Dopaminergic modulation of the praxis network in Parkinson's disease

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ABSTRACT

Apraxia is a deficit in central motor planning impairing praxis functions such as gesture production or tool use that affects a substantial number of patients with advanced Parkinson's disease. We investigated the functional connectivity of the praxis network in patients in early stages of Parkinson's disease having an increased risk for apraxia and evaluated the influence of dopaminergic therapy on praxis abilities and related networks.

13 patients with mild to moderate Parkinson's disease (ON and OFF dopaminergic therapy) and 13 healthy controls completed a praxis sensitive functional MRI task and apraxia assessments. Functional connectivity analyses included a graph theoretical approach analyzing the global efficiency within the praxis network followed by a seed-to-voxel functional connectivity analysis.

Patients in the OFF but not in the ON state showed significantly lower praxis scores than controls. Patients in both states displayed higher global efficiency within the praxis network than controls revealing the bilateral supramarginal gyri as hubs. Seed-to-voxel functional connectivity analyses showed aberrations of right-hemispheric praxis areas in the OFF but not in the ON state. Patients in the ON state exhibited a significantly higher functional connectivity between the supramarginal gyrus and the primary motor cortex, basal ganglia, and frontal areas than in the OFF state.

Dopaminergic therapy seems to normalize praxis abilities and related praxis networks in early stages of Parkinson's disease potentially by facilitating the propagation of long-term representations of object-related actions to motor execution areas.

1. Introduction

Apraxia is a cognitive motor disorder affecting the performance of skilled and purposeful movements such as tool use or gesture production (Leiguarda and Marsden, 2000). Deficits in praxis functions can have obstructive effects on the activities of daily living and can significantly impair the patients' ability to live autonomously (Dovern et al., 2012; Foundas et al., 1995; Hanna–Pladdy et al., 2003). Apraxia occurs in a variety of neurological diseases including stroke, dementia, and movement disorders (Park, 2017; Zadikoff and Lang, 2005). With a prevalence rate varying between 17 and 64%, a substantial number of patients with Parkinson's disease (PD) suffer from apraxic symptoms (Grossman et al., 1991; Leiguarda et al., 1997; Vanbellingen et al.,

2012). Besides different methods to assess apraxia, this variability regarding the prevalence figures might also be attributed to different disease stages. Indeed, Vanbellingen et al. (2012) showed that the prevalence rate increases with disease severity, ranging from 0% in Hoehn and Yahr stage 1 up to approximately 40% in stage 4, implying that patients in early stages are at risk for developing apraxia later in the course of the disease. As the neurodegenerative nature of PD entails that motor and non-motor symptoms gradually evolve it is likely to observe changes in brain function and connectivity before symptoms become clinically overt. Indeed, we previously demonstrated evidence of a compensatory increased recruitment of left-hemispheric core regions of the praxis network during pantomime of object use in patients in early stages of PD without clinically evident apraxia (Matt et al.,

2017). While this classical functional magnetic resonance imaging (fMRI) analysis is suitable for investigating the specialization of brain regions for specific functions, functional connectivity (FC) addresses the functional integration of localized neuronal processing across widely distributed brain regions with distinct functional specializations (Friston, 2011).

Previous FC studies in PD reported aberrations of the sensorimotor networks (Baudrexel et al., 2011; Burciu et al., 2015; Helmich et al., 2010; Kurani et al., 2015; Sharman et al., 2013; Wu et al., 2011) but also altered networks of associative cortical regions (Chen et al., 2015; Putcha et al., 2015; Zhang et al., 2015). Functional connectivity alterations were found to be related to motor and non-motor symptoms such as cognitive impairment in PD (Gao and Wu, 2016; Hohenfeld et al., 2018). Yet, it is not clear how such functional connectivity alterations in PD might be related to praxis abilities interfacing cognition and motor functions. Specifically, praxis functions have been shown to rely on a predominantly left-hemispheric fronto-parietal network, as functional imaging studies in healthy individuals and structural lesion studies suggest (Bieńkiewicz et al., 2014; Vry et al., 2015; Niessen et al., 2014). However, apraxia might also be related to right-hemispheric lesions or structural alterations (De Renzi et al., 1980; Manuel et al., 2013; Stegmayer et al., 2016). Functional imaging studies in clinical samples are rare, but suggest a potential for compensating dysfunctions or lesions of praxis core areas by upregulation within the network (Matt et al., 2017) or by recruiting right-hemispheric homologue regions (Martin et al., 2016).

To specifically address the FC aberrations of the praxis network we used data of PD patients and healthy controls that have already been used to investigate task-based activation (Matt et al., 2017). One of the most commonly used FC approaches is the seed-to-voxel analysis that involves the correlation of the signal time-course of a pre-defined seed area with the time-courses of all other voxels. However, this analysis requires strong a priory hypotheses about which region to select as seed. As for praxis functions a variety of brain regions have been reported to subserve praxis functions – leading to the description of the so called praxis network (Vry et al., 2015; Niessen et al., 2014) – we subjected this network to a graph theoretical analysis to specify our seed region for the follow-up seed-to-voxel analysis. Further, we evaluated the influence of dopaminergic therapy on the praxis network by comparing patients with and without individually optimized medication.

We assumed that the observed compensatory mechanisms concerning the task-related activations in PD patients (Matt et al., 2017) are reflected by FC changes, potentially by an upregulation of the functional connectivity within or outside the praxis network. We further hypothesized that dopaminergic therapy affects the FC of the praxis network and related areas. Finally, we expect an association between the FC of the praxis network and behavioral praxis abilities.

2. Material and methods

2.1. Participants

Fourteen patients with a diagnosis of mild to moderate PD (Hoehn and Yahr stage 1–2) participated in this study. One patient was not able to perform the experiment without dopaminergic therapy and was excluded from the analysis. For the resulting 13 patients (six female, mean 60.23 years) the mean disease duration was 6.31 years (Table 1). To be included, patients had to be right-handed as assessed with the Edinburgh Handedness Inventory (Salmaso and Longoni, 1985) and not older than 85 years of age. None of the patients showed a coexistence of other neurological diseases, a history of psychosis, significant head tremor, or disabling rest or action tremor according to the Unified Parkinson's Disease Rating Scale (UPDRS action tremor >2). Further exclusion criteria were cognitive impairment according to the Mini-Mental State Examination (MMSE; Folstein et al., 1975) using a cut-off

value of <26 (Kukull et al., 1994), and abnormal sensory functions as assessed by clinical examinations. Fourteen healthy control subjects were recruited from the general population and matched for age and gender of the patients. One healthy subject was excluded from final analysis due to insufficient data quality of the structural image. Six of the remaining 13 control subjects were female and their average age was 56.77 years (Table 1). Control subjects had a normal neurological and psychiatric status without any history of central nervous system disease or a first grade relative with a primary movement disorder. The data for this study was previously used to investigate task-related activation (Matt et al., 2017). The study was approved by the ethics committee of the Medical University of Vienna and all participants gave their written informed consents according to the Declaration of Helsinki.

2.2. Experimental design

For the patients fMRI experiments and behavioral and clinical examinations were performed once with individually optimized dopaminergic medication (ON) and once without (OFF). Patients in the OFF state were measured at least 12 h after their last dopaminergic medication, or in case of extended-release preparations after at least 48 h. Scans ON and OFF were conducted in a randomized order (seven patients performed ON first, six OFF first) within 14 days. Before each fMRI measurement (ON and OFF) patients underwent a neurological examination including Hoehn and Yahr scale and the motor evaluation (Part III) of the UPDRS.

The healthy controls performed only one fMRI measurement preceded by evaluations of praxis functions using the De Renzi Ideomotor apraxia test and the De Renzi Demonstration-of-Use test. The Ideomotor apraxia test (De Renzi et al., 1980) consists of 24 unilateral right and left hand gestures (12 of them additionally involve arm movements) that are produced by the experimenter. Patients were asked to imitate these gestures and were given 3 points if the gesture was appropriate after the first demonstration, 2 points after the second demonstration, 1 point after the third demonstration, and 0 points for incorrect gestures after the third demonstration. The cut-off for clinical apraxia was 62 out of the maximum of 72 points. During the Demonstration-of-Use test (De Renzi and Lucchelli, 1988) ten common objects (e.g. a hammer) were presented and the patients were required to demonstrate their use with the right hand. Flawless performance in the first trial was scored with 2 points, in the second with 1 point, and 0 points were given for an incorrect gesture. These apraxia tests were also completed by the patients before each fMRI measurement.

During fMRI participants performed a pantomime task in which they imitated the use of visually presented objects with their right hand and a reference task with standardized finger tapping with the right index finger (see Matt et al., 2017 for further details). The block-designed fMRI experiment consisted of 10 runs with four reference and three pantomime periods (each lasting 20 s). Intrascan pantomime performance was rated by the experimenter in the scanner room and ranged from 0 for wrong gestures to 3 for appropriate gesture production (Leiguarda et al., 1997).

2.3. MRI data acquisition

MRI measurements were performed with a 3 Tesla TIM-TRIO system (Siemens Healthcare, Erlangen, Germany) using a 32 channel Siemens head coil. Functional images were acquired using a 2D single shot echo planar imaging sequence (repetition time = 2500 ms, echo time = 28 ms, flip angle = 90°, in-plane acceleration = GRAPPA 2) with 34 axial slices covering the whole brain (field of view = 230 mm, voxel size = $1.8 \times 1.8 \times 3.0$ mm, no gap). Each of the 10 functional runs consisted of 56 volumes and lasted 140 s. A T_1-weighted structural image was acquired using a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence (repetition time = 2300 ms, echo

Table 1
Subject characteristics and behavioral data.

	Patients (N = 13)		HC (N = 13)	Group comparisons
	ON	OFF		
Gender	6 female, 7 male		6 female, 7 male	
Age (years)	60.23 (12.18)		56.77 (9.97)	Patients vs. HC† P = .139, d = 0.31
Disease duration (years)	6.31 (4.70)			
No. Patients H&Y 2/2.5/3	8/5/0	5/7/1		
UPDRS III	22.46 (7.80)	30.23 (12.18)		ON vs. OFF‡ P = .011, d = 0.76
De Renzi Ideomotor apraxia score	70.92 (1.26)	70.17 (1.64)	71.59 (0.66)	ON vs. HC† P = .558, d = 0.67 OFF vs. HC† P = .027, d = 1.14 ON vs. OFF‡ P = .486, d = 0.51
Pantomime Rating	2.59 (0.35)	2.48 (0.56)	2.82 (0.20)	ON vs. HC† P = .216, d = 0.81 OFF vs. HC† P = .057, d = 0.81 ON vs. OFF‡ P = .999, d = 0.24

Data as mean (standard deviation), *P*-values and effect size (Cohen's d) for the group comparisons († unpaired *t*-test, ‡ paired *t*-test, Bonferroni correction for multiple comparisons). HC = healthy controls, H&Y = Hoehn and Yahr stage, UPDRS III = Unified Parkinson's Disease Rating Scale Part III.

Table 2
Regions of interests (ROIs) comprising the praxis network.

Praxis network ROIs (Harvard-Oxford-Atlas)	Acronym	ROI volume[a]	
		Left	Right
Middle Frontal Gyrus	MFG	2927	2740
Inferior Frontal Gyrus, pars triangularis	IFG tri	650	555
Inferior Frontal Gyrus, pars opercularis	IFG oper	686	766
Middle Temporal Gyrus, temporooccipital part	toMTG	866	1162
Superior Parietal Lobule	SPL	1460	1476
Supramarginal Gyrus, anterior division	aSMG	954	801
Supramarginal Gyrus, posterior division	pSMG	1064	1235
Angular Gyrus	ANG	950	1469
Lateral Occipital Cortex, superior division	sLOC	4967	4813

[a] Number of voxels at a resolution of 2 mm isotropic.

time = 3.36 ms, inversion time = 900 ms, flip angle = 9°, voxel size = 0.9 mm isotropic. To minimize head motion artefacts, individually constructed plaster cast helmets were used (Edward et al., 2000).

2.4. Functional connectivity analysis

All preprocessing procedures and FC analyses were performed using the CONN toolbox v17 (Whitfield-Gabrieli and Nieto-Castanon, 2012). The CONN default preprocessing pipeline was applied including realignment, unwarping, slice-time correction, structural segmentation, normalization, outlier detection, and smoothing (8 mm full-width at half-maximum isotropic Gaussian kernel). Denoising of the functional data consisted of a high-pass filter of 0.01 Hz to reduce effects from low-frequency drifts and removal of confounding covariates by first level linear regression. These confounds include six rigid-body head motion parameters derived from the realignment procedure and their first derivatives as well as white matter and cerebrospinal fluid signals (five principal components extracted from the cerebrospinal fluid and the white matter masks). The main condition effect was modeled as pantomime block regressors convolved with the hemodynamic response function and was entered as a confounding covariate in the first level analysis as well. First level statistics was performed with a weighted general linear model testing for the bivariate correlation of the corrected time series between anatomical regions of interests (ROI-to-ROI

analysis) or voxels (seed-to-voxel analysis).

Second level analysis was performed using a graph theoretical approach followed by a seed-to-voxel analysis. The graph theoretical measure global efficiency (GE) is defined as the inverse of the shortest path length between each pair of nodes of the network and is a measure of the network's capacity for parallel information transfer between nodes via multiple series of edges (Achard and Bullmore, 2007). The GE was analyzed on ROI- and network-level (Whitfield-Gabrieli and Nieto-Castanon, 2012) within the predefined praxis network with core areas according to previous studies in healthy subjects (Vry et al., 2015; Niessen et al., 2014). Previous data in clinical samples demonstrated a potential involvement of right-hemispheric homologue areas (Martin et al., 2016; Stegmayer et al., 2016), thus, we analyzed the praxis network bilaterally. Core areas were transferred to the Harvard-Oxford atlas as implemented in the CONN-toolbox beforehand. Specifically, the praxis network includes bilateral inferior (anterior and posterior supramarginal gyrus, angular gyrus) and superior parietal areas, the superior part of the lateral occipital lobe, inferior (triangular and opercular parts) and middle frontal gyri, as well as the temporo-occipital middle temporal gyrus (Table 2).

The graph theoretical analysis was performed with an adjacency matrix threshold set to cost = 0.1, which represents 10% of all possible edges between all network nodes. By using this threshold the GE is estimated for a low-cost network (Achard and Bullmore, 2007). Group comparisons of the GE values were performed with unpaired *t*-tests between the patients ON / OFF and the controls and paired *t*-tests between the ON and OFF phase in the patients (network level *P* < .05 uncorr., ROI level P < .05 FDR corr.). ROIs within the networks that showed a significant difference between the experimental groups according to the graph theoretical analysis were subjected to a seed-to-voxel analysis. Between group comparisons of the first level seed-to-voxel connectivity maps were performed with appropriate *t*-tests (*P* < .001 uncorr., cluster-size *P*-FDR corr. threshold .05).

2.5. Clinical and behavioral data analysis

Statistical analyses of clinical and behavioral data were performed with SPSS (version 24). As the pantomime ratings, De Renzi Ideomotor apraxia scores, and the UPDRS III scores were not normally distributed appropriate non-parametric tests were applied for the comparison between groups (Wilcoxon-Test for comparing patients ON vs. OFF,

Mann-Whitney-*U* Test for comparing patients with the controls; two-tailed, Bonferroni corrected *P*-values, alpha level set at $P < .05$). In addition, Cohen's d effect size was calculated for the group comparisons. FC measures between the network hubs as identified with the graph theoretical analysis and the other ROIs of the praxis networks were extracted for each subject individually (correlations between ROI time-series, Fisher-z-transformed values) and correlated with the individual pantomime and apraxia scores using the non-parametric Spearman correlation analysis (without correction for multiple comparisons). Correlation analysis was performed for all subjects pooled together, and additionally separately for the controls and the patients (ON and OFF).

3. Results

3.1. Behavioral data

Subject characteristics including clinical and behavioral assessments are summarized in Table 1. The patients and the healthy controls did not significantly differ according to their age. Patients OFF exhibited significantly severer motor signs than patients ON (UPDRS III-score). Hoehn and Yahr stage increased 0.5 points in four patients in the OFF state, while for the other nine patients Hoehn and Yahr stages remained stable across ON and OFF states. All participants achieved the maximum score of 20 in the De Renzi Demonstration-of-Use Test and none of the patients showed apraxic symptoms according to the De Renzi Ideomotor apraxia score with a clinical cutoff value of 62 (De Renzi et al., 1980). There was no significant difference between patients in the ON and OFF state in this apraxia score or in the intrascan pantomime performance. However, patients OFF but not patients ON had significantly lower De Renzi Ideomotor apraxia scores ($P = .027$, d = 1.14). The differences between the patients and the controls regarding the intrascan pantomime score did not survive Bonferroni correction.
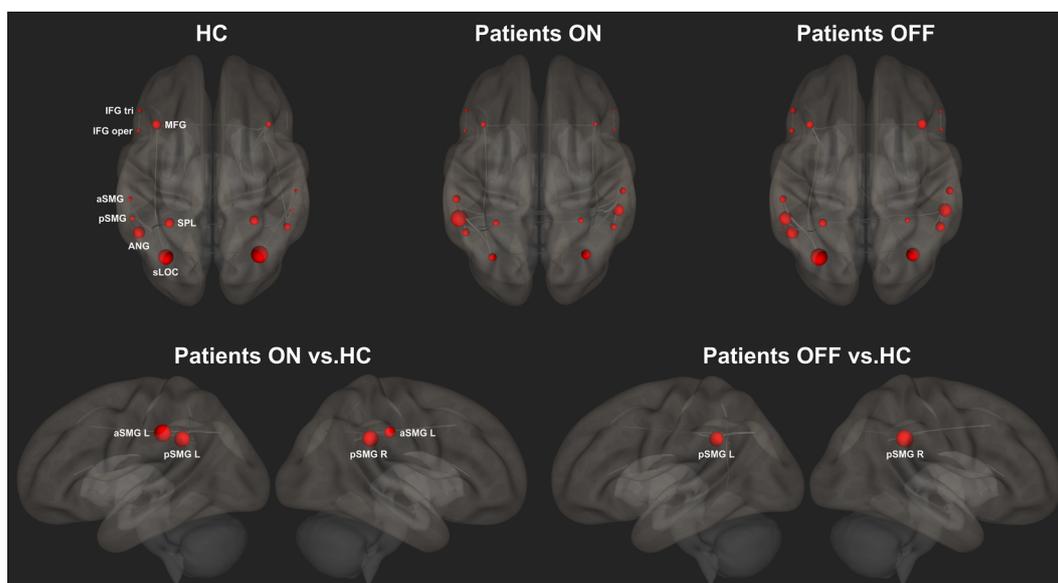
3.2. Global efficiency

The praxis network with each ROI's sphere size weighted according to the GE values for all experimental groups are depicted in Fig. 1. Regarding the GE of the praxis network ROIs, inferior parietal and frontal areas were clearly lateralized to the left hemisphere in the controls, while in patients ON and OFF an increased involvement of right-hemispheric areas was found. The direct contrast between patients and controls revealed a significantly increased GE within the whole praxis network for the patients in the ON and in the OFF state (Table 3) while the contrast between the ON and OFF state was not significant ($P = .276$). The bilateral supramarginal gyri (SMG) turned out as hubs in this network with significantly increased GE in posterior parts of the SMG (pSMG) in both states. Additionally, the bilateral anterior SMG showed significantly higher GE values in the patients ON compared to controls (Fig. 1, Table 3).

3.3. Seed-to-voxel functional connectivity

As the graph theoretical analysis revealed an aberrant GE of the left and right pSMG in the patients in both states compared to the controls, the seed-to-voxel FC analysis was restricted to these seed regions. The FC map of the left pSMG seed showed a network of adjacent left parietal areas and the right SMG as well as bilateral temporal and inferior frontal areas in the healthy controls (Fig. 2). Patients in the OFF state exhibited an increased and more widespread functional network of the left pSMG seed that involved bilateral posterior parietal areas, major parts of the right inferior parietal lobe, inferior and middle frontal gyri with a right-hemispheric dominance, and bilateral superior temporal areas (Fig. 2).

The significant differences between the experimental groups regarding FC of the SMG are listed in Table 4, including the specification of the result regions with cluster peak MNI coordinates and cluster size. Compared to the controls, patients OFF displayed a significantly increased connectivity of the left pSMG to the right homologue area and to the right inferior frontal gyrus (IFG) as well as between the right pSMG and the right superior lateral occipital cortex (Fig. 2, Table 4). The FC map of the left pSMG in the patients ON appeared as a transition between the controls and the OFF state; patients in the ON state showed more involvement of surrounding parietal areas and right fronto-parietal areas than the controls but less than in the OFF state. Indeed, a

Fig. 1. The regions of interest of the praxis network with sphere size weighted according to global efficiency values for the healthy controls (HC), patients ON and OFF separately, and for the contrasts between patients and controls. IFG tri = inferior frontal gyrus pars triangularis, IFG oper = inferior frontal gyrus pars opercularis, MFG = middle frontal gyrus, aSMG = anterior supramarginal gyrus, pSMG = posterior supramarginal gyrus, SPL = superior parietal lobule, ANG = angular gyrus, sLOC = superior lateral occipital cortex.

Table 3
Global efficiency values (GE) for the praxis network and its ROIs showing significant differences between patients and healthy controls.

	HC	Patients ON	ON vs. HC		Patients OFF	OFF vs. HC	
	Mean GE (SD)	Mean GE (SD)	T	P	Mean GE (SD)	T	P
Praxis network	0.169 (0.024)	0.213 (0.038)	30.45	.001	0.199 (0.032)	20.66	.007
aSMG L	0.103 (0.093)	0.284 (0.116)	40.40	.001†	0.197 (0.138)		
pSMG L	0.173 (0.125)	0.330 (0.062)	40.08	.001†	0.301 (0.107)	20.81	.043†
aSMG R	0.103 (0.099)	0.223 (0.110)	20.93	.016†	0.193 (0.123)		
pSMG R	0.128 (0.126)	0.301 (0.083)	40.12	.001†	0.278 (0.101)	30.34	.025†

HC = healthy controls, GE = global efficiency, SD = standard deviation, aSMG = anterior supramarginal gyrus, pSMG = posterior supramarginal gyrus, L = left, R = right. † FDR 0.05 corrected P-values.
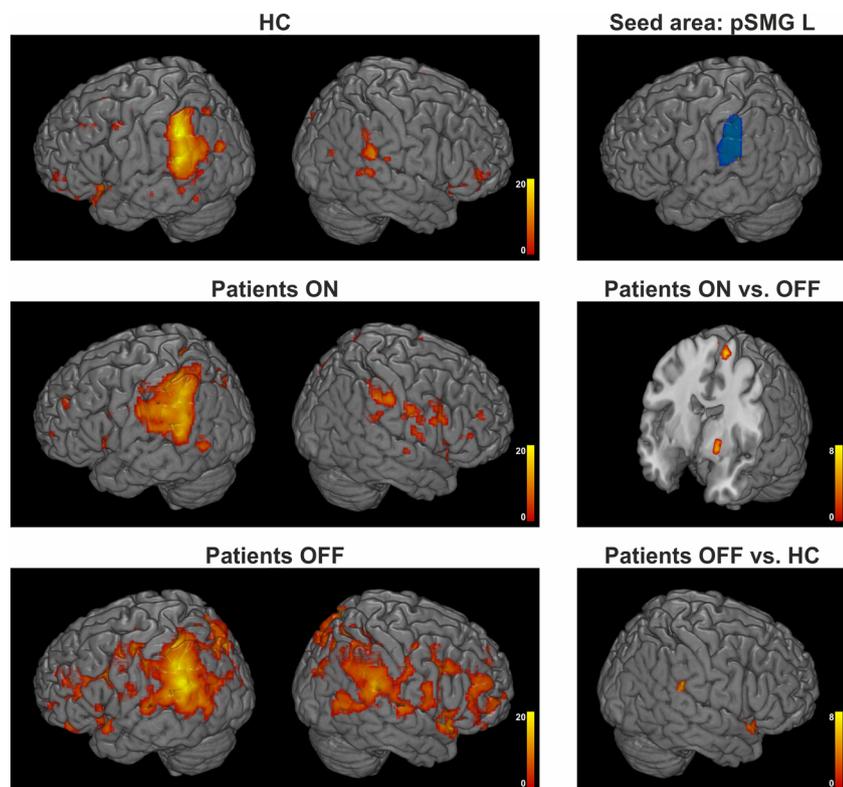
Fig. 2. Seed-to-voxel functional connectivity maps for the left posterior supramarginal gyrus (pSMG L) as seed area (blue) for the experimental groups separately and for significant group contrasts. Between group comparisons of the first level seed-to-voxel connectivity maps (Fisher-z-transformed correlation of the corrected time series between seed ROI and all voxels) were performed with paired (patients ON vs. OFF) and unpaired t-tests (patients vs. healthy controls (HC); $P < .001$ uncorr., cluster-size P-FDR corr. threshold .05).

direct contrast between patients ON and the controls was not significant. However, the comparison between the ON and OFF state revealed an increased FC of the left pSMG to the left precentral gyrus and the left pallidum as well as to the right IFG in the patients ON. An increased FC to the precentral gyrus and right superior frontal gyrus was also found for the right pSMG as seed in the ON compared to the OFF state.

3.4. Correlations with behavioral scores

Initially, the correlation analysis was planned for testing the relation between behavioral scores and the FC within the praxis network only. As we found significant modulations of FC between the SMG and motor areas (precentral gyrus and pallidum) by dopaminergic medication we also included these ROIs in the correlation analysis. Further, we conducted an additional partial correlation analysis with the UPDRS score

Table 4
Significant differences between groups regarding the functional connectivity of the left and right posterior supramarginal gyri as seed areas.

Seed	Contrast	Result region	Cluster peak MNI coordinates			Peak T value	Cluster size
pSMG L	OFF > HC	IFG pars opercularis R	54	18	− 08	4.91	96
		Posterior SMG R	60	− 38	28	6.08	64
	ON > OFF	Precentral gyrus L	− 10	− 24	70	8.95	92
		IFG pars triangularis R	40	34	10	8.89	35
		Pallidum L	− 22	− 02	− 04	6.57	30
pSMG R	OFF > HC	Superior LOC R	32	− 70	30	5.13	73
	ON > OFF	Precentral gyrus R	36	− 22	70	5.45	50
		Superior frontal gyrus R	20	− 08	76	4.88	37

OFF = patients OFF, ON = patients ON, HC = healthy controls, pSMG = posterior supramarginal gyrus, IFG = inferior frontal gyrus, LOC = lateral occipital cortex, L = left, R = right.

Table 5

Significant correlations between the De Renzi score and the functional connectivity of the bilateral posterior supramarginal gyri.

Target ROI		Seed: pSMG L				Seed: pSMG R			
		All	HC	Patients	Patients†	All	HC	Patients	Patients†
MFG R	r	0.272	0.217	0.394	**0.464**	−0.102	0.079	−0.197	−0.153
	P	.109	.523	.051	**.022**	.555	.817	.344	.475
MFG L	r	**0.341**	0.111	0.387	**0.418**	0.255	0.438	0.189	0.203
	P	**.042**	.745	.056	**.042**	.133	.178	.365	.342
IFG tri R	r	0.190	0.090	0.311	0.141	0.190	−0.338	**0.443**	0.290
	P	.267	.793	.130	.511	.268	.309	**.027**	.169
IFG oper R	r	0.243	−0.095	**0.405**	0.272	−0.017	−0.127	0.021	−0.070
	P	.154	.781	**.044**	.198	.921	.710	.919	.744
SPL R	r	**0.343**	0.132	**0.463**	0.196	0.048	0.391	0.041	−0.051
	P	**.041**	.699	**.020**	.359	.779	.235	.844	.813
SPL L	r	0.221	0.037	**0.461**	0.221	−0.033	0.259	−0.041	−0.104
	P	.195	.914	**.020**	.299	.850	.442	.846	.629
ANG R	r	0.026	0.201	0.097	0.039	−0.094	**0.782**	−0.152	−0.119
	P	.880	.554	.646	.856	.587	**.004**	.469	.581
PreCG R	r	**0.363**	0.132	**0.444**	**0.441**	0.023	0.217	−0.085	−0.179
	P	**.029**	.699	**.026**	**.031**	.896	.523	.687	.403
PreCG L	r	**0.413**	0.259	**0.472**	0.376	0.167	0.201	0.143	−0.016
	P	**.012**	.442	**.017**	.070	.329	.554	.496	.941
Pall R	r	**0.362**	−0.042	0.386	0.339	**0.334**	−0.121	0.343	**0.422**
	P	**.030**	.902	.057	.105	**.047**	.722	.093	**.040**
Pall L	r	**0.431**	0.222	**0.508**	**0.455**	**0.373**	0.048	**0.527**	**0.507**
	P	**.009**	.512	**.010**	**.026**	**.025**	.890	**.007**	**.011**

Results for the Spearman correlation analysis with correlation coefficients (*r*) and *P*-values for target areas with a significant correlation in any group (significant results in bold). † Adjusted for basal motor symptoms (score of the Unified Parkinson's Disease Rating Scale Part III as control variable in partial Spearman correlation analyses). MFG = middle frontal gyrus, IFG tri = inferior frontal gyrus pars triangularis, IFG oper = inferior frontal gyrus pars opercularis, pSMG = posterior supramarginal gyrus, SPL = superior parietal lobule, ANG = angular gyrus, PreCG = precentral gyrus, Pall = Pallidum. L = left, R = right.

as control variable to adjust for basal motor symptoms in the patients. For the intrascan pantomime score we found a significant relation between the FC of the left pSMG to the triangular part of the left IFG for the healthy controls ($r = -0.644$, $P = .018$). The right pSMG FC to the right triangular IFG was negatively correlated with the pantomime score for all subjects pooled together ($r = -0.342$, $P = .033$) and for the patients if adjusting for the UPDRS ($r = -0.438$, $P = .029$).

The correlations between the De Renzi apraxia score and the FC of the bilateral pSMG are listed in Table 5. The De Renzi apraxia score was significantly related to the left pSMG connectivity to the left middle frontal gyrus, to the right superior parietal lobule, as well as to the bilateral precentral gyri and the bilateral pallidum for all subjects analyzed together. In the patients (ON and OFF) significant correlations with the apraxia score were found for the left pSMG connectivity to the right IFG (opercular part) and the left pallidum, as well as to bilateral superior parietal lobules and precentral gyri. After controlling for the UPDRS, correlations with the right precentral gyrus and the left pallidum FC remained significant and new significant relations between the left pSMG and the bilateral middle frontal gyri emerged. While the FC of the left pSMG to the target areas was not significantly related to the De Renzi score in the healthy controls, the right pSMG FC to the right angular gyrus was positively correlated with this score. In the patients the right SMG FC to the right IFG (triangular part) was related to the apraxia score if not controlling for the basal motor abilities. The FC of the right pSMG to the bilateral pallidum was significantly related to the De Renzi score in all participants and in patients after controlling for the UPDRS.

4. Discussion

Although the neuronal basis of praxis functions has been comprehensively investigated in healthy individuals (Bieńkiewicz et al., 2014; Niessen et al., 2014) functional imaging studies targeting these abilities including their impairments in clinical samples are still rare (Kübel et al., 2018; Martin et al., 2016; Matt et al., 2017). Here we investigated the functional connectivity of the praxis network in patients in early

stages of PD with and without dopaminergic medication. Critically, the patients investigated were not apraxic according to clinical standard evaluations but had an increased risk for developing praxis dysfunctions (Vanbellingen et al., 2012). Yet, global efficiency in the praxis network was increased in the patients and functional connectivity of the supramarginal gyrus as a hub in this network showed remarkable differences between the patients OFF and controls. These findings complement the results of our task-based activation analysis demonstrating hyperactivation in left-hemispheric praxis regions in the PD patients (Matt et al., 2017). FC analysis further revealed a spreading of the praxis network to right-hemispheric areas as well as a modulatory effect of dopaminergic therapy on the praxis network. The latter result may indicate that FC analyses are more sensitive to these subtle changes in functional organization of the brain than classical fMRI analysis.

4.1. Altered global efficiency in the praxis network in PD

Despite the fact that PD patients with and without dopaminergic therapy were not apraxic according to clinical apraxia tests, we observed a significant increase in GE within the praxis network with the bilateral SMG as hubs. The left inferior parietal lobe, in particular the left SMG, was proposed as a key area for transitive praxis functions as it is thought to contain long-term representations of object-related actions (Heilman et al., 1982; Binkofski and Buxbaum, 2013). Functional imaging studies consistently demonstrated the involvement of the left SMG during the performance of object- or tool-related actions (Vry et al., 2015; Imazu et al., 2007; Króliczak and Frey, 2009; Ohgami et al., 2004; Vingerhoets et al., 2011). Moreover, this area is a prominent part of the left-hemispheric "ventro-dorsal" route for visually triggered gesture production which originates from visual areas and projects via superior temporal areas and inferior parietal areas to the ventral premotor cortex (Binkofski and Buxbaum, 2013). Lesions affecting this stream, particularly inferior parietal areas, were shown to produce apraxic symptoms such as impairments in pantomime or tool use (Buxbaum et al., 2007; Goldenberg and Spatt, 2009; Hoeren et al., 2014). A recent arterial spin labeling study by Kübel et al. (2018) found

that the regional resting state cerebral blood flow of the left inferior parietal lobe was correlated with gestural performance in heathy controls and in PD patients. Interestingly, the perfusion levels were not significantly different between patients and controls indicating a relatively preserved function of the left inferior parietal lobe in PD patients (Kübel et al., 2018).

Our finding of an increased GE in the left-hemispheric SMG implies that the key role of this region for object-related actions within the praxis network is strengthened in the patients. While the GE of the praxis network in the controls showed a clear left-hemispheric dominance of regions supporting the ventro-dorsal stream including its projections to left inferior and middle frontal areas (Vry et al., 2015), the patients showed a more bilateral pattern of the praxis network GE. Potentially, this increased recruitment of the right hemisphere was driven by the interaction between the left SMG and its right-hemispheric homologue area leading to the emergence of the bilateral SMG as hubs in the patients. These findings suggest that the left-hemispheric ventro-dorsal route for gesture production is extended to the right hemisphere in the patients.

In contrast, the typically bilateral dorso-dorsal route connecting superior visual areas, superior parietal areas and the dorsal premotor cortex suggested to support the online control of visually guided movements (Binkofski and Buxbaum, 2013) showed similar GE values across the hemispheres in all groups suggesting no shift in the hemispheric dominance of this stream in the patients. The partial correlation analysis concerning the relation between SMG FC and behavioral scores revealed an interesting interaction between basal motor abilities and behavioral implications of the FC. The patients showed a positive relation between apraxia score and functional connectivity of the SMG to superior parietal areas that was found to be explainable by the UPDRS score. On the other side, the SMG FC to middle frontal areas showed to be significantly correlated with the apraxia score only after controlling for the parkinsonian symptoms. These results imply that basal motor difficulties might trigger an increased need for movement monitoring via the dorso-dorsal stream while the increased parieto-frontal connectivity seems to be unaffected by the motor symptoms.

4.2. Increased SMG functional connectivity in PD

Using the left pSMG as a seed, FC maps revealed increased connectivity to left frontal and to right-hemispheric areas in the patients, particularly in the OFF state. Compared to controls, patients OFF displayed an increased FC of the left SMG to contralateral areas of the praxis network – the right SMG and the right IFG – as well as an increased connectivity between the right pSMG and the right superior lateral occipital cortex. As the patients OFF had significantly lower praxis scores than the controls this apparent expansion of the predominantly left-hemispheric praxis network to right-hemispheric homologue areas does not seem to be beneficial. In addition, correlation analysis revealed that an increased right-hemispheric connectivity between the SMG and the IFG was significantly related to worse pantomime performance in the scanner. Contrary to the OFF state, a significant difference between patients in the ON state and the controls was found neither for the left nor the right SMG seed. Together with the non-significant difference of the patients ON compared to controls regarding the De Renzi apraxia score and the pantomime score a normalization of the praxis network connectivity and related behavioral performance induced by dopaminergic therapy seems reasonable. This finding is in line with previous resting state FC studies that have reported a normalization of aberrant sensorimotor networks due to dopaminergic medication in PD (Esposito et al., 2013; Kwak et al., 2012; Wu et al., 2009). Further, the comparison between the ON and OFF state demonstrated an increased SMG FC to the basal ganglia and primary motor areas due to dopaminergic therapy. The significant correlation of the connectivity between these areas with the De Renzi score implies that these connections are critical for gesture production

potentially by facilitating the propagation of object-related action representations stored in the SMG (Heilman et al., 1982) to areas of movement execution. Critically, the correlation between the De Renzi score and the FC of the SMG to basal ganglia and primary motor cortex remained significant after correcting for the UPDRS score. Thus, the relation between praxis abilities and SMG connectivity cannot be explained by basal motor abilities including their improvement due to medication. In contrast to the UPDRS score, a direct comparison of the apraxia and pantomime scores between the ON and OFF state did not reach significance, potentially due to the small sample size and the low variability in these scores. Yet, an investigation of PD patients with variable praxis difficulties did not find a benefit of dopaminergic therapy on apraxia scores either (Leiguarda et al., 1997). Thus, the dopaminergic facilitation of behavioral praxis functions might be subtle and restricted to early stages of PD.

4.3. Relation between functional connectivity and task-related activation

In the present study an increased FC between the left SMG as a key area of the praxis network and left frontal areas in the PD patients was found which fits well to the patients' frontal and inferior parietal hyperactivations found in the task-related activation analysis (Matt et al., 2017). Both task-related activation and FC analyses demonstrated that left frontal areas were particularly engaged in the OFF state. Opposed to the classical fMRI analysis that showed task-related hyperactivation predominantly in the left hemisphere, the FC analysis revealed a more bilateral praxis network in the patients. The increased FC between the left SMG and right-hemispheric areas was more prominent in the OFF state resulting a significant difference compared to the controls in the right SMG and the right IFG. In the task-related analysis these areas did not show any significant difference between the patients and controls indicating that this right-hemispheric extended praxis network in the patients is not exceedingly recruited during the task.

Further, we found a significantly increased FC of the bilateral SMG to basal ganglia and primary motor areas in the ON compared to the OFF state. In contrast, task-related differences for the praxis task between the ON and OFF state turned out to be not significant implying that the seed-to-voxel FC analysis might be more sensitive to detect differences induced by dopaminergic therapy. Potentially, dopaminergic medication exhibits a specific effect on low-frequency BOLD signal fluctuations as targeted in FC analysis (Kwak et al., 2012). However, task-related hyperactivation in the basal ganglia and in the primary motor cortex were found in the patients ON but not in the patients OFF, both compared to healthy controls. Thus, the increased functional coupling between the SMG and these motor areas as found in the seed-to-voxel analysis might be the underlying functional mechanism that promotes the task-related hyperactivation of motor areas in patients with dopaminergic therapy. Indeed, the coherent spontaneous activity fluctuations within a network assessed with FC analysis have been proposed to provide the context for neuronal responsiveness to external stimuli or task requirements (Vincent et al., 2006). The increased FC in the praxis network found in PD patients may provide the framework for the hyperactivations found in the classical fMRI approach. Some of the areas with an increased FC in the patients such as left frontal areas were indeed significantly stronger recruited during the task. In contrast, the increased FC in the right-hemispheric praxis network areas that were particularly evident in the patients OFF did not have an equivalence in the task-related activation analysis. However, these alterations might be a preparation for an increased need to compensate for praxis difficulties in later stages of the disease that might later result in an increased task-related recruitment of right-hemispheric praxis areas.

4.4. Limitations

Apraxia is defined as a cognitive motor disorder that is not explainable by elemental sensory or motor deficits. However, subtle motor difficulties related to tremor or bradykinesia might influence the

overall impression of a gesture and might bias the rating during the pantomime task and the apraxia tests. Indeed, controlling for the UPDRS score changed some results in the correlation between FC and behavioral scores and identified praxis related areas which are prone to basal motor confounds such as the superior parietal lobe. Yet, the increased FC of the SMG to motor execution areas remained significant after adjusting for the UPDRS suggesting that the dopaminergic modulation of the SMG-motor network connectivity is not driven by changes in parkinsonian symptoms. Due to methodological constraints of an MR study, we excluded PD patients with disabling tremor. This certainly limits the generalizability of this study to a certain extent, but would affect studies in more advanced stages of PD even more. Critically, apraxia is more common in later stages of the disease when parkinsonian neuropathology spreads towards cortical association cortices (Vanbellingen et al., 2012). However, at this stage motor symptoms are severe and might disguise apraxic difficulties (Zadikoff and Lang, 2005). Thus, it seems reasonable to investigate early phases of the disease with subclinical praxis symptoms. The differences between the patients and controls regarding the apraxia and pantomime scores were indeed subtle, with non-significant results partially owed to the low variability in these scores but also to the moderate sample size. To further elucidate the relation between functional connectivity, aberrant praxis related activation, and behavioral apraxic symptoms future studies with PD patients with and without clinical apraxia as well as longitudinal investigations are required.

5. Conclusion

While PD patients without dopaminergic therapy showed significantly reduced praxis performance combined with a significantly increased FC in right-hemispheric praxis related brain areas compared to healthy controls the praxis performance and the FC of the praxis network normalized in patients ON medication. Dopaminergic therapy induced an increased FC between the supramarginal gyrus and motor areas that might facilitate the propagation of long-term representations of object-related actions to motor execution areas. Besides the well-known effects on basal motor functions dopaminergic therapy seems to support higher-order cognitive motor functions such as praxis abilities and related networks – at least in early stages of PD.

Declaration of Competing Interest

None.

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