

ORIGINAL ARTICLE

Functional Connectivity Changes of Key Regions for Motor Initiation in Parkinson's Disease

Lukas Hensel^{1,2}, Felix Hoffstaedter^{3,4}, Julian Caspers^{5,6}, Jochen Michely^{1,7}, Christian Mathys⁶, Julia Heller^{8,9}, Claudia R. Eickhoff^{5,10}, Kathrin Reetz^{8,9}, Martin Südmeyer^{10,11}, Gereon R. Fink^{1,2}, Alfons Schnitzler^{10,11}, Christian Grefkes^{1,2} and Simon B. Eickhoff^{3,4}

¹Department of Neurology, Cologne University Hospital, Cologne D-50937, Germany, ²Institute of Neuroscience and Medicine, (INM-3: Cognitive Neuroscience), Research Centre Jülich, Jülich D-52425, Germany, ³Institute of Systems Neuroscience, Heinrich Heine University Düsseldorf, Düsseldorf D-40225, Germany, ⁴Institute of Neuroscience and Medicine, (INM-7: Brain and Behaviour), Research Centre Jülich, Jülich D-52425, Germany, ⁵Institute of Neuroscience and Medicine, (INM1: Structural and Functional Organization of the Brain), Research Centre Jülich, Jülich D-52425, Germany, ⁶Department of Diagnostic and Interventional Radiology, University Düsseldorf, Medical Faculty, Düsseldorf D-40225, Germany, ⁷Wellcome Centre for Human Neuroimaging, University College London, London WC1N 3AR, UK, ⁸Department of Neurology, RWTH Aachen University, Aachen D-52074, Germany, ⁹JARA-BRAIN Institute Molecular Neuroscience and Neuroimaging, Research Centre Jülich, Jülich D-52425, Germany, ¹⁰Medical Faculty, Institute of Clinical Neuroscience and Medical Psychology, Heinrich Heine University, Düsseldorf D-40225, Germany and ¹¹Medical Faculty, Department of Neurology, Center for Movement Disorders and Neuromodulation, Heinrich Heine University, Düsseldorf D-40225, Germany

Address correspondence to Simon Eickhoff, Institut für Neurowissenschaften und Medizin (INM-7), Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany. Email: S.Eickhoff@fz-juelich.de

Abstract

Akinesia, a cardinal symptom of Parkinson's disease, has been linked to abnormal activation in putamen and posterior medial frontal cortex (pmFC). However, little is known whether clinical severity of akinesia is linked to dysfunctional connectivity of these regions. Using a seed-based approach, we here investigated resting-state functional connectivity (RSFC) of putamen, pmFC and primary motor cortex (M1) in 60 patients with Parkinson's disease on regular medication and 72 healthy controls. We found that in patients putamen featured decreases of connectivity for a number of cortical and subcortical areas engaged in sensorimotor and cognitive processing. In contrast, the pmFC showed reduced connectivity with a more focal cortical network involved in higher-level motor-cognition. Finally, M1 featured a selective disruption of connectivity in a network specifically connected with M1. Correlating clinical impairment with connectivity changes revealed a relationship between akinesia and reduced RSFC between pmFC and left intraparietal

lobule (IPL). Together, the present study demonstrated RSFC decreases in networks for motor initiation and execution in Parkinson's disease. Moreover, results suggest a relationship between pMFC-IPL decoupling and the manifestation of akinetic symptoms.

Key words: akinesia, functional connectivity, motor initiation, Parkinson's disease

Introduction

Akinesia, the impairment to initiate spontaneous movements (Hallett et al. 1991), is one of the cardinal symptoms of Parkinson's disease critically affecting patients' quality of life (Schrug et al. 2000; Chapuis et al. 2005). James Parkinson described akinesia as the inability of the patient to perform movements "with the promptitude that the will directs" (Parkinson 1817). Later, Kinier Wilson referred to akinesia as a "paralysis of the will", suspecting its pathomechanism at the "highest level" of motor control (Wilson 1925). Since then, considerable progress has been made in the discovery of the neural mechanisms underlying motor symptoms of Parkinson's disease at the systems level. Current pathophysiological models of the disease suggest that akinesia arises from dysfunctional cortico-striatal processing, induced by a functional imbalance between direct and indirect basal-ganglia pathways (Wichmann and DeLong 2002; Grafton 2004; Wichmann et al. 2011; Jellinger 2014). Here, the putamen is most prominently affected by the deprivation of dopaminergic input originating from the substantia nigra (Bernheimer et al. 1973; Hornykiewicz and Kish 1987; Morrish et al. 1995; Forno 1996; Rajput et al. 2008). These findings are in line with *in vivo* neuroimaging studies, showing decreased activation of the putamen in Parkinson patients (for a recent meta-analysis see Herz et al. 2013). At the cortical level, the posterior medial frontal cortex (pMFC) has been suggested to contribute to patients' impairment in voluntary movement initiation (e.g. MacDonald ; Grafton 2004). This region is considered a central interface mediating cognitive (Ridderinkhof et al. 2004; Dosenbach et al. 2007, 2008; Nachev et al. 2008), motivational, and motor processes (Bush et al. 2002; Rushworth et al. 2004).

In the context of Parkinson's disease, neuroimaging studies have indicated abnormal activity in the pMFC during self-initiated movements (Playford et al. 1992; Jahanshahi et al. 1995; Haslinger et al. 2001), which ameliorated under dopamine replacement (Jenkins et al. 1992; Rascol et al. 1992; Haslinger et al. 2001) or deep brain stimulation (Davis et al. 1997; Limousin et al. 1997; Fukuda et al. 2001). Moreover, single cell recordings in the macaque pMFC revealed specific neural responses to movement instructions (Escola et al. 2003), which were distorted after inducing akinesia by lesioning this region. Correspondingly, clinical case reports in humans also noted akinetic symptoms resulting from lesions affecting the pMFC (Dick et al. 1986; Meador et al. 1986; Haussermann et al. 2001). Together, these findings suggest that akinesia might arise from a dysfunctional interaction between the pMFC and basal ganglia, especially the putamen (Grafton 2004; Vercruyse et al. 2014).

Of note, both of these regions' have been described as key nodes in a larger network linked to volitional behavior (Jahanshahi 1998; Hallett 2007; Brass and Haggard 2008; Kranick and Hallett 2013) and self-generated movements (Hoffstaedter et al. 2013, 2014). This cortical network includes lateral and medial prefrontal cortex, mid- and anterior cingulate cortex, insula as well as posterior parietal regions. Recently, an increasing number of fMRI studies have begun to investigate resting-state functional connectivity (RSFC) in Parkinson's disease (for a systematic

overview on RSFC studies in Parkinson's disease see Tahmasian et al. 2015). However, most of these studies have focused on subcortical seeds, revealing that striatal seeds feature reduced RSFC with the sensorimotor cortex (Helmich et al. 2010; Wu, Long, et al. 2011; Sharman et al. 2013; Luo et al. 2014; Müller-Oehring et al. 2015) and subcortical nuclei including thalamus, subthalamic nucleus, and midbrain (Hacker et al. 2012; Wu et al. 2012). In contrast, the cortical network for movement initiation remains poorly understood with respect to RSFC alterations in Parkinson's disease.

Hence, the present study aimed at analyzing RSFC of both striatal as well as pMFC seeds and their relation to akinesia in Parkinson's disease. To this end, 3 seeds in bilateral putamen and pMFC (comprising both hemispheres) were functionally defined based on a coordinate-based meta-analysis of neuroimaging experiments that included the free timing of movements (Hoffstaedter et al. 2014). Furthermore, 2 seeds were placed in bilateral primary motor cortices (M1) to compare RSFC of pMFC and putamen with connectivity in systems related to direct motor execution. All of the aforementioned regions are known to play a crucial role in motor function and were expected to show abnormal connectivity patterns in Parkinson's disease. However, we hypothesized that akinesia was particularly related to connectivity changes with regions involved in motor initiation, especially the pMFC. To test this hypothesis, we first analyzed RSFC between seeds in Parkinson patients and healthy controls, assessing the configuration of the preselected network in both groups. Next, whole-brain RSFC was computed for each of the 5 seeds in control subjects to identify extended resting-state networks specifically connected to the putamen, M1, and pMFC. These networks, were used to allocate the subsequently assessed aberrations of RSFC in patients. Finally, every seed's RSFC was tested for correlations with clinical scores of akinesia. In sum, the present study analyzed RSFC of bilateral putamen, bilateral M1, and pMFC to characterize seed-specific resting-state networks in healthy controls, their alterations in Parkinson's disease, and their potential roles in the manifestation of akinesia.

Materials and Methods

Subjects

Resting-state fMRI data of 60 patients with idiopathic Parkinson's disease (mean disease duration 6.5 ± 5.5 [SD] years) and 72 healthy participants were included in the analysis. Patients and healthy participants were matched for age, gender, and head movements within the MRI-scanner (please see Table 1 for further sample characteristics). Data were acquired at 2 sites, Aachen University Hospital (31 patients, 32 healthy controls) and Düsseldorf University Hospital (29 patients, 40 healthy controls). Overall disease durations ranged from 0 to 21 years (Düsseldorf: 9.3 ± 5.9 , range 0–21 years, Aachen: 3.9 ± 3.5 , range 0–15 years). All patients were examined while on their regular dopaminergic medication (mean levodopa equivalent dose 786 ± 517 mg per day, estimated based on Tomlinson et al. 2010). Patients' general

Table 1 Sample characteristics

	HHU Düsseldorf		RWTH Aachen		Overall sample	
	Parkinson patients	Healthy controls	Parkinson patients	Healthy controls	Parkinson patients	Healthy controls
Age [years]	59.8 ± 9.2	57.1 ± 10.0	63.3 ± 10.9	62.7 ± 5.6	61.6 ± 10.2	59.6 ± 8.8
P (t-test)	0.262		0.749		0.216	
Gender (m/f) ^a	(18/11)	(22/18)	(19/12)	(20/12)	(37/23)	(42/30)
P (χ ² -test)	0.557		0.921		0.697	
Movement (FD) ^b	0.41 ± 0.18	0.36 ± 0.16	0.36 ± 0.17	0.34 ± 0.15	0.39 ± 0.17	0.35 ± 0.16
P (t-test)	0.226		0.597		0.242	
UPDRS III (ON)	14.7 ± 7.5		24.3 ± 15.5		20.0 ± 13.2	
L-Dopa equivalent dose	1113.4 ± 400.1		395.9 ± 402.2		725.9 ± 532.9	
Disease Duration [years]	9.3 ± 5.9		3.9 ± 3.5		6.6 ± 5.5	
Laterality index ^c	-0.03 ± 0.43		0.23 ± 0.50		0.13 ± 0.47	
MMSE	n.a.		28.6 ± 1.2			
MDRS	136.8 ± 5.8		n.a.			
Measurement Parameters ^d	3 T / 300 / 2.2 / 30 / 90° / 3.1 × 3.1 × 3.1 mm ³		3 T / 165 / 2.2 / 30 / 90° / 3.1 × 3.1 × 3.1 mm ³			

HHU, Heinrich Heine University; RWTH, Rheinisch–Westfälische Technische Hochschule.

Mini-Mental State Examination; MDRS, Mattis Dementia Rating Scale.

^am = male, f = female.

^bFD: Framewise displacement (within scanner movement).

^cLaterality index: Right minus left UPDRS III scores, divided by the sum of right and left scores (Tomer et al. 1993).

^dMeasurement parameters: Magnetic field strength/volumes/repetition time [s]/echo time [ms]/flip angle/voxel size.

motor impairment was quantified by part III of the Unified Parkinson's Disease Rating Scale (UPDRS, [Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease 2003](#)). Across all patients, the average UPDRS III (on their regular dopaminergic medication) score was 19.6 ± 13.1 . As part of this score, item 31 assesses the global spontaneity of movements on a scale from zero (no symptoms) to 4 (severe symptoms). This item was used to rate clinical severity of akinesia and relate it to RSFC alterations in the fMRI analysis. Examinations at all data acquisition sites as well as pooled analysis were approved by the local ethics committees and carried out in accordance with the Declaration of Helsinki. All participants gave informed written consent before entering the study.

Regions of Interest

Five spherical regions of interest (ROI, 5 mm radius) were chosen for the RSFC analysis, centered around Montreal Neurological Institute (MNI x y z) coordinates based on the previous literature. The goal of the present study was to examine ROIs consistently associated with motor initiation with respect to Parkinson's disease. Therefore, coordinates in the pMFC (0 14 48) and bilateral centromedial putamen (left: -28 -2 2; right: 24 2 -2) were derived from local maxima of an activation likelihood estimation meta-analysis examining 103 neuroimaging experiments on volitional hand movements (Hoffstaedter et al. 2014). These seeds were motivated by the observation that movement initiation tasks (i.e., tasks with a free choice of movement initiation) are associated with increased activation in the aforementioned cortico-striatal network formed by the putamen and pMFC. Importantly, the pMFC was not only associated with self-selected timing, but also choice of movement (e.g., between different movement effectors), indicating the region's central role in different aspects of movement initiation (Hoffstaedter et al. 2013). For comparison, the 4th and 5th ROIs in bilateral primary motor hand areas (M1, left: -34 -26 56; right: 34 -24 52; cf. Roski et al. 2014) were included as control seeds, since

M1 is known to be one of the least affected areas by neurodegenerative processes in Parkinson's disease (Braak et al. 2004).

Seed-Based Resting-State fMRI Analysis

BOLD signal time series were measured using Siemens MAGNETOM TIM Trio 3 Tesla whole body scanners (Erlangen, Germany) at both study sites. For each participant, whole-brain volumes of gradient-echo EPI pulse sequences were acquired (details for each acquisition site are provided in Table 1). Preprocessing was conducted using the SPM8 software package (<http://www.fil.ion.ucl.ac.uk/spm>). The first 4 scans served as “dummy” images to allow for magnetic field saturation and were discarded prior to further preprocessing. The remaining EPI images were first corrected for head movement by affine registration using a 2-pass procedure, first creating a mean EPI and then realigning all scans to it. The mean EPI image of each participant was then spatially normalized to the MNI non-linear average FSL template using the “unified segmentation” approach (Ashburner and Friston 2005). The ensuing deformation was then applied to the individual EPI volumes. Then, images were smoothed by a 5-mm FWHM Gaussian kernel to account for residual anatomical variation and to meet the requirements of normal distribution of the residuals for Gaussian random field inference to correct for multiple comparisons. Movement effects in the scanner were corrected via regression of 24 movement parameters including the 6 motion parameters derived from the image realignment and their first derivative from the realignment as first and second order term (Power et al. 2012) before band pass filtering between 0.01 and 0.08 Hz (Cordes et al. 2001).

In order to compare the configuration of the predefined network between patients and healthy controls, pairwise RSFC was estimated between all seeds. Therefore, partial temporal correlations were computed using the FSLNets toolbox (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets>). For each pairwise connection,

Fisher's z-transformed FC values were submitted to one-sample t-tests. The resulting t values, reflecting connection strength as well as consistency across the sample, were z-transformed (i.e., into units of the standard normal distribution) and then fed into an agglomerative hierarchical cluster analysis. Cluster analysis was based on Ward's method as implemented in Matlab. Although this method does not reveal a finite parcellation (into a specific number of clusters), it aims at the heuristic identification of functionally interpretable subclusters within a given network. Data from healthy controls and patients were analyzed separately to assess network configurations of each group.

After the between-seed RSFC analysis, whole-brain RSFC was computed for each ROI in both patients and healthy controls to account for connectivity alterations in extended resting-state networks of each region. Accordingly, for each subject, linear (Pearson) correlation coefficients were computed between each seed's time series and those of all other gray matter voxels in the brain. Voxel-wise correlation coefficients were then transformed into Fisher's z-scores, and tested for consistency across subjects by a second-level analysis of variance (ANOVA). Therefore each seed's RSFC was entered in a general linear model (GLM), as implemented in SPM8. Additionally, to assess akinesia-related RSFC changes across the whole-brain for each ROI, UPDRS item 31 was introduced as a covariate for each seed's RSFC in the GLM. Additionally, measurement site (Aachen, Düsseldorf) was added as a covariate of no interest for all analyses to account for site-related effects.

To identify Parkinson patients' connectivity changes in the context of physiological resting-state networks, we first examined RSFC of the healthy participants. Based on healthy subjects' RSFC, conjunction analyses were used to delineate 3 networks specifically connected to bilateral putamen, bilateral M1, and pMFC.

That is, specific RSFC with the pMFC was obtained by contrasting RSFC of this region to the RSFC of all remaining seeds: $(RSFC_{pMFC}) \wedge (RSFC_{pMFC} - RSFC_{bilateral\ putamen}) \wedge (RSFC_{pMFC} - RSFC_{bilateral\ M1})$. Resting-state networks specifically connected with bilateral putamen and M1 were computed in analogous fashion. Similar analyses have been employed in previous studies, aiming at disentangling specific connectivity maps related to different ROIs (i.e., Cieslik et al. 2012; Eickhoff et al. 2016; Genon et al. 2017). In sum, the ensuing networks from these conjunctions comprise those regions that were specifically stronger connected with a particular seed, as opposed to the other ones. It is important to note, however, that each seed may feature RSFC and possibly Parkinson-related changes in all 3 networks, which was tested in the following analysis.

In the next step, the 3 maps derived from healthy controls were used to assign connectivity alterations related to Parkinson's disease. Altered connectivity in patients tested by comparing RSFC of each seed between patients and controls. For example, patients' connectivity *decreases* of the putamen were computed using the conjunction: $(healthy\ RSFC_{bilateral\ putamen}) \wedge (healthy\ RSFC_{bilateral\ putamen} - patients'\ RSFC_{bilateral\ putamen})$. In turn, *increased* RSFC with the putamen in Parkinson's disease was tested in the conjunction: $(healthy\ RSFC_{bilateral\ putamen}) \wedge (patients'\ RSFC_{bilateral\ putamen} - healthy\ RSFC_{bilateral\ putamen})$. These conjunctions were likewise applied to contrast patients' changes in bilateral M1 and pMFC. Besides testing for altered connectivity in Parkinson's disease, we probed co-variation between akinesia-scores and every ROI's RSFC. All of the ensuing disease- and symptom-related connectivity maps were then masked by each of the 3 networks, previously derived from healthy controls. This

allowed for dissociating pathological connectivity patterns in putamen-, M1-, or pMFC-specific resting-state networks.

Finally, conjunction analyses were used to test whether altered RSFC patterns of the different seeds were localized in converging brain regions. For example, overlap of RSFC decrease between putamen and pMFC was tested by the conjunction: $(healthy\ RSFC_{bilateral\ putamen}) \wedge (patients'\ RSFC_{bilateral\ putamen} - healthy\ RSFC_{bilateral\ putamen}) \wedge (healthy\ RSFC_{pMFC}) \wedge (patients'\ RSFC_{pMFC} - healthy\ RSFC_{pMFC})$. All results were whole-brain, cluster-level ($P < 0.05$) corrected for multiple comparisons.

Principal Component Analyses on the UPDRS III

RSFC was further related to the remaining UPDRS III (motor) items, including items which are used to assess bradykinesia, rigor and tremor. In this alternative approach, we aimed to reduce dimensionality of UPDRS III items using a principal component analysis as implemented in Matlab. Patients' scores of the ensuing components explaining most variance across UPDRS items were then related to each seed's RSFC, analogous to the connectivity analysis on akinesia, described in the previous paragraph. Methods and results of these analyses are in detail provided in the online Supplementary Material.

Anatomical Localization

The SPM Anatomy Toolbox v2.0 (Eickhoff et al. 2005, 2007) was used to allow for investigator-independent anatomical localization of the results. By means of maximum probability maps, activation clusters were automatically assigned to the most likely cytoarchitectonic area.

Results

Hierarchical Clustering Based on RSFC Between Seeds

Cross-correlations between all seeds' time series (bilateral putamen, bilateral M1, pMFC) enabled us to group seeds based on their connectivity strengths between each other. This hierarchical clustering analysis was separately performed for healthy controls and patients (Fig. 1). In both groups, strongest connectivity was found for interhemispheric interactions between anatomically homolog regions, leading to their consistent clustering as pairs. Moreover, in the healthy control group, bilateral putamen and pMFC were clustered in one group, separated from bilateral M1. In contrast, Parkinson patients featured stronger connectivity between pMFC and M1, clearly separated from bilateral putamen. Hence, we observed a distinct hierarchical clustering between regions of movement initiation and execution in patients compared to controls.

RSFC Networks in Healthy Participants

For each ROI, brain regions showing strongest connectivity estimates compared to all other seeds were isolated in healthy controls. For example, the analysis of specific RSFC of bilateral putamen only yielded those brain regions, that were (1) functionally connected to bilateral putamen, and (2) stronger connected to bilateral putamen than to bilateral M1 and pMFC seeds. This putamen-specific network comprised bilateral basal ganglia, midbrain, thalamus, left amygdala, right posterior insula, and bilateral cerebellum (bilateral lobules IV and V; Diedrichsen et al. 2009) (Fig. 2).

Equivalent contrast analyses identified specific resting-state networks for bilateral M1 (regions stronger connected with

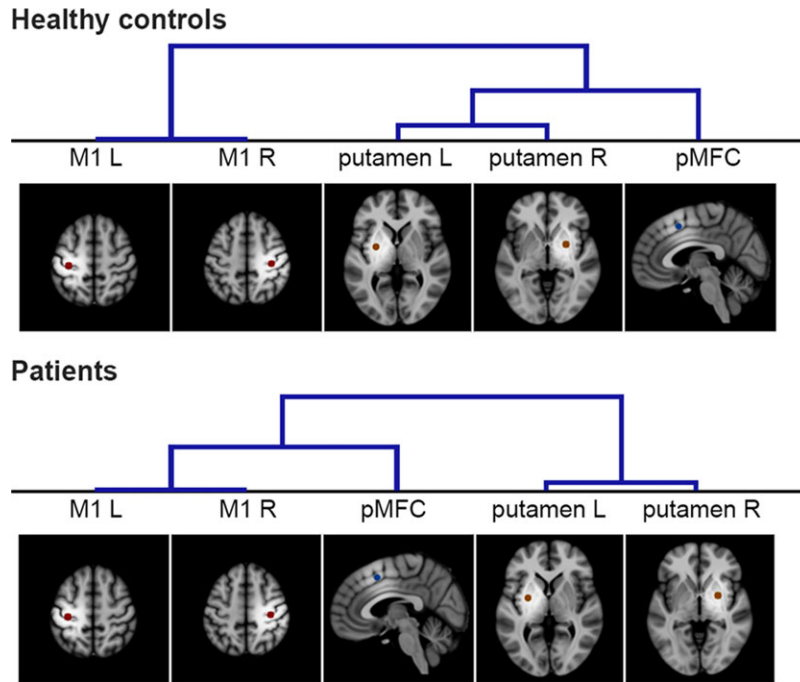


Figure 1. Hierarchical clustering of ROIs. Hierarchical clustering of ROIs based on their RSFC in healthy participants (top) and Parkinson patients (bottom). Using FSLNets, seeds with relatively strong RSFC were grouped first as illustrated by lower branches in the cluster trees. The qualitative comparison of both hierarchies indicates a shift of pMFC connectivity from homolog putamen to homolog M1 ROIs in Parkinson's disease.

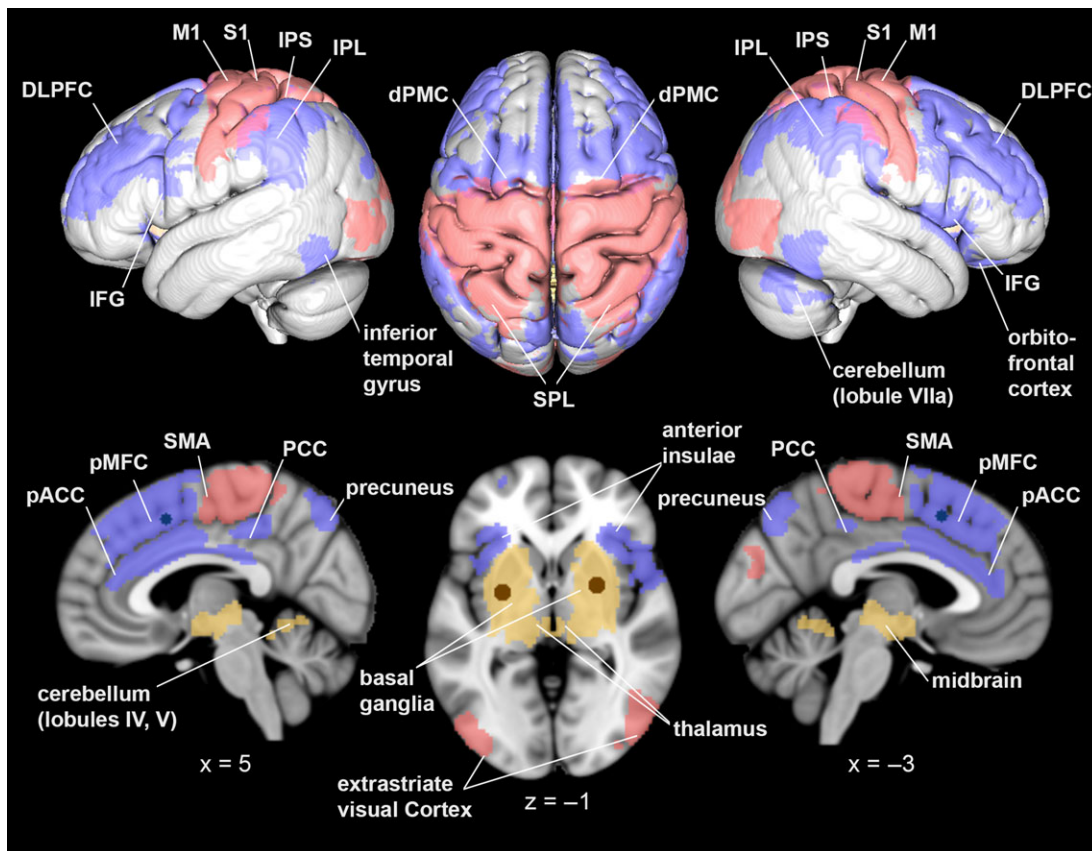


Figure 2. Resting-state functional connectivity networks in healthy controls. Differentiation of 3 resting-state networks in healthy participants: these yielded stronger connectivity to bilateral putamen (yellow), bilateral M1 (red), and pMFC (blue), as contrasted to the respective other seeds. All results were cluster-level corrected at $P < 0.05$. Images were rendered into a T1-weighted MNI single subject template using mango (<http://ric.uthscsa.edu/mango/>).

bilateral M1 than bilateral putamen and pMFC seeds) and pMFC (regions stronger connected with pMFC than with bilateral putamen and M1 seeds). The M1-specific network comprised the medial and lateral primary motor cortex, the posterior portion of the supplementary motor area (SMA; Geyer 2004), the dorsal premotor cortex (dPMC), primary somatosensory cortex (S1), superior parietal lobule (SPL), the medial bank of the intraparietal sulcus (IPS), extrastriate visual cortex, and right parietal operculum.

Finally, the resting-state network specifically connected with pMFC contained bilateral inferior frontal gyri (IFG; areas 44 and 45), perigenual anterior cingulate cortex (pACC), and posterior cingulate cortex (PCC; Vogt et al. 2004; Palomero-Gallagher et al. 2009), pMFC, dPMC, dorsolateral prefrontal cortex (DLPFC), anterior insulae, inferior parietal lobules (IPL), the lateral bank of the IPS, posterior areas of the SPL (7 P, 5 Ci; Scheperjans et al. 2008), precuneus, inferior temporal gyri, right orbitofrontal cortex, and right cerebellum (lobule VIIa crus I).

In summary, 3 networks specifically connected to putamen, M1 and pMFC were dissected by contrasting seeds' RSFC (Fig. 2). Importantly, these networks were solely derived from healthy participants' data. Thus, they provided representative functional connectivity maps to test for pathological connectivity changes.

RSFC Changes in Parkinson's Disease

Connectivity changes in Parkinson's disease were analyzed within the 3 seed-specific networks. There were only connectivity decreases in patients compared to healthy controls (Fig. 3), whereas no significant increases were found. The putamen seeds showed RSFC decreases in all 3 examined networks, that is the putamen-, pMFC-, and M1-specific network. First, in the putamen-specific network, we identified decreased putamenal RSFC with bilateral thalamus, putamen, and pallidum. Second, in the M1-specific network, putamen exhibited reduced

connectivity with bilateral SMA, S1, M1, SPL, IPS, extrastriate visual cortex, and right dPMC. Third, in the pMFC-specific network, putamen showed reduced RSFC with bilateral IPS, pMFC, left DLPFC, and left IPL.

Likewise, the pMFC was tested for RSFC abnormalities in Parkinson's disease. Within the M1-specific network, the pMFC seed showed decreased connectivity to bilateral S1 and right SPL. Additionally, in the pMFC-specific network, the pMFC seed exhibited decreased RSFC with bilateral anterior insulae and left DLPFC.

Furthermore, pathological connectivity changes were tested in M1 as a control region. RSFC decreases with bilateral M1 were mainly found in the M1-specific network including SMA, dPMC, M1, S1, SPL, IPS, and extrastriate visual cortex. In addition, an M1 connectivity decrease was observed in the pre-SMA. As revealed by the RSFC analysis in healthy controls, this region is part of the pMFC-specific network, which includes medial frontal regions rostral to the SMA. In contrast to the M1- and pMFC-specific networks, M1 did not show significantly altered connectivity in the putamen-specific network.

Finally, the aforementioned RSFC alterations in Parkinson's disease were tested for overlapping effects across seeds (Fig. 4). Convergent connectivity reductions were especially found for putamen and M1. Both regions featured reduced connectivity with the SMA, dPMC, and M1 in the right hemisphere as well as bilateral S1, SPL, IPS, and extrastriate visual cortex. Putamen seeds furthermore showed overlapping RSFC changes with the pMFC seed, namely in bilateral S1 and right SPL. No significant overlap was found when conjoining patients' RSFC reductions of M1 and the pMFC.

Akinesia-Related RSFC Changes in Parkinson's Disease

To analyze the relationship of akinesia and RSFC alterations in Parkinson's disease, akinesia scores were included in the GLM for each seed. Thus, RSFC with every seed was tested for

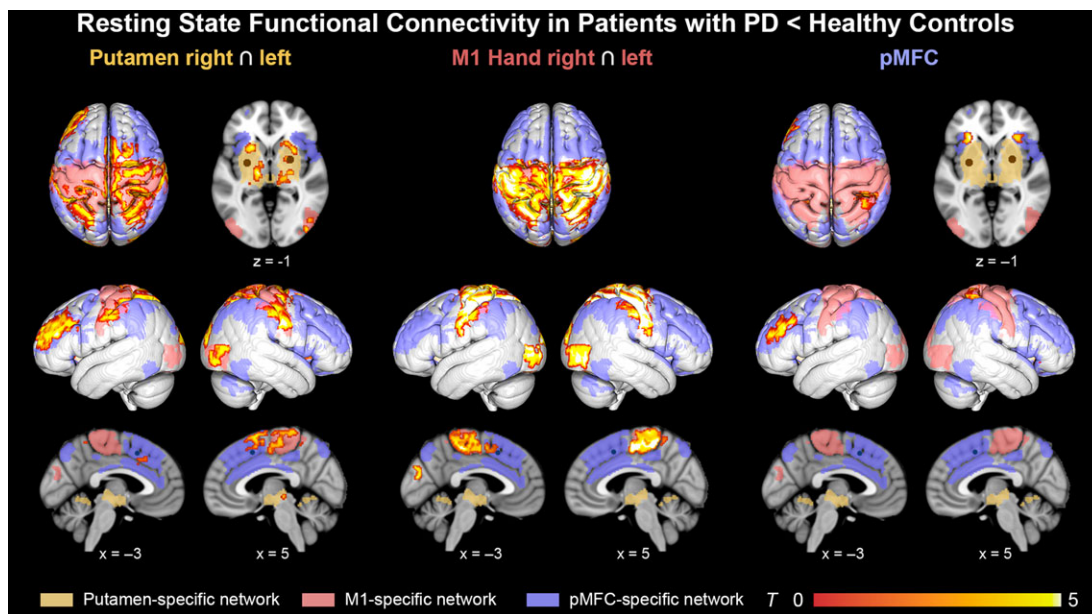


Figure 3. Resting-state functional connectivity decrease in Parkinson's disease. RSFC decrease in Parkinson patients assigned to the 3 resting-state networks as defined in the healthy group. These networks were rendered in yellow (putamen-specific network), red (M1-specific network), and blue (pMFC-specific network). Left column: RSFC with bilateral putamen was reduced in regions from all 3 networks. Middle column: RSFC with bilateral M1 declined most selectively in the M1-related network. Right column: Focal reductions of RSFC with the pMFC seed were found in pMFC- and M1-related networks. All results were cluster-level corrected at $P < 0.05$.

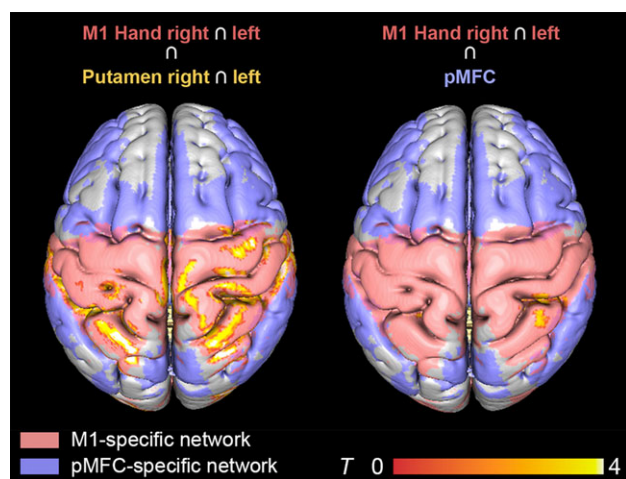


Figure 4. Overlap in resting-state connectivity decrease across seeds. Overlapping patterns of RSFC decrease were observed between M1 and putamen (left) as well as M1 and pMFC (right). All results were cluster-level corrected at $P < 0.05$.

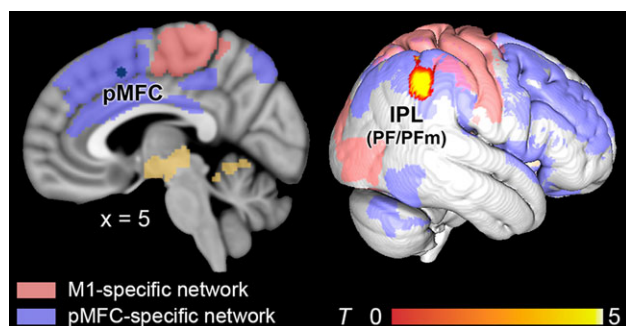


Figure 5. Connectivity decrease related to patients' global spontaneity of movements. Decreased RSFC between the pMFC seed and the inferior parietal lobule (IPL, areas PF/PFm) correlated with impaired spontaneity of movement initiation in Parkinson's disease. Resting-state networks from healthy controls were rendered in yellow (putamen-related regions), red (M1-related regions), and blue (pMFC-related regions). All results were cluster-level corrected at $P < 0.05$.

correlations with akinesia. While no association between akinesia and RSFC could be found within the putamen-, or M1-specific networks, connectivity within the pMFC-specific network was related to akinesia in Parkinson's disease. That is, RSFC between pMFC and right IPL (PF, PFm, Caspers et al. 2006) showed a negative correlation with akinesia scores. That is, higher impairment was correlated with a decline of RSFC between the pMFC seed and right IPL (Fig. 5).

Discussion

The pMFC and putamen are considered key regions for the spontaneous initiation of movements, which is critically impaired in Parkinson's disease. The present study elucidated abnormal RSFC changes of these regions, and 2 control seeds in bilateral M1, in a cohort of 60 Parkinson's patients and 72 healthy controls. First, the examination of RSFC between the 5 seeds indicated disturbed connectivity between putamen and pMFC seeds in patients. Alterations of RSFC were further examined in 3 seed-specific resting-state networks, reflecting preferential connections with a given seed (relative to the others) in the

healthy control group (Fig. 2). In Parkinson's disease, all seeds showed reduced RSFC within their respective network. For example, M1 showed a RSFC decrease mainly in the M1-specific sensorimotor network, pMFC lost RSFC with both anterior insulae and left DLFPFC (pMFC-specific network), and bilateral putamen showed marked RSFC loss within the putamen-specific subcortical network (Fig. 3). Finally, decreasing RSFC between pMFC and right IPL correlated with higher scores of akinesia in Parkinson's disease.

Network Hierarchy Amongst Seeds

Based on inter seed correlations, hierarchical clustering analyses yielded different network hierarchies in healthy controls as compared to Parkinson patients (Fig. 1). In controls, pMFC and putamen were clustered in one group, separate from bilateral M1 seeds. This network configuration is consistent with the seeds' different functional implications: While putamen and pMFC have been associated with the initiation of movements (Goldberg 1985; Deiber et al. 1999; Jenkins et al. 2000; Cunnington et al. 2002; Hoffstaedter et al. 2013, 2014), the primary motor cortex is mainly related to motor execution (Chen et al. 1991; Tanji and Mushiaki 1996; Roski et al. 2014). The strong functional connectivity between pMFC and centromedial putamen seeds, as observed during motor initiation tasks, furthermore parallels their structural interconnectivity, indicated by probabilistic tractography in diffusion weighted imaging data (Draganski et al. 2008; Helmich et al. 2010; Tziortzi et al. 2014; Neggers et al. 2015). Interestingly, RSFC across seeds yielded a different network hierarchy in Parkinson's disease. That is, patients' pMFC was less connected with putamen than M1. This separation of cortical and subcortical seeds in patients (Fig. 1) indicates dysfunctional cortico-striatal connectivity, which has been frequently observed in functional connectivity studies (Helmich et al. 2010; Kwak et al. 2010; Luo et al. 2014; Michely et al. 2015; Müller-Oehring et al. 2015). In relation to the decreased cortico-striatal connectivity, the hierarchical clustering suggested stronger connectivity between cortical seeds (M1, pMFC) in patients. In line with this observation, neuropathological changes in Parkinson's disease are known to start subcortically, whereas cortical regions are affected at later stages of the disease (Braak et al. 2004). By quantitatively comparing RSFC between patients and HC, the following paragraphs provide a detailed analysis of altered cortico-striatal and cortico-cortical connectivity in Parkinson's disease.

Subcortical and Cortico-Striatal Connectivity in Parkinson's Disease

In healthy subjects, a subcortical network was identified by its specific RSFC to bilateral putamen, in contrast to M1 and pMFC (Fig. 2). This putamen-specific network included bilateral caudate nuclei, pallidum, midbrain, thalamus and subthalamic nuclei, which are known to be also structurally interconnected (Kalil 1978; Albin et al. 1989; Nakano et al. 1990; Redgrave et al. 2010). Within this subcortical network, Parkinson patients showed reduced RSFC of bilateral putamen with pallidum and thalamus. Moreover, subcortical connectivity reductions were related to symptoms of bradykinesia as shown in detail in the online Supplementary Material of this article (Supplementary Fig. 4S). This is in line with previous studies reporting decreased RSFC between subcortical nodes, for example between putamen and thalamus (Hacker et al. 2012; Wu et al. 2012). Notably, these regions are predominantly involved in

cortico-striatal circuits, which play a crucial role in pathophysiological models of Parkinson's disease (Alexander et al. 1986; Redgrave et al. 2010). Accordingly, dopaminergic depletion in the putamen arises from the degeneration of dopaminergic neurons in the substantia nigra pars compacta (Hornykiewicz and Kish 1987; Morrish et al. 1995; Forno 1996). This, in turn, affects intrinsic basal-ganglia processing but importantly also its interaction with cortical regions (DeLong 1983; Jahanshahi 1998; Wichmann and DeLong 2002; Grafton 2004; Wichmann et al. 2011). Well in line, the present results not only show reduced putamen RSFC with subcortical nodes, but also extensive decoupling across cortical regions that are functionally stronger connected with M1 or pMFC (Fig. 3), including the primary and secondary motor- and somatosensory cortex, SMA, pre-SMA, right dPMC, extrastriate visual cortex, and left DLPFC. The former regions participate in cortico-striatal loops, whose dysfunction may explain sensorimotor and habitual dysfunction in Parkinson's disease (Abbruzzese and Berardelli 2003; Graybiel 2008; Redgrave et al. 2010). Correspondingly, previous RSFC studies in Parkinson patients have reported cortico-striatal decoupling mainly with sensorimotor regions, especially when selecting seeds in the posterior putamen (Helmich et al. 2010; Luo et al. 2014). The centromedial putamen examined in the present study is located between posterior and anterior aspects of the putamen, as it was defined by its involvement in voluntary motor initiation (Hoffstaedter et al. 2014). As opposed to posterior putamen seeds, central regions of the putamen feature stronger structural connections to frontal premotor regions and more rostral putamen seeds have been shown to connect with prefrontal areas in humans (Lehericy, Ducros, Krainik, et al. 2004; Lehericy, Ducros, Van de Moortele, et al. 2004; Draganski et al. 2008; Tziortzi et al. 2014). In agreement with the subregional organization of the putamen, the presently used seeds in the putamen show RSFC reductions with bilateral pre-SMA, dPMC, and left DLPFC. This network has been associated with cognitive motor functions such as action selection (Rowe et al. 2010) and planning (Nachev et al. 2005; Tanji and Hoshi 2008). Thereby, the observed dysconnectivity between central parts of the putamen and prefrontal systems for motor-cognition complements previous analyses on posterior versus anterior putamen in Parkinson's disease (Helmich et al. 2010; Luo et al. 2014). In sum, the centromedial putamen shows a widespread decoupling from subcortical and cortical regions involved in both movement initiation and execution in patients. In sum, the present findings outline dysfunctional circuits between aspects of the putamen usually involved in motor initiation, and cortical networks, associated with sensory, motor, and cognitive processing.

pMFC-Related Connectivity in Parkinson's Disease

In healthy participants, the pMFC seed featured strongest RSFC with the DLPFC, IFG, anterior insulae, pre-SMA, anterior mid-cingulate cortex, IPS, and IPL (Fig. 2). These regions have been consistently related to cognitive, i.e., higher motor control (Jenkins et al. 2000; Boecker et al. 2008; Brass and Haggard 2008; François-Brosseau et al. 2009; Rowe and Siebner 2012; Hoffstaedter et al. 2013) as well as to non-motor tasks, and motivational processing (Niendam et al. 2012; Rottschy et al. 2012; Chong et al. 2017). Within this network, the pMFC has been suggested to play a key role in movement initiation (Deiber et al. 1999; Cunnington et al. 2002; Hoffstaedter et al. 2013). Correspondingly, subdural stimulation of this region has

been reported to trigger motor responses, often with the experience of an "urge" to move (Fried et al. 1991). Moreover, clinical case reports have described akinetic symptoms after pMFC lesions (Dick et al. 1986; Meador et al. 1986; Haussermann et al. 2001). Importantly, functional neuroimaging studies on voluntary movements performed by Parkinson patients have identified abnormal activation not solely in the pMFC, but also areas like the DLPFC, insulae, and IPL (Playford et al. 1992; Jahanshahi et al. 1995; Samuel et al. 1997; Kikuchi et al. 2001). Yet, it is unclear whether—and how—pathological interactions between the pMFC and these regions relate to akinesia. Interestingly, although the present findings show a relatively preserved pMFC connectivity, focal reductions were found within the pMFC-specific network. In this network, the pMFC showed focal reductions of RSFC with bilateral anterior insulae as well as the left DLPFC. This suggests dysfunctional processing in a core network for multiple cognitive demands, including working memory, attention, and inhibition (Alvarez and Emory 2006; Duncan 2010; Müller et al. 2015). Atrophy within this network, specifically in the pMFC and anterior insulae, has been commonly observed across several neuropsychiatric disorders (Goodkind et al. 2015). With respect to Parkinson's disease, these regions are known to be amongst the first neocortical regions showing disease-specific neurodegeneration (Braak et al. 1996, 2004, 2006), and neurotransmitter dysfunction (Pavese et al. 2010; Christopher et al. 2014, 2015). Recently, PET studies have increasingly linked reduced dopamine receptor binding in anterior insulae with Parkinson patients' cognitive symptoms (Christopher et al. 2014, 2015). Moreover, reduced cerebral blood flow in the right insula has been associated with higher UPDRS scores (Hsu et al. 2007).

Besides motor initiation, pMFC, DLPFC, and insula have also been linked to motivational processing, motor vigor and the integration of effort costs and rewards during decision making (Walton et al. 2003; Schweimer and Hauber 2006; Croxson et al. 2009; Chong et al. 2017). Both motivational and motor deficits have been shown to respond to dopaminergic modulation in PD, indicating an overlapping neural system underlying apathy and akinesia (Chong et al. 2015; Le Bouc et al. 2016; Le Heron et al. 2018). Although the present study did not assess patients' motivational deficits, it suggests decreased connectivity in systems associated with higher-level motivational processing.

Further, DLPFC dysfunction in Parkinson patients has been associated with deficits in attention demanding tasks (Brown et al. 1998; Dimberger et al. 2005; Zgaljardic et al. 2006; Trujillo et al. 2015), as well as compromised cognitive motor control (Rowe et al. 2002). Rowe et al. (2002) observed that during action monitoring healthy individuals' effective connectivity between DLPFC and pMFC increases, whereas patients failed to show this attention-modulated increase. Dopaminergic medication, however, led to an increase of DLPFC-pMFC connectivity, which correlated with the improvement of motor performance (Michely et al. 2015). Based on resting-state fMRI data, the present study suggests a decoupling between DLPFC and pMFC in Parkinson patients, also in the absence of a task. In sum, the pMFC shows reduced RSFC with regions that are commonly involved in both higher cognitive, motivational and basic motor functions and their decline.

Interestingly, reduction of pMFC connectivity with the right IPL (areas PF, PFM, Fig. 5) was related to the degree of akinesia in the patient group. Evidence from functional neuroimaging studies in humans (Corbetta et al. 2008; Seghier 2013) and single cell recordings in monkeys (Fogassi 2005) has consistently highlighted the IPL's role in integrating multimodal perceptual

information and higher-order conceptual representations (Caspers et al. 2012). Further, fMRI (Farrer et al. 2008) and lesion studies (Sirigu et al. 2004) in humans suggest that the IPL strongly contributes to the awareness of self-generated actions. While healthy individuals are able to report their intention to move about 250 ms before movement onset, patients with IPL lesions were impaired in this ability (Sirigu et al. 2004). This suggests a key role of the IPL in the subjective experience of voluntary movement initiation before its onset. This suggestion is supported by electrophysiological work by Desmurget et al. (2009), who showed that direct electrical stimulation of the IPL triggered the conscious sense of “wanting to move” (Desmurget et al. 2009). However, in striking contrast to pMFC stimulation (Fried et al. 1991), IPL stimulation did not result in muscular responses, even at stronger stimulation intensities. A recent review of electrophysiological, clinical, and behavioral studies therefore indicated that the IPL may process earlier stages of intentional movement generation, whereas the pMFC regulates responses shortly before their execution (Desmurget and Sirigu 2012). Interestingly, akinesia in Parkinson's disease has been suggested to arise from an impaired conversion from intentional motor plans into “overt actions” (Jahanshahi 1998). The present results suggest that this impairment is associated with a reduction of RSFC between right IPL and pMFC, thereby highlighting the importance of functional interaction between these regions with respect to the manifestation of akinesia in Parkinson's disease.

M1-Related Connectivity in Parkinson's Disease

The M1-specific resting-state network was delineated by contrasting M1 seeds' RSFC to all other seeds' connectivity in the healthy control group. The resulting network comprised the primary and secondary sensorimotor cortex, SMA, and dPMC, IPS, SPL, as well as extrastriate visual areas (Fig. 2). Especially the former regions are well known as a structurally interconnected network (Cavada and Goldman-Rakic 1989; Krubitzer and Kaas 1990; Dum and Strick 2005) engaged in sensorimotor integration (Johnson et al. 1993; Caminiti et al. 1996; Corbetta et al. 2000; Caspers et al. 2012) and motor execution (Kurata and Tanji 1986; He et al. 1993; Dum and Strick 1996; Grèzes and Decety 2001). Strikingly, M1 connectivity with all of these regions was significantly reduced in Parkinson patients compared to controls (Fig. 3). In contrast, patients' M1 connectivity with the subcortical, putamen-specific network was not significantly different. M1 also featured normal connectivity with most regions of the frontoparietal, pMFC-specific network, except for the pre-SMA (Fig. 3). This finding agrees with previous studies (Wu, Long, et al. 2011; Michely et al. 2015), which did not find significantly altered M1 connectivity with prefrontal regions in Parkinson's disease, compared with healthy individuals (but see Wu, Wang, et al. 2011). Hence, the present results suggest a selective decline of M1 connectivity with a broader sensorimotor network, which normally features strong RSFC with M1 in the healthy brain (Fig. 2). This finding might be linked to previous behavioral (Abbruzzese and Berardelli 2003) and electrophysiological (Lefaucheur 2005) evidence for dysfunctional sensorimotor processing in Parkinson's disease. For example, hand movements (Rickards and Cody 1997; Khudados et al. 1999) and transcranial magnetic stimulation (TMS)-induced motor responses (Sailer et al. 2003; Wagle Shukla et al. 2013) were less amenable to somatosensory input in Parkinson patients. Such indicators for deficient sensorimotor processing are in line with the marked RSFC decrease between M1 and the

adjacent sensorimotor cortex. Yet, disturbed RSFC in these regions is in striking contrast to the histopathological distribution of Parkinson's disease-related Lewy-body accumulation, which are rarely observed in the primary motor cortex even during late stages of Parkinson's disease (Braak et al. 2003, 2004). It is therefore unlikely that the decreased connectivity with M1 arises from this region's neurodegeneration *per se*. Rather, functional connectivity with M1 may be affected by distant regions that degenerate earlier in the course of Parkinson's disease, such as the putamen. Indeed, conjunction analyses revealed that M1 and putamen share dysconnectivity in almost all regions of the M1-specific network, including the right SMA and dPMC as well as bilateral primary and secondary sensorimotor cortex, IPS, SPL, and extrastriate visual areas (Fig. 4). Assuming that these regions are primarily affected by an insufficient striatal facilitation in Parkinson's disease (DeLong 1983; Jahanshahi 1998; Wichmann and DeLong 2002; Grafton 2004; Wichmann et al. 2011), their decoupling from M1 might develop as a secondary effect. In sum, the present study demonstrates a selective RSFC loss between M1 and a functionally related sensorimotor network, possibly reflecting an extension of network pathology from cortico-striatal to cortico-cortical connectivity in Parkinson's disease.

Limitations

A limitation of the present study is that all patients were assessed under regular dopaminergic medication. Thus, drug effects cannot be distinguished from neuropathological alterations in patients' functional connectivity. Unfortunately, a differentiation of the latter underlies practical challenges especially in later disease stages, since dopamine replacement therapies are known to induce long term effects, persisting under dopamine withdrawal (Lesser et al. 1979; Chase 1998). While some of the effects observed in the present study, such as the reduction of cortico-striatal RSFC, has also been observed in drug-naïve patients (Luo et al. 2014), longitudinal monitoring of RSFC before and after dopaminergic treatment may further disentangle effects induced by drugs and degeneration, respectively. Moreover, the clinical assessment of akinesia was limited to the UPDRS. Given the results of the present study, a more detailed examination of akinetic symptoms appears promising for future studies, allowing a more detailed analysis of clinical deficits in relation to functional connectivity in Parkinson's disease.

Conclusion

The present study investigated altered connectivity in parkinson's disease, analyzing seed-based RSFC of bilateral putamen and pMFC, functionally defined by motor initiation tasks, as well as M1, defined by motor execution. While, hierarchical clustering based on inter seed connectivity indicated a decoupling between regions involved in motor initiation (putamen and pMFC), an extended RSFC analysis in seed-specific networks revealed Parkinson-related connectivity alterations on the subcortical and cortical level. In line with pathophysiological models of Parkinson's disease, putamen showed reduced connectivity with basal ganglia, sensorimotor areas, but also regions involved in higher-level cognitive functions such as the left DLPFC. In contrast, altered connectivity with M1 was restricted to a cortical sensorimotor network. Of note, pMFC showed reduced connectivity in a core network for higher cognitive demands and its decreased connectivity with the right

IPL was related to patients' impairment of spontaneous movement generation. We thereby provide evidence that cortical networks associated with cognitive motor control are involved in the manifestation of akinesia in Parkinson's disease.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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Notes

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