainstem and the olfactory bulb, later progressing to the substantia nigra (SN) and finally to limbic regions and the neocortex (Braak et al., 2003). However, it remains unclear if any of these regions and pathways are affected during the prodromal phase of PD. Neuroimaging provides a useful non-invasive means of addressing this question. In particular, altered functional connectivity between the SN and the putamen and SN and parieto-occipital cortical regions were reported in patients with RBD, when compared to controls (Ellmore et al., 2013). More recently reduced resting-state coactivation within a large-scale network of brain regions including the putamen, middle, medial and orbital frontal cortices was found in patients with RBD compared to age-matched controls (Rolinski et al., 2016). Together, these two studies suggest that functional interactions between the putamen and other cortical and subcortical regions are disrupted in the prodromal phase of PD. However, findings from other imaging modalities suggest that other regions in basal ganglia may be affected (Postuma and Berg, 2016). For example, molecular imaging studies have found alterations in dopaminergic

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neurotransmion in patients with idiopathic RBD in both the putamen and the caudate (Eisensehr et al., 2000; Iranzo et al., 2010). These findings join data on aberrant functional connectivity (Rolinski et al., 2015) and regional atrophy (Zeighami et al., 2015) in early PD found in the caudate and pallidum, as well as in the putamen. Communication between the caudate and putamen, the input structures of the BG and the pallidum which consists of both intrinsic (GPe) and output (GPi) BG nuclei are a central feature in mechanistic models of PD (Lanciego et al., 2012). Still, the time course of neuropathological changes within the BG, and in particular the extent to which intrinsic functional connectivity between the input and output structures in this circuity is altered in the prodromal phase of PD remains insufficiently understood. Here, we set out to examine if the prodromal phase of PD is associated with specific alterations in functional connectivity within the basal ganglia and between the BG and other cortical and subcortical regions.

Materials and Methods

Subjects: Data from 35 participants were analyzed, including 17 participants in a prodromal PD group (mean age= 67.88 ± 4.8, 12 males) and 18 age-matched controls (mean age 64.22 ± 9.77, 14 males). The data were obtained from the Parkinson's Progression Markers Initiative (http://www.ppmi-info.org), a comprehensive observational, international, multi-center study designed to identify PD progression biomarkers (Marek et al., 2011). All participants provided written informed consent and the procedures were approved by the Institutional Review Boards of the participating centers. All resting-state and anatomical scans provided by the PPMI for both groups were included in the analysis. To be included in the prodromal PD group participants had to be at least 60 years of age and present at least one of the two following clinical characteristics: a) hyposmia, as confirmed using the University of Pennsylvania Smell Identification Test (UPSIT)(Doty et al., 1984), with a cutoff at or below the 10th percentile adjusted by age and gender. b) polysomnography meeting the criteria of RBD and/or a clinical diagnosis of RBD by site investigator including existing PSG. Current or active clinically significant neurological or psychiatric disorders including a current diagnosis of PD were defined as exclusion criteria in this group. For the control group, current or active clinically significant

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neurological disorder or a first degree relative with idiopathic PD were defined as exclusion criteria. Full inclusion and exclusion criteria for the two groups are available online (http://www.ppmi-info.org). Data from 2 subjects in the prodromal group and 1 in the control group were excluded because of excessive head motion during scanning (see bellow), therefore the final dataset included 15 participants in a prodromal group (mean age=68.06±5.07, 11 males) and 17 age-matched controls (mean age=63.64 ±9.75, 14 males).

Cognitive evaluation: As part of the PPMI protocol, subjects underwent basic screening for cognitive function, using the Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005).

Imaging data acquisition: Imaging data were acquired with Siemens 3T scanners (either Prisma or TimTrio). Structural images were acquired with an MPRAGE sequence using GRAPPA (TE=2.98, TR=2300 ms, FA=9°, 1 mm^3 isotropic voxel). Resting-state functional MRI (fMRI) scans were acquired from the same subjects with an echo-planar sequence (total of 210 volumes [164 in 2 of the prodromal subjects), 40 axial slices, acquired in ascending order, TE=25.0 ms; TR=2400.0 ms, Flip Angle=80.0° voxel size = 3.3 mm3 [3.0 mm in 2 of the prodromal subjects]. For the resting state scans subjects were instructed to rest quietly with their eyes open while trying not to fall asleep.

Imaging data analysis: Data analysis was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the Conn toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) version 16b, both running on MATLAB R2016b (MathWorks, Natick, MA, USA). Functional images were realigned, unwarped and slice-time corrected; grey-matter, white-matter and cerebrospinal fluid (CSF) were segmented and the functional data were normalized to the MNI template. Motion artifacts were further detected using the ART-based scrubbing method (see, Power et al., 2012), implemented in Conn (setting a threshold of 2 mm subject motion and a global signal threshold of Z=9) and the data were spatially smoothed with a Gaussian kernel set at 8mm full width at half maximum. Unsmoothed data was used in the region-to-region analysis (see bellow). Signals from white matter and CSF (the first five principal

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components from each), as well as the 6 motion realignment parameters and their first order derivatives were regressed out of the signal, and so were outlier volumes (including the single volumes preceding the outliers) detected in the ART-based scrubbing procedure. The data was also linearly detrended. Data from 2 subjects in the prodromal group and 1 subject in the control groups were excluded, because of excessive head motion (>50% of volumes detected as outliers), leaving 15 subjects in the prodromal groups and 17 in the control group. The residual signals were then band-pass filtered (0.008Hz to 0.09Hz).

Two types of analyses were conducted. First, interactions between regions of interest (ROIs) in the BG were tested with region-to-region analysis. In the first level of analysis region-to-region connectivity matrices were computed for each subject. ROIs in the caudate, putamen and the pallidum, defined based the probabilistic Harvard-Oxford atlas, were used in this analysis. In an additional analysis spherical ROIs in the SN were also included in the region-to-region analysis, defined based on published coordinates (Tomasi and Volkow, 2014). Each subject's fisher-Z transformed connectivity matrices were then subjected to a second-level non-parametric network-based statistics analysis (Zalesky et al., 2010), testing differences between the prodromal and control groups, with a connection-level threshold set at False Discovery Rate (pFDR)<0.05. Second, functional connectivity between the BG and other cortical and subcortical regions was tested using a seed-to-voxel approach. In the first level of the analysis, seed-to-voxel maps were computed for each subject, with seed regions comprising right and left putamen, both defined based on the Harvard-Oxford atlas. The single-subject seed-to-voxel maps were then subjected to a random effect second-level general linear model testing for differences between the groups. A voxel-level threshold of p>0.001 was used, qFDR (>0.05) corrected for multiple comparisons at the cluster level.

Results

Our objective was to examine if intrinsic functional interactions within the BG and between the BG and other cortical and subcrotical regions differ in patients who are suspected to be in the prodromal phase of PD, relative to age-matched controls. We analyzed resting-state fMRI data acquired from a group of individuals who had a confirmed diagnosis of RBD and/or were

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hyposmic, two established markers of prodromal PD (Postuma and Berg, 2016). Data acquired from age-matched controls was used as a comparison.

The prodromal and control groups did not differ in age (t_{30}=1.574, p>0.1), male/female distributions (Kolmogorov-Smirnov Z=0.255, p>0.1) or cognitive function, assessed with the MOCA (t_{30}=-0.934, p>0.1). In addition, we did not find statistically significant differences between the groups in the total amount of head movement during scanning (t_{30}=1.467, p>0.1) or the number of outliers detected in the ART-based scrubbing procedure (Mann-Whitney U=117, p>0.1), ruling out possible confounds which may have been introduced by head motion during scanning.

Region-to-region functional connectivity in the basal ganglia

To identify possible functional connectivity alterations within the BG found in the prodromal group, relative to the control group we first subjected the bilateral putamen, caudate and pallidum ROIs to network-based statistics analysis (Zalesky et al., 2010). Functional connectivity within the BG was first derived for the prodromal (**Fig 1a**), the control (**Fig 1b**) groups. A comparison between the groups (with a connection-level threshold set at pFDR<0.05) revealed that, relative to controls, the prodromal group displayed reduced interhemispheric functional connectivity (**Fig. 1c**) between right putamen and left pallidum (p= 0.0021), right caudate and left putamen (p=0.0295), right caudate and the left pallidum (p= 0.0023), right pallidum and left caudate (p=0.0131) and between right and left putamen (p= 0.0004), caudate (p= 0.0005) and pallidum (p= 0.0095). Additionally, the prodromal group showed reduced intrahemshpric connectivity (**Fig. 1C**) between left putamen and pallidum (p= 0.0457), left putamen and caudate (p= 0.0238) and left caudate and pallidum (P= 0.0003).

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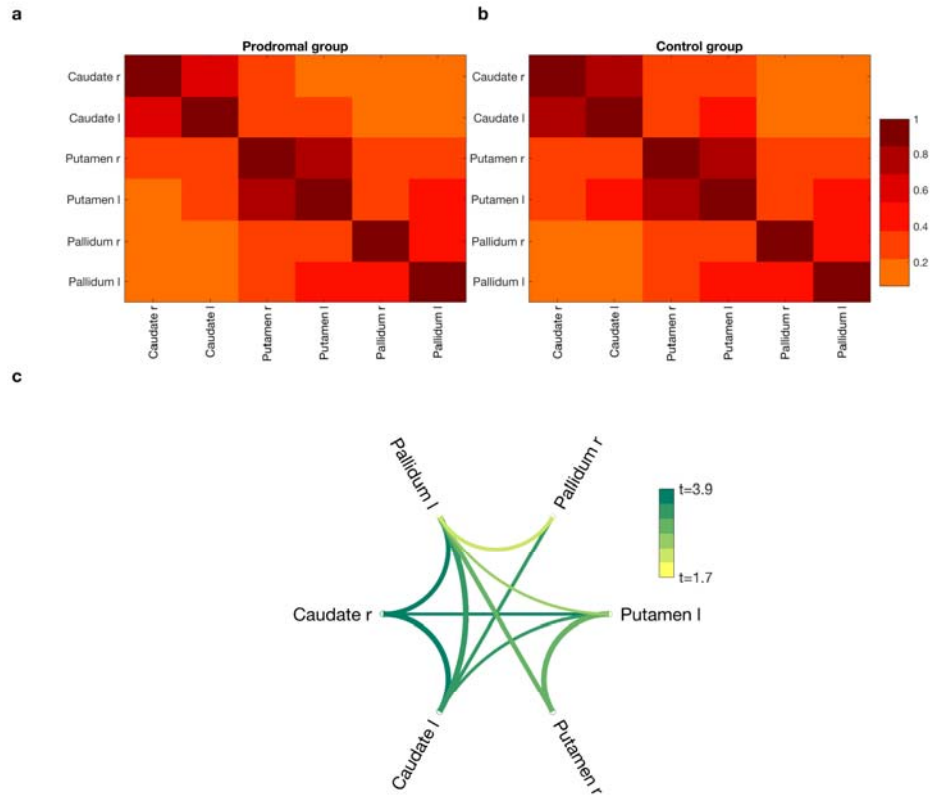

Figure 1. Region-to-region functional interactions in the basal ganglia. (a) average connectivity within the basal ganglia network in the prodromal group (b). Average BG functional connectivity in the control group. All correlation values were inverse Fisher Z transformed (to Pearson's r values) for visualization purposes. (c) functional connections for which the prodromal group showed reduced connectivity relative to the control group, based on a non-parametric network-based statistics analysis with a connection-level threshold set at pFDR < 0.05.

Seed-to-voxel functional connectivity in the basal ganglia

The results above suggest that an extensive set of intrinsic functional connections within the BG differentiated the two groups. We next tested whether the intrinsic alterations in functional connectivity found in the prodromal group, relative to the control group, were restricted to the BG, or rather were also evident in interactions between the BG and other cortical and subcortical regions. We therefore extracted the fMRI signals from right and left putamen and used these as seed regions in a seed-to-voxel analysis. We focused on functional connectivity with the putamen, as its interactions with other cortical and subcortical regions have been shown to be disrupted in the prodromal phase of PD (Ellmore et al., 2013; Rolinski et al., 2016).

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The results of this analysis suggest that BG connectivity differences between the prodromal and the control groups were primarily limited to functional interactions within the BG. The prodromal group showed reduced functional connectivity between the right putamen seed and a cluster encompassing contralateral putamen and pallidum ($p<0.0001$, FDR corrected at the cluster level). The prodromal group also showed reduced functional connectivity between the left putamen seed and a cluster encompassing bilateral pallidum, putamen and caudate ($p< 0.0001$, FDR corrected at the cluster level).

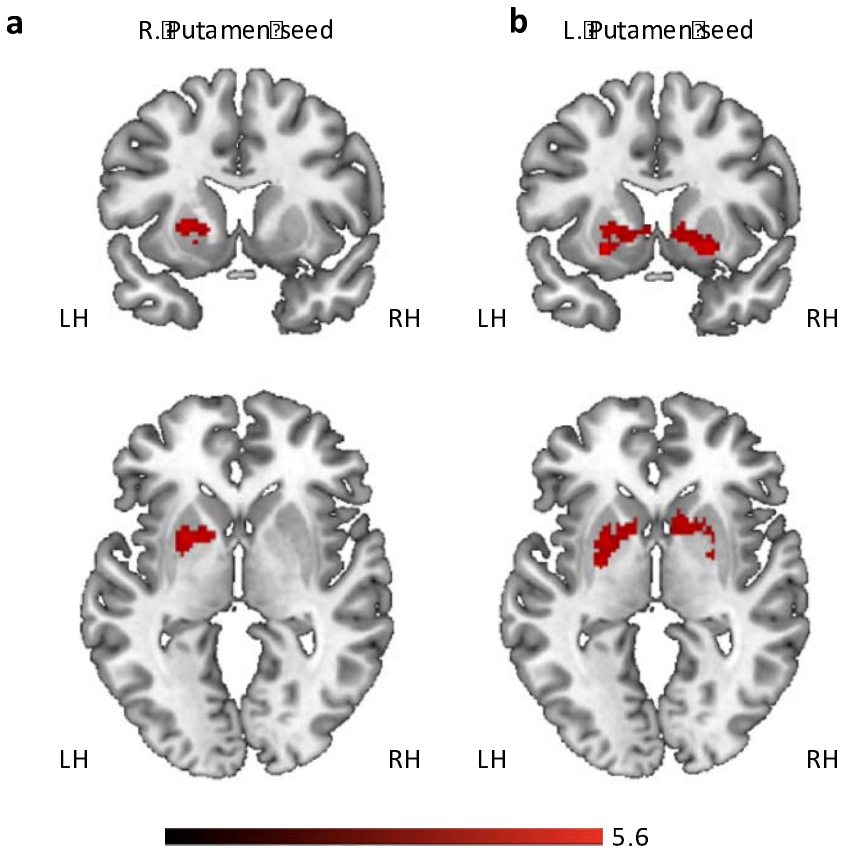

Figure 2. Seed to voxel functional connectivity analysis. (a) Relative to the control group, the prodromal group displayed reduced functional connectivity between right putamen and a cluster encompassing left putamen and pallidum. (b) Reduced functional connectivity in the prodromal relative to the control group was also found between left putamen and clusters in the left pallidum, and right putamen and pallidum. LH, left hemisphere. RH, right hemisphere.

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Cluster X,Y,Z	Locations	Cluster size	Cluster pFDR	Peak p
R. Putamen seed				
-22, 6, 2	Putamen (L), Pallidum (L)	359	0.0012	<0.0001
L. Putamen seed				
24, 12, -8	Putamen (L,R), Caudate (L,R) Pallidum (L,R)	654	<0.0001	<0.0001

Table 1. Seed-to-voxel analysis. Clusters showing reduced functional connective in the prodromal group, relative to the control group.

Functional connectivity between striatal and pallidal structures and substantia nigra

Previous results suggested that functional connectivity between the SN and the putamen is disrupted in patients with RBD, when compared to controls (Ellmore et al., 2013). We thus next examined if the prodromal and control groups showed differing functional connections between the 6 striatal and pallidal ROIs (see above) and ROIs in left and right SN (MNI coordinates: ±12, -12, -12, (Tomasi and Volkow, 2014)). This analysis did not reveal any significant differences between the two groups in striato-pallidal-SN functional connectivity.

Discussion

The results demonstrate that functional connectivity between the different compartments of the BG is disrupted in individuals who are likely in the prodromal phases of PD, relative to age-matched controls. Subjects in the prodromal group showed reduced interhemispheric functional connectivity in each of the tested BG nuclei (putamen, caudate, pallidum) as well as reduced striato-pallidal inter- and intrahemshpric connectivity. Connectivity changes were confined to striato-pallidal structures in the BG and were not found between these structures and other cortical and subcortical regions.

In the classical model of BG organization (for a recent review, see Lanciego et al., 2012), cortical signals flow through the striatum, forming two pathways. In the direct pathway, output from the striatum reaches directly to the substantia nigra pars reticulata (SNr) /internal globus pallidus (GPi). In the indirect pathway, striatal output reaches the SNr/GPi via the external

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globus pallidus (GPe) and the Subthalamic nucleus (STN). Signals from the SNr/GPi then project back to the cortex through the thalamus. Functional interactions between the putamen and caudate, the input structures of the BG, and pallidum which consists of both intrinsic (GPe) and output (GPi) nuclei are thus a major feature of normal BG function, and disruption in this circuity, as demonstrated here in the prodromal group, is a central feature in mechanistic models of PD (Lanciego et al., 2012)

Our results join two other recent studies (Ellmore et al., 2013; Rolinski et al., 2016) in reporting intrinsic functional connectivity alterations which are manifested already in the prodromal phase of PD. The current results differ from these earlier reports in our focus on connectivity within striato-pallidal structures in the BG. The first study (Ellmore et al., 2013) utilized seed-based connectivity analysis, with the right and left SN as seed regions, and found differences between RBD patients and controls in functional connectivity between right SN and right parieto-occipital cortical regions and left SN and the left putamen (Ellmore et al., 2013). A second study used a data-driven approach and found reduced resting state-coactivation in RBD patients, relative to controls, in an extensive network encompassing the putamen, and prefrontal cortex. Thus, while these results both suggest that functional interactions of cortical and subcortical regions with the putamen are altered in prodromal PD, the methods used do not specifically focus on connectivity between the different input and output structures of the BG, as tested here. Our results specifically point to disruptions in local striato-pallidal interactions, but not in functional connectivity between the BG and other cortical and subcortical regions, or between SN and striato-pallidal structures. One challenge in comparing results between studies is that, as a progressive process, the prodromal phase of PD may be manifested differently in groups of subjects that are not matched closely in various attributes such as current clinical diagnosis and disease duration. It thus remains to be tested how functional connectivity within the BG and between the BG and other cortical and subcortical regions changes along the progression of the prodromal phase of PD.

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Several limitations in the current study should be taken into account. First, the prodromal PD cohort analyzed here consisted of patients with RBD and/or hyposmia. It is currently unclear if these markers of prodromal PD (Berg et al., 2015; Mahlknecht et al., 2015; Postuma and Berg, 2016) are associated with differing intrinsic functional interactions within the BG, and a larger sample would be needed to test this question. Second, the current results focus on a cross sectional single-time point comparison and it remains to be tested if the strength of BG connectivity could predict conversion from prodromal to clinical PD. Future adequately powered longitudinal studies will be needed in order to address this question (Heinzel et al., 2016).

Circuit- and network-based accounts of neurological (Sharp et al., 2014; Stam, 2014) and neuropsychiatric (Gunaydin and Kreitzer, 2016) disease states have been prevalent in recent years. Similar accounts have been proposed for PD, with data pointing to disruptions in multiple motor and non-motor brain systems and their interactions (Baudrexel et al., 2011; Dayan et al., 2012; Jaywant et al., 2016; Luo et al., 2014). With the current results in mind, it appears that a systems-level account for PD (Caligiore et al., 2016) may also offer new insight on its prodromal phase and the progression from the prodromal to the clinical phase of the disease.

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