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Altered praxis network underlying limb kinetic apraxia in Parkinson's disease - an fMRI study

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ABSTRACT

Parkinson's disease (PD) patients frequently suffer from dexterous deficits impeding activities of daily living. There is controversy whether impaired fine motor skill may stem from limb kinetic apraxia (LKA) rather than bradykinesia. Based on classical models of limb praxis LKA is thought to result when premotor transmission of time-space information of skilled movements to primary motor representations is interrupted. Therefore, using functional magnetic resonance imaging (fMRI) we tested the hypothesis that dexterous deficits in PD are associated with altered activity and connectivity in left parieto-premotor praxis network. Whole-brain analysis of fMRI activity during a task for LKA (coin rotation) showed increased activation of superior and inferior parietal lobule (SPL, IPL) and ventral premotor cortex (vPM) in PD patients compared to controls. For bradykinesia (assessed by finger tapping) a decreased fMRI activity could be detected in patients. Additionally, psychophysical interaction analysis showed increased functional connectivity between IPL and the posterior hippocampi in patients with PD. By contrast, functional connectivity to the right dorsolateral prefrontal cortex was decreased in patients with PD compared to controls.

In conclusion, our data demonstrates that dexterous deficits in PD were associated with enhanced fMRI activation of the left praxis network upstream to primary motor areas, mirroring a neural correlate for the behavioral dissociation of LKA and bradykinesia. Furthermore, the findings suggest that patients recruit temporal areas of motor memory as an attempt to compensate for impaired motor skills. Finally, dysexecutive function may contribute to the deficit.

1. Introduction

Patients with Parkinson's disease (PD) frequently suffer from loss of fine motor skills. Dexterous difficulties in PD are only partly explained by elemental motor deficits such as bradykinesia (Gebhardt et al., 2008). They may develop even at an early stage of the disease (Koop et al., 2008; Proud and Morris, 2010) and have been linked to poor outcome (Pohar and Allyson Jones, 2009). Indeed, dexterous difficulties not exclusively explained by bradykinesia significantly impair activities of daily living (ADL) (Foki et al., 2016). Therefore, exploring the neural mechanism of impaired fine motor skills in PD is of clinical interest.

It has been suggested to introduce the notion of limb kinetic apraxia (LKA) to describe dexterous difficulty in PD (Gebhardt et al., 2008; Quencer et al., 2007). LKA adopts an intermediate position between higher-order (i.e. apraxic) and elemental motor disorders. It is characterized by impaired control of selective and coordinated hand and finger movements, but not explained by weakness or sensory deficits (Heilman, 2010). LKA can be assessed by the so-called coin rotation (CR) task. CR is a relatively simple and fast administered task to assess

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manual dexterity in clinical settings (Barkemeyer et al., 1998; Gebhardt et al., 2008; Hill et al., 2010).

To perform a skilled movement, temporal and spatial information of the movement must be retrieved and translated into motor output. According to the movement representation hypothesis (Geschwind, 1975), brain areas forming part of the so-called praxis network (Niessen et al., 2014) are involved. Specifically, it is assumed that the inferior parietal lobule (IPL) conveys spatial and temporal content of a movement (Heilman et al., 1982; Rothi et al., 1985) to left premotor cortex (Barrett et al., 1998; Haaland et al., 2000; Kolb and Milner, 1981) and probably to the supplementary motor area (SMA) (Watson et al., 1986). The premotor regions finally program movement execution by transmitting information to motor representations of the primary motor cortex (M1). In fact, in healthy subjects, the premotor cortex is critical to perform skilled finger movements as demonstrated by functional MRI (fMRI) (Nirkko et al., 2001).

As expected from the neural basis of motor skills, LKA may result from structural and functional alterations of the praxis network. For instance, premotor lesions can cause LKA (Freund and Hummelsheim, 1985). Furthermore, premotor white matter density correlates with limb kinetic deficits in corticobasal syndrome (Borroni et al., 2008). In addition, detailed clinico-anatomical case studies have demonstrated that early LKA in corticobasal syndrome is associated with predominant premotor atrophy (Tsuchiya et al., 1997). Finally, the sensorimotor and posterior parietal cortices showed reduced cerebral blood flow in corticobasal syndrome patients with LKA (Okuda et al., 1998).

In PD neuroimaging findings of LKA are sparse. In fact, to the best of our knowledge, only one group has investigated functional correlates of LKA (altered CR) in PD (Foki et al., 2010). This study found an increased activation in parietal areas, as well as subcortical, sensory, premotor, and supplementary motor areas associated with LKA in PD. However, there was some methodological criticism (Bohlhalter et al., 2011). For instance, self and fixed paced conditions were different across tasks (CR and index finger tapping). Furthermore, unspecific activation cannot be ruled out as the kinematic (finger tapping with one finger vs. coin rotation with tree fingers) and somatosensory requirements (finger tapping without object manipulation vs. coin rotation) differed for the two fMRI tasks. Moreover, the design lacked a true baseline.

Therefore, robust imaging data on LKA in PD at the level of praxis networks is not available. Moreover, previous reports in PD point towards compensatory increased functional connectivity within the motor network during motor tasks (Wu et al., 2010a, 2010b; Yan et al., 2015) and decreased functional connectivity of attentional and executive control areas during higher order control tasks (e.g. working memory) (de Bondt et al., 2016; Helmich et al., 2009; Trujillo et al., 2015). However, functional interactions between relevant praxis areas remain to be explored.

The goal of the present study was to assess the functional brain activity during skilled fine motor tasks, as measured by the CR, in PD compared to healthy controls. Furthermore, we investigated for the first time dynamic functional connectivity within the praxis network during CR. We hypothesized increased activation and altered functional coupling of areas of the praxis network in PD, in particular, of premotor areas and the left inferior parietal lobule as well as executive control and attention areas.

2. Methods

2.1. Subjects

In total, 22 PD patients and 13 age and handedness-matched healthy controls participated in this study. Patients were recruited at the Department of Neurology, Inselspital, University Hospital of Bern. Controls were recruited from the local community. The study was performed according to the Declaration of Helsinki and was approved by the local Ethics Committee. All participants provided written informed consent.

Patients were included if they had an established diagnosis of PD, as determined by the UK Brain Bank diagnostic criteria (Hughes et al., 1992). Exclusion criteria for all participants were sedating medication, severe medical or psychiatric conditions, as well as general exclusion criteria for magnetic resonance imaging (i.e. claustrophobia or metal implants). Further exclusion criteria for healthy controls were any neurological disorder in general, and for patients any neurological disorder other than PD. In both groups we assessed hand dominance with the Edinburgh Handedness Inventory (Oldfield, 1971) and cognitive impairment with the Mini–mental status examination (MMSE) (Folstein et al., 1975). Additionally, the forward and backward digit span (Wechsler, 1997) test was performed for specific neuropsychological testing of short-term verbal memory. In patients, disease stage was determined according to the Hoehn & Yahr criteria (Goetz et al., 2004). In addition, we measured bradykinesia-rigidity using the modified Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2008). Twelve patients received dopaminergic medication and ten patients were drug-naïve.

2.2. Experimental design

All participants underwent the same acquisition of clinical and behavioral data. Prior to imaging data acquisition, we provided detailed task instructions and training to ensure understanding of task procedures and accurate execution. If patients received antiparkinsonian medication, PD patients were tested in their best ON state (60 to 90 min after their last dose of dopaminergic medication). In general, all patients used their clinically less affected hand (right hand performance: n = 12/60%) to minimize confounding effects of bradykinesia. Controls performed the task with the same hand as patients (right hand performance n = 9/75%). Therefore, four participants performed with the left hand.

We employed an fMRI block design. Each of the eight blocks consisted of one of two movement tasks (Fig. 1). The order of the two movement task blocks was pseudo-randomized to control for sequence effects. Each block consisted of 3 trials.

In detail, each experimental trial (Fig. 1) started with a brief written instruction (4 s) indicating the upcoming movement task followed by an active movement phase of 26 s, followed by a 16 s rest phase. A green cross in the middle of the screen signaled the start of the active movement phase. During the resting phase a white fixation cross was presented and participants were asked to relax and not to move.

During the active movement phase, participants were instructed to perform one of two movement tasks: the CR (Barkemeyer et al., 1998; Hill et al., 2010) or a modified finger tapping (FT) task (Goetz and Stebbins, 2004; Reitan, 1969). Briefly, during CR, subjects were asked to rotate a Swiss 50-Rappen coin (18 mm in diameter) through 180°-turns between thumb, index, and middle finger. During the modified FT task subjects were asked to simply tap their fingers following an alternating sequence. The sequence was as follows: 1-2-1-3-1-2-1-3-1-2-1-3, in which 1, 2 and 3 refer to thumb, index and middle finger, respectively. Participants executed tapping on an MRI compatible response box. We used a repetitive finger tapping sequence, as it is sensitive to test bradykinesia. Furthermore, the finger sequence allowed minimizing unspecific activation based on differences in sensory-motor processing. Thus, the modified FT is closer to the kinematic and sensory demands of the CR task (i.e. same fingers involved as in the coin rotation task and some sensory component by the tapping on the box). CR and FT were performed self-paced (i.e. as fast as possible).

Performance of motor tasks was video recorded and evaluated by an independent rater blinded for diagnosis and clinical status. CR performance scores reflect mean numbers of half-turns adjusted for coin drops (Barkemeyer et al., 1998). FT performance scores reflect the number of alternating sequences (Goetz and Stebbins, 2004; Reitan, 1969). Thus

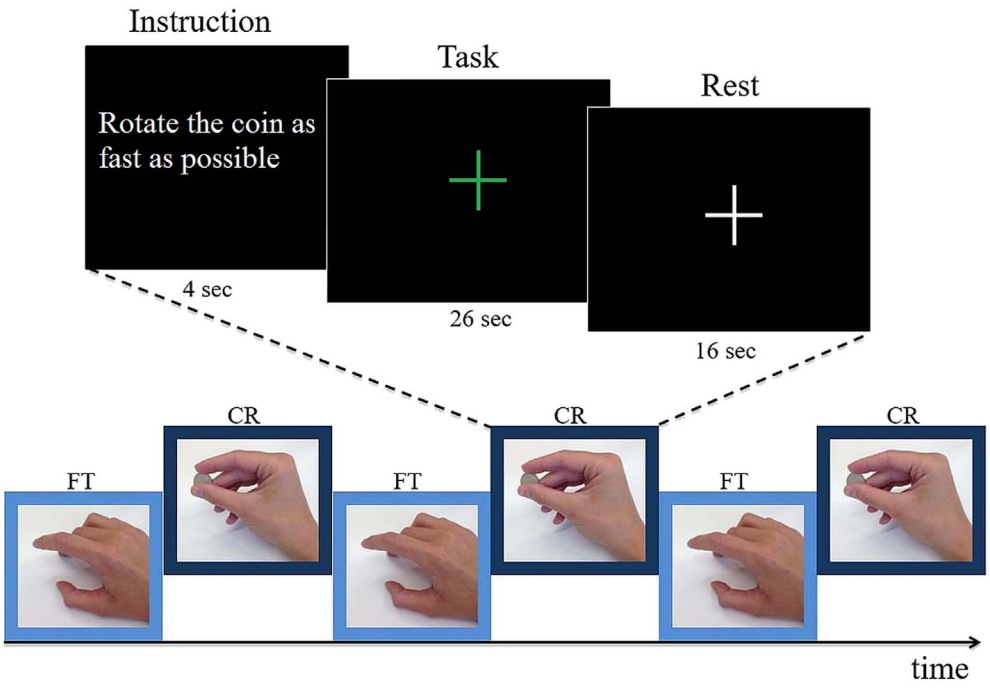

Fig 1. Limb kinetic and bradykinesia fMRI task. General block design and a single trial of the limb kinetic apraxia task. FT = finger tapping (bradykinesia task); CR = coin rotation (limb kinetic apraxia task).

high numbers represent a good performance in both tasks (Barkemeyer et al., 1998; Hill et al., 2010).

2.3. Structural and functional MRI acquisition

High-resolution T1-structural and T2*-weighted functional images were obtained using a whole-body 3 T scanner (Siemens Trio, Erlangen, Germany) with a 12-channel head matrix coil. T1-weighted structural images were acquired using the Modified Driven Equilibrium Fourier Transform sequence [TE = 2.48 ms, TR = 7.92 ms, flip angle 16°, FOV = 256 × 256 mm^2, matrix size 256 × 256 mm^2 yielding a nominal isotropic resolution of 1 mm^3)]. T2*-weighted gradient-echo echo planar imaging sequence was used to obtain functional images sensitive to BOLD signal [TE = 30 ms, TR = 2000 ms, flip angle 90°, FOV = 230 × 230 mm^2, voxel dimension: 3.6 mm × 3.6 mm × 3 mm, matrix size 64 × 64 mm^2 and slice thickness = 3 mm].

2.4. Structural and functional MRI acquisition and data processing

Image data was analyzed using SPM (Version 8; Wellcome Trust Centre for Neuroimaging, London). Preprocessing encompassed slice time correction, spatial realignment, co-registration, normalization to the Montreal Neurological Institute T1 template and spatial smoothing with an isotropic Gaussian kernel of 8 mm full-width at half maximum (Ashburner and Friston, 2005).

2.5. Data and MRI analysis

Behavioral data analysis was performed using IBM SPSS (Version 22). The Shapiro-Wilk test was used to test for normality. Two-sample *t*-test and chi-square (χ^2) tests were used to compare categorical and continuous variables between patients and controls, respectively. Level of significance was set at $P < 0.05$, two tailed.

Our main interest was to assess brain activation specific for a LKA task in PD. We therefore set one general linear model to analyze brain activity during both motor tasks for each subject using the canonical hemodynamic response function available in SPM. Realignment parameters were included in the general linear model as regressors of no interest in order to correct for residual motion. Next, statistical parametric maps from each individual were entered into a second-level random effects analysis. To investigate brain activation associated with the motor tasks, both conditions were contrasted with the instruction condition (CR vs instruction and FT vs instruction). The instruction condition served as control condition because longer resting conditions may be confounded by mental activity due to unconstrained thoughts (Stark and Squire, 2001). Furthermore, reading the instruction controlled for unspecific attention and visual processing but lacked any specific demands in motor execution. To control for differences in motor performance, we included the parameters of motor output as regressors of no interest. In addition, the levodopa equivalent was included as regressor of no interest to control for unspecific effects due to medication. We computed a factorial design with the factors group and task execution to reveal the interaction of group and task (F-test: task-by-group; group = patients and healthy controls; task = FT and CR).

We extracted mean beta estimates of significant clusters of the whole brain interaction analysis using the MarsBaR toolbox for SPM (Brett et al., 2002). In detail, mean beta estimate values in regions of interest (ROIs) were extracted from the modulated, normalized and smoothed fMRI images of the flexible factorial designs for each subject and each task and were compared between patients and controls using multivariate analysis corrected for multiple testing (Sidak correction for familywise error rate).

In a next step, we examined task specific functional connectivity applying the psychophysiological interactions (PPI) approach and the PPI toolbox integrated in SPM (Friston et al., 1997). Briefly, PPI analyses allow the examination of process-specific functional interaction between brain regions. We entered three factors in the design matrix: one factor, termed the physiological factor, represents the average time series of activity of all voxels in the seed region i.e. the left IPL, the second factor reflects the task context termed psychological factor (CR task versus cue) and the third factor, termed PPI factor, is the product of the two factors. To test for significant whole brain correlations with the left IPL during the CR task, PPI single subject data was then entered into a random effects analysis model. We then calculated significant functional correlations within and between groups within one factorial design (*t*-tests: controls; patients; controls > patients and patients > controls).

Further, in an exploratory analysis, we examined whether functional connectivity of brain networks correlate with CR performance. We performed individual Pearson correlations between the mean of the

PPI regressor and CR performance for each of the 8 target regions (see Supplementary material analysis A). The PPI regressor was derived from individual time series for each target region for each subject and was further mean-corrected.

To examine the role of possible grey matter density differences between healthy controls and patients on brain activity, we performed an additional whole-brain voxel based morphometry (VBM) analysis. We used total brain volume and the same regressors as in the main analysis (see Supplementary material analysis B).

For all contrasts we used a uniform voxel-level threshold of $P < 0.005$ (uncorrected); minimum cluster size 17 voxels (tables and figures). This threshold is equivalent to a map-wise false positive rate of alpha < 0.005 using a Monte Carlo procedure as implemented in the AlphaSim program in the Analysis of Functional Neuroimages software package (Stepens et al., 2010). All reported significant clusters were anatomically labeled using the Jülich atlas included in the SPM Anatomy Toolbox Version 1.8 (Eickhoff et al., 2005). Images were produced using SPM8 and MRIcron (Rorden et al., 2007).

3. Results

3.1. Behavioral and clinical data

Demographic and clinical data are given in Table 1. Two patients had to be excluded as MRI acquisition had to be stopped prematurely due to intolerance of the supine position in the scanner. One participant was excluded due to a coin rotation deficit to rule out any confounding effects based on musculoskeletal impairments. Thus, the data of 20 PD patients and 12 healthy controls remained for final analysis. As expected, patients performed worse than controls in the CR task. Twelve patients showed CR deficits according to Hill and colleagues (Hill et al., 2010) (deficit = mean in 10 s < 13 rotations adjusted for coin drop). However, five patients and no healthy control participant were classified as showing clear-cut LKA (LKA = mean in 10 s < 10 rotations adjusted for coin drop) (Barkemeyer et al., 1998). In contrast, although FT was slightly diminished in patients, the difference was not statistically significant. Furthermore, no task-by-group interaction was detected.

Table 1
Clinical characteristics and demographic data of Parkinson's disease patients and healthy controls.

	Controls (n = 12)		Patients (n = 20)		Between group tests		
Gender (n)	Men/women		Men/women		*df*	χ^2	*P*
	5/8		4/16		1	1.742	0.187
Handedness	Right/left		Right/left		*df*	χ^2	*P*
	11/1		19/1		*1*	*0.142*	*0.706*
	M	D	M	SD	*f*	*T*	*P*
Age (y)	63 [34,75]	10	62 [37,75]	10	30	0.263	0.794
Coin rotation (CR/10s)	17.08 [13,21]	2.7	12.6 [6,21]	3.2	30	4.03	< **0.001**
Finger tapping (FT/10s)	32.7 [20,46]	8.3	28.3 [14,49]	10.9	30	1.152	0.259
MMSE	28.9 [26,30]	1.3	28.2 [25,30]	1.6	30	1.161	0.255
Forward digit span	7.08 [5,11]	2.0	7.15 [4,11]	1.8	30	0.096	0.924
Backward digit span	5.17 [3,9]	1.9	5.5 [3,10]	1.9	30	0.484	0.630
Levodopa equivalent (mg/day)	–	–	438.3 [0,1600]	532.2	–	–	–
Disease duration (y)	–	–	2.9 [0,8]	3.1	–	–	–
Hoehn & Yahr stage (ON)	–	–	1.9 [1,2]	0.4	–	–	–
MDS-UPDRS III	–	–	22.4 [7,34]	8.2	–	–	–

M = mean; y = years; MMSE = mini-mental state examination; MDS-UPDRS III = Movement Disorders Society-Unified Parkinson disease rating scale motor part; the values in the brackets represent the minimum and maximum value.

3.2. Differential fMRI activation of the left IPL, SPL, SFG and vPM in Parkinson's disease

We found a significant task-by-group interaction effect in brain areas forming part of the praxis network (Figs. 2, 3): left IPL ($F_{(1, 56)} = 14.17$), left superior parietal lobule (SPL) ($F_{(1, 56)} = 13.58$), left superior frontal gyrus (DMPFC; $F_{(1, 56)} = 11.6$), and left ventral premotor area (vPM) ($F_{(1, 56)} = 11.54$). Post-hoc *t*-tests (Fig. 3) of extracted fMRI activity values in these areas indicated increased activity in patients compared to controls during CR (IPL, $T_{(30)} = 2{,}77$, $P = 0.009$; SPL, $T_{(30)} = 2.61$, $P = 0.014$; vPM, $T_{(30)} = 3{,}33$, $P = 0.002$). In contrast, for the FT task fMRI, activity in patients was decreased significantly in IPL ($T_{(30)} = 2{,}38$, $P = 0.024$), SPL ($T_{(30)} = 2{,}35$, $P = 0.026$), and in SFG ($T_{(30)} = 3{,}2$, $P = 0.003$). In vPM fMRI activation of FT was not different ($T_{(30)} = 1.15$, $P = 0.258$). These results show that the increased activation during CR in left praxis areas is not a general group effect, but specifically modulated by the task. Furthermore, the CR task differentially activates the left praxis network in patients regardless of the hand involved.

3.3. Increased functional coupling of the left IPL with posterior hippocampi

We detected an increased functional connectivity in patients of the left IPL bilaterally to posterior hippocampus, extending from precuneus on the right. Furthermore, stronger connectivity of left IPL was found with lateral temporal areas including left middle and right superior temporal gyrus, as well as the left cuneus (Fig. 4; Table 2). In addition, patients showed a disturbed connectivity with the frontal lobe. We detected a decreased connectivity of the left IPL and the dorsolateral prefrontal cortex (DLPFC: right middle frontal gyrus) in patients compared to controls (Fig. 4; Table 2).

Correlation analysis revealed that functional connectivity of the left IPL with the left middle temporal gyrus (MTG) was associated with better CR performance in patients (see Supplementary material analysis A).

3.4. Grey matter volume decrease in bilaterally frontal brain areas

VBM analysis revealed a slight decrease of grey matter volume in widespread brain areas including the left inferior frontal gyrus and bilaterally the primary motor cortices in patients compared to controls (see Supplementary material analysis B, Table SI).

4. Discussion

Patients with PD frequently suffer from loss of fine motor skills. Clinical studies (Foki et al., 2016; Gebhardt et al., 2008; Quencer et al., 2007; Vanbellingen et al., 2011) suggested that LKA, apart from bradykinesia, is implicated. However, whether dexterous impairment in PD is explained by apraxia is still a matter of debate (Foki et al., 2015, 2016; Gebhardt et al., 2008; Landau and Mink, 2007; Quencer et al., 2007; Swash et al., 2007; Vanbellingen et al., 2011).

Therefore, the goal of the present study was to assess the functional brain activity during skilled fine motor tasks, as measured by the coin rotation (LKA) task in PD compared to matched healthy controls. Furthermore, we investigated for the first time dynamic functional connectivity within the praxis network during CR. We hypothesized to detect increased activation in areas of the praxis network in PD patients during the CR task, which is the neural correlate of LKA. Furthermore, we expected an altered functional connectivity of the praxis network during a limb kinetic task.

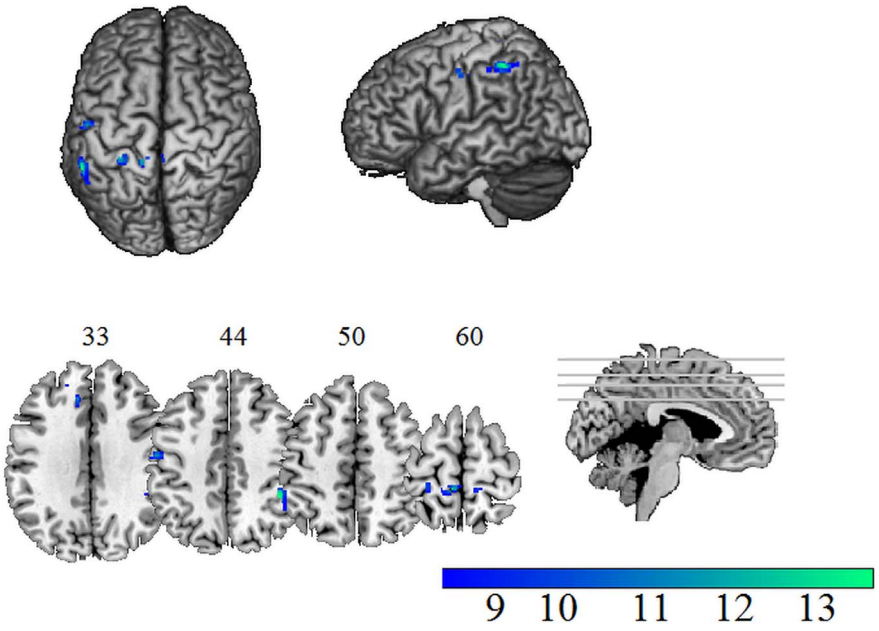

Fig. 2. Brain areas with significant task-by-group interaction. Effect in patients with Parkinson's disease and healthy controls during a bradykinesia (finger tapping) and a limb kinetic apraxia task (coin rotation). Significant whole brain task-by-group interaction was detected within the left inferior parietal lobule, superior parietal lobule, superior frontal gyrus and ventral premotor area. The color bars show F statistic. L = left; R = Right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

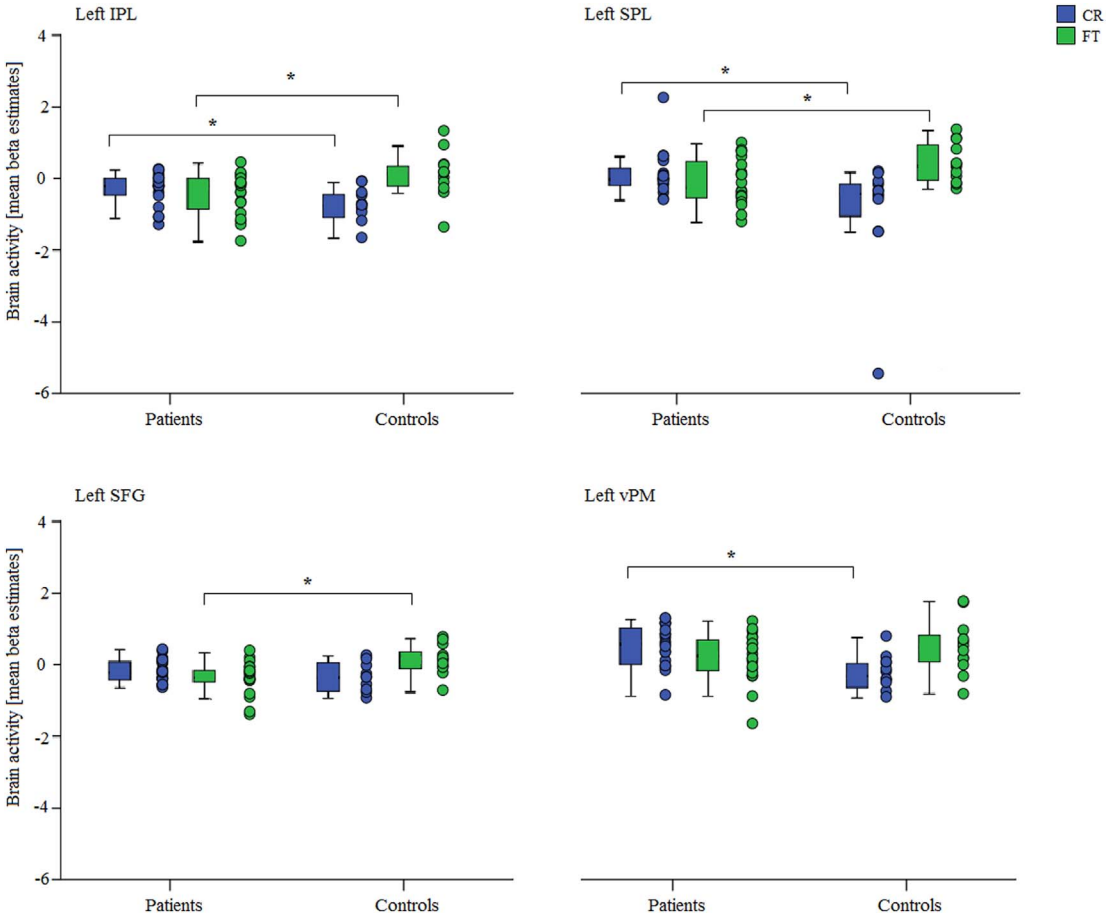

Fig. 3. Between group differences of brain activity within significant clusters of the interaction analysis.
Brain activity in the left inferior parietal lobule (IPL), superior parietal lobule (SPL) and superior frontal gyrus (SFG) was enhanced in patients compared to controls during the limb kinetic apraxia task (CR) and decreased in the IPL, SPL and vPM during the bradykinesia task (FT). Significant differences of post-hoc pairwise group comparisons are indicated with asterisks ($P < 0.05$). Note: CR = coin rotation in green; FT = finger tapping in blue, error bars: ± 1 standard error.(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

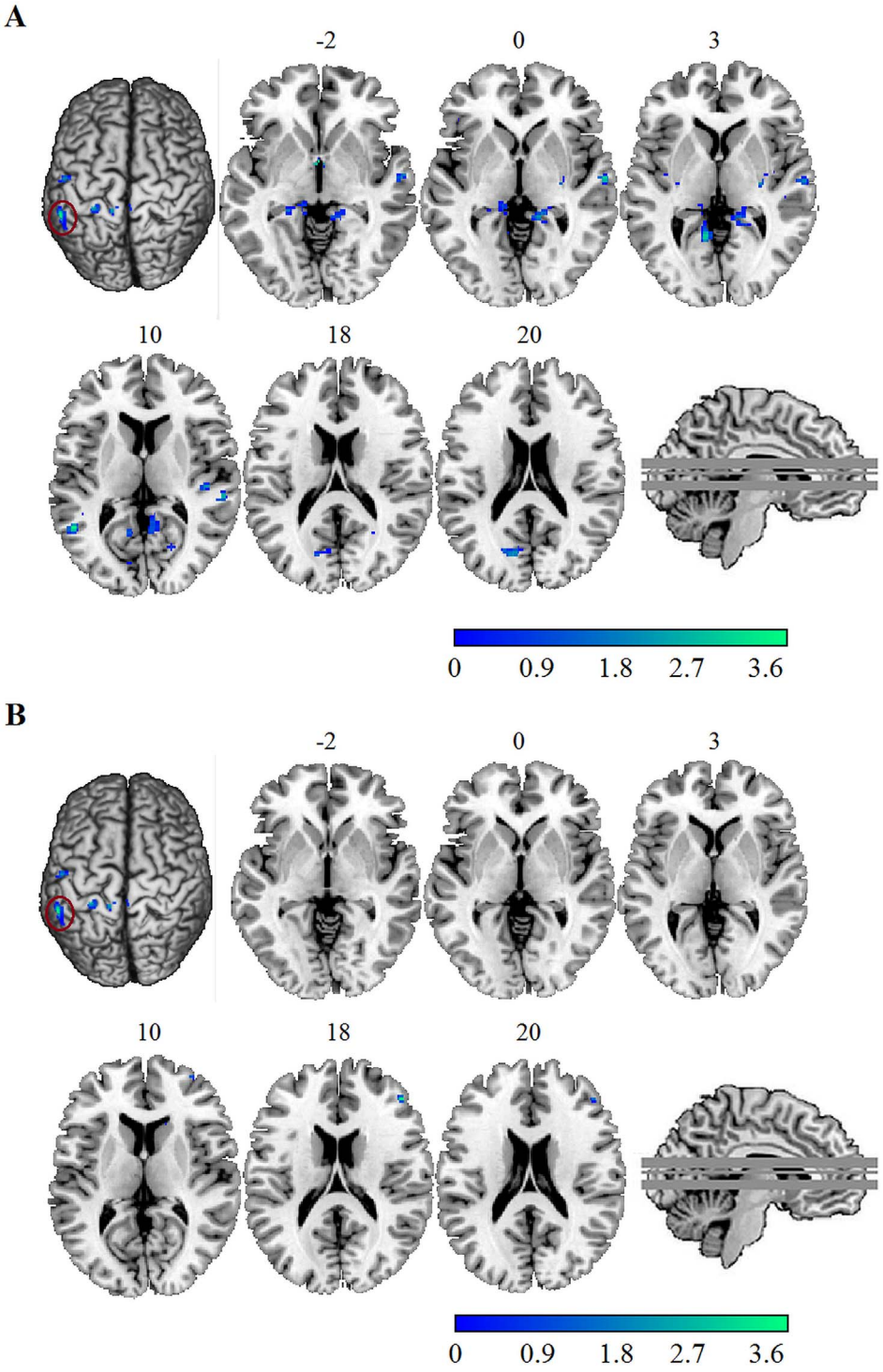

Fig. 4. Between group results of functional connectivity during limb kinetic apraxia task performance.
A. Significant enhanced functional connectivity between the inferior parietal lobule and the posterior body of the hippocampus on both sides and B. significant decreased connectivity between the inferior parietal lobule and the middle frontal gyrus (DLPFC) in patients compared to healthy controls. The color bars show T values. L = left; R = right; DLPFC = dorsolateral prefrontal cortex.(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

As predicted, and in line with current models of apraxia, we detected differential activation in key areas of the left praxis network (i.e. left IPL, SPL and vPM) and additionally the DMPFC, regardless of the hand involved. These results fit nicely with the literature that shows the association of apraxic deficits with left parietal and premotor regions and thus support the notion that indeed dexterous deficits in PD stem from LKA. We confirmed our hypothesis of altered functional coupling within the praxis network associated with the LKA task. In particular, we detected increased functional connectivity of the IPL in patients with several brain areas including an area involved in visual-spatial memory (posterior hippocampus). Furthermore, unlike controls, patients failed to functionally connect the IPL with regions of executive control during the LKA task.

4.1. Differential neuronal activation of limb kinetic apraxia and bradykinesia

Altered activation of IPL is frequently found in PD (Herz et al., 2014; Samuel et al., 1997; Wu and Hallett, 2005). Moreover, the IPL is relevant for skilled fine movements (Buxbaum et al., 2007; Pause et al., 1989) and is a key region in apraxia (Buxbaum et al., 2007; Goldenberg, 2009; Heilman, 2010). In particular, time and spatial content of a movement is hypothesized to be stored in the IPL (Buxbaum et al., 2014; Heilman et al., 1982; Rothi et al., 1985). In addition, the

Table 2
Altered functional connectivity of the left inferior parietal lobule linked to limb kinetic apraxia in patients and controls: between-group analysis (Parkinson's disease patients > healthy controls; healthy controls > Parkinson's disease patients.

Whole brain functional connectivity of the inferior parietal lobule during coin rotation														
	Patients > controls							Controls > patients						
	Cluster		Peak		MNI coordinates			Cluster		Peak		MNI Coordinates		
Brain region	$p_{(FWE-corr)}$	k	$p_{(FWE-corr)}$	$T_{(31)}$	x	y	z	$p_{(FWE-corr)}$	k	$p_{(FWE-corr)}$	$T_{(31)}$	x	y	z
L Middle temporal gyrus	0.996	40	0.572	4.331	−52	−54	8	*n.s.*						
L Cuneus	0.979	59	0.996	3.420	−12	−74	20	*n.s.*						
L Hippocampus	1.000	19	0.999	3.230	−22	−36	−2	*n.s.*						
L Parahippal gyrus extending to hippocampus	1.000	23	0.999	3.070	−12	−36	0							
L Calcerin gyrus	0.798	115	0.647	4.220	−10	−54	4	*n.s.*						
R Middle frontal gyrus	*n.s.*							1.000	23	0.971	3.650	46	40	18
R Superior temporal gyrus	0.995	42	0.989	3.580	62	−12	0	*n.s.*						
	1.000	25	0.993	3.920	46	−24	8	*n.s.*						
R Precuneus extending to hippocampus	0.643	146	0.938	3.760	18	−46	4	*n.s.*						

L = left; MNI = Montreal Neurological Institute; n.s. = not significant: R = right.

premotor areas and supplementary motor area via primary motor cortex are hypothesized to transmit time and spatial information to motor representation for final motor execution (Babiloni et al., 2003; Penfield and Penfield and Welch, 1951). In general, functional imaging studies highlight the involvement of left lateralized premotor-posterior parietal areas in praxis related tasks such as pantomiming (Bohlhalter, 2009; Choi et al., 2001; Fridman et al., 2006; Króliczak and Frey, 2009; Mäki-Marttunen et al., 2014; Ohgami et al., 2004; Vingerhoets et al., 2011; Vry et al., 2015) or real tool use (Brandi et al., 2014; Imazu et al., 2007). In PD the hyper-activation of inferior frontal and inferior parietal areas is associated with diminishing pantomime skills (Matt et al., 2016). Furthermore, several studies showed increased fMRI activation reflecting a compensatory (although dysfunctional) mechanism for diminished task performance (e.g. diminished working memory) (Rottschy et al., 2013; Trujillo et al., 2015). However, so far only one group investigated functional correlates of LKA in PD (Foki et al., 2010, 2015). This study showed bilateral hyper-activity in widespread areas of the frontal and the parietal cortex (Foki et al., 2010). Hence, except for weak hypo-activity in somatosensory cortex, the findings largely lacked specificity, which may be explained by methodological issues (Bohlhalter et al., 2011).

Strikingly, we revealed differential neuronal activation of LKA within the IPL, SPL and premotor areas. Therefore, our findings fit well with the left-predominant posterior-anterior control of praxis function, in which limb kinetic deficits result if the neuronal transmission to final motor output is impaired. The dysfunction upstream to primary motor representations is further corroborated as the interaction effect of fMRI activity was controlled for performance and therefore cannot be explained by differences in motor output per se. The VBM analysis showed diminished grey matter volume in various inferior frontal and temporo-parietal brain regions as known from the literature (Borghammer et al., 2010; Postuma and Dagher, 2006; Potgieser et al., 2014). No diminished grey matter volume was found in the praxis relevant areas associated with the CR task. Therefore, the VBM findings cannot account for LKA-related fMRI alterations in PD.

For the bradykinesia task, we detected decreased activity in the left SPL, IPL and SFG in patients compared to controls. Several factors may account for this observation. Hypo-activity in cortical structures such as the primary motor cortex (Rascol et al., 1992), SPL (Haslinger et al., 2001), SMA (Rascol et al., 1992) and DLPFC (Playford et al., 1992) has been reported as a general feature of PD and has also been linked to bradykinesia (Rascol et al., 1992). Furthermore, basal ganglia and cortical activation likely depend on the medication status, as most functional imaging studies in PD demonstrated hypo-activation in OFF state and hyper-activation in ON (Buhmann et al., 2003; Kraft et al., 2009; Leenders et al., 1985; Lewis et al., 2007). Therefore, we may speculate that cortical hypo-activity associated with bradykinesia observed herein may be explained by the fact that almost half of the patients were drug naïve. Finally, the patients reached normal performance in the modified finger tapping task despite hypo-activation. This constellation may reflect the earlier disease stage of our cohort, when compensatory cortical hyper-activity is only necessary with higher and specific task demands such as for digital dexterity associated with the CR task.

4.2. Altered functional coupling with visual-spatial and executive brain areas

Previous task-based network investigations of motor performance (fMRI) detected mostly increased connectivity in PD patients in the motor network compared to healthy controls e.g. during action planning (i.e. skilled finger movements) (Wu et al., 2010b; Yan et al., 2015) and motor learning (Wu et al., 2010a). These increased connectivity patterns in patients were interpreted as compensatory mechanisms during motor control in PD (Eckert et al., 2006; Katschnig et al., 2011; Mallol et al., 2007; Yu et al., 2007). Likewise, altered functional connectivity during general higher-level planning, such as task-shifting (de Bondt et al., 2016; Helmich et al., 2009) and working memory (Trujillo et al., 2015; Weder et al., 1999), have repeatedly been demonstrated in PD. In detail, De Bondt and colleagues found a hyper-activation together with decreased connectivity between key areas of task-shifting, such as the DLPFC, superior frontal gyrus and posterior parietal cortex. Participants performing a visual-spatial working memory task showed decreased functional coupling with the DLPFC but an increased connectivity of the fronto-parietal network, including the IPL (Trujillo et al., 2015). Thus, previous studies mostly suggest increased connectivity within brain areas of the motor networks during motor performance together with decreased connectivity within attentional and executive brain areas during cognitive tasks. In contrast, studies investigating functional connectivity in PD during a LKA task are missing.

Here we reported increased connectivity of the IPL in patients with the temporal lobe, the cuneus, the precuneus, and the calcerine gyrus. In addition, increased connectivity of the IPL with the posterior hippocampi on both sides was shown. Thus, we failed to detect increased connectivity with brain areas of cortical motor networks previously reported for motor performance tasks. Instead, we detected increased connectivity with the posterior hippocampus and the left MTG. The hippocampus is hypothesized to integrate object-related information and to store and retrieve time and spatial information of a movement (Behrendt, 2013). In healthy controls, the hippocampus was detected as important also for encoding and retrieval of event related memories (Eldridge et al., 2000) and context coding (Kalisch et al., 2006).

Moreover, the hippocampus as well as the MTG seem to play important roles in retrieval of semantic knowledge about the use of a tool (Goldenberg and Randerath, 2015). Thus, corresponding lesions can cause pantomime impairments and lead to ideo-motor apraxia (Speach et al., 1998). In addition, the hippocampus plays a role in movement planning (Dagher et al., 2001), motor learning (Schendan et al., 2003) and in retaining motor knowledge (Albouy et al., 2008). Therefore, the increased connectivity in patients may be a dysfunctional compensatory mechanism during the LKA task. Specifically, increased coupling of the IPL with the posterior hippocampus may reflect the attempt to retrieve temporo-spatial information from the hippocampus for movement planning, which is normally done in the IPL. Similarly, the association between CR performance and the connectivity of IPL to MTG in PD patients may point to a compensatory recall of motor engrams. In addition, one PET study showed the recruitment of the hippocampus to overcome the striatal deficits during planning of movement sequence in PD (Dagher et al., 2001). In addition, it was generally hypothesized that cortical reorganization in PD patients involves the modification of the type and strength of connectivity to maintain a normal performance (Husárová et al., 2013). However, whether increased connectivity with the IPL is the cause or the consequence of possible altered IPL function in PD needs to be further evaluated.

Furthermore, unlike controls, patients failed to connect the IPL functionally with the DLPFC during the LKA task. Decreased functional connectivity with the DLPFC during the LKA task is in line with studies examining general higher-level planning (de Bondt et al., 2016; Rowe et al., 2002). Moreover, the decreased coupling of the IPL with the DLPFC fits to one previous task-based fMRI study investigating novel and automatic finger sequences using a psycho-physiological interaction approach in PD (Wu et al., 2010a). The authors detected stronger functional connectivity of motor areas with the DLPFC during novel sequences in healthy subjects, showing that execution of more complex motor tasks, in contrast to automatic movements, shifted brain connectivity from more subcortical to more executive control areas compared to PD (Wu et al., 2010a). Accordingly, decreased IPL and DLPFC coupling in our patients may reflect impairments in executive functions (Trujillo et al., 2015) during the limb apraxia task, thereby adding to dexterous impairment.

Finally, the altered pattern of functional brain connectivity may be interpreted together with the differential neuronal activation of LKA and bradykinesia. PD patients often suffer from cognitive impairments in the course of the disease, specifically in memory and visual-spatial domains (Aarsland et al., 2010). Therefore, one may speculate that altered functional coupling together with the increased neural activation of brain areas of the praxis network reflects additional recruitment of regions to overcome general cognitive impairments in PD. Yet, it is unlikely that the detected altered pattern of activity and connectivity simply stem from cognitive performance deficits, particularly as cognitive performance (MMSE, digit span test) did not differ between patients and controls.

4.3. Limitations

There are several limitations of our study. Patients with PD received medical treatment which may affect brain activation. In fact, if patients received medical treatment, they performed the fMRI task in best ON medication. The focus of our study, however, was on LKA underlying PD independent of confounding effects due to bradykinesia. Therefore, to minimize unspecific effects due to medication we controlled for the levodopa equivalent. Furthermore, studies on the effect of PD medication on brain activity are inconclusive (Cools et al., 2002; Fera et al., 2007; Haslinger et al., 2001; Jubault et al., 2009; Martinu et al., 2012; Rascol et al., 1994) and pinpoint to a normalizing effect of Levodopa on fMRI activation of PD patients (Haslinger et al., 2001; Ng et al., 2010). In addition, a general limitation of functional connectivity analysis with the PPI approach is that direction of connectivity between brain regions cannot be detected (Friston et al., 1997) and may not follow structural routes. Further studies e.g. with diffusion tensor imaging need to explore structural connectivity alterations associated with LKA in PD. Finally, the adaption of the finger tapping task (involving three fingers) introduced elements of selective finger innervation that is a hallmark of Liepmann's LKA concept. Therefore, the modified paradigm for bradykinesia may have reduced the power of detecting specific differential activation with LKA as measured by the CR task.

5. Conclusion

Our data demonstrates differentially altered activations within the praxis network of left hemisphere associated with LKA in PD. Moreover, for the first time, we provide evidence of decreased functional connectivity of the IPL with the DLPFC and increased connectivity of the IPL with the hippocampi, which may reflect an attempt to compensate for dexterous deficits. These results strongly support the notion that LKA, apart from bradykinesia, is implicated in dexterous deficits in PD. In addition, our findings demonstrate that CR is a valid clinical test for LKA in PD.

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Appendix A. Supplementary data

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