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Dopamine substitution alters effective connectivity of cortical prefrontal, premotor, and motor regions during complex bimanual finger movements in Parkinson's disease

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ABSTRACT

Bimanual coordination is impaired in Parkinson's disease (PD), affecting patients' quality of life. Besides dysfunction of the basal ganglia network, alterations of cortical oscillatory coupling, particularly between prefrontal and (pre-)motoric areas, are thought to underlie this impairment. Here, we studied 16 PD patients OFF and ON medication and age-matched healthy controls recording high-resolution electroencephalography (EEG) during performance of spatially coupled and uncoupled bimanual finger movements. Dynamic causal modeling (DCM) for induced responses was used to infer task-induced effective connectivity within a network comprising bilateral prefrontal cortex (PFC), lateral premotor cortex (lPM), supplementary motor area (SMA), and primary motor cortex (M1). Performing spatially coupled movements, excitatory left-hemispheric PFC to lPM coupling was significantly stronger in controls compared to unmedicated PD patients. Levodopa-induced enhancement of this connection correlated with increased movement accuracy. During performance of spatially uncoupled movements, PD patients OFF medication exhibited inhibitory connectivity from left PFC to SMA. Levodopa intake diminished these inhibitory influences and restored excitatory PFC to lPM coupling. This restoration, however, did not improve motor function.

Concluding, our results indicate that lateralization of prefrontal to premotor connectivity in PD can be augmented by levodopa substitution and is of compensatory nature up to a certain extent of complexity.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting tens of millions of people worldwide (Pringsheim et al., 2014). Clinical manifestations include motor-symptoms typically characterized by slowness of movement (bradykinesia), increased muscle tone (rigidity), resting tremor, and postural instability (Lang and Lozano, 1998). The hallmark of the underlying pathophysiology is a loss of dopaminergic neurons in the substantia nigra pars compacta. This deprivation of dopaminergic influence causes aberrant neuronal processing within the cortico-striato-thalamo-cortical circuit, consequently affecting oscillatory activity in the cerebral cortex (Cassidy et al., 2002; Hammond et al., 2007; Redgrave et al., 2010). Particularly, excessive beta synchronization exhibited by the subthalamic nucleus is thought to affect the basal ganglia-cortical circuitry (Brown, 2007; Weinberger et al., 2006). Increased synchronization in the beta band was also detected between primary motor cortex and subthalamic nucleus during movement and was associated with impaired motor control (Kühn et al., 2008).

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High-frequency deep brain stimulation as well as levodopa replacement therapy can suppress the pathological synchronization, thereby alleviating motor symptoms (Brown et al., 2001; Kühn et al., 2008; Priori et al., 2004). Furthermore, pathological firing of the basal ganglia entrains oscillations within supplementary motor area (SMA), lateral premotor cortex (lPM), as well as frontal areas in various frequency bands (Cassidy et al., 2002; Fogelson et al., 2006; Hammond et al., 2007; Kühn et al., 2008; Timmermann and Fink, 2011).

Integrity of the prefrontal-(pre-)motor network, however, is needed for the complex orchestration of neuronal information underlying bimanual coordination (Loehrer et al., 2016). PD patients commonly display impaired bimanual coordination, especially during complex movements, affecting their activities of daily living and quality of life (Johnson et al., 1998; Peto et al., 1995; Ponsen et al., 2006; Serrien et al., 2000). Numerous imaging studies investigating bimanual movements in PD described distinct alterations of activity as well as connectivity patterns within the prefrontal-(pre-)motor network. Specifically, studies employing fMRI showed that PD patients exhibited enhanced activity in right hemispheric M1 and bilateral lPM whereas SMA showed reduced activity (Haslinger et al., 2001; Sabatini et al., 2000; Wu et al., 2010). Although conflicting results regarding left hemispheric M1 activity exist, a meta-analysis of 283 patients showed activity of left M1 to be reduced depending on the movement studied (Herz et al., 2014a). Furthermore, coupling from prefrontal cortex (PFC) to SMA was shown to be reduced in PD (Rowe et al., 2002). This is thought to be an expression of impaired attention to action (Rowe et al., 2002) since PFC is crucial for online monitoring of movement (Durstewitz et al., 2000; Jueptner et al., 1997; Ullsperger and von Cramon, 2006).

Employing electroencephalography (EEG), Herz et al. were the first to show that levodopa restores oscillatory coupling between PFC and premotor areas in PD patients performing simple unimanual flexion-extension finger movements leading to better motor performance (Herz et al., 2014c). Cortical interactions, however, strongly depend on the movement studied, i.e. connectivity patterns in unimanual tasks significantly differ from those in bimanual movements (Aramaki et al., 2006a; Liuzzi et al., 2011; Loehrer et al., 2016).

As of today, very limited studies have investigated oscillatory coupling between prefrontal and (pre-)motor areas induced by bimanual movements in PD. Understanding pathophysiological alterations, however, is fundamental to develop new treatment strategies and to quantify disease progression. In the present study, patients with PD, both OFF and ON medication, as well as matched healthy controls performed complex bimanual motor tasks, while a 128-channel EEG was recorded. The paradigm comprised a simple and a more complex task in order to reveal weather task complexity influences prefrontal to premotor coupling patterns in PD patients and its modifiability by dopaminergic medication. Besides prefrontal to premotor connectivity we wanted to examine PD-related changes of interhemispheric crosstalk. To enhance differences in interhemispheric connectivity, we increased complexity of our tasks by spatially uncoupling finger movements. Dynamic Causal Modeling (DCM) for induced responses (Chen et al., 2008) was employed to investigate PD associated changes of effective connectivity within a network comprising bilateral PFC, lPM, SMA, and M1. Based on findings of our previous study and the results of Herz et al. we hypothesized that:

1. Compared to healthy controls, PD patients OFF medication exhibit problems performing bimanual finger movements, especially emerging when movements are spatially uncoupled.
2. Performance deficits in PD patients in the medication OFF are associated with changes of oscillatory prefrontal (PFC) to premotor (lPM and SMA) and interhemispheric M1-M1 couplings.
3. Levodopa substitution improves motor performance and modulates PFC to lPM and SMA as well as interhemispheric M1-M1 connectivity.

Material and methods

Participants

33 patients with idiopathic Parkinson's disease and 32 age-matched controls participated in this study. It has to be noted, that data of the control group has been published before. Here, healthy elderly subjects were compared with a younger group to reveal age-related changes (Loehrer et al., 2016). Inclusion criteria comprised a clinical diagnosis of PD according to the UK PD Brain Bank Criteria; with normal MR imaging; without deep brain stimulation (DBS) treatment; age $\leq$ 65 years; and no history of other neurological or psychiatric disease. Participants were right-handed as revealed by Edinburgh Handedness Inventory (Oldfield, 1971) and did not play any musical instruments regularly (<5 h per month, revealed by self-designed musical questionnaire). 17 patients and 4 controls were excluded subsequently (see "Data Acquisition and Preprocessing") leaving 16 patients (age 57.6 $\pm$ 6.0 years, 7 female) and 28 controls (age 60.9 $\pm$ 7.1 years, 12 female) for further analysis. Anti-parkinsonian medication was ceased 12 (standard L-dopa) and 24 h (dopamine receptor agonists, controlled release L-dopa) prior to the experiment. To quantify parkinsonian motor symptoms, a unified Parkinson's Disease Rating Scale (UPDRS) examination Part III (UPDRS-III) was conducted beforehand and results together with sociodemographic characteristics are outlined in Table 1. The study was approved by the local ethics committee (study-nr: 13–394) and participants gave written informed consent in accordance with the Declaration of Helsinki prior to study participation.

Table 1
Sociodemographic information of patients, severity of parkinsonism, standard medication, and side predominantly affected by PD symptoms. F = female; M = male.

Age (years)	Gender	UPDRS motor score OFF	UPDRS motor score ON	Disease Duration	L-dopa daily intake (mg)	Predominantly affected side
52	M	34	23	9	870	right dominant
51	M	19	4	4	1195	right dominant
48	F	17	7	3	395	right dominant
63	F	29	15	9	1025	right dominant
64	F	20	7	6	320	right dominant
60	F	29	20	7	630	right dominant
49	M	41	18	8	610	right dominant
57	F	22	10	2	300	right dominant
61	M	14	5	3	262	right dominant
64	M	10	4	6	420	right dominant
65	M	20	10	3	297	right dominant
61	F	20	11	6	1110	left dominant
58	F	16	9	2	280	left dominant
56	M	17	10	4	715	right dominant
47	M	25	15	5	257	right dominant
57	M	9	2	5	100	right dominant
Mean 57.06		Mean 21.38	Mean 10.63	Mean 5.13	Mean 549.13	
SD 6.04		SD 8.52	SD 6.10	SD 2.31	SD 342.48	

Experimental conditions and behavioral paradigm

In the present study, we employed the same behavioral task as in Loehrer and Nettersheim et al. (Loehrer et al., 2016). Participants were seated in a comfortable chair in an electrically and acoustically shielded chamber with their fingers placed on a response pad (Cedrus, San Pedro, USA). The response pad consisted of eight buttons, four for each hand, and a number was allocated to each finger (left and right thumb = 1; left and right index finger = 2; left and right middle finger = 3; left and right ring finger = 4). A computer screen was placed in front of the chair and it was ensured that participants had a sharp vision of instructions presented on the monitor. Participants received a comprehensive standardized instruction on the motor task. This was followed by a practice session. To avoid a learning bias between subjects, length of the practice session was determined by the participant's ability to accurately execute the requested trials. Our experimental design demanded strict synchronicity of bilateral tapping. Therefore, we additionally assessed if participants tapped simultaneously before they commenced the task. At the end of each practice session it was evident that movements were highly synchronous and a ceiling of errors had occurred in all participants.

Since PD patients had to execute the task ON and OFF medication we reduced the number of complexity levels to two (please see Loehrer et al., 2016 for a detailed description and graphic representation of our paradigm).

In short, two major tasks had to be performed:

(I) During performance of the task "temporally coupled and spatially coupled" (SC), participants had to execute a random sequence of four button presses, whereby left and right hand had to tap an identical sequence. SC condition consisted of 40 trials.

(II) The second task "temporally coupled and spatially uncoupled" (SU) requested strict synchronous tapping (temporally coupled) of different sequences (spatially uncoupled). First, participants were instructed to memorize a sequence of four button presses for one hand so that they could automatically enter this sequence. During the following task "SU", participants had to execute the memorized sequence with the requested hand while tapping a different sequence with the other hand. Sequences for the "non-memorizing" hand were presented on a screen and changed for each trial. Memorized sequences were performed with the right and left hand. Participants were randomly allocated to start SU condition with either the right or left hand. Two levels of complexity were determined based on tapping-direction and changes of direction of one sequence (SU level 1. A: 1|2|3|4, SU level 1. B: 4|3|2|1; SU level 2. A: 1|3|2|4 and SU level 2. B: 2|1|4|3). To avoid learning effects and maintain comparability between groups PD-patients executed SU levels 1 and 2 A in their clinical OFF state, whereas SU levels 1 and 2 B had to be executed in their clinical ON. Healthy controls had to sequentially execute both sequences of each complexity level. For the control group each SU level consisted of 20 trials. Altogether, healthy subjects therefore had to perform 80 trials of SU level 1 and 80 trials of SU level 2. To take into account that PD patients performed one half of the trials OFF medication and the other half ON medication, we slightly increased the number of sequences to 24. Consequently, PD patients had to perform 48 trials of SU level 1 and 48 trials of SU level 2 in both medication states (OFF and ON).

Measurements of PD patients were conducted in the morning after overnight withdrawal of dopaminergic medication (OFF). Motor symptom severity was assessed prior to EEG-examination using the UPDRS-III.

After performing the task in their OFF, patients received a 200 mg tablet of fast-release soluble levodopa (Madopar LT®, Roche, Basel, Switzerland). Thirty minutes after levodopa intake, the UPDRS-III score was reassessed. Medication ON was defined as an improvement in UPDRS-III scores of at least 15% compared to medication OFF. Patients with less than 15% improvement received additional doses of levodopa (100 mg) and were reassessed using the UPDRS-III until medication ON was reached.

Behavioral data analysis

Mean error rates for each condition were derived from the ratio of the number of correct trials to the overall number of trials. The time between presentation of the go-signal (i.e. switch of the presented sequence from red to green color) and the last button press was measured during the experiment and is referred to as *performance time*. Subsequent data analysis was performed using SPSS 22.0 (IBM, Armonk, USA). As a first step, arcsine transformed error rates and performance times for PD patients were separately entered into a repeated measures analysis of variance (ANOVA) with the within-subject factors "medication state" (OFF vs. ON), "complexity" (SC vs. SU level 1 vs. SU level 2) and "hand" (left vs. right, comparing memorized sequences that were pressed with left or right hand) as well as the between-subject factor "starting hand" (left vs. right). Secondly, error rates and performance times for PD patients (in the OFF and ON state) and control subjects were compared within a mixed design ANOVA for the factors "group" (PD OFF vs. Control and PD ON vs. Control) and "complexity" (SC vs. SU level 1 vs. SU level 2) using Greenhouse-Geisser correction for non-sphericity.

Data acquisition and preprocessing

Magnetic resonance imaging

Prior to EEG measurements T_1-weighted structural magnetic resonance images (MRI) were acquired using a 3D-modified driven equilibrium Fourier transform sequence at 3 T, repeat time 1930 ms, echo time 650 ms, flip-angle = 18°, and slice-thickness = 1,25 mm.

Electroencephalography

An EEG-cap (Easy-cap, Herrsching, Germany) with 128-electrodes mounted in a spherical array (according to the 5 percent electrode system) was placed upon the subject's head and correct positioning was ascertained by measuring the electrodes distances to nasion, inion and preauricular fiducials. EEG-data were recorded using a 128-channel EEG system (Brainproducts, Gilching, Germany) after assuring that electrode impedances were below 10 kΩ. An electrically shielded room ensured low noise levels. EEG-signals were amplified, band-pass filtered from 0.1 to 1000 Hz, and digitized at a sampling rate of 5000 Hz. Trials with errors or incompletely executed trials were excluded from further analysis. Subsequently, data were transformed to SPM data-format (SPM12, update revision number 6225 (Wellcome Trust Centre for Neuroimaging, London, UK)). In SPM, EEG-data were epoched to single trials, high-pass filtered (1 Hz), downsampled to 250 Hz using an anti-aliasing filter, low-pass filtered (48 Hz), and baseline-corrected employing a prestimulus interval of 600 ms. Furthermore, we visually inspected all trials and excluded those, which were obviously not artifact-free. To ensure the largest possible number of trials for DCM analysis and increase reliability of the results the different complexity levels of the spatially uncoupled task were merged to a single SU condition. 12 patients and three control subjects failed to have the minimum number of five correct and artifact-free trials per condition. Four patients and one healthy participant could not complete MRI scans due to claustrophobia. One patient got severely nauseous after intake of 200 mg of levodopa and could not perform the task in the ON-state. These participants were therefore excluded from further analysis. Due to technical issues, trials of one subject's SC condition were not recorded. Since SU condition of this patient complied with our standards, we, however, refrained from excluding the patient from further analysis.

Source specification

Similar to other studies investigating cortical activity in motor tasks

using functional magnetic resonance imaging (fMRI) we defined a core motor network (Haslinger et al., 2001; Rowe et al., 2010; Sabatini et al., 2000). This network comprised SMA as well as bilateral M1, lPM, and dorsolateral PFC. The coordinates were adopted from previous PD studies employing EEG (Herz et al., 2014b, 2014c).

To examine whether sources specified by MNI coordinates were consistently activated during motor execution, we co-registered electrode positions with individual MRIs and performed source localization using SPM. Here, we calculated a forward model (Symmetric Boundary Element Method, BEM) for each subject employing a cortical mesh with 8196 vertices. We inverted source activity for the active time window of −100 to 360 ms using the minimum norm solution as implemented in SPM for correctly performed trials. A 100 ms prestimulus baseline period was used to reference and compare inversion results employing t-statistics. Afterwards, p-values were calculated for clusters of activated voxels using family wise error (FWE) correction thresholded at $< .05$ at the cluster-level. A deviation of ±10 mm from our ROIs (for MNI coordinates please see Supplementary Table 1) was allowed for each source to account for the low spatial resolution of EEG source reconstruction (Herz et al., 2012). Sources were confirmed to be active in participants used for analysis and results of source analysis of a representative patient can be found in Supplementary Fig. 1.

Dynamic causal modeling

As in our previous study (Loehrer et al., 2016), in the remaining 16 PD patients and 28 control subjects we performed DCM for induced responses as introduced by Chen et al. (Chen et al., 2010, 2009, 2008).

Spectral densities were computed with a Morlet wavelet transform using a wavelet number of 7 (Chen et al., 2010) and a bandwidth from 4 to 48 Hz to avoid a 50 Hz electric current artifact and to include low frequencies. Baseline used to compute the time-frequency spectra included the first 1/8 samples of the peristimulus time window (in this case 57.7 ms), which corresponds to the DCM default settings. We set the time-window from -100 ms before to 360 ms after the first button press (physiological input). For a thorough explanation of this approach please see Loehrer et al., 2016. The power spectra of the 7 sources for each subject were reduced in their dimensionality by singular value decomposition (SVD) to 6 principal frequency modes, which reduced computational load (please see Supplementary Fig. 2 for an illustration of frequency modes of a representative patient). Similarity of observed time-frequency spectra and spectral responses as predicted by our models was confirmed by visual inspection of the whole interval.

Definition of model space

The model space was adopted from Loehrer and Nettersheim et al. (Loehrer et al., 2016). It was comprised of eighteen models that were inverted using DCM (Supplementary Fig. 3). In Models 1 to 9 coupling within and between sources could be modeled within and across frequencies (linear and nonlinear intrinsic and extrinsic connections (INEN)). Models 10 to 18 featured equivalent model structures and extrinsic coupling was allowed to be linear and nonlinear. Intrinsic couplings, however, were linear (ILEN) (Chen et al., 2010; Herz et al., 2012). Furthermore, models differed in terms of PFC to premotor and interhemispheric M1-M1 connections. PFC was connected to lPM (models 1, 4, 7; Lateral-Family), SMA (models 2, 5, 8; Medial-Family), or both lPM and SMA (models 3, 6, 9; Bilateral-Family). M1-M1 connections were allowed to be reciprocal (models 1–3), from left M1 to right M1 only (models 4–6), or from right M1 to left M1 only (models 7–9). The input to the network was set to SMA which was found to be an appropriate candidate for external input in EEG as well as MEG by previous studies (Bonstrup et al., 2016; Chen et al., 2012; Loehrer et al., 2016). Note that due to its medial position on the cortex, bilateral SMA was considered as one single source in all models.

After model specification, Bayesian model inversion was performed for $M = 18$ models, a total of $N_1 = 16$ patients and $O_1 = 6$ conditions (SC, SU left hand and SU right hand, OFF and ON medication), as well as $N_2 = 28$ control subjects and $O_2 = 3$ conditions (SC, SU left hand and SU right hand). Overall, $M \times (N_1 \times O_1 + N_2 \times O_2) = 3240$ DCMs were inverted. Here, parameters are estimated by minimizing the relative entropy defined via the data and model outcome using an expectation maximization algorithm (Chen et al., 2008).

Bayesian model selection

Bayesian model selection (BMS) enables the researcher to obtain the probability of a model given the observed data and accounting for its complexity (Penny et al., 2004). Using the same approach as in Loehrer and Nettersheim et al. (Loehrer et al., 2016), we performed an extensive model comparison employing family level inference for random effects to focus on model structure of nested models and to avoid model dilution as described in (Penny et al., 2010). In a first step, we tested models of the INEN-Family against models within the ILEN-Family. Subsequently, models of the winning family were used to compare the Lateral-, Medial-, and Bilateral-Family. In a last step, BMS for random effects was used on a partitioned model space to infer parameter estimates (Penny et al., 2010; Stephan et al., 2010, 2009). Here, models are selected according to the highest posterior exceedance probability, i.e., the highest probability compared to any other model considered (Litvak et al., 2011; Stephan et al., 2010). To evaluate whether handedness influenced model selection we performed BMS for left and right SU conditions separately.

Inference on coupling parameters

Results of our behavioral analysis and our model selection prompted us to merge left and right SU conditions which avoided excessive data output. Coupling parameters were obtained from the model describing the data best (Model 3) and represent the frequency-to-frequency coupling for the respective connection. Here, individual coupling parameters of significant connections of interest were averaged for the respective frequency band (δ-band (1–3 Hz), θ-band (4–7 Hz), α-band (8–12 Hz), β-band (13–29 Hz) und γ-band (30–80 Hz); classification of frequency bands adopted from Timmermann et al. (2007). Coupling parameters were extracted, smoothed with a Gaussian kernel (full-width half-maximum of 6 Hz) and analyzed with conventional SPM analysis. F- and t-statistics were employed to calculate statistical parametric maps for each connection and different conditions. Significant frequency-specific coupling is reported for p-values $< .005$ (uncorrected) for single connections (Chen et al., 2010). To verify that connections found to be significant in SU condition were indeed stronger compared to SC condition we analyzed a DCM with a model structure equivalent to Model 3 modeling SU condition as a modulation of SC condition using a B-matrix. Here, we reported significant connections for p-values $< .005$ (uncorrected) for single connections. In order to reveal statistical dependencies between significant couplings and motor performance we used Spearman's rank correlation coefficient. Here, coupling parameters were averaged across respective frequency bands. Ratios for comparison between ON and OFF were obtained by dividing a subject's mean ON scores by mean OFF scores. All ratios are reported in arbitrary unit. We controlled the false discovery rate using Benjamini-Hochberg method to correct type I errors for multiple comparisons and report corrected p-values for significant correlations. Between group effects were determined by calculating F- and t-statistics for significant connections reporting p-values $< .05$ family wise error (FWE) corrected. Here, we contrasted PD OFF vs. Control and PD ON vs. Control using two-sample t-tests, and PD OFF vs. PD ON employing paired *t*-test. To ensure that changes in oscillatory coupling were not confounded by power differences between groups we compared time-frequency spectra of all groups, using t-tests.

Table 2
Mean numbers of trials after exclusion.

Artifact-free and correctly performed trials [mean (standard deviation)]	SC	SU 1	SU 2
PD OFF	25.44 (10.91)	21.81 (7.86)	19.00 (10.30)
PD ON	31.44 (4.55)	22.63 (7.32)	16.81 (8.99)
Control	28.86 (7.06)	46.21 (13.80)	42.32 (14.22)

Note: To ensure the largest possible number of trials and make the results more reliable, for DCM analysis SU 1 and SU 2 were merged to a single SU condition.

Results

The average numbers of artifact-free and correctly performed trials that were used for DCM analysis are indicated in Table 2.

Behavioral results

Results of behavioral analysis are displayed in Fig. 1. There was no significant difference in mean error rates between PD patients in the OFF and ON state. However, ON medication PD patients had significantly faster performance times than OFF medication ($p = .04$, Table 3). Examining conditions separately, in SC condition error rates and performance times of PD patients in the OFF and ON state did not show any significant distinctions ($p > .05$). Though, in SU condition behavioral analysis revealed the same significant performance differences between the groups as for the whole task, i.e. ON medication patients performed significantly faster than OFF medication ($p = .046$) and error rates did not differ significantly.

PD patients OFF medication made significantly more mistakes than healthy participants (Greenhouse–Geisser $F(1, 42) = 8.166$, $p = .007$, partial $\eta^2 = .163$). However, performance times did not significantly differ between the groups (Greenhouse–Geisser $F(1, 42) = .624$, $p = .434$, partial $\eta^2 = .015$). Whereas comparison of unmedicated PD patients and control subjects revealed a significant difference for error rates, there were no statistically significant interactions between conditions and groups, neither for error rates (Greenhouse–Geisser $F(1.305, 54.80) = .003$, $p = .983$, partial $\eta^2 < .001$) nor for performance times (Greenhouse–Geisser $F(1.416, 59.47) = .709$, $p = .450$, partial $\eta^2 = .017$). Performances of unmedicated PD patients and healthy controls were additionally compared by only considering the first conditions (i.e. SC and SU 1) to ensure that constantly testing PD patients OFF medication in the very beginning of the experiment did not confound the detected group differences. This supplementary comparison revealed the same results as for the whole trail: unmedicated PD patients made more errors than healthy participants (Greenhouse–Geisser $F(1, 42) = 4.875$, $p = .033$, partial $\eta^2 = .104$), whereas performance times did not differ significantly (Greenhouse–Geisser $F(1, 42) = .342$, $p = .562$, partial $\eta^2 = .008$). There were no statistically significant interactions between conditions and groups, neither for error rates (Greenhouse–Geisser $F(1, 42) = .166$, $p = .686$, partial $\eta^2 = .004$) nor for performance times (Greenhouse–Geisser $F(1, 42) = 1.207$, $p = .278$, partial $\eta^2 = .028$). Comparison of PD patients ON medication and control subjects revealed

Table 3
Group comparison of mean error rates and performance times.

	Mean error rate [% (standard deviation %)]	Mean performance time [s (standard deviation s)]
PD OFF	43.34 (24.50)	2.71 (0.64)
PD ON	38.86 (17.58)	2.47 (0.69)
Control	29.21 (19.72)	2.58 (0.65)

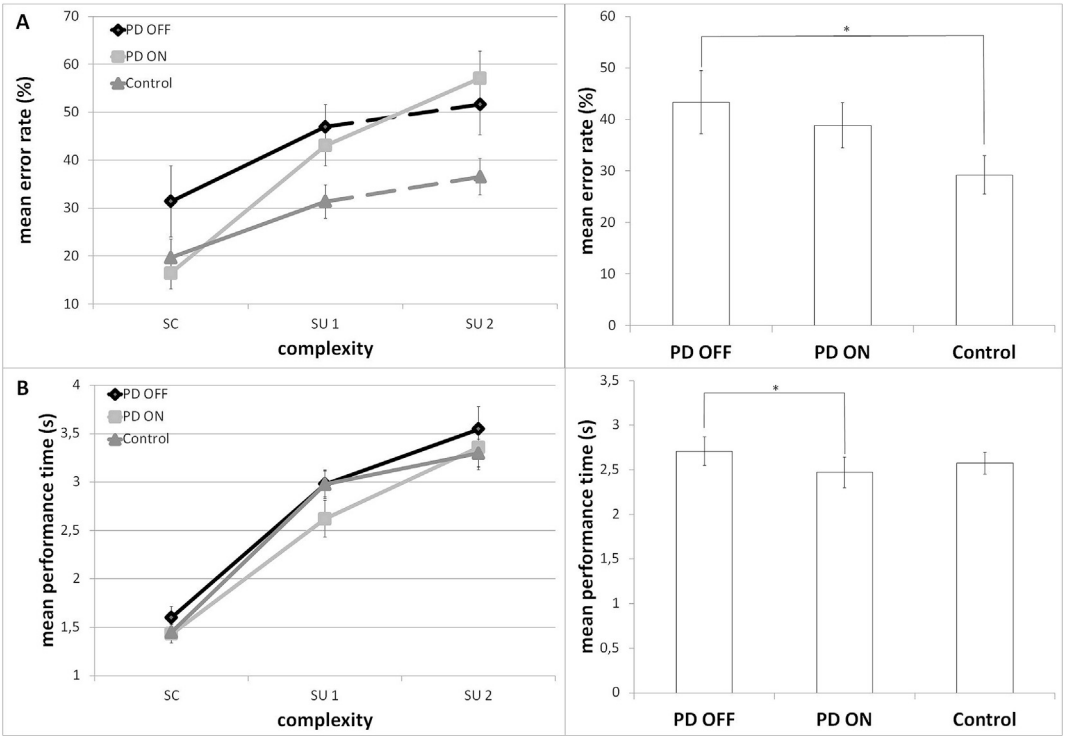

Fig. 1. A: Mean error rates and standard error of the mean for the different complexity levels. In all groups error rates were significantly higher in SU 1 as compared to SC condition. Additionally, PD patients ON medication had significantly higher error rates in SU 2 than in SU 1 condition (left side). Mean error rates significantly differed between PD patients OFF medication and control group (right side). **B:** Mean performance time and standard error of the mean for the different complexity levels. All groups performed significantly slower the more complex the task (left side). Furthermore, performance time differed significantly between PD patients ON and OFF medication (right side). On the left side, significant differences between conditions are shown as solid lines and missing significances are highlighted by dashed lines. On the right side, significant group differences are denoted by a starlet.

Table 4
Comparison of mean error rates and performance times for different complexity levels.

Mean error rate [% (standard deviation %)]	SC	SU 1	SU 2	p-value SC vs. SU 1	p-value SU 1 vs. SU 2
PD OFF	31.40 (29.61)	46.95 (18.51)	51.68 (25.39)	<.001	.377
PD ON	16.43 (12.96)	43.06 (16.99)	57.08 (22.80)	<.001	.002
Control	19.68 (20.44)	31.39 (18.57)	36.57 (20.16)	.004	.087
Mean performance time [s (standard deviation s)]					
PD OFF	1.60 (0.45)	2.98 (0.53)	3.55 (0.93)	<.001	<.001
PD ON	1.43 (0.38)	2.62 (0.75)	3.36 (0.92)	<.001	<.001
Control	1.45 (0.41)	2.98 (0.78)	3.30 (0.76)	<.001	<.001

a statistically significant interaction between conditions and groups for error rates (Greenhouse–Geisser $F(1.645, 69.08) = 7.008$, $p = .003$, partial $\eta^2 = .143$), but not for performance times (Greenhouse–Geisser $F(1.595, 67.01) = 2.640$, $p = .090$, partial $\eta^2 = .059$). With regard to the whole task neither error rates (Greenhouse–Geisser $F(1, 42) = 3.616$, $p = .064$, partial $\eta^2 = .079$) nor performance times (Greenhouse–Geisser $F(1, 42) = .351$, $p = .557$, partial $\eta^2 = .008$) differed significantly between the groups. However, PD patients ON medication had significantly higher error rates than control subjects in SU conditions, whereas there was no difference in SC condition (SC: $p = .738$, SU 1: $p = .041$, SU 2:

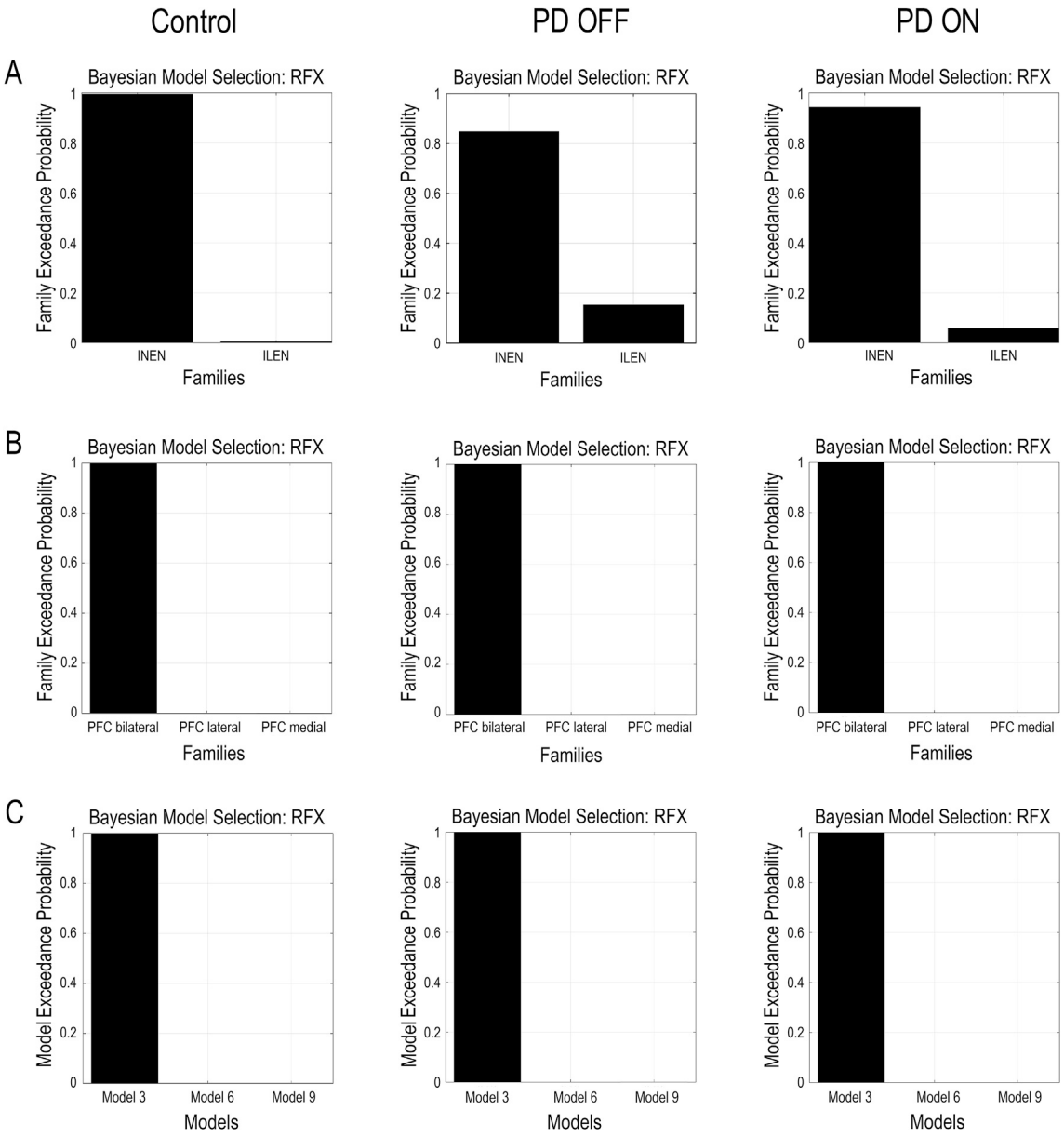

Fig. 2. Bayesian model selection (BMS). **A:** Family level comparison of INEN- and ILEN-family. In all groups, the INEN-model-family, characterized by linear and nonlinear couplings in intrinsic and extrinsic connections, described data better **B:** Comparison of PFC-families. The "PFC-bilateral" model-family, characterized by PFC to lPM *and* SMA connectivity, was highly preferred over "PFC-medial-family" (PFC-SMA connection only) and "PFC-lateral-family" (PFC-lPM connection only). **C:** BMS of INEN/PFC bilateral family. Models 3, 6, and 9 differed in terms of M1-M1 connectivity (Model 3: reciprocal M1-M1 connections; Model 6: left to right M1-M1 connection; Model 9: right to left M1-M1 connection). Model 3 highly outranked the other models.

p = .007).

Neither the factors "hand" nor "starting hand" had significant effects on error rates or performance times.

In all groups error rates were significantly higher in SU conditions than in the SC condition, whereas significant differences of error rates between SU 1 and 2 conditions could only be observed in PD patients ON medication. Performance times significantly increased with rising complexity, i.e. there were significant differences between SC and SU 1, as well as between SU 1 and 2 conditions in all groups (Table 4).

Bayesian model selection and model fit

Results of BMS were consistent in all groups (Fig. 2). Family level inference for random effects strongly favored a model family that allowed for cross- and within-frequency coupling in intrinsic as well as extrinsic connections (INEN, Fig. 2A). Within the INEN model-family, family level inference strongly favored the "PFC bilateral" model-family, allowing connections between PFC and lPM as well as between PFC and SMA (Fig. 2B). Finally, we compared Model 3, 6, and 9 representing the "PFC bilateral" model-family, which differed with respect to M1-M1 connectivity. BMS for random effects revealed that Model 3, allowing reciprocal M1-M1 couplings, described the data best (Fig. 2C). Exceedance probabilities were almost 1 for all groups and all conditions. For this reason, second level analysis of coupling parameters was based on this model. Model 3 explained approximately 99% of the original spectral variance (PD OFF: 99.07% ± 0.49; PD ON: 99.15% ± 0.63; Control: 99.33% ± 0.48). Additionally, visual inspection confirmed that observed spectral responses of the whole trial were accurately predicted by Model 3 (time-frequency spectra of a representative subject are shown in Supplementary Fig. 4).

Between-group comparison of time-frequency spectra showed that power at 15 Hz of PD patients ON medication was significantly stronger in left M1 as compared to control subjects (Supplementary Fig. 5). Apart from this, no significant distinctions in the studied regions or frequency bands were detected, demonstrating that observed differences in oscillatory coupling were not undermined by divergence in power.

Task-induced changes in effective connectivity

Oscillatory couplings induced by motor onset were statistically evaluated and significant reciprocal M1 to M1 and PFC to premotor frequency-to-frequency couplings are reported in Table 5. In all groups linear, i.e. within frequency, as well as nonlinear coupling (between frequencies) could be detected.

Oscillatory coupling between left and right primary motor cortices

With respect to M1-M1 coupling, we found an influence of left hemispheric M1 on its right hemispheric counterpart to be consistently present in all groups during performance of SC condition (Fig. 3). Particularly, controls exhibited γ-γ-coupling whereas unmedicated PD patients expressed β-γ coupling and, after administration of levodopa, γ-β coupling. Influence of left to right M1 coupling was negative in the control group, whereas it was positive in PD patients OFF and ON medication. Positive right to left hemispheric M1 coupling was present in medicated PD patients only. In SU condition, only controls exerted interhemispheric M1 coupling. PD patients did not express any significant couplings in this condition.

Effective connectivity from prefrontal cortex to premotor regions

Healthy subjects exhibited significant positive left PFC to left lPM

Table 5
Significant frequency-to-frequency couplings of the winning model (Model 3).

Connection	Frequency bands (peak)	p-Value (uncorrected (FWE-corrected))	Influence	Significant group-effect		
				vs. Control	vs. OFF	vs. ON
Condition: SC Control						
left PFC → left lPM	α-β (9–14 Hz)	<.001 (.028)	+		X	X
left M1 → right M1	γ-γ (43–45 Hz)	.002 (.173)	–			
Condition: SC PD OFF						
left PFC → left lPM	γ-α (35–8 Hz) γ-γ (37–46 Hz) α-β (12–21 Hz)	.001 (.148) .001 (.150) .002 (.307)	+ + -			
left M1 → right M1	β-γ (18–48 Hz) β-γ (14–38 Hz)	.001 (.191) .003 (.335)	+ +			
right PFC → right lPM	θ-θ (5–6 Hz) θ-γ (5–30 Hz)	.001 (.121) .004 (.419)	+ +	X		
Condition: SC PD ON						
left PFC → left lPM	γ-γ (45–45 Hz)	<.001 (.060)	+	X		
left M1 → right M1	γ-β (37–13 Hz)	.002 (.260)	+			
right M1 → left M1	β-β (13–23 Hz)	.003 (.329)	+			
right PFC → right lPM	α-α (11–9 Hz)	.002 (.236)	+	X		
Condition: SU Control						
left PFC → left lPM	γ-γ (41–45 Hz) α-θ (9–7 Hz)	<.001 (.038) < .001 (.040)	+ +		X	X
right PFC → SMA	γ-β (46–22 Hz)	.002 (.165)	+			
right PFC → right lPM	θ-θ (7–4 Hz)	.002 (.177)	+			
left M1 → right M1	β-β (14–25 Hz) θ-β (5–14 Hz)	<.001 (.041) .001 (.083)	- -		X	
right M1 → left M1	β-θ (19–4 Hz)	<.001 (.042)	+			X
Condition SU PD OFF						
left PFC → SMA	β-β (22–18 Hz)	<.001 (.049)	–	X		X
right PFC → right lPM	β-α (13–12 Hz) β-γ (18–34 Hz)	<.001 (.033) .002 (.199)	+ -			
Condition: SU PD ON						
left PFC → left lPM	β-β (17–19 Hz)	.002 (.245)	+		X	
right PFC → SMA	β-β (29–17 Hz)	.003 (.256)	+			

X Significant between group effect for respective condition vs. indicated group.
Note: F-statistics were performed to calculate statistical parametric maps for each connection. T-statistics were employed to differentiate, whether a coupling was positive (+) or negative (−), i.e., if the respective connection induced an increased or decreased power in the target region. Couplings for single connections are reported for p-values < .005 (uncorrected). For reasons of transparency FWE corrected p-values are also shown. F- and t-statistics were used to calculate significant between group effects, reported at p < .05 (FWE corrected).

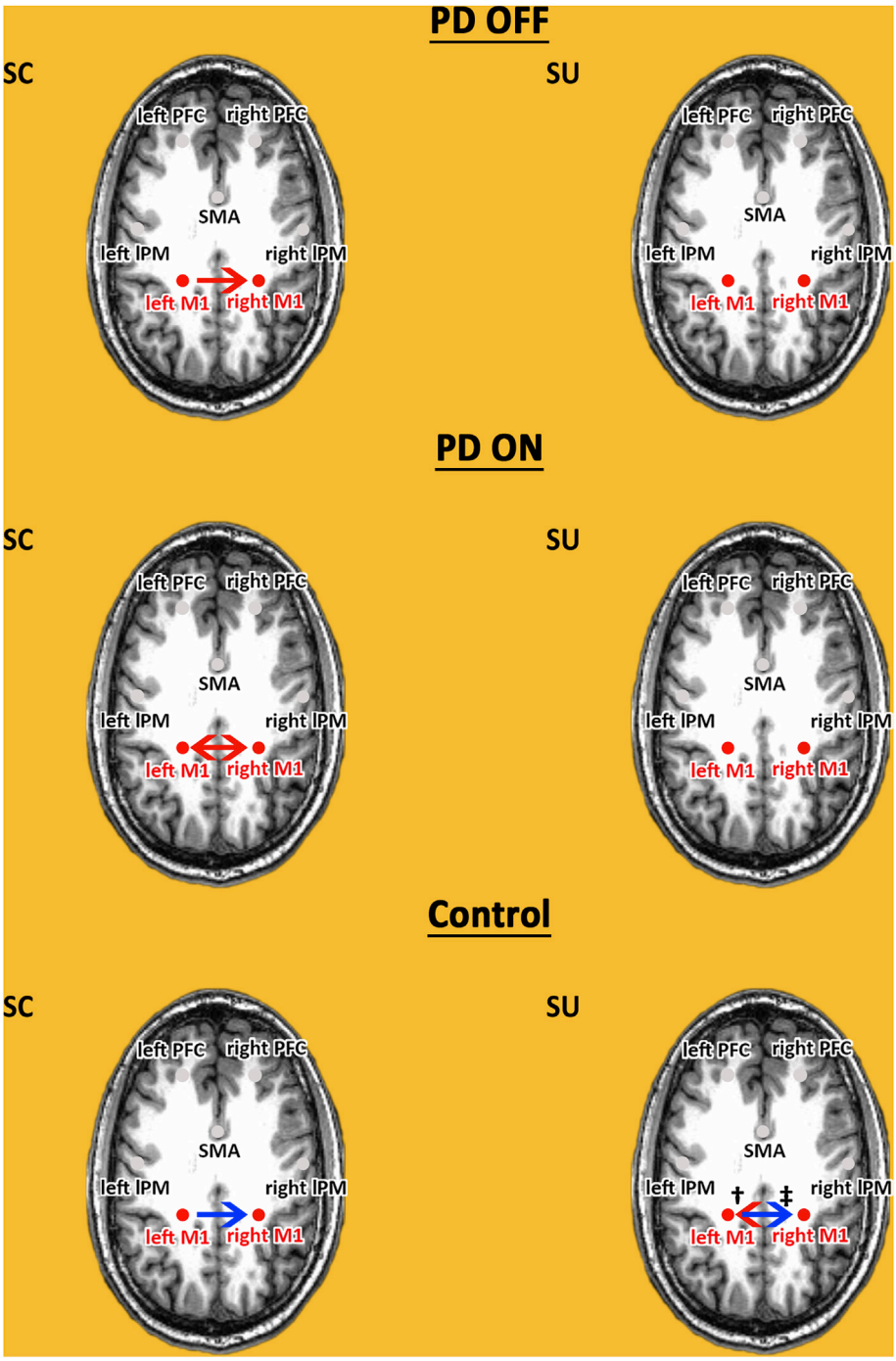

Fig. 3. Task induced frequency-specific coupling between left and right M1. Red arrows denote positive couplings, blue arrows denote negative couplings. ‡: connection significantly stronger as compared to PD OFF; †: connection significantly stronger as compared to PD ON. (Illustrations are for schematic purposes only, i.e., coordinates of the regions are not displayed correctly.)

coupling in all conditions (Fig. 4). In the SC condition, identical connectivity patterns (positive left PFC-lPM coupling) within higher frequency bands could be revealed for PD patients OFF and ON medication. In medicated PD patients, γ-γ coupling between left PFC and lPM was modulated significantly stronger compared to controls. Healthy participants exhibited α-β-coupling between left PFC and lPM that was stronger as compared to PD patients ON and OFF medication. Right PFC to right lPM coupling was positive and present in PD patients only. In SU condition, PD patients in the OFF state failed to express left PFC to lPM coupling. Rather, patients in their clinical OFF exhibited negative β-β coupling between left PFC and SMA which was modulated significantly stronger compared to controls and medicated patients. In PD patients ON medication, positive left PFC to lPM coupling was restored within the β-band. This connection was expressed significantly stronger compared to unmedicated patients. Furthermore, distinct differences in right PFC to premotor coupling were identified between groups. Positive right PFC to lPM and SMA coupling was present in controls, whereas there were significant positive as well as negative couplings from right PFC to right lPM in PD patients OFF medication. This connectivity disappeared in the ON and positive right PFC to SMA coupling could be revealed.

Second level analysis of DCMs contrasting SU against SC condition revealed significant left PFC to SMA coupling in the OFF as well as left

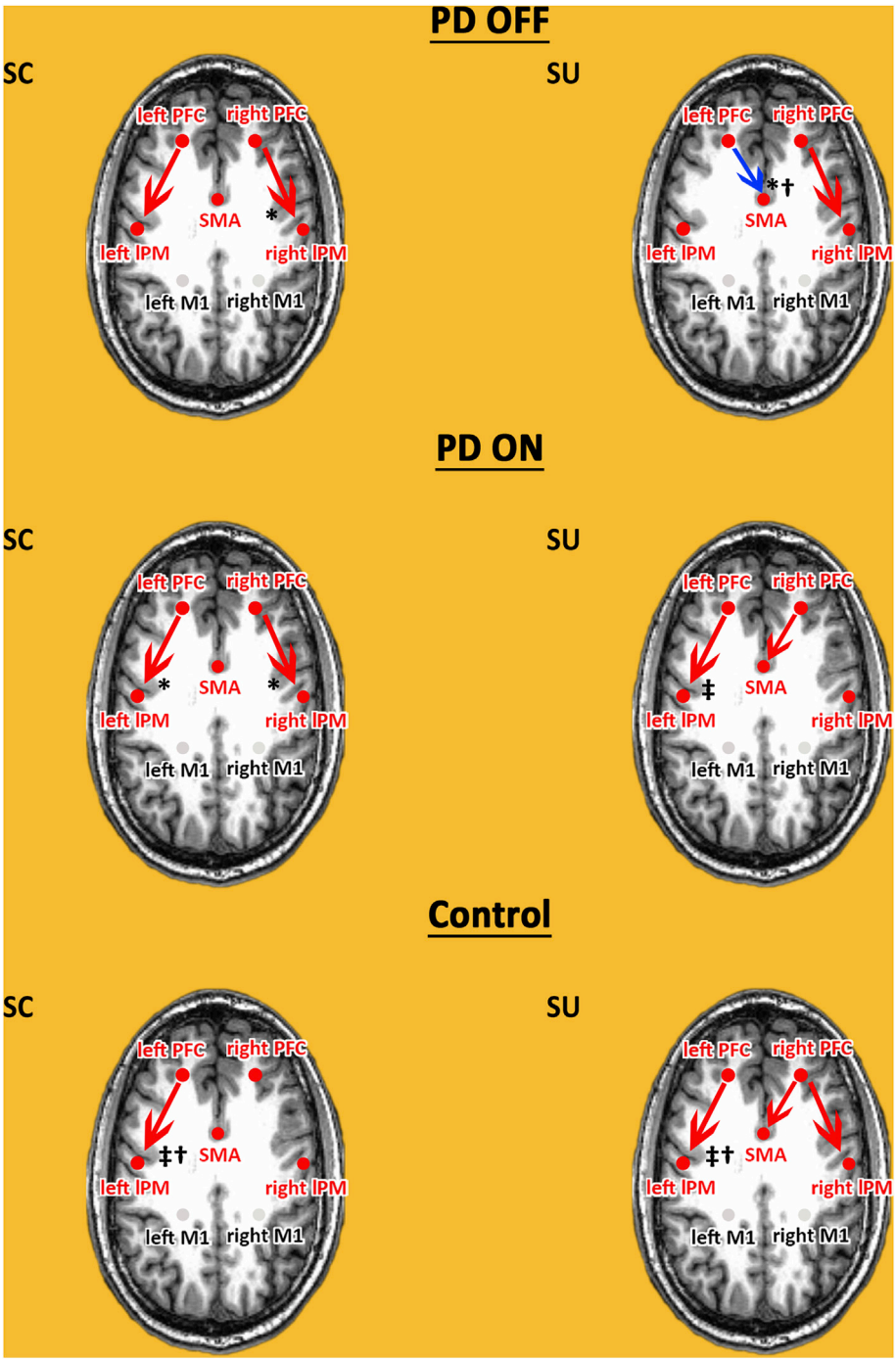

Fig. 4. Effective connectivity from prefrontal cortex (PFC) to premotor regions. Red arrows denote positive couplings, blue arrows denote negative couplings. *: connection significantly stronger as compared to control subjects ‡: connection significantly stronger as compared to PD OFF; †: connection significantly stronger as compared to PD ON. (Illustrations are for schematic purposes only, i.e., coordinates of the regions are not displayed correctly.)

PFC to lPM coupling in the ON that occurred within the same frequency bands as compared to the contrast of SU condition versus baseline (Supplementary Table 2).

Correlation between oscillatory coupling and motor function

Correlations between oscillatory coupling and motor function revealed distinct alterations of connectivity patterns that underlie motor impairment in PD and are depicted in Fig. 5, reporting corrected p-values. There was a significant correlation between left to right M1 connectivity and performance time in the SC condition in unmedicated PD patients (rho = .639, p = .047). The stronger β to γ cross-frequency coupling was expressed, the more pronounced were deficits in motor performance. Furthermore, levodopa-induced alterations of left PFC to lPM coupling correlated negatively with error rates (rho = -.657, p = .047). Here, stronger within-frequency γ-γ coupling from PFC to lPM in the ON compared to the OFF was associated with reduced error rates. Additionally, UPDRS values correlated positively with error rates (rho = .738, p = .014) in the clinical ON.

Discussion

In the present study, we investigated the causal interplay between

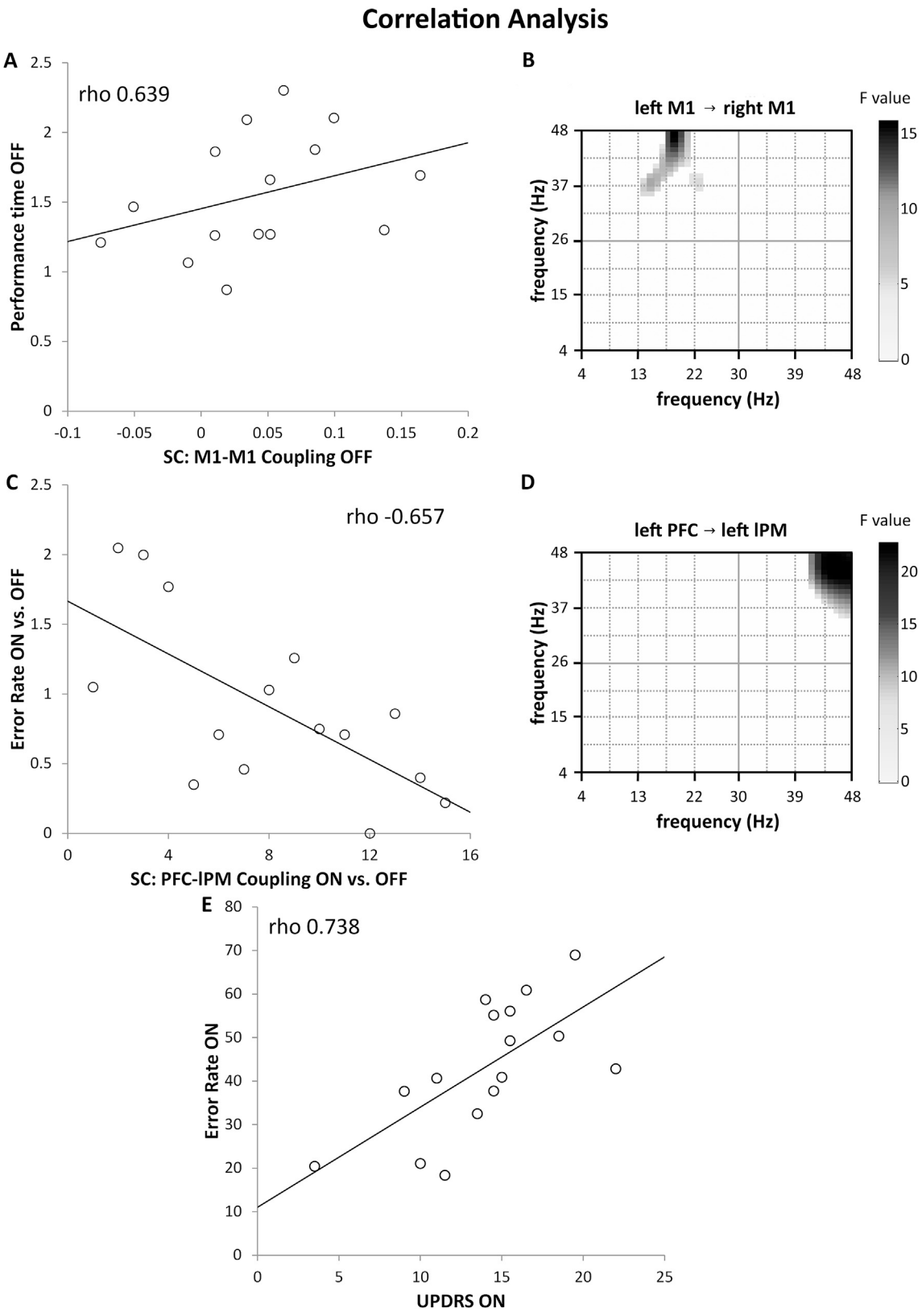

Fig. 5. Correlation Analysis. **A:** Significant β-γ-cross-frequency coupling between left and right primary motor cortex was present in SC condition of PD patients. The stronger this excitatory connection was expressed, the more prolonged was performance time (rho = .639, p = .047). **B:** Frequency-frequency plots of left M1 to right M1 connectivity in SC condition. **C:** Negative correlation between left PFC to lPM γ-γ-coupling and error rates in the ON vs. OFF state in the SC condition. The more levodopa enhanced PFC-lPM coupling compared to the OFF, the less errors were made (rho = -.657, p = .047). **D:** Frequency-frequency plots of left PFC to lPM connectivity in SC condition **E:** UPDRS values for patients on medication correlated with total error rates (SC plus SU condition). The higher UPDRS scores were, the more mistakes were made (rho = .738, p = .014).

prefrontal, premotor, and motor areas in a bihemispheric core-motor-network using dynamic causal modeling. In DCM for induced responses, coupling between two regions is characterized as a function of source and target frequencies. Hence, positive coupling indicates that the source region has an excitatory effect on the target region, i.e. it increases frequency-specific power whereas negative coupling indicates inhibitory effects, i.e. reduces frequency-specific power. It is important to note, however, that enhancement of frequency specific power does not necessarily translate to stronger activation of a region as measured by fMRI.

Behavioral performance

In PD patients OFF and ON medication as well as control subjects, error rates and performance times significantly increased with rising task complexity. In line with this, it has been demonstrated repeatedly, that especially PD patients but also healthy subjects have more difficulties performing uncoupled, e.g. anti-phasic, than coupled, e.g. phasic, bimanual movements (Almeida et al., 2002; Johnson et al., 1998; Ponsen et al., 2006; Serrien et al., 2000; van den Berg et al., 2000; Wu et al., 2010). With regard to our study, the significant decline of motor performance in all groups proofs that our predefined complexity levels, indeed, differed in terms of task difficulty.

Medicated PD patients performed tasks significantly faster than patients OFF medication. This effect especially emerged when performing spatially uncoupled, i.e. more complex, bimanual movements. In line with this, it has been shown that dopaminergic medication predominantly enhances movement speed (Brown and Almeida, 2011; Espay et al., 2011; Müller et al., 2013).

Nevertheless, levodopa substitution was also associated with better and more accurate motor coordination (Fattapposta et al., 2002; Park et al., 2014). In our study, direct comparison of patients in the OFF and ON state did not reveal significant differences of error rates. However, PD patients OFF medication made significantly more mistakes than healthy participants, whereas such difference could no longer be observed after levodopa substitution. This finding supports the idea that levodopa substitution not only improves velocity but may also increase movement accuracy. Interestingly, comparison of PD patients ON medication with healthy participants revealed an interaction between conditions and groups for error rates. In the SC condition no significant distinction of error rates between medicated PD patients and control subjects could be detected. However, during performance of spatially uncoupled movements PD patients in the ON state made significantly more errors than the control group. Huang and colleagues showed that levodopa substitution is associated with higher error rates in the moving-dots task when task complexity varied (Huang et al., 2015). The authors concluded that dopaminergic medication may disturb the accumulation of sensory information and, therefore, impair perceptual decision making in PD patients. Likewise, in our study dopamine-induced deficits in integration of sensory information and decision making may have contributed to the pronounced increase of error rates in medicated PD patients with rising task complexity. Specifically, in SU condition integration of a variety of information had to be accomplished and considerably exceeded information processing of SC condition. Another possible explanation is that the benefit of levodopa substitution in PD on movement accuracy may be limited to less demanding motor tasks. Particularly, it may help patients to perform spatially coupled movements more accurate, but not enable patients to preserve accuracy during performance of uncoupled movements. This consideration is well in line with a wide range of studies, demonstrating that PD patients perform coupled bimanual movements in a comparable fashion to healthy subjects but accuracy distinctly deteriorates when movements become increasingly uncoupled (Almeida et al., 2002; Johnson et al., 1998; Ponsen et al., 2006; Serrien et al., 2000; Wu et al., 2010). Given that already early-stage PD patients exhibit problems in performing uncoupled bimanual movements, it has been suggested that this could represent a sensitive test for evaluation of motor function in PD (Johnson et al., 1998; Ponsen et al., 2006). Our results provide further support for this suggestion.

Left and right primary motor area interplay

In all groups BMS identified a model including reciprocal connections between left and right primary motor cortex. This indicates the importance of bidirectional interhemispheric communication for performing bimanual movements. In general, influence, directionality, and strength of interhemispheric crosstalk follow a distinct chronological sequence and crucially depend on the movement executed (Heinrichs-Graham et al., 2014b; Liuzzi et al., 2010, 2011; Loehrer et al., 2016). During mirror-symmetric movements reduced activity in right M1 seems to be important for correct motor output in healthy subjects (Aramaki et al., 2006b). Inhibitory asymmetric interactions from left to right M1 are thought to contribute to this decrease and have been associated with stabilisation of mirror-symmetric movements and increased motor performance (Loehrer et al., 2016; Maki et al., 2008). In this study, participants used mirror-symmetric movements during the SC condition. Here, healthy controls expressed inhibitory γ-γ-connectivity from left to right M1, which is in convergence with previous findings. In contrary, PD patients OFF and ON medication expressed excitatory coupling from left to right M1. This suggests that PD patients are still able to lateralize interhemispheric interactions as required for mirror-symmetric movements. Influence of this asymmetric interhemispheric connection, however, could not be maintained and coupling from left to right M1 was excitatory. This finding is in line with a fMRI study by Wu and colleagues investigating activation patterns during bimanual mirror-symmetric movements. Here, the authors revealed that activity of right hemispheric M1 is increased in PD patients compared to healthy controls (Wu et al., 2010). Our data suggest that excitatory influence from left M1 on right M1 could potentially contribute to this enhancement of right-hemispheric M1-activity during mirror-symmetric movements. The finding that left to right M1 coupling is excitatory in PD patients is particularly interesting since mainly right dominant (RD) PD patients participated in this study. Recent data suggested that in RD patients oscillatory pathology is pronounced in right M1 during simple unimanual tapping (Heinrichs-Graham et al., 2017). However, it has not yet been investigated whether symptom dominance influences oscillatory coupling during bimanual movements as well and further studies are required to assess this issue.

When interpreting these results, it is important to note that cortical activation as well as connectivity patterns differ for bimanual movements requiring the use of homologous muscles (i.e. mirror-symmetric) and movements in which non-homologous muscle groups are activated. Furthermore, neuroimaging studies yielded inconsistent results regarding movement-related activation of left hemispheric primary motor cortex and SMA in PD (Haslinger et al., 2001; Sabatini et al., 2000; Yu et al., 2007). In a meta-analysis addressing this issue Herz and colleagues found activity of left hemispheric M1 to be decreased in patients ON and OFF medication (Herz et al., 2014a). However, left M1 activity was not decreased in unmedicated PD patients when internally paced movements were studied. These findings underline the influence of the movement studied when comparing and interpreting study results.

It is worth noting that in our study β-activity in the dominant left-hemispheric M1 exerted γ-activity in right M1 in unmedicated patients. In general, oscillatory synchronization in PD tends to arise in the beta band (Hammond et al., 2007). Interestingly, during rest, beta activity seems to be reduced in comparison to healthy controls (Heinrichs-Graham et al., 2014a). During movement, however, failure to suppress beta activity has been described (Heinrichs-Graham et al., 2014b) and various studies reported pathological beta synchronization between M1 and the basal ganglia (Brown, 2007; Kühn et al., 2008). Furthermore, recent findings of cross-frequency coupling revealed an exaggerated coupling between beta phase and gamma amplitude in primary motor cortex which was characteristic for Parkinson's disease (de Hemptinne et al.,

2013). Phase-amplitude coupling was also present within subthalamic nucleus (STN) and between STN and oscillations in M1 which could be linked to severity of motor impairment and bradykinesia respectively (Shimamoto et al., 2013; van Wijk et al., 2016). Crucially, the pathological β-γ-phase-amplitude coupling in M1 could be suppressed by STN DBS rendering activity in M1 a potential biomarker for adaptive DBS (de Hemptinne et al., 2015).

In our study unmedicated patients expressed beta activity in left primary motor cortex during SC condition. Crucially, the β-γ-coupling from left to right M1 correlated positively with prolonged performance time, indicating that stronger β-γ-coupling resulted in poorer motor performance. This demonstrates the relevance of intact interhemispheric cross-frequency coupling for motor output and could inform further studies investigating the potential relevance of left to right M1 beta-gamma phase amplitude coupling.

Several studies have suggested that PD patients have difficulties switching between antikinetic β-band and prokinetic γ-band (Lindenbach and Bishop, 2013; Schnitzler and Gross, 2005) but that dopaminergic replacement therapy helps to reinstate γ-band activity (Herz et al., 2014c; Schnitzler and Gross, 2005). Indeed, we found that, after administration of levodopa, γ-activity in left M1 significantly modulated β-band activity in right M1. However, this connection failed to correlate with motor performance.

During SU condition, participants had to execute movements using non-homologous muscles. In young adults functional integration between both primary motor cortices declines during performance of uncoupled movements (Meister et al., 2010). Interestingly, in our study elderly control subjects continued to express inhibitory left to right M1 connectivity (for a further discussion the reader is referred to Loehrer et al., 2016). PD patients OFF and ON medication, on the other hand, failed to express significant coupling between primary motor cortices. However, it remains inconclusive whether the absence of this connection reflects a compensatory mechanism or represents pathology in terms of decreased cortical activation.

In left M1 medicated PD patients expressed significantly stronger power at 15 Hz (i.e. in the β-band) as compared to control subjects. However, in PD patients ON medication β-oscillations in left M1 were not significantly coupled to oscillations in any other region. Therefore, it has to be stressed, that the observed difference in power did not influence effective connectivity.

Prefrontal to premotor oscillatory coupling

The complex bimanual finger movements in this study required a high level of attention, especially in spatially uncoupled conditions. Other studies showed, that this kind of demand of movement monitoring is associated with increased PFC activation (Durstewitz et al., 2000; Garavan et al., 2002; Jueptner et al., 1997). Moreover, premotor regions (lPM and SMA) have been revealed to figure prominently in bimanual movement coordination (Liuzzi et al., 2011; Meister et al., 2010). PD is related to changes of prefrontal and premotor activity as well as connectivity during motor performance (Herz et al., 2014c; Jahanshahi et al., 1995; Rowe et al., 2002, 2010; Schönberger et al., 2013; Wu et al., 2010). The extent of these changes depends on the motor demand, i.e. alterations especially emerge in complex bimanual movements (Wu et al., 2010). Accordingly, in our study, alterations of left PFC to premotor coupling associated with PD were pronounced in more demanding conditions. We additionally provide evidence that levodopa substitution restores PD-related connectivity loss. In line with this, it has been demonstrated that activity patterns (Jenkins et al., 1992; Rascol et al., 1992) as well as connectivity patterns (Herz et al., 2014c) within the prefrontal-premotor network can be normalized by dopaminergic medication.

Lateralization of PFC to premotor connectivity in spatially coupled movements

During performance of temporally and spatially coupled movements PD patients OFF and ON medication as well as control subjects exclusively exhibited left PFC to lPM coupling (i.e. PFC to SMA coupling failed to be significant in all groups). Medicated patients expressed stronger γ-γ left PFC-lPM coupling as compared to control subjects, whereas controls showed stronger α-β left PFC-lPM coupling as compared to patients in the OFF and ON. However, motor performance did not significantly differ between the groups. Complex hand movements in PD patients are associated with decreased SMA and enhanced lPM activity (Samuel et al., 1997; Wu et al., 2010). In line with our findings, previous studies have provided evidence that these altered activity patterns are accompanied by changes of left PFC to premotor connectivity, namely a switch from medial (PFC to SMA) to lateral (PFC to lPM) coupling (Rowe et al., 2010). Decreased PFC to SMA connectivity and SMA dysfunction in PD were suggested to cause difficulties in coordination of complex hand movements (Rowe et al., 2002; Wu et al., 2010). Furthermore, it was assumed that enhancement of additional connections and increased activity in certain brain regions, such as lPM, might represent a compensatory mechanism (Rowe et al., 2010; Wu et al., 2010). In our study, left PFC to lPM γ-γ coupling in patients OFF medication was not associated with better motor performance. In the ON state, however, the individual levodopa-induced increase of this coupling significantly correlated with better movement accuracy (i.e. lower error rates). Our data therefore supports the idea that lateralization of left PFC to premotor coupling in PD patients during motor performance may be of compensatory nature and, essentially, adds to the discussion that dopaminergic medication may pronounce this mechanism.

In summary, lateralized prefrontal to premotor connectivity was found in elderly healthy controls as well as PD patients executing bimanual movements. In recent studies, younger healthy individuals performing the same task with less mistakes and higher velocity than elderly (Loehrer et al., 2016) and healthy subjects exposed to a fairly simple demand, i.e. unimanual finger tapping (Herz et al., 2014c) expressed excitatory PFC to SMA coupling instead. We therefore hypothesize that lateralization of prefrontal to premotor connectivity particularly occurs in individuals faced with challenging motor tasks.

Levodopa restores PD-related loss of left PFC to lPM connectivity in uncoupled movements

During performance of spatially uncoupled movements healthy subjects continued to express left PFC to lPM coupling, whereas in PD patients OFF medication this connection failed to be present. Instead, in the OFF state left PFC exerted inhibitory influences on β-power in SMA. We therefore suggest that alterations of prefrontal to premotor coupling in PD more strongly emerge when complexity increases. Accordingly, it has been demonstrated that PD-related loss of left PFC to premotor connectivity especially occurs when high attention to action is required (Rowe et al., 2002).

After levodopa application the medial inhibitory PFC to premotor pathway diminished and lateral excitatory coupling was restored as β-β coupling. These findings resemble the results described by Herz et al. (2014c). Performing relatively simple, externally paced unimanual finger movements, PD patients in the OFF state failed to express any left PFC to premotor connectivity. ON medication, however, excitatory left PFC to SMA as well as lPM couplings could be observed (Herz et al., 2014c). Crucially, it was shown that levodopa-induced enhancement of the lateral connection (i.e. PFC to lPM) was positively correlated with individual improvement of motor function (represented by UPDRS-III scores) (Herz et al., 2014c). In SU condition we could not reveal any significant correlations between the individual strengths of left PFC to lPM coupling, which was restored by dopaminergic medication, and motor performance. As described above, in SC condition, however, the individual levodopa-induced increase of left-sided lateral PFC to premotor connectivity significantly correlated with better movement accuracy. Our results extend the findings from Herz et al. by suggesting that enhancement of lateral prefrontal to premotor coupling by dopaminergic medication in PD is not limited to relatively simple motor tasks but also emerges during

more complex movements. Crucially, our data suggests that this mechanism can contribute for compensation of disease-related performance loss only up to a certain extent of complexity. Furthermore, in our study we showed that coupling parameters correlated with actual motor performance rather than a surrogate parameter for motor function (UPDRS-III).

Contrasting SU against SC condition yielded equivalent coupling patterns compared to SU condition. Here, left PFC to SMA coupling was modulated significantly stronger in SU condition compared to SC in unmedicated patients. In medicated patients, left PFC to lPM coupling was significantly stronger modulated in SU compared to SC. Furthermore, second level analysis revealed that couplings were modulated in the same frequency bands as compared to SU condition. Results, thus, were shown to be stable.

Right hemispheric prefrontal-premotor oscillatory coupling

Performing spatially coupled movements, PD patients OFF and ON medication expressed right hemispheric PFC to lPM excitatory coupling that failed to be significant in control subjects. Furthermore, all groups showed right prefrontal to premotor connectivity in SU condition. In previous studies, right PFC activation was found to be involved in suppression of automated behavior (i.e. response inhibition) (Garavan et al., 2002) and shown to be particularly activated during phase-transition of bimanual movements (Aramaki et al., 2006a). Accordingly, we previously assumed right PFC to premotor coupling to be particularly involved in performance of uncoupled bimanual movements (Loehrer et al., 2016). In the present study, however, in PD patients right prefrontal to premotor connectivity was also present in spatially coupled movements. Since we could not find any correlation to motor performance, it remains unclear whether that connection might be compensatory or reflect neurodegenerative spread of activity. However, it is of great interest to further asses the relevance of right hemispheric prefrontal to premotor connectivity and its possible relation to motor performance.

Limitations

In the present study, we employed the same motor task, model space and subsequent parameter estimation (i.e. second level analysis) as previously used in Loehrer et al. (2016). Regarding limitations concerning task, model space, and coupling parameters we therefore refer the reader to this study. In short, our model based analysis represents a region of interest approach and does only allow inferences on a limited number of cortical sources. In other words, several brain regions, that have been found to be involved in movement coordination, are not represented by our models. Since oscillatory coupling during bimanual coordination in PD is poorly examined, further studies are required to prove the specific relevance of our interpretations. A general problem of analysing adjacent cortical areas (such as the motor regions analyzed in this study) using EEG recordings is that volume conduction could have influenced neighbouring regions. Further limitations of this study are underlying inaccuracies in the SPM for M/EEG package which cannot be excluded. In 2016 Eklund et al. demonstrated that false assumptions in underlying spatial autocorrelation functions can lead to an increased risk of false positive results when using parametric statistical approaches like the FWE in SPM for fMRI (Eklund et al., 2016). While we do not assume that this directly translates to SPM for M/EEG this highlights the need for large data repository driven studies to confirm or reject the underlying hypotheses of software packages like SPM. Additionally, Eklund et al. demonstrated that nonparametric statistical methods might be less prone to such errors and are thus an important alternative to the parametric statistics used in this study (Eklund et al., 2016). A large number of PD patients had to be excluded because they failed to have enough artifact-free and correctly performed trials. Although, we distinctly aimed to cognitively challenge participants, especially the most difficult sequences of the spatially uncoupled task might have been too complex for patients. Choosing a less complex task could have prevented exclusion of so many participants. Due to the design of our study, in SU conditions PD patients had to perform fewer trials compared to control subjects. Since the absolute number of trials was still sufficient (i.e. at least about 40 trials) we do not think that electrophysiological findings were affected by a difference in trial quantity. Nevertheless, an equal number of trials would have been advantageous.

Conclusion

In the present study, we show that impaired bimanual motor control in Parkinson's Disease is associated with alterations of oscillatory coupling within a prefrontal-(pre-)motor network which can partially be normalized by levodopa substitution. In PD patients OFF medication, excitatory influence from dominant left hemispheric M1 to its right hemispheric counterpart correlated with slower performance of spatially coupled movements. Furthermore, excitatory left prefrontal to lateral premotor connectivity was reduced in the OFF state as compared to healthy participants. Crucially, levodopa induced enhancement of this connection was associated with increased accuracy of spatially coupled movements. When spatially uncoupled movements had to be performed, unmedicated PD patients actually exhibited inhibitory left PFC to SMA coupling instead of excitatory prefrontal to lPM connectivity. Levodopa induced a shift from this inhibitory medial to excitatory lateral PFC to premotor connectivity. Here, restoration of the lateral coupling, however, was not associated with better motor performance. Our results suggest that levodopa therapy enhances lateral prefrontal to premotor coupling within the left hemisphere in PD patients. Up to a certain extent of task complexity, this enhancement eventually results in increased motor control.

Conflict of interest statement

Lars Timmermann received payments as a consultant for Medtronic Inc, Boston Scientific, SAPIENS, St. Jude Medical, GE Medical, Bayer Healthcare, UCB Schwarz Pharma, Archimedes Pharma. L.T. received honoraria as a speaker on symposia sponsored by Zambon Pharma, TEVA Pharma, Lundbeck Pharma, Bracco, Gianni PR, Medas Pharma, UCB Schwarz Pharma, Desitin Pharma, Boehringer Ingelheim, GlaxoSmithKline, Eumecom, Orion Pharma, Medtronic, Boston Scientific, Cephalon, Abott, GE Medical, Archimedes, Bayer, ProsStrakan Pharma. The institution of L.T., not L.T. personally received funding by the German Research Foundation, the German Ministry of Education and Research, Manfred und Ursula Müller Stiftung, Klüh Stiftung, Hoffnungsbaum e. V., NBIA DISORDERS SOCIETY USA, Köln Fortune, Medtronic, Deutsche Parkinson Vereinigung. Archimedes Pharma, Abott, Bayer, UCB, zur Rose Pharma, TEVA. Neither L.T. nor any member of his family holds stocks, stock options, patents or financial interests in any of the above mentioned companies or their competitors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.04.030.

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