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Functional Neuroimaging of Motor Control in Parkinson's Disease: A Meta-Analysis

Damian M. Herz,[1]* Simon B. Eickhoff,[2,3] Annemette Løkkegaard,[4] and Hartwig R. Siebner[1]

[1]*Danish Research Center for Magnetic Resonance, Center for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark*
[2]*Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine University, Duesseldorf, Germany*
[3]*Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, Germany*
[4]*Department of Neurology, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark*

Abstract: Functional neuroimaging has been widely used to study the activation patterns of the motor network in patients with Parkinson's disease (PD), but these studies have yielded conflicting results. This meta-analysis of previous neuroimaging studies was performed to identify patterns of abnormal movement-related activation in PD that were consistent across studies. We applied activation likelihood estimation (ALE) of functional neuroimaging studies probing motor function in patients with PD. The meta-analysis encompassed data from 283 patients with PD reported in 24 functional neuroimaging studies and yielded consistent alterations in neural activity in patients with PD. Differences in cortical activation between PD patients and healthy controls converged in a left-lateralized fronto-parietal network comprising the presupplementary motor area, primary motor cortex, inferior parietal cortex, and superior parietal lobule. Both, increases as well as decreases in motor cortical activity, which were related to differences in movement timing and selection in the applied motor tasks, were reported in these cortical areas. In the basal ganglia, PD patients expressed a decrease of motor activation in the posterior motor putamen, which improved with dopaminergic medication. The likelihood of detecting a decrease in putaminal activity increased with motor impairment. This reduced motor activation of the posterior putamen across previous neuroimaging studies indicates that nigrostriatal dopaminergic denervation affects neural processing in the denervated striatal motor territory. In contrast, fronto-parietal motor areas display both increases as well as decreases in movement related activation. This points to a more complex relationship between altered cortical physiology and nigrostriatal dopaminergic denervation in PD. *Hum Brain Mapp 35:3227–3237, 2014.* © **2013 Wiley Periodicals, Inc.**

Key words: Parkinson's disease; functional magnetic resonance imaging; positron emission tomography; meta analysis; motor

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*Correspondence to: Damian M. Herz, Danish Research Center for Magnetic Resonance, MR Department 714, Copenhagen University Hospital Hvidovre, Kettegaard Allé 30, 2650 Hvidovre, Denmark. E-mail: damianh@drcmr.dk

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INTRODUCTION

Parkinson's disease is a chronic disabling neurological disease characterized by akinesia, rigidity, tremor, and postural instability [Jankovic, 2008]. The pathophysiological hallmark of PD is progressing degeneration of nigrostriatal dopaminergic neurons [Lang and Lozano, 1998a,b], but it remains elusive exactly how the loss of dopaminergic neurons leads to the clinical motor symptoms of PD. To address this question, functional neuroimaging studies including functional magnetic resonance imaging (fMRI) and H_2O-positron emission tomography (H_2O-PET) have been used in numerous studies over the last two decades. These studies have reported changes in cortical motor activity in PD, yet the distribution as well as the direction of regional activation changes varied across studies [Grafton, 2004, Rowe and Siebner, 2012, Stoessl et al., 2011]. This raises the question whether functional neuroimaging studies are useful in revealing general mechanisms underlying motor impairment in PD, or if the observed activation patterns are specific to the patient group or motor task tested in the respective experiment. In the current study, we aimed to overcome typical constraints and limitations of functional neuroimaging studies such as small sample sizes, and heterogeneity of the studied patient group by using a coordinate-based quantitative meta-analysis approach. This enabled us to identify core features of abnormal motor activation in PD, which are consistently expressed across a range of motor tasks and patient cohorts.

METHODS

Literature Search and Study Selection

A literature search was conducted on Pubmed (www.pubmed.org) using the following search strings: "Parkinson's disease" OR "Parkinson disease" OR "Parkinsons disease" AND "functional magnetic resonance" OR "fMRI" OR "positron emission tomography" OR "PET." This search resulted in 1,698 studies on the final search on January 18, 2013. Further studies were identified through review papers and reference tracing of retrieved articles. Only fMRI or H_2O-PET studies that used motor paradigms and that were written in English language were screened for eligibility. Exclusion criteria were as follows:

i. review articles reporting no original data,
ii. studies testing passive movements, motor learning or executive control (e.g., task switching), since these tasks assess neural processes that are distinct to movement execution,
iii. motor tasks were tested against each other rather than against baseline or a control task (e.g., fixation),
iv. the contrasts "PD OFF medication vs. healthy controls," "PD ON medication vs. healthy controls," or "PD ON medication vs. PD OFF medication" were not reported,
v. analyses were based on regions of interest (i.e., not whole brain analyses), multivariate analyses or covariance analyses,
vi. less than 6 PD patients were included,
vii. studies in which PD patients were treated with deep brain stimulation or other drugs than levodopa (e.g., apomorphine), because these treatments induce distinct effects on the sensorimotor system in PD [Bradberry et al., 2012, Ko et al., 2013].

Another study [Schwingenschuh et al., 2013] had to be excluded because of a significant age difference between the PD and control group. If a publication did not report the group stereotactic coordinates of activation maxima, we contacted the authors by email. This procedure resulted in 24 studies that were included in the meta-analysis (Table I) [Baglio et al., 2011; Buhmann et al., 2003; Cerasa et al., 2006; Eckert et al., 2006; Gonzalez-Garcia et al., 2011; Haslinger et al., 2001; Holiga et al., 2012; Hughes et al.; 2010, Katschnig et al., 2011; Kraft et al., 2009; Maillet et al., 2012; Mallol et al., 2007; Mattay et al., 2002; Payoux et al., 2010; Pinto et al., 2011; Rowe et al., 2002; Sabatini et al., 2000; Samuel et al., 1997; Tessa et al., 2010, 2012, 2013; Turner et al., 2003; Wu and Hallett, 2005; Wu et al., 2010].

Meta-analysis Based on Activation Likelihood Estimation

The meta-analyses were carried out using the revised version [Eickhoff et al., 2012] of the activation likelihood estimation (ALE) approach for coordinate-based meta-analyses [Turkeltaub et al., 2002]. ALE tests for a significant convergence between activation foci from different experiments as compared to a random distribution of foci. The term "experiment" refers to a contrast of interest (e.g., PD-ON vs. PD-OFF) for a given study, i.e., one study can comprise several experiments. A detailed description of the ALE technique can be found elsewhere [Eickhoff et al., 2009, 2012; Turkeltaub et al., 2012]. In short, activation foci from different experiments were modelled as spatial 3D Gaussian probability distributions, where the size of the distribution depends on the sample size (number of participants) in the respective experiment. Combining probabilities for foci in each experiment resulted in a modelled activation (MA) map. Subsequently, voxel-wise ALE scores were computed by taking the union of the MA maps describing the convergence of results across experiments at each grey matter voxel. The nonparametric P values of ALE scores were derived by the proportion of equal or higher values obtained under the random (null) distribution and thresholded at a cluster level-corrected threshold

TABLE I. Studies included in the meta-analysis

Study	Modality	# PD	# C	UPDRS-III OFF	UPDRS-III ON	Age PD	Age C	# Foci	Contrast
Baglio et al., 2011	fMRI	15	11		21.5	66.5	66.9	6	ON vs. C
Task:	Button presses with right index finger (timing: external, selection: external)								
Buhmann et al., 2003	fMRI	8	10			54	57	2	ON vs. OFF
Task:	Random finger opposition task at 0.33 Hz with right and left hand (timing: external, selection: internal)								
Cerasa et al., 2006	fMRI	10	11	27.5		64.2	63.4	8	OFF vs. C
Task:	Synchronized tapping with right index finger at 1.33 Hz (timing: external, selection: external)								
	fMRI	10	11	27.5		64.2	63.4	3	OFF vs. C
Task:	Continuation of the tapping with right index finger without stimulus (timing: internal, selection: external)								
Eckert et al., 2006	fMRI	9	9	20.6	10.7	63.3	60.6	18	OFF vs. C
	fMRI	9	9	20.6	10.7	63.3	60.6	9	ON vs. C
	fMRI	9	9	20.6	10.7	63.3	60.6	4	ON vs. OFF
Task:	Opening and closing of right fist at ~1 Hz (timing: internal, selection: external)								
Gonzalez-Garcia et al., 2011	fMRI	17	10		41	64.4		8	ON vs. C
Task:	Button presses with right and left hand in pre-defined order (timing: external, selection: external)								
	fMRI	17	10		41	64.4		5	ON vs. C
Task:	Button presses with right and left hand in random order (timing: external, selection: external)								
Haslinger et al., 2001	fMRI	8	8	15.8	11.8	60.8	54.4	7	OFF vs. C
	fMRI	8	8	15.8	11.8	60.8	54.4	8	ON vs. C
	fMRI	8	8	15.8	11.8	60.8	54.4	10	ON vs. OFF
Task:	Joystick-movements with right hand with four spatial dof (timing: external, selection: internal)								
Holiga et al., 2012	fMRI	12		33.5	9.6	56		5	ON vs. OFF
Task:	Index-to-thumb opposition movements with right and left hand at 1 Hz (timing: external, selection: external)								
Hughes et al., 2010	fMRI	16	15	31.3	18.9	63.9	66.5	10	ON vs. C
Task:	Specified and chosen button presses with right hand (timing: external, selection: both)								
Katschnig et al., 2011	fMRI	20	20	37.9		66.8	62.3	2	OFF vs. C
Task:	Dorsiflexion of right and left ankle at 1 Hz (timing: external, selection: external)								
Kraft et al., 2009	fMRI	12	12	21	13.9	60.8	53	12	OFF vs. C
	fMRI	12	12	21	13.9	60.8	53	8	ON vs. C
	fMRI	12	12	21	13.9	60.8	53	4	ON vs. OFF
Task:	Grip-force task with right and left hand simultaneously (timing: external, selection: external)								
	fMRI	12	12	21	13.9	60.8	53	13	OFF vs. C
	fMRI	12	12	21	13.9	60.8	53	4	ON vs. C
	fMRI	12	12	21	13.9	60.8	53	4	ON vs. OFF
Task:	Grip-force task with right and left hand alternating (timing: external, selection: external)								
Maillet et al., 2012	fMRI	12		40.3	10	59.8		2	ON vs. OFF
Task:	Joystick-movements with right hand with four spatial dof at 0.5 Hz (timing: external, selection: internal)								
Mallol et al., 2007	fMRI	13	11	22.6		64.9	61.9	13	OFF vs. C
Task:	Finger-to-thumb opposition and rotating movements of right hand (timing: internal, selection: external)								
Mattay et al. 2002	fMRI	7		8.8	5	55		7	ON vs. OFF
Task:	Button presses with right hand (0-back task) (timing: external, selection: external)								
Payoux et al., 2011	PET	8	10	22	12	62	67	3	OFF vs. C
	PET	8	10	22	12	62	67	1	ON vs. OFF
Task:	Joystick-movements with right hand with four spatial dof at 0.33 Hz (timing: external, selection: internal)								
Pinto et al., 2011	fMRI	9	15	33		59	55	6	OFF vs. C
Task:	Joystick-movements with right hand with four spatial dof at 0.5 Hz (timing: external, selection: internal)								
Rowe et al., 2002	fMRI	12	12	33.7		62	62	2	OFF vs. C
Task:	Sequential finger movements of right hand at 0.33 Hz (timing: external, selection: external)								
Sabatini et al., 2000	fMRI	6	6	16		61	59	15	OFF vs. C
Task:	Finger-to-thumb opposition movements and fist clenching with right hand (timing: external, selection: external)								
Samuel et al., 1997	PET	6	6	17.7		70.2	64.3	7	OFF vs. C
Task:	Sequential finger movements of right hand at 0.33 Hz (timing: external, selection: external)								
	PET	6	6	17.7		70.2	64.3	10	OFF vs. C
Task:	Bimanual sequential finger movements at 0.33 Hz (timing: external, selection: external)								
Tessa et al., 2010	fMRI	15	11	16.1		70.1	69	12	OFF vs. C
Task:	Continuous tapping of right hand (timing: internal, selection: external)								
Tessa et al., 2012	fMRI	15	13	16.3		68.1	64.2	4	OFF vs. C

TABLE I. (continued).

Study	Modality	# PD	# C	UPDRS-III OFF	UPDRS-III ON	Age PD	Age C	# Foci	Contrast
Task:	Continuous writing of "8"-figures with right hand (timing: internal, selection: external)								
Tessa et al., 2013	fMRI	11	10	13.5		67.7	64	6	OFF vs. C
Task:	Continuous tapping of left hand (timing: internal, selection: external)								
Turner et al., 2003	PET	12	12	41.4		57	58	9	OFF vs. C
Task:	Tracking task with right hand (timing: external, selection: external)								
Wu et al., 2005	fMRI	12	12	25.5		61.2	61.8	12	OFF vs. C
Task:	Sequential finger tapping with right hand at ~0.5 Hz (timing: internal, selection: external)								
Wu et al., 2010	fMRI	15	15	20.7		59.7	60.3	15	OFF vs. C
Task:	In-phase movements of both index fingers at ~0.5 Hz (timing: internal, selection: external)								
	fMRI	15	15	20.7		59.7	60.3	20	OFF vs. C
Task:	Anti-phase movements of both index fingers at ~0.5 Hz (timing: internal, selection: external)								

PD # C, number of PD patients and controls enrolled in the respective study; # Foci, number of activation foci reported in the respective study; dof, degrees of freedom.

of $P < 0.05$ family-wise error (FWE)-corrected. When pooling contrasts (e.g. "PD-OFF vs. controls" comprised the contrasts "PD-OFF > controls" and "controls > PD-OFF") we subsequently assessed the contribution of experiments reporting respectively increased and decreased activity to each cluster. This was computed by the ratio of ALE-values at the cluster with and without the experiments in question.

We hypothesized that some of the heterogeneity in reported activation differences between PD patients and healthy controls might be due to differences in the applied motor tasks, for instance related to the mode of movement selection. There is some evidence that PD patients rely more strongly on external cues during motor control than healthy participants [Brown and Marsden, 1988, Georgiou et al., 1994]. Because internally and externally specified movements are associated with distinct neural activation patterns [Hoffstaedter et al., 2013], we labeled each experiment according to the mode of movement timing (internally vs. externally paced) and movement selection (internally generated vs. externally specified movement). This allowed us to conduct separate meta-analyses for internally vs. externally paced movements as well as internally generated vs. externally specified movements.

Finally, we assessed putative correlations between activation likelihood and motor impairment by computing voxel-wise Spearman rank correlations between the activation likelihood and the mean Unified Parkinson's Disease Rating Scale-III (UPDRS-III) score [Fahn, 1987] of each experiment [Nickl-Jockschat et al., 2012; Rehme et al., 2012]. The mean UPDRS-III score was reported in 21 studies for PD patients OFF medication and in 10 studies for PD patients ON medication. Results of the correlation analysis were thresholded at $P < 0.05$.

Localization of significant effects was guided by the SPM Anatomy Toolbox v1.7 [Eickhoff et al., 2007] and the Harvard-Oxford subcortical structural atlas [Makris et al., 1999] for cortical and subcortical areas, respectively.

RESULTS

Twenty-four publications (21 fMRI, 3 H2O-PET) with an average sample size of 11.8 ± 3.5 (mean ± SD) PD patients and 11.4 ± 3.2 control participants were included (Table I). These publications collectively reported results from 56 experiments and 283 individual patients. Results from 35 experiments and 193 patients were reported for the contrasts "PD-OFF vs. controls," 11 experiments and 77 patients for the contrasts "PD-ON vs. controls," and 10 experiments and 79 patients for the contrasts "PD-ON vs. PD-OFF."

Differences in Motor Activation Between PD Patients and Healthy Controls

An overview of significant convergence of activation maxima for the different analyses is given in Table II. The meta-analysis for differences between activation in PD patients OFF medication and healthy control participants yielded significant convergence of activation in the right posterior putamen, left inferior parietal cortex (IPC), left primary motor cortex (M1), presupplementary motor area (preSMA), and left superior parietal lobule (SPL) (Fig. 1A). The neuroimaging experiments contributing to the cluster in the right posterior putamen consistently reported decreased activity. A reduction in motor activation was detected in 33.3% of all experiments (Fig. 1B). Conversely, the experiments contributing to the cluster in the left SPL consistently reported an increase in motor activity. Increased motor activation of left SPL was observed in 29.4% of all experiments (Fig. 1C). For the remaining regions, the direction of activation differences between PD-OFF and Controls were inconsistent across experiments: Experiments reporting decreased activation in PD contributed 75% to the cluster in left M1, 61% to the cluster in left IPC and 60% to the cluster in preSMA, while

TABLE II. Activation-likelihood-estimation analyses for between group contrasts

Neural region	Side	MNI coordinates X	Y	Z	Z value
Difference in activation between PD-OFF and controls (35 experiments, 193 patients)					
Putamen	right	26	−4	−8	5.09
Inferior parietal cortex	left	−60	−22	22	5.04
Precentral gyrus (M1)	left	−36	−20	62	4.65
Presupplementary motor area	right	6	12	60	4.30
Superior parietal lobule	left	−34	−46	62	3.99
Decreased activation in PD-OFF compared to controls (18 experiments, 171 patients)					
Putamen	right	26	−4	−8	5.72
Increased activation in PD-OFF compared to controls (17 experiments, 157 patients)					
Superior parietal lobule	left	−26	−48	60	4.04
Difference in activation between PD-ON and controls (11 experiments, 77 patients)					
Precentral Gyrus (M1)	left	−34	−24	60	5.2
Decreased activation in PD-ON compared to controls (7 experiments, 61 patients)					
Precentral Gyrus (M1)	left	−34	−24	60	5.28
Difference in activation between PD-ON and PD-OFF (10 experiments, 79 patients)					
Middle Frontal Gyrus	right	34	4	48	4.2
Putamen	right	26	3	−6	4.06
Increased activation in PD-ON compared to PD-OFF (7 experiments, 58 patients)					
Putamen	left	−28	−4	−2	4.35

Clusters with convergence of activation maxima are reported at a statistical threshold of $P < 0.05$ cluster-corrected. There were no significant activations for the contrasts PD-ON > Controls and PD-OFF > PD-ON.

experiments reporting an increased activation in PD patients contributed respectively, 25, 39, and 40%.

Additional analyses focused on the mode of movement selection (i.e., externally vs. internally paced as well as externally specified vs. internally chosen movements). These analyses revealed that M1 activation was significantly decreased in PD patients OFF medication compared to healthy controls during externally-, but not internally paced and generated movements. Conversely, activation of parietal areas, namely IPC and SPL, was significantly increased in PD patients OFF medication during externally specified, but not internally chosen movements. Activation differences of preSMA remained inconsistent even after separating experiments according to movement timing and selection.

Analysis for difference in activation between PD patients ON medication and healthy controls revealed significant convergence of activation in the left M1 only. In the ON state, task-related motor activation of M1 was consistently decreased in PD patients relative to healthy controls. A reduction in movement-related M1 activity was present in 42.9% of all experiments (Fig. 1D).

Effect of Dopaminergic Medication on Motor Activation in PD Patients

Significant convergence of activation maxima for the contrasts comparing PD patients ON and OFF medication were found in the right middle frontal gyrus (MFG) and right putamen (Fig. 2A). Activation differences in these regions, however, were inconsistent across experiments: Experiments reporting increased activation in PD ON contributed 74% to the cluster in right putamen and 62% to the cluster in right MFG, while experiments reporting decreased activation in PD ON contributed respectively, 26 and 38%. These inconsistencies could not be explained by separating experiments according to motor timing and selection (external vs. internal). Conversely, activity of the left putamen was consistently increased after dopaminergic medication, which was detected in 42.9% of all experiments (Fig. 2B).

Correlation Between Motor Activation and Motor Impairment

Motor impairment as indexed by the mean UPDRS-III OFF score correlated with likelihood of decreased activity in the right putamen in PD patients OFF medication compared to healthy controls (peak: 25 −5 −6, MNI coordinates; rho = 0.63, $P < 0.05$), indicating that decrease of motor activation of right putamen was more pronounced in PD patients with stronger motor impairment (Fig. 3). A mean UPDRS-III OFF score of ∼20 could be identified as cut-off point. Patient cohorts with a mean UPDRS-III OFF score of more than 20 expressed deficient task-related activation in the putamen. Of note, the only study with a high mean UPDRS-OFF score, in which decreased activation of the putamen was not reported, studied ankle movements. That study failed to induce a consistent activation of the putamen in PD patients and healthy controls [Katschnig et al., 2011]. There were no other significant correlations between activation likelihood and UPDRS-III scores.

DISCUSSION

Using this meta-analysis approach we were able to detect consistent patterns of abnormal neural activity during movements in PD as revealed by fMRI and H2O-PET studies. Differences in neural activity between PD patients OFF medication and healthy controls converged in a left-lateralized fronto-parietal cortical network comprising pre-SMA, M1, IPC, and SPL. With the exception of left SPL where PD was associated with increased levels of motor activation, PD patients expressed both, decreased as well as increased motor activation in these frontoparietal regions, which could partly be explained by differences in

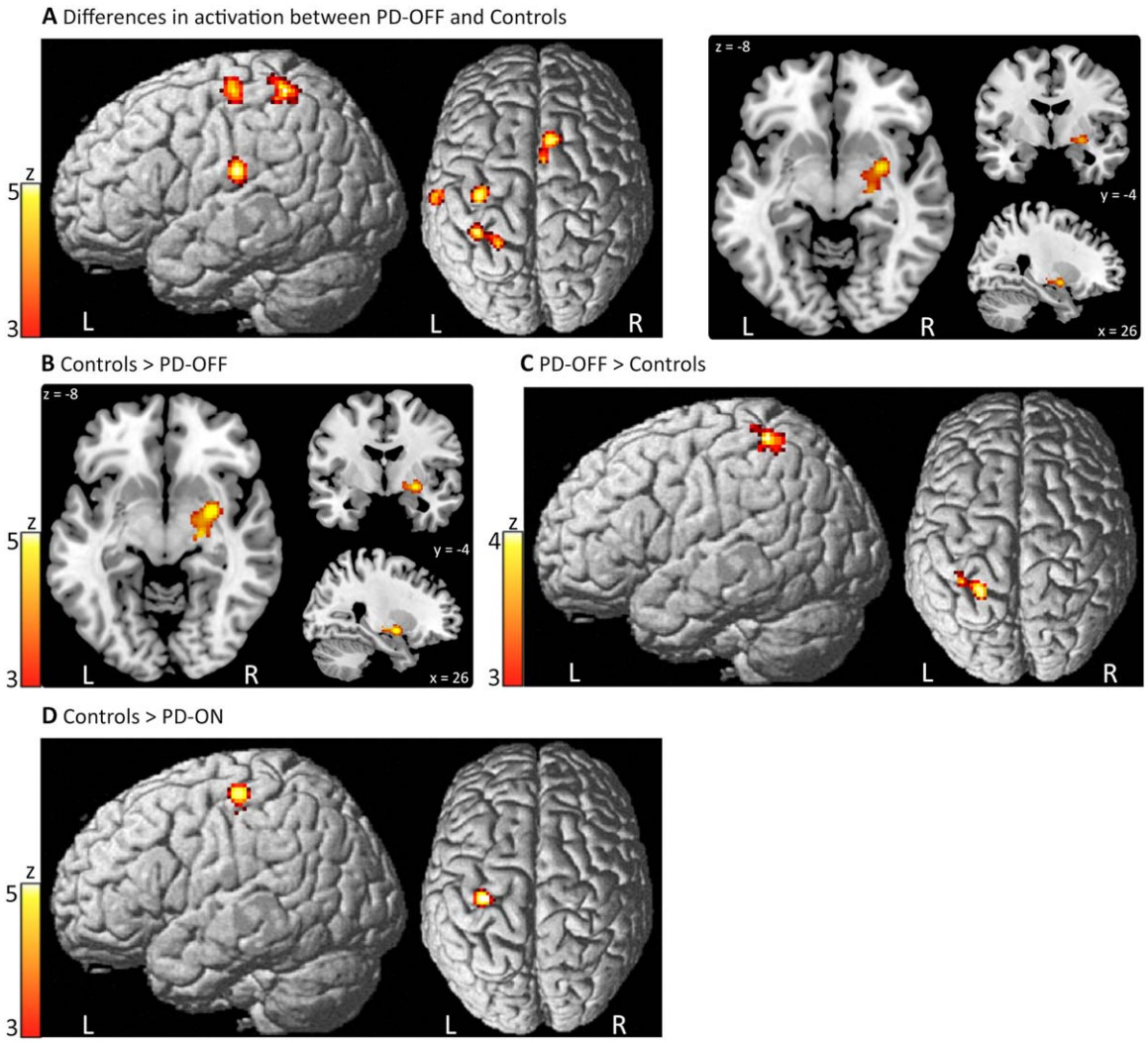

Figure 1.

Convergence of activation maxima for the group comparison between PD patients and healthy controls. **A**: Significant results for the contrast PD-OFF vs. Controls (i.e., "PD-OFF > Controls" or "Controls > PD-OFF"). **B**: Decreased activation in PD-OFF compared to Controls. **C**: Increased activation in PD-OFF compared to Controls. **D**: Decreased activation in PD-ON compared to Controls. Significant activation maxima for the contrast "PD-ON vs. Controls" are omitted, since they are identical to results of the contrast "Controls > PD-ON" shown in 1D. L, left; R, right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

movement timing and selection in the applied motor tasks. In the basal ganglia, PD patients OFF medication showed an attenuation of motor activity in the posterior putamen. Decreased motor activity in the putamen correlated with motor impairment in PD patients OFF medication.

Deficient Motor Activation of the Putamen in PD

The pathophysiological hallmark of PD is a progressive loss of dopaminergic neurons of the substantia nigra pars compacta (SNc) causing nigrostriatal denervation, especially in the posterior motor part of the putamen [Lang and Lozano, 1998a,b]. Dopamine signalling from SNc to the putamen is thought to have a movement facilitating effect by modulating distinct pathways linking the basal ganglia and cortical motor areas [Alexander et al., 1986]. In agreement with this pathophysiological model, we found a consistent decrease of motor-related activity of the putamen in PD patients who have paused dopaminergic medication.

The likelihood of detecting decreased activity in the right posterior putamen correlated positively with the mean UPDRS-III scores. This correlation suggests that

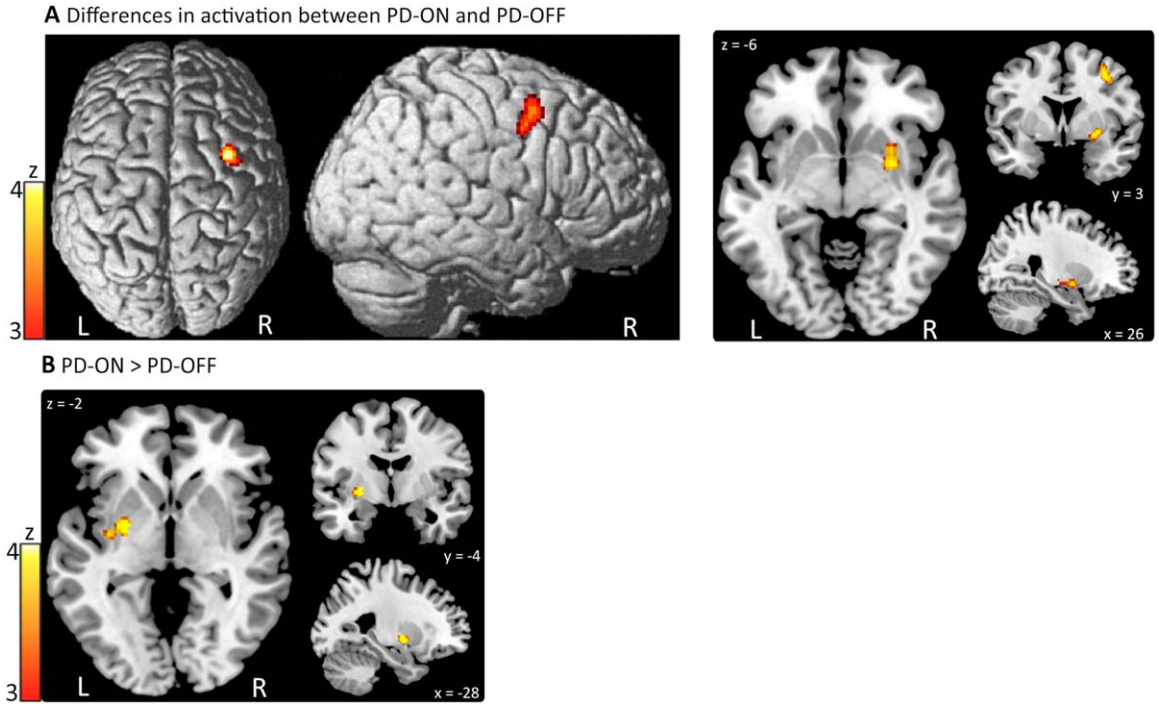

Figure 2.

Convergence of activation maxima for the comparison between PD patients ON and OFF medication. **A**: Significant results for the contrast PD-ON vs. PD-OFF (i.e., "PD-ON > PD-OFF" or "PD-OFF > PD-ON"). **B**: Increased activation in PD-ON compared to PD-OFF. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the magnitude of motor activation in the putamen decreases with progression of motor impairment. In the OFF medication state, decreased motor activation in the putamen was present in PD cohorts with a mean UPDRS-III group score of about 20. However, recent fMRI studies using regions of interest (ROI) approaches [Holden et al., 2006; Prodoehl et al., 2010; Spraker et al., 2010] showed that decreased motor activation of the putamen could already be detected in patient groups with a lower mean UPDRS-score (UPDRS-III OFF scores: 15.7, 16.2, and 17.9, respectively), when the statistical sensitivity for detecting activity changes in the putamen is increased. While PD patients in these studies all had developed symptoms, it is of great clinical interest to detect abnormal neural activity already in presymptomatic disease stages, before symptoms become apparent. Future prospective studies need to evaluate at which stage abnormal neural activity can be detected in PD using fMRI and H_2O-PET.

Our meta-analysis revealed that dopaminergic medication (PD-ON > PD-OFF) significantly augmented motor activation in the left putamen in PD patients. Likewise, neurophysiological studies have shown that dopaminergic medication facilitates high-frequency coupling from the basal ganglia to the cortex [Litvak et al., 2012; Williams et al., 2002]. Together, these findings provide converging evidence that dopaminergic medication mediates its therapeutic effect primarily at the side of nigrostriatal denervation and hereby, improving neural processing in the cortico-basal ganglia thalamo-cortical motor loop.

Motor Activation of Cortical Motor Areas in PD

Previous functional neuroimaging studies in PD have mainly reported changes in activation of cortical motor areas [Grafton, 2004; Rowe and Siebner, 2012]. However, when systematically reviewing previous studies, inconsistencies in the observed cortical activation patterns between different experiments become apparent [Rowe and Siebner, 2012]. For example early studies using single-photon emission computed tomography (SPECT) [Rascol et al., 1994, 1997], PET [Jahanshahi et al., 1995; Playford et al., 1992] and fMRI [Buhmann et al., 2003; Haslinger et al., 2001] have shown that the preSMA/SMA is hypoactive in PD. Consecutive studies, however, also reported the opposite finding, namely an increase of preSMA activity in PD [Cerasa et al., 2006; Eckert et al., 2006; Turner et al., 2003]. Our meta-analysis confirmed this discrepancy by showing that there is a significant difference in preSMA activity between PD patients off medication and healthy controls, but that the direction of activity changes (i.e., an increase or decrease in activity) is not consistent across studies. The

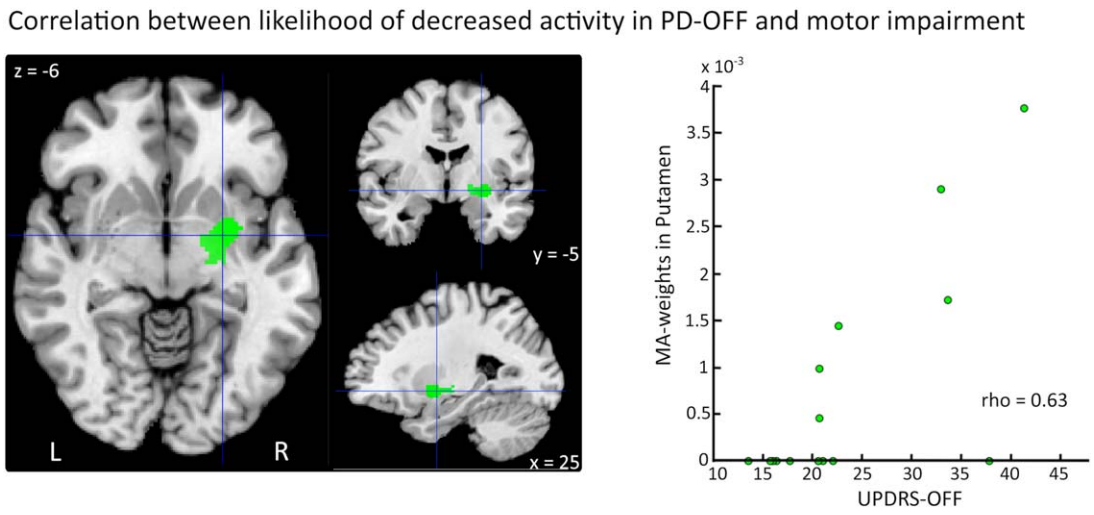

Figure 3.

Voxel-wise Spearman correlations between activation likelihood and UPDRS-III scores. There was a significant correlation between likelihood of decreased activity in the right Putamen in PD patients ("Control > PD-OFF") and motor impairment (rho = 0.63, $P < 0.05$). Studies that do not report activations of the respective region have an MA-value of 0. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

left IPC and M1 showed a similar heterogeneity with respect to the direction of activity changes in PD patients relative to healthy controls. A likely explanation for the lateralization of the detected cortical network to the left hemisphere is that the majority of studies tested movements of the right hand (Table I), which was the dominant hand of most patients (21 of the 24 included studies restricted their analysis to right-handed patients). Task-specific recruitment of cortical motor networks could also partly explain inconsistencies in terms of regional increases or decreases in motor activation. We deliberately restricted this meta-analysis to studies probing motor execution, and excluded paradigms probing motor learning or executive control (e.g., response inhibition or task switching). Yet, the included studies still covered a wide variety of motor execution tasks, such as internally and externally paced as well as internally chosen and externally specified movements. When taking into account the mode of movement timing and selection (external vs. internal), our meta-analyses were able to resolve some of the reported inconsistencies. Activity in M1 was decreased in PD patients OFF medication during externally (but not internally) specified and paced movements, whereas activity of parietal areas (SPL and IPC) was increased in PD patients OFF medication during externally specified, but not internally chosen movements. These findings demonstrate that activation differences between PD patients and healthy participants are task-dependent and highlight the critical role of external cues on the motor system in PD [Brown and Marsden, 1988].

Of note, the inconsistencies in reported activation differences of preSMA between PD patients and healthy controls could not be explained by differences in motor timing and selection. An important factor determining changes in preSMA activation is the amount of attention that is assigned to the motor task [Rowe et al., 2002]. Rowe et al. found that PD patients OFF medication had increased motor-related activity in SMA compared to healthy controls in a task, which did not require subjects to attend to their actions. In contrast to healthy controls, PD patients failed to augment SMA activity when asked to attend to their actions [Rowe et al., 2002]. These findings suggest that PD patients "by default" pay attention to their actions, even if this is not explicitly required. Hence, they are not able to further increase their attentional control of movements, when being explicitly asked to do so.

Analysis of resting state (RS) activity has been increasingly recognized as a valuable method for studying task-independent abnormal neural activation patterns in PD. Interestingly, a recent RS study has demonstrated decreased connectivity between SMA/preSMA and the sensorimotor system in PD, suggesting that such abnormal connectivity patterns of the SMA/preSMA might be central to the pathophysiology underlying PD [Esposito et al., 2013]. However, even in the absence of a task, both increases as well as decreases in connectivity between SMA and other cortico-subcortical motor regions have been reported [Esposito et al., 2013; Kwak et al., 2010; Wu et al., 2011; Yu et al., 2013]. These inconsistencies might partly be due to differences in preprocessing and statistical analysis of RS fMRI data, and it remains to be elucidated to what extent RS studies can advance our understanding of the abnormal neural mechanisms underlying PD.

An interesting finding of this meta-analysis was the increased activation of parietal areas in PD patients OFF medication compared to healthy controls. Because parietal motor areas are involved in sensory-motor transformation and visually-guided movements [Buneo and Andersen, 2006], one might speculate whether this finding could be related to the increased dependency on external cues that can be observed in some PD patients [Brown and Marsden, 1988; Georgiou et al., 1994]. In line with this hypothesis, we found that SPL as well as IPC were significantly increased in PD patients OFF medication during externally specified, but not internally chosen movements, suggesting a potential compensational role of parietal motor areas in PD. These results grant further research about the functional role of parietal motor areas during motor control in PD.

PD patients ON medication showed a consistent decrease of activity of left M1 as the only significant finding. It is important to note, however, that only relatively few neuroimaging studies actually reported motor activation in the ON medication state. Eleven experiments that were included in the meta-analysis examined motor activity while patients were ON medication, whereas 35 experiments assessed motor activity in the OFF medication state. Given the small number of studies, the lack of significant differences in cortical activity in nonprimary motor cortical areas in medicated PD patients might simply be due to a lack of power. This negative finding should not be interpreted as evidence for a partial normalization of neural activity after dopaminergic medication.

Limitations

An advantage of meta-analyses encompassing data from many different experiments is an increase in external validity, i.e., the results are not restricted to a specific small patient group. However, one has to bear in mind that functional neuroimaging studies almost exclusively study PD patients with predominantly akinetic-rigid symptoms. Tremor-dominant PD patients are usually excluded because movement artefacts evoked by the tremor heavily interfere with data acquisition. Thus, the drawn conclusions are not necessarily valid for patients with tremor-dominant PD, who constitute the majority of PD patients [Jankovic et al., 1990]. Recently, methods have been developed to control for movement artefacts induced by tremor, allowing functional neuroimaging studies in tremor-dominant PD patients [Helmich et al., 2011; Prodoehl et al., 2013]. Future studies are needed to assess to what extent the findings from studies in akinetic-rigid patients hold true for tremor-dominant PD patients.

A second limitation is the limited field of view that has been applied during data acquisition particularly in early studies, i.e. not the whole brain was covered during scanning. This limitation mainly affects the orbitofrontal cortex, occipital cortex and the cerebellum. Therefore, our meta-analysis might lack sufficient sensitivity to detect abnormal activations of these areas, such as an increased activation of the cerebellum in patients with PD. Indeed it has been suggested that cerebellar activity might increase in PD to compensate for deficient cortico-basal ganglia-thalamo cortical loops via cereballar-thalamo-cortical projections [Wu and Hallett, 2013].

Additionally, fMRI and H_2O-PET studies have a limited resolution of several mm. This makes it difficult to study smaller structures of the basal ganglia, such as the substantia nigra or the subthalamic nucleus, particularly in early studies. Recent advances in fMRI imaging using higher field strength will allow a more detailed analysis of movement-related activation of smaller basal ganglia structures in PD, which are likely to be involved in motor dysfunction. Finally, only functional neuroimaging studies using classical univariate approaches were included in this meta-analysis. It is important to note that other approaches, such as multivariate analyses of metabolic [Niethammer and Eidelberg, 2012] or perfusion patterns [Melzer et al., 2011] have been successfully applied to neuroimaging of PD over the last years. For methodological reasons, these studies could not be included in the meta-analysis, but are nevertheless valuable for studying abnormal neural networks in PD.

CONCLUSION

This meta-analysis of previous studies that used fMRI and H_2O-PET to examine motor activation in PD shifts the focus from functional alterations at the cortical level to impaired activation in the basal ganglia. The reported activation peaks in the putamen indicate that the OFF-medication state is associated with a deficient motor activation across different motor tasks and neuroimaging studies. Dopaminergic medication consistently improves motor activation in the putamen, whereas deficient putaminal activation correlates positively with motor impairment in PD. We conclude that functional neuroimaging studies using fMRI and H_2O-PET are useful for mapping abnormal neural activity caused by dopaminergic denervation of the putamen in patients with PD. Cortical changes in motor activation can also be captured with functional neuroimaging, but here the functional alterations are not consistent in terms of PD-related up- or down-regulation of regional cortical activity, and rely more strongly on the applied motor task.

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