Brain motor network changes in Parkinson's disease: Evidence from meta-analytic modeling.

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Abstract:

Background: Motor-related brain activity in Parkinson's disease has been investigated in a multitude of functional neuroimaging studies, which often yielded apparently conflicting results. Our previous meta-analysis did not resolve inconsistencies regarding cortical activation differences in Parkinson's disease (Herz et al., 2014), which might be related to the limited number of studies that could be included. Therefore, we conducted a revised meta-analysis including a larger number of studies.

Objectives: To elucidate brain areas that consistently show abnormal motor-related activation in Parkinson's disease and to reveal their functional connectivity profiles using meta-analytic approaches.

Methods: We applied a quantitative meta-analysis of functional neuroimaging studies testing limb movements in Parkinson's disease comprising data from 39 studies of which 15 studies (285 of 571 individual patients) were published after the previous meta-analysis. We also conducted meta-analytic connectivity modeling to elucidate the connectivity profiles of areas showing abnormal activation.

Results: We found consistent motor-related underactivation of bilateral posterior putamen and cerebellum in Parkinson's disease. Primary motor cortex and supplementary motor area also showed deficient activation, while cortical regions localized directly anterior to these areas expressed overactivation. Connectivity modeling revealed that areas showing decreased activation shared a common pathway through the posterior putamen, while areas showing increased activation were connected to the anterior putamen.

Conclusions: Despite of conflicting results in individual neuroimaging studies, this revised meta-analytic approach identified consistent patterns of abnormal motor-related activation in Parkinson's disease. The distinct patterns of decreased and increased activity might be determined by their connectivity with different sub-regions of the putamen.

Introduction:

Parkinson's disease (PD) is a common and disabling neurodegenerative disorder. Even though many patients develop non-motor symptoms, such as depression or autonomic dysfunction, the disease is still considered a movement disorder and is defined by the hallmark presence of bradykinesia, i.e. the slowing of movement initiation and progressive reduction in speed and amplitude of repetitive movements[1, 2]. Bradykinesia can be conceptualized as an impaired ability to 'energize' or 'charge' movements and has been attributed to an impaired modulation of movement vigor[3, 4]. In order to better understand the neural underpinning of this motor impairment, a multitude of studies have been conducted using neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and H_2O^{15} positron emission tomography (PET), whilst patients perform a motor task. However, the results of these studies often seem conflicting. For example, several studies reported decreased activity in the medial prefrontal and frontal cortex in PD[5-8], while other studies reported activity in these areas to be increased[9-12]. One approach to address these inconsistencies is to conduct meta-analyses in order to overcome some of the shortcomings of neuroimaging studies in PD, such as low sample size and heterogeneity of the studied patient group. Furthermore, it allows the generalization of findings beyond the precise experimental setup and task design of a specific study. Thus, meta-analyses allow assessing whether there are differences in neural activation in PD that are consistent across individual patient groups and motor tasks. We previously conducted a meta-analysis of neuroimaging studies in PD[13] using a quantitative, coordinate-based approach termed activation likelihood estimation (ALE). This analysis pinpointed the motor territory of the striatum, the posterior putamen, as the brain region that was most consistently underactivated during motor tasks in PD. At the cortical level, the observed frontal and parietal activation differences were less consistent regarding the directionality of changes (i.e. increased or decreased in PD relative to healthy controls) and appeared to rely more strongly on the applied motor task. This raises the question whether cortical activation changes in PD are task-dependent rather than reflecting a general disease-related neural dysfunction. An alternative explanation for the discordant results from our previous meta-analysis is the limited number of studies that

could be included at the time, because meta-analyses with a low number of included studies have relatively low statistical power and can be strongly affected by results from individual experiments[14]. To address this, we conducted a revised ALE meta-analysis, which included an additional 15 studies, reporting data from an additional 285 patients, that were published after our previous meta-analysis. Furthermore, we computed functional connectivity profiles of the abnormally activated areas in order to further characterize the dysfunctional motor networks underlying PD.

Methods:

Literature search and study selection:

We conducted a search on pubmed using the identical search strings as in our previous meta analysis [13]: ("Parkinson's disease" OR "Parkinson disease" OR "Parkinsons disease") AND ("functional magnetic resonance" OR "fMRI" OR "positron emission tomography" OR "PET"). The final search was conducted on June 30th 2020 and resulted in 3841 studies. We did not find any additional papers through review papers and reference tracing. We only screened studies using fMRI or H_2O^{15}-PET during motor paradigms, that were written in English language, resulting in 170 studies that were further assessed by reading the abstract and / or main text. The following exclusion criteria were then applied for all experiments:

(i) review articles reporting no original data or PET studies other than H_2O^{15}-PET (n=20),

(ii) studies testing passive movements, eye movements (saccades), speech, motor learning or executive control (e.g. task switching) (n=28),

(iii) motor tasks were tested against each other rather than against baseline or a non-motor control task (e.g. fixation) (n=19),

(iv) neither of the contrasts "PD OFF medication vs. healthy controls", "PD ON medication vs. healthy controls" or "PD ON medication vs. PD OFF medication" were statistically compared (n=19),

(v) analyses were based on regions of interest (n=29). These most commonly comprised the putamen and other basal ganglia areas, primary motor cortex, supplementary motor areas, cerebellum and, less

frequently, parietal or other cortical areas. Some studies, in particular early publications, did not cover the whole brain. These studies, however, were not excluded since they did not include regions based on a-priori assumptions and in many studies the field of view was not reported. Likewise we did not exclude studies, which masked the between-group comparisons based on task-related activity in the control group, since this was not based on a-priori assumptions about the brain areas of interest,

(vi) multivariate analyses or covariance analyses (n=6),

(vii) less than 6 PD patients were included (n=2),

(viii) studies in which PD patients were treated with deep brain stimulation or received acute challenges with other drugs than levodopa (e.g. apomorphine), because these treatments induce distinct effects on the sensorimotor system in PD[15, 16] (n=5).

As in our previous meta-analysis, another study[17] was excluded because of a significant age difference between the PD and control group. If coordinates were not reported, we contacted the corresponding author by email (coordinates could not be obtained in 3 studies). This procedure resulted in the exclusion of 131 studies leaving 39 studies that were included[5, 6, 8-12, 18-49]. Fifteen of these studies were published after our previous meta-analysis and allowed us to conduct a well-powered meta-analysis. For an overview of the included studies please see table 1.

Activation likelihood estimation (ALE) meta-analysis:

The meta-analyses were carried out using the revised version[50] of the activation likelihood estimation approach for coordinate-based meta-analyses[51]. ALE tests whether there is a significant convergence between activation foci from different experiments compared to a random distribution of foci. Since the term “experiment” refers to a contrast of interest (e.g. PD-ON vs. PD-OFF) for a given study, one study can contribute with several experiments to the ALE. A detailed description of the ALE technique can be found elsewhere[50, 52]. In short, activation foci from different experiments were modelled as spatial 3D Gaussian

probability distributions, where the size of the distribution depends on the number of participants in the respective experiment (in case of different number of participants for the PD and healthy control group, the lower number was used). If coordinates were reported in Talairach space, they were transformed to Montral Neurological Institute (MNI) space using the tal2icbm method[53]. 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 non-parametric p-values of ALE scores were derived by the proportion of equal or higher values obtained under the assumption of random spatial association and thresholded at a cluster level-corrected threshold of $P < 0.05$ familiy-wise error (cFWE)-corrected.

Since publication of our first meta-analysis[13], it has been demonstrated that the results of meta-analyses comprising only few experiments are driven by single studies. We therefore now only conducted meta-analyses for contrasts based on > 20 experiments[14]. Thus, no meta-analyses were conducted for the contrasts PD-ON vs. healthy controls (13 experiments for HC > PD-ON and 7 experiments PD-ON > HC) or PD-ON vs. PD-OFF (10 experiments for PD-ON > PD-OFF and 5 experiments for PD-OFF > PD-ON). For the same reason we did not conduct analyses separately for motor tasks that were externally or internally cued (there were < 20 experiments for all contrasts with internally-timed and internally-chosen movements). There were sufficient experiments to conduct meta-analyses for the contrasts “PD-OFF > HC” (34 experiments) and “HC > PD-OFF” (36 experiments). We also conducted meta-analyses comparing HC and PD patients irrespective of medication (i.e. irrespective of whether patients were ON or OFF medication), which included 41 experiments for the contrast “PD > HC” and 49 experiments for the contrast “HC > PD”.

Even though there is currently no optimal approach to conduct ALE correlation analyses across the whole brain, we attempted to relate the observed underactivation in PD to disease severity as indexed by the mean UPDRS scores of the individual studies. To this end we computed how much individual studies

contributed to a given cluster and then entered this variable into a non-parametric Spearman correlation with the mean UPDRS-score.

We also computed the probability of experiments detecting abnormal activation of the putamen in PD. To this end, we assessed whether or not a given experiment activated the putamen in the control group (detected in 25 experiments) and whether this experiment found decreased putamen activity in PD. This additional analysis was motivated by the observation that in many experiments the motor task mainly induced activation in cortical areas and less frequently in the basal ganglia. Given the important role of putamen in motor symptoms in PD[2], this lack of striatal engagement seemed surprising and might be due to the specific experimental design and data acquisition. This analysis thus tries to circumvent this problem by only looking at the sub-sample of studies revealing putamen activation in healthy participants. We could not perform the same analysis for cortical and cerebellar changes, since the exact localization of activation in healthy controls was often not given and we could not distinguish between activation of e.g. preSMA vs SMA or rostral premotor vs precentral gyrus. On the other hand, in case of basal ganglia activation, it was explicitly mentioned whether the putamen was activated in almost all studies.

Meta-analytic connectivity modelling (MACM):

After having established which foci showed consistent differences in activation between PD patients and healthy controls, we further analysed these foci regarding their functional task-related connectivity profiles. MACM tests consistent co-activation patterns of a volume of interest (VOI) with the rest of the brain. In short, experiments in healthy subjects, which report activation at the VOI (here: the foci with consistent activation differences from the ALE analysis) were retrieved from the BrainMap database[54, 55]. A coordinate-based meta-analysis was then performed using ALE, which generates a co-activation pattern across the whole brain for each voxel in each VOI. In other words, the computed pattern reflects which brain areas a given region is commonly co-activated with in healthy subjects reflecting its functional task-related connectivity profile. For more details see reference[56]. Since dopaminergic de-afferentiation of the putamen

in PD shows a rostral-caudal gradient with the most pronounced de-afferentiation in the caudal (posterior) putamen and relatively preserved innervation of the rostral (anterior) putamen, we hypothesized that activity of cortical areas that are primarily connected with the posterior putamen might be more affected in PD compared to cortical areas that are connected to more anterior parts of the putamen. To test this, we analysed where the co-activation patterns of the different VOIs overlapped indicating common functional connectivity. To minimize lateralization (e.g. left M1 is primarily connected with left putamen) we only used cortical VOIs from the hemisphere contralateral to the most frequently used right hand (only respectively 5 and 6 experiments used the left hand for the contrasts C>PD and PD>C) in case of bilateral VOIs. Thus, based on the results from the ALE analysis (see below) we used left M1, SMA and right cerebellum as VOIs for the contrast "HC > PD", and left rostral precentral gyrus/middle frontal gyrus and preSMA as VOIs for the contrast "PD > HC". We then computed two overlap images, one of the MACM maps of each of the VOIs for the contrast "HC > PD" and one for the VOIs for the contrast "PD > HC". These two overlap images reflect which functional connectivity patterns are common for all VOIs of each contrast. Since we were mostly interested in the putamen (see above), we then used a mask of the bilateral putamen created using the automated anatomical labelling atlas[57] to assess which areas of the putamen were consistently co-activated with areas that were respectively more and less activated in PD.

Results:

Thirty-nine publications (36 fMRI, 3 H_2O^{15}-PET) were included. Meta-analyses were conducted for contrasts comparing HC with PD patients irrespective of medication as well as contrasts comparing HC with PD patients OFF medication. Since only 3 studies used H_2O^{15}-PET, we also conducted the same meta-analyses without including H_2O^{15}-PET studies, which yielded identical results. The number of experiments was too low for comparing HC with PD patients ON medication or comparing PD patients ON vs. OFF medication (see methods for more details).

Decreased activation in patients with PD:

We first assessed areas that consistently showed decreased motor-related activation in PD. Forty-nine experiments (420 unique subjects, average sample size 14.0) reported results for the contrast “HC > PD”. The meta-analysis revealed significant convergence of activation differences in left and right posterior putamen (detected in 17 and 18 experiments corresponding to 35% and 37% of all experiments, respectively), left and right precentral gyrus (12 and 10 experiments corresponding to 24% and 20%, respectively), SMA (11 experiments, 22%) and right cerebellar lobule 6 (8 experiments, 16%), see figure 1A and table 2. When only considering studies where PD patients were tested off dopaminergic medication, there were 36 experiments with 345 unique subjects and an average sample size of 14.0 that reported results for the contrast “HC > PD-OFF”. Activation differences converged in the left and right posterior putamen (detected in respectively 13 and 14 experiments corresponding to 36% and 39%), left precentral gyrus (8 experiments, 22%), and left cerebellar lobule 5/vermis (7 experiments, 19%), see figure 1B and table 2. None of the detected areas showing decreased activation in PD correlated with differences in disease severity across studies as indexed by mean UPDRS-scores (all $P_{\text{uncorrected}} > 0.05$, see methods for more details).

Increased activation in PD:

We then analyzed which areas consistently showed increased motor-related activation in PD. Forty-one experiments with 369 unique subjects and an average sample size of 13.9 reported results for the contrast “PD > HC”. We found significant convergence of activation differences in pre-supplementary motor area (detected in 13 experiments corresponding to 32%), as well as left and right rostral precentral gyrus/middle frontal gyrus (both detected in 13 experiments corresponding to 32%), see figure 1A and table 2. When limiting the meta-analysis to studies of PD patients off medication there were 34 experiments with 300 unique subjects and an average sample size of 13.7 that reported results for the contrast “PD-OFF > HC”. This meta-analysis showed significant convergence of activation differences in the left and right rostral

precentral gyrus/middle frontal gyrus (detected in respectively 8 and 11 experiments corresponding to 24 and 32%), see figure 1B and table 2.

Probability of detecting decreased putamen activation in PD:

Even though the posterior putamen was the area that was most consistently underactivated in PD, it was only reported in roughly a third of all experiments (see above), which is somewhat surprising given the pivotal role of the putamen in pathophysiological models of PD[2]. Since we observed that many of the included studies used motor tasks that primarily induced cortical activation, we hypothesized that some of these studies were not suited to detect decreased activation of the putamen in PD, because the experimental task or study design were suboptimal for detecting task-related activity in the putamen. To test this, we analyzed whether a given experiment induced activation of the putamen in the control group and, if so, whether this experiment found abnormal putamen activation in PD. This analysis showed that 21 of the 25 experiments where putamen activation was found in the healthy control group were able to detect decreased activation of the putamen in PD (corresponding to 84%), while only four of these experiments (i.e. 16%) were not able to detect this difference. There were no experiments that found decreased activation of the putamen in PD without detecting putamen activity in the healthy control group. Thus, when using experimental paradigms that robustly activate the putamen, the probability of detecting hypoactivation in PD is much higher than reflected by the ALE analysis across all tasks (84 % vs. 35-39 %).

Meta-analytic connectivity modeling:

Since dopaminergic deafferentiation of the putamen in PD shows a prominent caudal-to-rostral gradient, we hypothesized that areas showing decreased and increased activation in PD might be connected to distinct subareas of the putamen, with areas showing decreased activity being mainly connected to the more affected caudal (posterior) putamen, which contains the motor territory of the striatum. To test this, we computed functional connectivity profiles of the areas showing abnormal activation in PD using MACM (see methods for more details). In line with our hypothesis we found that areas, which showed decreased

activation in PD, were mainly connected with the posterior putamen, while areas showing increased activation in PD were connected with more anterior parts of the putamen (figure 2).

Discussion:

Using a meta-analytic ALE approach we found consistent patterns of motor-related hypo- and hyperactivation in several cortical and subcortical areas in PD. The area that most consistently showed decreased activation in PD was the posterior putamen (ca. 35-39% of experiments). This finding is in good agreement with previous meta-analyses[13, 58] as well as SPECT and PET studies showing marked dopaminergic denervation of the posterior putamen in PD[59]. We also found consistent hypoactivation of bilateral M1 and SMA (between 20-24% of experiments)**.** While decreased activation of these areas was less often reported, both areas have long been implicated in the pathophysiology of PD[19, 60, 61]. Finally, there was consistent hypoactivation in the cerebellum. While only relatively few studies reported decreased cerebellar activation (between 16-19% of experiments) it should be noted that most of the early studies had a limited field of view, which did not include the cerebellum. Furthermore, several studies reported increased activation of the cerebellum in PD[62, 63]. These discrepancies might be related to differences in the applied motor tasks, different PD phenotypes or different sub-areas of the cerebellum. Future meta-analyses comprising a larger number of studies testing cerebellar activation in PD might help to further clarify the role of altered cerebellar activation in PD. We did not find correlations between reduced activity in these areas and the mean UPDRS-scores of the individual studies suggesting that the observed activity changes do not closely reflect disease progression or, alternatively, that the group-average UPDRS-scores are not sensitive enough for elucidating this relationship.

Most included studies did not report activation changes in all, but only in a subset of these areas, and a common underactivation only became evident in this meta-analytic approach. However, there is evidence from multivariate analyses of neuroimaging data that PD is related to a network dysfunction rather than abnormal function of isolated neural areas[64]. Overlaying meta-analytic functional connectivity maps of the

hypoactivated cortical areas on an anatomical map of the putamen revealed that these areas share a common pathway through the posterior putamen, the striatal area that is most affected by dopaminergic denervation in PD[65]. Dopaminergic denervation is thought to result in an imbalance between a net inhibitory (indirect) and net facilitatory (direct) pathway that connect the cortex with the basal ganglia in a closed-loop fashion[66]. This results in abnormal inhibition of the cortex by the basal ganglia that can be further modified by the cerebellum, which shares reciprocal di-synaptic connections with the basal ganglia[67]. The loop running through the posterior putamen is often referred to as 'motor loop', since it is thought to be primarily involved in processes related to movement execution and habitual movements[66].

Does the reduced task-related activation of this network in PD have a correlate at the behavioral level? While reverse inference should be taken with caution[68], there is strong evidence from neuroimaging and electrophysiological studies for a critical role of this network in the modulation of movement vigor. This has been demonstrated for the posterior putamen[69-72], SMA[70, 73], M1[72, 74-77] and the cerebellum[71, 72, 77-79]. Furthermore, it should be noted that this meta-analysis was conducted in studies using a variety of motor tasks implying that any detected difference should not be specific to a certain kind of movement, but rather a general process underlying motor execution. We speculate that the process that is probed in many of these neuroimaging studies in PD might be the modulation of movement vigor, which is a crucial aspect of motor control[80] and reduced movement vigor constitutes a core motor impairment in PD (clinically termed bradykinesia). This idea is supported by several neuroimaging studies in PD which directly tested movement vigor, e.g. by recording force production, and found decreased activation in posterior putamen, precentral gyrus, SMA and cerebellum[5, 7, 36, 79].

We also detected areas that consistently showed increased activation in PD; a midline cluster primarily involving the pre-SMA (32% of experiments) and the bilateral rostral precentral gyrus / middle frontal gyrus (24-32% of experiments). Interestingly, both the midline cluster as well as the more lateral clusters were localized directly anterior to areas that showed decreased activation in PD, namely SMA and bilateral

precentral gyrus (see figure 1). Anatomical studies have demonstrated a rostro-caudal gradient in both medial prefrontal cortex (comprising pre-SMA and SMA) and premotor cortex, where the more rostral areas are connected with prefrontal areas, while the more caudal areas are connected to primary motor cortex and the spinal cord[81]. This gradient is also reflected in distinct connectivity patterns with the basal ganglia where more rostral cortical areas are connected to more rostral (and ventral) parts of the striatum[82]. The more rostrally localized loop is often referred to as the 'associative' loop and is thought to be primarily related to executive control of movements and goal-directed behavior[66, 83]. In line with these previous studies, the meta-analytic functional connectivity profiles of preSMA and premotor cortex in the MACM analysis showed common co-activation with the anterior putamen, which is relatively spared of dopaminergic denervation in PD. Of note, this co-activation was observed bilaterally, which might indicate less lateralization of this loop compared to the motor loop running through the posterior putamen. It has previously been suggested that PD patients might rely more on effortful or 'goal-directed' behavior, which is related to the associative cortical-BG loop, since more 'automatic' motor behavior, which has been related to the motor cortical-BG loop, is impaired[84]. Similarly, it has been suggested that PD patients recruit areas that are involved in externally cued movements to compensate for impairments in internally generated movements[85]. This remains, however, speculative, and it should be noted that increased cortical activation of rostral motor areas in PD might not exclusively have compensatory effects but could also have deleterious effects. For example, increased activation of the pre-SMA in PD has been demonstrated in patients developing involuntary 'dyskinesia' movements as a side-effect to dopaminergic therapy[86, 87]. Elucidating the role of these areas in PD warrants further research.

In conclusion, we were able to detect distinct neural networks showing decreased and increased motor-related activation in PD using a meta-analytic approach. Meta-analyses should be continuously updated, since the increasing number of studies that can be included further increases the sample size and reduces ambiguity of the results (see e.g. the current meta-analysis and our previous analysis from 2014). This might also allow analyzing contrasts that we were not able to test in the current analysis due to the limited

number of individual experiments, such as PD-ON vs. PD-OFF in order to elucidate effects of dopaminergic medication on neural activity in PD. To facilitate this, we will make all data from this meta-analysis publicly available on ANIMA (anima.inm7.de), incl. excel sheets with the coordinates from all studies, the ALE software and corresponding scripts. This allows replication of the results and will hopefully facilitate revised meta-analyses in the future.

Authors' roles:

DMH: Research project conception, organization, execution. Statistical analysis design, execution. Manuscript writing of the first draft.

DM: Research project execution. Statistical analysis execution. Manuscript review and critique.

JC: Statistical analysis design, execution. Manuscript review and critique.

SBE: Research project conception, organization. Statistical analysis review and critique. Manuscript review and critique.

HRS: Research project conception, organization. Statistical analysis review and critique. Manuscript review and critique.

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Figure legends:

Figure 1: A. Significant clusters for the comparison of motor-related activity between PD patients and HC. B. Significant clusters for the comparison between PD patients off dopaminergic medication and HC. L, left; R, right; PD, Parkinson's disease; HC, healthy controls.

Figure 2: Functional connectivity profiles of areas with decreased and increased activity in PD with the putamen. Functional connectivity was computed using meta-analytic connectivity modeling and revealed a rostro-caudal gradient for areas with increased vs. decreased activity in PD. PD, Parkinson's disease.

Tables:

Table 1: 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	HC vs. ON
Task:	Button press with right index finger								
Buhmann et al., 2003	fMRI	8	n/a			54	n/a	2	ON vs. OFF
Task:	Random finger opposition task at 0.33 Hz with right and left hand								
Burciu et al., 2015	fMRI	20	20	31.9		65.8	64.8	20	HC vs. OFF
Task:	Grip force task with or without feedback with more affected hand								
Caproni et al., 2013	fMRI	11	11	20		65	65.1	7	HC vs. OFF
Task:	Tapping with right index finger								
	fMRI	11	11	20		65	65.1	15	HC vs. OFF
Task:	Sequence from dig I to V with right hand								
	fMRI	11	11	20		65	65.1	13	HC vs. OFF
Task:	Sequence with order dig I, III, V, II, IV with right hand								
Cerasa et al., 2006	fMRI	10	11	27.5		64.2	63.4	8	HC vs. OFF
Task:	Synchronized tapping with right index finger at 1.33 Hz								
	fMRI	10	11	27.5		64.2	63.4	3	HC vs. OFF
Task:	Continuation of the tapping with right index finger without stimulus								
Drucker et al., 2019	fMRI	22	19	33.9		67.7	64.7	4	HC vs. OFF
Task:	Externally-cued foot tapping sequence								
	fMRI	22	19	33.9		67.7	64.7	6	HC vs. OFF
Task:	Internally-cued foot tapping sequence								
Eckert et al., 2006	fMRI	9	9	20.6	10.7	63.3	60.6	18	HC vs. OFF
	fMRI	9	9	20.6	10.7	63.3	60.6	9	HC vs. ON
	fMRI	9	n/a	20.6	10.7	63.3	n/a	4	ON vs. OFF
Task:	Opening and closing of right fist at ~ 1 Hz								
Gonzalez-Garcia et al., 2011	fMRI	17	10		41	64.4		8	HC vs. ON
Task:	Button presses with right and left hand in pre-defined order								
	fMRI	17	10		41	64.4		5	HC vs. ON
Task:	Button presses with right and left hand in random order								
Haslinger et al., 2001	fMRI	8	8	15.8	11.8	60.8	54.4	7	HC vs. OFF
	fMRI	8	8	15.8	11.8	60.8	54.4	8	HC vs. ON
	fMRI	8	n/a	15.8	11.8	60.8	n/a	10	ON vs. OFF
Task:	Joystick-movements with right hand with 4 spatial dof								
Holiga et al., 2012	fMRI	12	n/a	33.5	9.6	56	n/a	5	ON vs. OFF
Task:	Index-to-thumb opposition movements with right and left hand at 1 Hz								
Hughes et al., 2010	fMRI	16	15	31.3	18.9	63.9	66.5	10	HC vs. ON
Task:	Specified and chosen button presses with right hand								
Jia et al., 2018	fMRI	22	22	16.45		61	60.6	8	HC vs. OFF
Task:	Self-initiated tapping with right index finger at approx. 0.5 Hz								
Katschnig et al., 2011	fMRI	20	20	37.9		66.8	62.3	2	HC vs. OFF
Task:	Dorsiflexion of right and left ankle at 1 Hz								

Kim et al., 2018		fMRI	16	15	36		63.1	64.1	6	HC vs. OFF
		fMRI	16	15	36		63.1	64.1	19	HC vs. ON
		fMRI	16	n/a	36		63.1	n/a	5	ON vs. OFF
	Task:	Two-choice forced response task with finger II and III of right hand								
Kraft et al., 2009		fMRI	12	12	21	13.9	60.8	53	12	HC vs. OFF
		fMRI	12	12	21	13.9	60.8	53	8	HC vs. ON
		fMRI	12	n/a	21	13.9	60.8	n/a	4	ON vs. OFF
	Task:	Grip-force task with right and left hand simultaneously								
		fMRI	12	12	21	13.9	60.8	53	13	HC vs. OFF
		fMRI	12	12	21	13.9	60.8	53	4	HC vs. ON
		fMRI	12	n/a	21	13.9	60.8	n/a	4	ON vs. OFF
	Task:	Grip-force task with right and left hand alternating								
Maillet et al., 2012		fMRI	12	n/a	40.3	10	59.8	n/a	2	ON vs. OFF
	Task:	Joystick-movements with right hand with 4 spatial dof at 0.5 Hz								
Mak et al., 2016		fMRI	26	21		29	61.4	60.9	3	HC vs. ON
	Task:	Self-initiated index finger tapping at ~ 0.2-0.3 Hz on most affected side								
		fMRI	26	21		29	61.4	60.9	3	HC vs. ON
	Task:	Cued index finger tapping at ~ 0.2-0.3 Hz on most affected side								
Mallol et al., 2007		fMRI	13	11	22.6		64.9	61.9	13	HC vs. OFF
	Task:	Finger-to-thumb opposition and rotating movements of right hand								
Martin et al., 2019		fMRI	22	22	15.6		53	48.5	13	HC vs. OFF
	Task:	Self-generated sequential button press with finger I-IV of most affected hand								
		fMRI	22	22	15.6		53	48.5	10	HC vs. OFF
	Task:	Self-generated sequential button press with finger I-IV of less affected hand								
		fMRI	22	22	15.6		53	48.5	13	HC vs. OFF
	Task:	Visually-cued sequential button press with finger I-IV of most affected hand								
		fMRI	22	22	15.6		53	48.5	5	HC vs. OFF
	Task:	Visually-cued sequential button press with finger I-IV of less affected hand								
Mattay et al. 2002		fMRI	7	n/a	8.8	5	55	n/a	7	ON vs. OFF
	Task:	Button presses with right hand (0-back task)								
Mohl et al., 2017		fMRI	26	21	33	24	62.2	61.6	1	HC vs. OFF
	Task:	1 Hz sequential tapping from finger I-V and vice versa with right hand								
Payoux et al., 2011		PET	8	10	22	12	62	67	3	HC vs. OFF
		PET	8	n/a	22	12	62	n/a	1	ON vs. OFF
	Task:	Joystick-movements with right hand with 4 spatial dof at 0.33 Hz								
Pinto et al., 2011		fMRI	9	15	33		59	55	6	HC vs. OFF
	Task:	Joystick-movements with right hand with 4 spatial dof at 0.5 Hz								
Planetta et al., 2015		fMRI	14	14	29.6		64	61.9	34	HC vs. OFF
	Task:	Cued & memorized pinch grip force task with most affected hand (collapsed)								
Poisson et al., 2013		fMRI	6	10	16		65	53.6	13	HC vs. OFF
	Task:	Finger-thumb tapping with right hand at 1 Hz								
Rottschy et al., 2013		fMRI	23	23		23.9	67.2	65	8	HC vs. ON
	Task:	Direct repeat of sequence of 4 or 5 finger movements with both hands								
		fMRI	23	23		23.9	67.2	65	14	HC vs. ON
	Task:	Delayed repeat of sequence of 4 or 5 finger movements with both hands								
Rowe et al. 2002		fMRI	12	12	33.7		62	62	2	HC vs. OFF
	Task:	Sequential finger movements of right hand at 0.33 Hz								

Sabatini et al., 2000		fMRI	6	6	16	61	59	15	HC vs. OFF
	Task:	Finger-to-thumb opposition movements and fist clenching with right hand							
Samuel et al., 1997		PET	6	6	17.7	70.2	64.3	7	HC vs. OFF
	Task:	Sequential finger movements of right hand at 0.33 Hz							
		PET	6	6	17.7	70.2	64.3	10	HC vs. OFF
	Task:	Bimanual sequential finger movements at 0.33 Hz							
Tessa et al., 2010		fMRI	15	11	16.1	70.1	69	12	HC vs. OFF
	Task:	Continuous tapping of right hand							
Tessa et al., 2012		fMRI	15	13	16.3	68.1	64.2	4	HC vs. OFF
	Task:	Continuous writing of "8"-figures with right hand							
Tessa et al., 2013		fMRI	11	10	13.5	67.7	64	6	HC vs. OFF
	Task:	Continuous tapping of left hand							
Turner et al., 2003		PET	12	12	41.4	57	58	9	HC vs. OFF
	Task:	Tracking task with right hand							
Wu et al., 2005		fMRI	12	12	25.5	61.2	61.8	12	HC vs. OFF
	Task:	Sequential finger tapping with right hand at ~ 0.5 Hz							
Wu et al., 2010		fMRI	15	15	20.7	59.7	60.3	15	HC vs. OFF
	Task:	In-phase movements of both index fingers at ~ 0.5 Hz							
		fMRI	15	15	20.7	59.7	60.3	20	HC vs. OFF
	Task:	Anti-phase movements of both index fingers at ~ 0.5 Hz							
Wu et al., 2015		fMRI	26	26	13	59	58.9	7	HC vs. OFF
	Task:	Tapping with right index finger at 0.3 - 0.5 Hz							
Wu et al., 2016		fMRI	18	18	20.4	60.4	59.9	11	HC vs. OFF
		fMRI	18	n/a	20.4	60.4	n/a	7	ON vs. OFF
	Task:	Free writing in PD patients with consistent micrographia							
		fMRI	18	18	19.1	59.6	60	9	HC vs. OFF
		fMRI	18	n/a	19.1	59.6	n/a	4	ON vs. OFF
	Task:	Free writing in PD patients with progressive micrographia							
Wurster et al., 2015		fMRI	10	10	20.7	66.4	64.9	2	HC vs. ON
	Task:	Auditory-cued button press with right index finger at 1, 2.5 and 4 Hz (collapsed)							
Yan et al., 2015		fMRI	11	12	20.1	61.5	65.5	5	HC vs. OFF
	Task:	Auditory-cued finger-to-thumb movement with left hand							
		fMRI	11	12	20.1	61.5	65.5	4	HC vs. OFF
	Task:	Auditory-cued finger-to-thumb movement with right hand							

HC, healthy control participants; OFF, Parkinson's disease patients off dopaminergic medication; ON, Parkinson's disease patients on dopaminergic medication; foci, number of activation foci reported in the respective study; n/a, not applicable.

Table 2: Results of ALE analyses for all between group contrasts.

	Side	MNI coordinates (at peak)			z-value (at peak)
		x	y	z	
Decreased activation in PD compared to HC					
Putamen	right	30	-10	6	5.78
Putamen	left	-30	-8	2	6.87
Precentral gyrus	left	-34	-22	62	7.03
Precentral gyrus	right	36	-20	72	5.18
Supplementary motor area	left	-4	-6	58	5.68
Cerebellum, lobule VI	right	26	-54	-30	4.27
Decreased activation in PD-OFF compared HC					
Putamen*	right	30	-10	6	5.26
Putamen	left	-30	-4	0	6.67
Precentral gyrus	left	-34	-22	62	5.68
Cerebellum, lobule V / vermis	left	-6	-60	-14	4.29
Increased activation in PD compared to HC					
Pre-supplementary motor area	left	-2	2	58	4.77
Precentral gyrus / middle frontal gyrus	left	-34	-6	58	4.81
Precentral gyrus / middle frontal gyrus	right	32	-6	56	4.99
Increased activation in PD-OFF compared to HC					
Precentral gyrus / middle frontal gyrus	right	30	-4	56	4.77
Precentral gyrus / middle frontal gyrus	left	-34	2	52	4.33

Clusters with convergence of activation maxima are reported at a threshold of 0.05 family-wise error corrected at the cluster level. *The second peak of the cluster is listed, since the first peak was localized in white matter.

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