Neuropsychologia 117 (2018) 491–499

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Motor cognition in patients treated with subthalamic nucleus deep brain stimulation: Limits of compensatory overactivity in Parkinson's disease

Klara Hagelweide[a,b,*], Anna R. Schönberger[a], Lutz W. Kracht[c], Theo O.J. Gründler[d,e], Gereon R. Fink[a,f], Ricarda I. Schubotz[a,b]

[a] Department of Neurology, University Hospital Cologne, Kerpener Str. 62, D-50937 Cologne, Germany
[b] Department of Psychology, University of Muenster, Fliednerstr. 21, D-48149 Münster, Germany
[c] Max Planck Institute for Metabolism Research, Gleueler Str. 50, D-50931 Cologne, Germany
[d] Center for Behavioral Brain Sciences, Otto-von-Guericke-University Magdeburg, Universitaetsplatz 2, 39106 Magdeburg, Germany
[e] Faculty of Economics and Management, Otto-von-Guericke-University Magdeburg, Universitaetsplatz 2, 39106 Magdeburg, Germany
[f] Institute of Neuroscience and Medicine (INM3), Cognitive Neuroscience, Research Centre Jülich, Leo-Brandt-Straße, D-52425 Jülich, Germany

ARTICLE INFO

Keywords:
Supplementary motor area
Premotor cortex
Serial prediction task
Positron emission tomography
Cognitive impairment
Motor loop

ABSTRACT

Recent fMRI findings revealed that impairment in a serial prediction task in patients suffering from Parkinson's disease (PD) results from hypoactivity of the SMA. Furthermore, hyperactivity of the lateral premotor cortex sustained performance after withdrawal of medication. To further explore these findings, we here examined the impact of deep brain stimulation of the subthalamic nucleus on the activity of the putamen and premotor areas while performing the serial prediction task. To this end, we measured eight male PD patients ON and OFF deep brain stimulation and eight healthy age-matched male controls using [^{15}O] water positron emission tomography to measure regional cerebral blood flow. As expected, PD patients showed poorer performance than healthy controls while performance did not differ between OFF and ON stimulation. Hypoactivity of the putamen and hyperactivity of the left lateral premotor cortex was found in patients compared to controls. Lateral premotor hyperactivity further increased OFF compared to ON stimulation and was positively related to task performance. These results confirm that the motor loop's dysfunction has impact on cognitive processes (here: prediction of serial stimuli) in PD. Extending prior data regarding the role of the lateral premotor cortex in cognitive compensation, our results indicate that lateral premotor cortex hyperactivity, while beneficial in moderate levels of impairment, might fail to preserve performance in more severe stages of the motor loop's degeneration.

1. Introduction

The hallmark of Parkinson's disease (PD) is the loss of dopaminergic neurons projecting from substantia nigra pars compacta to the striatum. The resulting dopamine deficiency in the basal ganglia causes bradykinesia, resting tremor, muscle rigidity, and posture and gait problems, but also depression and cognitive decline (Rodriguez-Oroz et al., 2009) via depletion of different cortico-basal ganglia-thalamo-cortical loops (Alexander et al., 1986; Sawamoto et al., 2008).

When cognitive deficits in PD are investigated, the focus is often put on impairments in executive functions, i.e., set shifting, planning, conflict resolution, response inhibition, and working memory (Dirnberger and Jahanshahi, 2013). Shortcomings in these domains, subsumed under the notion of a dysexecutive syndrome, are ascribed to a dysfunction of the dorsolateral prefrontal loop (e.g., Brück et al., 2001; Gawrys et al., 2014; Owen, 2004; Rinne et al., 2000; Saint-Cyr et al., 1988), the anterior cingulate and the orbitofrontal loop (Polito et al., 2012; Zgaljardic et al., 2006).

On the contrary, the motor loop, which bundles input from the supplementary motor area (SMA), lateral premotor cortex (PM), and primary motor and sensory cortices to the putamen and projects back to the SMA via the internal globus pallidus and thalamus, is often neglected in relation to cognitive deficits. While some studies suggest the dysexecutive syndrome to be distinct of motor impairment (Cooper et al., 1991; Lewis et al., 2003; Muslimović et al., 2005), others considered them to be interdependent (Elgh et al., 2009; Mortimer et al., 1982; Poletti et al., 2012; Williams et al., 2007). For instance, Nagano-Saito et al. (2014) found that patients with mild cognitive impairment showed premotor hypoactivity during the execution of set-shifting in a computer version of the Wisconsin Card Sorting Test, suggesting that

* Correspondence to: Department of Psychology, University of Münster, Fliednerstr. 21, 48149 Münster, Germany.
E-mail address: klara.hagelweide@wwu.de (K. Hagelweide).

https://doi.org/10.1016/j.neuropsychologia.2018.07.007
Received 31 October 2017; Received in revised form 7 May 2018; Accepted 6 July 2018
Available online 09 July 2018
0028-3932/

the motor loop may contribute to cognitive processes involved in executive functions.

We examined the motor loop's contribution to cognitive processes in two previous studies by testing PD patients 'on' and 'off' dopaminergic medication in the serial prediction task (Schönberger et al., 2013, 2015). This task requires participants to monitor stimulus sequences and indicate violations of the sequences' structure. Patients showed poor task performance related to motor impairment (Schönberger et al., 2013), particularly in a modified task version (SPT+) which heightened the need for internal sequence representation as supported by the SMA (Goldberg, 1985). In both studies medication mitigated performance deficits which were associated with hypoactivity of the SMA and putamen while successful performance was related to higher SMA activity. After withdrawal of medication, PM hyperactivity emerged, supposedly reflecting a compensatory mechanism as suggested by a positive correlation with serial prediction (Schönberger et al., 2015). Importantly, these results are reminiscent of a pattern also observed in motor tasks, namely SMA hypoactivity in PD patients co-occurring with PM hyperactivity (Haslinger et al., 2001; Mallol et al., 2007; Sabatini et al., 2000; Samuel et al., 1997) when performance is preserved under external guidance (Hanakawa et al., 1999; Michely et al., 2015).

To confirm and extend these findings, the influence of subthalamic nucleus (STN) deep brain stimulation (DBS) on serial prediction performance and its neural underpinnings was examined in the current study. Similar to dopaminergic medication, DBS significantly improves patients' motor symptoms and quality of life (Perestelo-Pérez et al., 2014), but the exact mechanism of DBS to date remains elusive (Alhourani et al., 2015; Chiken and Nambu, 2016; Udupa and Chen, 2015). A plausible hypothesis is that stimulation of STN disrupts the pathological synchronization in the beta frequency band (Silberstein et al., 2005). In particular, DBS may normalize the exaggerated phase amplitude coupling between the beta rhythm in STN and gamma activity in primary motor cortex (De Hemptinne et al., 2013; Oswal et al., 2013) by reducing the pathological beta rhythms' coherence between STN and SMA (Oswal et al., 2016). Studies examining DBS influences on brain activity show that DBS at rest increases activity in the STN region, thalamus, posterior cerebellum, and precuneus while metabolism is reduced in a network including the PM, SMA, dorsolateral prefrontal cortex, and anterior cingulate cortex (Alhourani et al., 2015; Boertien et al., 2011). On the contrary, DBS during tone-paced joystick movements is associated with increased cerebral blood flow in thalamus and putamen (Thobois et al., 2002), PM (Ceballos-Baumann et al., 1999; Grafton et al., 2006), rostral SMA (Ceballos-Baumann et al., 1999; Grafton et al., 2006; Limousin et al., 1997; Strafella et al., 2003), dorsolateral prefrontal cortex (Ceballos-Baumann et al., 1999; Limousin et al., 1997; Strafella et al., 2003; Thobois et al., 2002) and anterior cingulate cortex (Ceballos-Baumann et al., 1999; Strafella et al., 2003). These activity changes are related to stable (Limousin et al., 1997) or reduced movement latencies under stimulation (Ceballos-Baumann et al., 1999; Strafella et al., 2003; Thobois et al., 2002) and are interpreted as normalization of pathological activity (Grafton et al., 2006).

Taken together, prior studies support the idea that DBS restores the normal function of the motor loop and improves sensory processing, while DBS effects on cognition are still debated (Boertien et al., 2011). Experiments testing for changes in cognitive functions with onset of stimulation found some tasks to be improved and some to be impaired during DBS (Boertien et al., 2011; Jahanshahi et al., 2000; Heo et al., 2008). A study which examined the effects of DBS on motor and cognitive symptoms in comparison to medical therapy in a large sample of patients found minor cognitive decrements in the patients receiving DBS compared to levodopa, while motor symptoms were clearly improved with DBS (Weaver et al., 2009). Furthermore, Carbon et al. (2003) investigated effects of internal pallidal DBS on a sequence motor learning task and found a significant enhancement in the underlying neural network resulting in better task performance, while a decrease in network activity and no behavioural changes were observed after levodopa infusion. These findings point to the idea that DBS may have a stronger positive effect on motor symptoms, while levodopa rather improves cognitive measures.

Against this background, we investigated whether performance in serial prediction is heightened during DBS. Similar to other cognitive tasks, serial prediction might not be significantly improved by DBS. But as serial prediction relies predominantly on the functionality of the motor network (Schubotz, 2007), while many other cognitive tasks rather depend on the prefrontal loops, we expected DBS to have positive effects on serial prediction performance. Drawing on our previous findings we hypothesized patients to show impaired serial prediction compared to healthy controls, especially i) with deactivated DBS, and ii) when the need for SMA engagement is heightened (SPT+; hypothesis 1). The performance deficit was expected to be positively correlated with patient's individual motor impairment and to co-occur with hypoactivity of SMA and putamen (hypothesis 2). In addition to the motor loop's dysfunction, we expected patients to show PM hyperactivity, in particular without DBS and in SPT+, providing a compensatory mechanism which therefore should be related to better performance (hypothesis 3).

2. Material and methods

2.1. Participants

Eight male patients suffering from Parkinson's disease according to the UK Parkinson's disease Society Brain Bank Criteria (Hughes et al., 1992) were included in the study. Patients had a mean age of 61.5 years (range: 54–69 years; for further demographical and clinical data see Table 1). In all patients quadripolar electrodes had been implanted bilaterally into the STN (for stimulation parameters see Table 1). The severity of symptoms measured according to Hoehn and Yahr (1967) ranged between II and III under regular medication. The motor score of the UPDRS (Fahn and Elton, 1987) was assessed by a movement disorder specialist once ON DBS and once OFF DBS. All patients received dopaminergic medication regularly which was discontinued at least fourteen hours before testing while withdrawal of long-acting dopamine agonists lasted up to thirty-six hours.

Eight healthy male participants comparable to the patients regarding age were measured as control subjects. No participant had a history of any psychiatric or other neurological disease or suffered from dementia as tested by the Parkinson neuropsychometric dementia assessment (PANDA; Kalbe et al., 2008). Two additional patients were excluded from the analysis due to behavioural performance at chance level for both SPT0 and SPT+.

All participants gave their written informed consent prior to participation. The study was performed according to the Declaration of Helsinki and approved by the local ethics committee of the Medical Faculty, University of Cologne, Germany (study number: 09–139). Permission to administer radioactive substances was obtained from the regulatory authorities (Bundesamt für Strahlenschutz).

2.2. Stimuli and tasks

We applied the serial prediction task in two versions (SPT0 and SPT+) in which participants had to indicate whether a sequence of 15 stimuli ended regularly or with a switch in the sequence's order (Fig. 1). Stimuli consisted of concentric circles with twelve differing sizes. To allow learning of the sequence, a triplet of three consecutively presented circles (1-2-3) was repeated five times per trial. In half of the trials a novel triplet with switched positions of two circles (1-3-2 or 2-1-3) was presented during the fifth repetition. Then participants had to decide whether the sequence contained a switch or not in a forced-choice-response phase of 3.5 s. Overall, one trial lasted 18.75 s including response and feedback. After feedback a fixation cross was presented for 2 s before the next trial started.

Table 1
Patient characteristics.

Pat	Age (years)	Disease duration (years)	Medication (mg/day)	LED (mg)	Hoehn & Yahr		UPDRS III		Resting tremor		DBS parameters	
					DBS ON	DBS OFF	DBS ON	DBS OFF	DBS ON (left/ right)	DBS OFF (left/ right)	Left electrode	Right electrode
1	66	15	8 mg ropinirole	160	2	2	17	32	1/0	1/0	4.3 mA, 60 µs, 174 Hz	4.3 mA, 60 µs, 130 Hz
2	62	4	1 rasagiline, 50 piribedil	150	2	2	13	22	0/0	2/0	1: 3.5 V, 90 µs, 130 Hz; 2: 3.5 V, 90 µs, 130 Hz	4.0 V, 60 µs, 130 Hz
3	59	7	1 rasagiline, 10 rotigotine	400	2	2	9	18	0/0	0/0	1: 2.5 V, 60 µs, 130 Hz; 2: 2.5 V 60 µs, 130 Hz	2.1 V, 60 µs, 130 Hz
4	69	11	500 L-Dopa, 50 carbidopa, 200 piribedil, 75 benserazide	700	2	3	29	50	0/0	2/2	1: 2.7 V, 60 µs, 125 Hz; 2: 1,0 V, 60 µs, 125 Hz	2.3 V, 60 µs, 125 Hz
5	54	20	400 L-Dopa, 100 carbidopa, 1.4 pramipexol, 400 amantadine, 800 entacapone	672	2	3	24	46	2/0	4/2	3.0 V, 60 µs, 130 Hz	2.4 V, 60 µs, 130 Hz
6	54	9	10 ropinirole, 1 rasagiline	300	2	3	13	27	0/1	0/3	1: 3.7 V, 90 µs, 150 Hz 2: 3.7 V, 90 µs, 150 Hz	1.5 V, 60 µs, 150 Hz
7	65	18	150 L-Dopa, 8 rotigotine, 75 benserazide	390	3	4	27	54	0/0	2/2	1.5 mA, 60 µs, 130 Hz	2.8 mA, 60 µs, 130 Hz
8	59	24	450 L-Dopa, 125 carbidopa, 800 entacapone, 25 benserazide, 150 amantadine	598,5	2	3	29	51	0/0	1/1	3.0 V, 60 µs, 130 Hz	2.7 V, 60 µs, 130 Hz

Pat. = Patient number; resting tremor = ratings of item 20 of UPDRS III. LED = Levodopa equivalent dose calculated according to Tomlinson et al. (2010).

Fig. 1. Set-up of the serial prediction task. SPT0: Participants were instructed to watch a triplet of circles (1st-2nd–3rd), which was repeated five times per trial to allow learning of the sequence. After presentation of a fixation cross (1 s) at the beginning of a trial every circle was presented for 600 ms with an inter stimulus interval of 125 ms. At the end of a trial participants had to respond in a forced-choice-response phase within maximum 3.5 s whether the sequence ended as predicted (50%: 1st–2nd-3rd) or not (25%: 1st–3rd-2nd; 25%: 2nd-1st-3rd). One response button was provided for answering "correct sequence" and one for responding "a sequential switch occurred". Answers were delivered with the right index and middle fingers. A valid feedback indicated a correct, false, or missing answer. SPT+: In modification of SPT0, 1–4 stimuli of every trial were replaced by wildcards: instead of a circle a blank card was shown. The first three stimuli of a trial were not replaced, and never two consecutive stimuli were replaced by wildcards. The last triplet contained maximal one wildcard.

The SPT+ condition was identical to SPT0 except for a parametric modulation of the necessity for internal sequential representations: In SPT+ trials two, three, or four stimuli were replaced by wildcards, i.e., non-informative stimuli that replaced standard circle-stimuli of the sequence.

The SPT+ and SPT0 conditions were presented in blocks of 10 trials each lasting 3.4 min. The experiment contained 12 blocks, always alternating between a SPT0 and SPT+ block. It was inter-individually balanced if the scanning session was started with an SPT+ or SPT0 block.

2.3. Procedure

Participants were measured with positron emission tomography (PET) because of safety concerns regarding functional magnetic resonance tomography in patients with DBS (Finelli et al., 2002; Georgi, Stippich, Tronnier, and Heiland, 2004; Shrivastava et al., 2012).

Every participant attended our study on two consecutive days. On the first day, every subject received training on SPT0 and SPT+ outside the scanner. Furthermore, subjects were asked to complete the PANDA, the Beck depression inventory-II, and the Barratt Impulsiveness Scale Version 11. On the second day the participants attended the experimental PET session. Patients' dopaminergic medication was discontinued at least fourteen hours before testing while withdrawal of long-acting dopamine agonists lasted up to thirty-six hours. The order of DBS ON and DBS OFF measurements was counterbalanced across patients to avoid confounds of the DBS effect with possible training or repetition effects on serial prediction performance. Therefore, the following procedure was applied: In four patients, DBS was switched OFF at least 30 min before the first PET scan and DBS OFF state UPDRS III scores were assessed. Then the patients received six PET scans while performing one task block per scan. The six scans took about 60 min including breaks to allow the radiation to decay between scans. DBS was switched ON again directly after the sixth PET scan. Before starting the seventh scan (after at least 30 min) the patients' UPDRS III scores

were assessed once again to document motor improvement ON DBS. In these patients, DBS stayed ON during the subsequent six PET scans that again lasted about 60 min. In the other four patients, UPDRS III scores were assessed ON DBS and the first six PET scans were performed. Right after the sixth scan, DBS was switched OFF. After at least 30 min, the decay of the stimulation effect was measured with UPDRS III, and the seventh scan was started. DBS remained OFF in these patients until the end of the twelfth PET scan and was switched ON right after the PET scanning. Healthy subjects also performed twelve blocks but were only exposed to six PET scans for reasons of radiation reduction. Because waiting times matching the patients' schedule were applied to the healthy controls, the PET session lasted 150–180 min in total in all participants.

2.4. PET scanning

Regional cerebral blood flow (rCBF) was measured by recording the regional distribution of cerebral radioactivity after the intravenous injection of [^{15}O] water. The PET measurements were carried out using an ECAT EXACT HRRT dedicated brain scanner (CTI Siemens, Knoxville, TN, USA) with a total axial field of view of 252 mm covering the whole brain (Wienhard et al., 2002). Data were acquired in three-dimensional mode. For each measurement of rCBF, 550 MBq of [^{15}O] water were given intravenously as a bolus injection. Each PET scan was started after the participants had performed two trials to make sure that they were involved in the serial prediction task. Emission data were thereafter collected over 45 s. This process was repeated for each emission scan, with 8 min between scans to allow for an adequate decay of radioactivity. All emission scan data were corrected for scattered events and for radiation attenuation by means of a transmission scan taken prior to the first emission measurement. The corrected data were reconstructed using OSEM3D into 207 transaxial images of 256 × 256 pixels (1.218750 mm isotropic voxels). The reconstructed PET images had a resolution of 2.2 mm in the center and 2.5 mm at 10 cm of axis and were regarded to represent rCBF qualitatively.

2.5. Analysis of PET scans

Image processing and statistical analysis of PET scans was conducted using MATLAB version 8.0 (The Mathworks Inc., Natick, MA) and statistical parametric mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK). All PET scans were realigned to the first scan of each session to correct for movements between scans. This resulted in 2 × 6 aligned images for each patient and 6 aligned images for each control plus a mean relative rCBF image compiled for each participant. This mean image was normalized to the standard SPM8 template in MNI space using linear as well as non-linear transformations (Friston et al., 1995) in order to apply this set of normalization parameters to the other scans. The spatially normalized PET images were smoothed using a low-pass Gaussian filter of 12 mm. The resulting voxel size in stereotactic space was 2 × 2 × 2 mm^3.

Finally, analyses of variance (ANOVA) were performed to compare rCBF of patients and healthy controls. Condition related differences in global CBF were removed by treating global activity as a covariate (Friston et al., 1990). Only activations that exceeded a statistical threshold of $p < .05$ (whole brain corrected for multiple comparisons) with a cluster size of at least five voxels were considered significant. In addition, six regions, i.e., left and right SMA, left and right PM and left and right putamen, were selected for region-of-interest (ROI) analyses. Identical to the approach in Schönberger et al. (2015), SMA and PM regions were based on coordinates of maximum activity during performance of SPT0 and SPT+ compared to a control task in young healthy participants (Schubotz and von Cramon, 2004). These peak voxel coordinates were converted from Talairach to MNI space and the resulting coordinates (left SMA: x = − 5, y = − 4, z = 56; right SMA: x = 1, y = 3, z = 53; left PM: x = − 53, y = 2, z = 37; right PM: x = 56, y = 6, z = 25) were used as the centres of spherical volumes of interest with 6 mm radius each. The ROI analysis of putamen activity was based on anatomic masks of the left and right putamen provided by the anatomical atlas (Tzourio-Mazoyer et al., 2002) implemented in the WFU pick-atlas toolbox (Maldjian et al., 2003). The statistical threshold was set to $p < .05$ (small-volume correction) and an extend threshold of at least five voxels was applied.

2.6. Behavioural analysis

The software package SPSS (SPSS Statistic 22.0, IBM, Chicago, IL) was used for statistical analyses. Behavioural performance was assessed by probability of recognition (Pr; Snodgrass and Corwin, 1988) defined as the difference of hit rate and false alarm rate (cf. Schönberger et al., 2013). All participants included in the statistical analysis performed above chance levels (0.22 in SPT0 and SPT+) in at least one version of the task. Note that faster responses do not reflect better performance as participants were instructed to give correct and non-speeded responses. Nevertheless, response times of correct answers were included in the analysis to suspend the possibility of a speed-accuracy trade off. Because of the small sample size, non-parametric tests were conducted. As patients and controls were matched for gender and age, all comparisons between groups were carried out using Wilcoxon tests, i.e., a non-parametric substitute for paired *t*-tests. Correlational analyses were conducted using Spearman's Rho, a rank-based non-parametric measure. Results with p-values < .05 were considered significant.

3. Results

3.1. Behavioural results of the PET study

Wilcoxon tests were conducted comparing age, PANDA, scores in Beck depression inventory-II and scores in the Barratt Impulsiveness Scale Version 11 of patients and controls. No significant differences were found (see Table 2). UPDRS III scores ON DBS (20.13 ± 8.1; mean ± standard deviation) and OFF DBS (37.5 ± 14.4) showed a significant effect of stimulation within the patient group ($Z = 2.53$; $p = .012$).

Performance of all participants was measured in two sessions. Group comparisons were conducted with the controls' data averaged over both sessions as neither performance in SPT0 ($Z = -0.255$, $p = .799$) and SPT+ ($Z = -0.73$, $p = .465$) nor reaction times in SPT0 ($Z = -0.28$, $p = .779$) and SPT+ ($Z = -0.14$, $p = .889$) differed between their two sessions. Average performance rates of controls and patients ON DBS and OFF DBS are depicted in Fig. 2.

While all eight patients performed sufficiently well in SPT0, the individual performance of four patients was below the chance level of

Table 2
Subject demographics and neuropsychological test data.

Characteristic	Mean ± standard deviation		p[a]
	Patients (n = 8)	Controls (n = 8)	
Age, years	61.5 ± 5.1	61.5 ± 6.7	.833
PANDA	27.8 ± 1.8	27.9 ± 1.8	.914
BDI-II	4.3 ± 5.8[b]	5.8 ± 6.6	.686
BIS-11	52.6 ± 7.7[c]	57.9 ± 11.8	.345

PANDA = Parkinson neuropsychometric dementia assessment (dementia cut-off < = 24; max. value = 30); BDI-II = Beck depression inventory-II (depression cut-off > = 19; max. value = 63); BIS-11 = Barratt Impulsiveness Scale Version 11 (scores > = 72 correspond to highly impulsive individuals; max. value = 120).

[a] Significance of differences between groups, computed with non-parametric Wilcoxon tests.

[b] n = 7.

[c] n = 6.

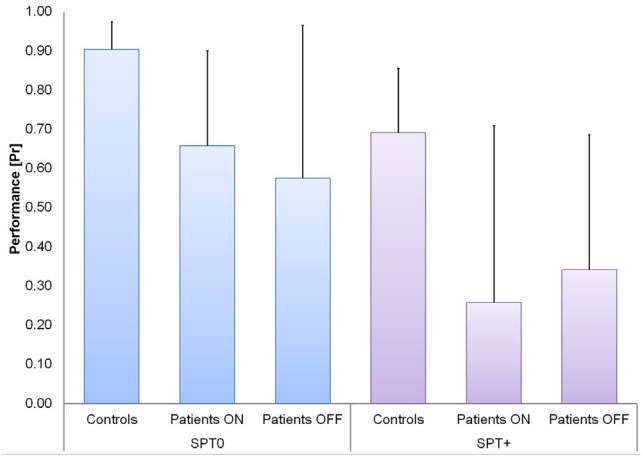

Fig. 2. Average performance in the two applied versions of the serial prediction task (SPT0 = serial prediction task with ongoing stimuli; SPT+ = serial prediction task with wildcard stimuli). Performance is measured as probability of recognition (Pr; Snodgrass and Corwin, 1988); Pr is calculated as the difference of hit rate and false alarm rate. Resulting values represent the ability to correctly differentiate deviant and non-deviant sequences. Values greater than 0.22 indicate performance above chance level. Whiskers depict the standard deviation.

Table 3
Individual performance during SPT0 and SPT+ calculated as probability of recognition.

	Patient		Control	
Number	SPT0	SPT+	SPT0	SPT+
1	0.47	**0.03**	0.97	0.93
2	0.40	**0.04**	0.87	0.50
3	0.97	0.73	0.94	0.87
4	0.27	**0.04**	0.90	0.67
5	0.90	0.64	0.77	0.54
6	0.97	0.80	1.00	0.80
7	0.63	0.30	0.90	0.53
8	0.34	**− 0.17**	0.90	0.70

SPT0 = serial prediction task with ongoing stimuli; SPT+ = serial prediction task with wildcard stimuli; Bold numbers mark performance rates below chance level (< 0.22).

0.22 in SPT+ (Table 3). Because of the poor performance of patients in the SPT+ version, all following analyses that include the patient group are restricted to results of the SPT0 task.

As hypothesized, controls performed significantly better than patients ON DBS in SPT0 ($Z = -2.10$, $p = .035$). Patients' performance OFF DBS showed a trend for deficits in SPT0 ($Z = -1.86$, $p = .063$). In congruence with our previous findings, controls showed higher performance rates in SPT0 than in SPT+ (controls: $Z = -2.53$, $p = .012$). Regarding the effect of DBS, no significant difference between ON and OFF state was found for SPT0 ($Z = -0.63$, $p = .528$).

To estimate the influence of patients' characteristics on their performance, non-parametric correlations were calculated. Age, PANDA scores, UPDRS III scores ON DBS, the years since the diagnosis of Parkinson's disease, and the effectiveness of DBS in ameliorating motor symptoms was correlated with performance in SPT0 in ON and OFF state. The DBS effectiveness was calculated as UPDRS III score OFF minus ON DBS divided by the score OFF DBS (cf. Evans et al., 2006; Weinberger et al., 2006). When testing for intercorrelations of the patients' characteristics, only the duration of Parkinson's disease and the UPDRS III scores ON DBS were found to be correlated ($\rho = .747$, $p = .033$). Results show a significant negative relation of the patients' age and their performance in SPT0 in OFF state, while there was no

Table 4
Correlations of participants' characteristics with performance calculated as Pr (probability of recognition).

Characteristic	Patients		Controls	
	Pr SPT0		Pr SPT0	Pr SPT+
	ON DBS	OFF DBS		
Age	− 0.51	− 0.83*	0.12	0.02
PANDA scores	0.15	0.68	− 0.15	− 0.49
UPDRS III scores ON	− 0.55	− 0.57	–	–
Years since diagnosis	− 0.07	− 0.11	–	–
DBS effectiveness	0.86*	0.74*	–	–

Correlation coefficients computed as Spearman's Rho; *p < .05. SPT0 = serial prediction task with ongoing stimuli; SPT+ = serial prediction task with wildcard stimuli; PANDA = Parkinson neuropsychometric dementia assessment.

significant influence of age in controls (see Table 4). The effectiveness of DBS was positively correlated with SPT0 performance ON and OFF DBS.

No significant differences in response times were found, neither between controls and patients ON DBS in SPT0 (controls: 828 ms ± 181 ms; patients ON: 994 ms ± 609 ms; $Z = -0.14$, $p = .889$), nor between controls and patients OFF DBS in SPT0 (patients OFF: 981 ms ± 626 ms; $Z = 0$, $p = 1$). Furthermore, patients in ON vs. OFF state did not differ in response times in SPT0 ($Z = -0.42$, $p = .671$).

3.2. PET imaging results

Notably, only four patients performed above chance level in SPT+. A statistical analysis based on these four data sets was discarded due to its low statistical power caused by too few independent measurements. Therefore, all eight data sets were used, but restricted to scans during SPT0 performance to ascertain that results reflect brain activity related to successful task performance. Consequently, all reported imaging results and their correlations with performance correspond to the successfully executed SPT0 task. Scans recorded during SPT0 were entered into a general linear model (GLM) comprising patients ON DBS, patients OFF DBS, and controls. Contrasts were calculated comparing controls vs. patients ON DBS, controls vs. patients OFF DBS, and patients ON vs. patients OFF DBS. As there was no baseline measurement included in the experimental protocol, these contrasts contain the pure network effect of stimulation and effects of the evolving resting tremor which was documented in three patients ON DBS and seven patients OFF DBS (see tremor scores in Table 1). Consequently, the stimulation effect is not distinguishable from task activations. To differentiate between patients' and controls' general differences and influences of the stimulation, conjunctions of the comparisons of controls with both patients ON DBS and patients OFF DBS were calculated [(controls vs. patients ON DBS) ∩ (controls vs. patients OFF DBS)]. This conjunction reveals group differences independent of confounding stimulation effects. The influence of DBS is directly tested by comparing patients ON DBS and patients OFF DBS. Resting tremor was previously found to activate a network of cerebellum, primary sensory and motor cortex, cingulate cortex and putamen (Mure et al., 2011) including SMA (Davis et al., 1997; Fukuda et al., 2004). To minimize activations due to resting tremor in all comparisons, the UPDRS III scores of item 20 coding for resting tremor were used as covariates in the following way: the sum of left hand and left foot scores were combined to a left side resting tremor score, and the sum of right hand and right foot were summed to a right side resting tremor score (see Table 1; no patient showed resting tremor of the head). These two measures were included in the GLM as covariates to parcel out the effect of resting tremor on the data. Finally, to test for significant relations between performance and rCBF, the probability of recognition corresponding to each scan was added as

Table 5
Results of the whole brain analysis.

Brain area	BA	H	Peak voxels' MNI coordinates			Peak *t*-value	k
			x	y	z		
(A) Areas hypoactive in patients [(controls > patients ON) ∩ (controls > patients OFF)]							
Thalamus		L	− 20	− 20	2	5.71	21
Medial temporal gyrus	37	L	− 48	− 56	2	5.91	13
Medial temporal gyrus	37/39	R	56	− 64	16	6.91	264
Temporal lobe	37	R	36	− 30	2	5.89	18
		L	− 42	− 30	4	5.47	5
Lingual gyrus/calcarinus/precuneus	18/30	L/R	5	− 56	10	7.33	305
Lingual gyrus	19	L	− 18	− 54	2	5.94	25
Cuneus	18/19	R	2	− 86	16	5.74	160
		L	− 22	− 88	20	6.62	121
		L	− 12	− 84	32	5.27	19
(B) Areas hyperactive in patients [(patients ON > controls) ∩ (patients OFF > controls)]							
Medial frontal gyrus	46/9	L	− 38	46	16	8.866	449
	46 /10	R	38	38	26	6.6375	257
Paracentral lobule	4	R	4	− 30	80	5.8361	79
(C) Areas with increased activity in patients ON (patients ON > patients OFF)							
Thalamus		R	8	− 18	14	5.5247	8
Medial orbital frontal cortex	11	R	20	32	− 20	5.7912	20
(D) Areas with increasing activity in relation to resting tremor (covariate left resting tremor)							
Supplementary motor area	6	L	− 2	0	68	5.5942	15
Inferior frontal gyrus	45	R	50	30	2	5.2773	7
Medial temporal gyrus	39	R	56	− 66	16	5.8124	65
	39	R	42	− 58	22	5.4806	8
(E) Area with increasing activity in relation to performance							
Medial temporal gyrus	39	R	62	− 48	10	5.2127	5

Significant activations at $p < .05$ after FWE correction for multiple comparisons. BA = Brodmann area; H = hemisphere; k = number of significant voxels.

covariate. Whole brain results of all contrasts and covariates are listed in Table 5.

The ROI analysis testing for increased activity in controls compared to patients confirmed the hypothesized hypoactivity in patients' left putamen (peak *T*-value = 4.81; cluster size k = 5), but not in SMA, and no difference of PM activity. Thus, a partial hypoactivity of the motor circuit was found to accompany the patients' deficits in task performance. When testing for increased activity in patients compared to controls, results matched the hypothesized pattern of hyperactivity in the left PM (T = 3.7; k = 41) with no differences of activity in SMA or putamen.

Regarding the stimulation effect, the expected hyperactivity of left PM when OFF compared to ON DBS (T = 4.16; k = 30) was confirmed, while SMA and putamen activity did not change. Patients ON DBS did not show higher activity than OFF DBS in any ROI.

When examining the relation of SPT0 performance and ROI activity, higher probability of recognition was related to increased activity in left PM (T = 3.83; k = 26). This result shows SPT0 blocks with better performance to be related to higher PM activity within each participant, i.e. in both patients and controls. The performance level was not associated with activity in SMA or putamen. No negative correlation of SPT0 performance and activity was found in any ROI. To test if left PM hyperactivity in patients was related to better performance, an additional analysis was conducted. A conjunction of the performance parameter and hyperactivity of patients vs. controls [performance ∩ (patients ON DBS > controls) ∩ (patients OFF DBS > controls)] revealed a significant activation in left PM (T = 3.39; k = 4). On the contrary, a conjunction of the performance parameter and hypoactivity of patients [performance ∩ (controls > patients ON DBS) ∩ (controls > patients OFF DBS)] revealed no significant activity in left PM.

To explore the relation of mean left PM activity to individual performance, which was found to be positive in patients of the fMRI study (Schönberger et al., 2015), the first eigenvariate of this ROI was extracted in SPM (Friston et al., 2006) to correlate the estimated mean rCBF with the individual probability of recognition of each participant (see Fig. 3). The resulting correlations demonstrate in which way the participants' mean activity in PM was related to their overall performance. While the controls' SPT0 performance showed descriptively a positive relationship with left PM activity ($\rho = .561$, $p = .148$), the opposite was found in patients ON DBS ($\rho = -.683$, $p = .062$). The correlation was not significant in patients OFF DBS ($\rho = -.361$, $p = .379$).

3.3. Comparison of the PET sample's disease severity with previous samples

It is noteworthy that only half of the patients performed above chance in the SPT+ task, as the previous studies found 27 of 36 PD patients to pass the SPT+ (Schönberger et al., 2013, 2015). To investigate reasons for the patients' poor SPT+ performance, characteristics of the current study's participants (labelled PET sample in the following) were compared to the previous samples' data (see Table 6). Mann-Whitney *U* tests showed the UPDRS III scores OFF DBS in the PET sample to be higher than the scores of patients OFF dopaminergic medication in the fMRI study (Schönberger et al., 2015) and, by trend, in the behavioural study (Schönberger et al., 2013). Therefore, the data suggest that the PET sample's more severe motor impairment might explain the striking deficits in task performance.

4. Discussion

To examine the effect of DBS on performance in a cognitive task we measured patients suffering from PD and matched healthy controls with PET while subjects performed a serial prediction task. Notably, the serial prediction task is a purely cognitive task, as participants do not give speeded responses, but evaluate the serial structure of visual events. This perceptual sequence processing recruits the SMA and PM in healthy individuals (Schubotz and von Cramon, 2003; Schubotz, 2007) and in PD patients (Schönberger et al., 2015). We hypothesized that performance would be impaired in patients (hypothesis 1) in concurrence with hypoactivity of the mesial motor loop, i.e., SMA and

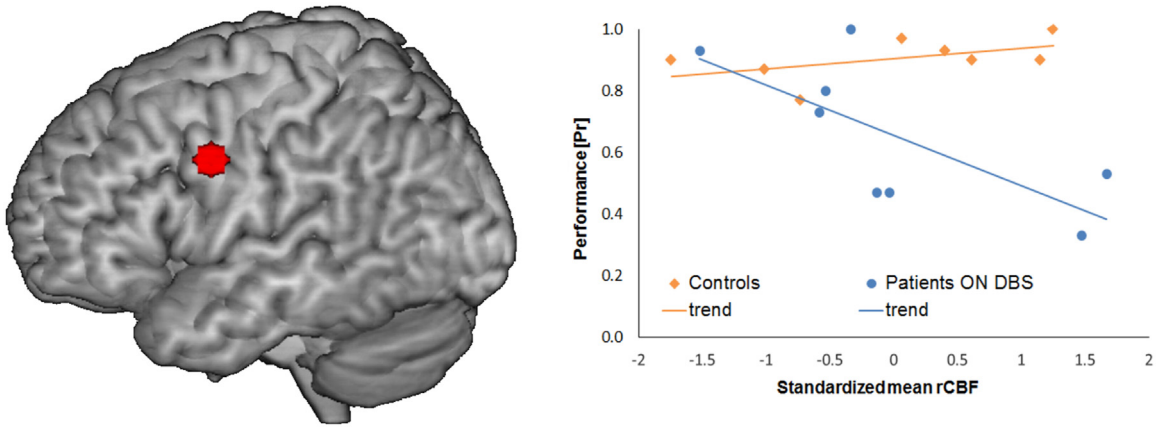

Fig. 3. Scatter plots show the relation of performance in serial prediction (SPT0) and mean regional cerebral blood flow (rCBF) in the left PM ROI in healthy controls and patients ON DBS. Spearman's Rho, a rank-based non-parametric measure, shows a significant correlation of performance and rCBF in patients ON DBS.

Table 6
Comparison of patients' characteristics of the current and previous samples.

Characteristic	Mean ± standard error of the mean			p[a]	
	PET sample (n = 8)	fMRI sample (n = 16)	Behav. sample (n = 20)	PET vs. fMRI	PET vs. Behav.
Age, years	61.5 ± 1.8	60.1 ± 2.1	57.9 ± 1.5	.759	.169
PANDA	27.8 ± 0.6	25.8 ± 0.9	25.7 ± 0.7	.370	.089
UPDRS III ON	20.1 ± 2.9	15.3 ± 1.5	17.6 ± 1.9	.159	.373
UPDRS III OFF	37.5 ± 5.1	23.6 ± 2.7	26.6 ± 2.0	.038	.059

PET sample = patients of the current study; fMRI sample = patients of the study described in Schönberger et al. (2015); behav. sample = patients of the study described in Schönberger et al. (2013); PANDA = Parkinson neuropsychometric dementia assessment. In the behavioural and the fMRI sample UPDRS III ON refers to motor scores under normal medication and UPDRS III OFF to motor scores after withdrawal of medication. In the PET sample, UPDRS III ON refers to motor scores ON DBS after withdrawal of medication, and UPDRS III OFF refers to motor scores after withdrawal of medication and OFF DBS.

[a] Significance of differences between groups, computed with Mann-Whitney *U* tests.

putamen (hypothesis 2). Additionally, we expected to find PM hyperactivity in patients, especially without deep brain stimulation (hypothesis 3). We concentrated on a ROI analysis of SMA, putamen, and PM driven by these hypotheses.

Supporting previous results (Schönberger et al., 2013, 2015), PD patients showed the hypothesized impaired serial prediction performance when compared to healthy controls (hypothesis 1). These deficits were unexpectedly large, as only half of the patients performed above chance level in the task version with increased load on the mesial motor loop (i.e., SPT+). Therefore, the results were limited to the (easier) task version (i.e., SPT0) with continuous stimuli that all participants performed successfully. The deficit in this task was accompanied by hypoactivity of putamen in patients compared to healthy controls, consistent with the expected dysfunction of the motor loop (hypothesis 2). As tremor scores were related to heightened activity of SMA located right dorsal to the area used in the ROI analysis (Table 5), the patients' resting tremor possibly interacted with sequence related processing, preventing to find hypoactivity of SMA as well. Importantly, we rather underestimated the patients' hypoactivity found in putamen because resting tremor activates the dorsal putamen (Mure et al., 2011). Finally, we found more activity in left PM in patients compared to controls and in patients OFF compared to ON stimulation, thereby supporting hypothesis 3.

Unexpectedly, there was no significant improvement of serial prediction performance ON compared to OFF DBS. This may be due to low statistical power because of the small sample size or other limiting factors such as the variability in individual medication and levodopa equivalent dose (see Table 1). However, DBS significantly reduced motor impairment, and therefore possibly was not as effective in restoring serial prediction performance as medication in our previous studies. Notably, DBS effectiveness in ameliorating motor symptoms was positively correlated to task performance in all conditions. Patients who show a good levodopa response and few non-responsive motor symptoms benefit more from DBS (Bronstein et al., 2011), suggesting that patients with a general loss of sensitivity to treatment performed poorly in serial prediction. We therefore argue that the cognitive performance level is attributable to patients' disease progression which causes deficient sequence processing normally provided by the SMA. Consistently, the current sample was more affected OFF DBS than the patients OFF medication in our previous studies.

Although there was no apparent effect of DBS on performance, DBS influenced activity in the motor loop, as patients ON DBS showed less activity of the left PM than patients OFF DBS. Therefore, the lack of performance differences OFF vs. ON DBS may also be related to the involvement of compensatory resources provided by PM hyperactivity when OFF DBS. Notably, PM activity showed specific correlations with serial prediction performance, thus rebutting the possibility that PM hyperactivity was caused by resting tremor: blocks with better performance were correlated to higher levels of PM activity in all participants. In contrast, the general level of PM activity showed a group specific pattern. While well performing controls tended to show more left PM engagement, patients performed the worse the higher levels of left PM activity they exhibited under stimulation (see Fig. 3). This pattern may clarify why half of the patients failed to perform the more difficult task version that challenges the mesial motor loop: The most parsimonious explanation is that DBS could not amplify the patients' severely affected motor loop activity to the required performance level, wherefore PM hyperactivity under these more challenging task conditions could not restore performance. In line with this interpretation, the extent of PM engagement differs from the previous fMRI study which found hyperactivity only when both the load on the mesial motor loop was increased and patients' dopaminergic medication was discontinued (Schönberger et al., 2015). In the current sample, PM hyperactivity was observed in the easier task version (i.e., SPT0) and in patients compared to controls independent of stimulation. This suggests that patients engaged in PM activation earlier, most likely because of advanced dysfunction of the motor loop. Notably, we previously found that the ability to increase SMA activity was related to good performance when internal sequence representation was challenged (Schönberger et al., 2015). This suggests that PM hyperactivity may preserve performance only for moderate PD stages with sufficient SMA engagement, while

compensation via PM involvement is no longer possible in more severe stages, also reflecting that compensatory mechanisms are limited.

Restrictions of compensation via increased activation have been described for the aging brain (Park and Reuter-Lorenz, 2009; Reuter-Lorenz, 2002; Steffener et al., 2009) and have also been observed in PD patients in a motor sequence learning task with different levels of task difficulty depending on sequence length (Mentis et al., 2003a, 2003b). In the latter study PD patients who showed task performance equal to controls exhibited an intensified activation of the same network including premotor and other frontal areas. Particularly, the left hemisphere was additionally activated compared to controls so that the patients showed almost normal performance when task difficulty was moderate. However, PD patients failed to learn long sequences that required bilateral activation in healthy participants. A further study implementing the same task suggested that the ability to compensate through elevated task-specific activation diminished with disease progression (Carbon et al., 2010), resulting in decremented task performance over time. These findings may parallel the limits of compensation via PM hyperactivity that were evident during serial prediction.

Regarding the influence of DBS on serial prediction, the question arises if DBS would have significantly improved performance in a less severely affected sample. It is plausible that DBS is less effective than medication in modulating task performance independent of the disease's progress, as shown in other cognitive tasks (Carbon et al., 2003). To answer this question, further research is needed, ideally comprising a group of DBS patients and non-DBS patients with similar disease status or comparing the effect of both therapies on serial prediction performance in one sample of DBS patients. Nevertheless, we replicated our previous results in the current sample of DBS patients, as we found the expected co-occurrence of hypoactivity in the putamen and cognitive impairments of PD patients. Furthermore, a compensatory involvement of the lateral premotor cortex was shown. We take the results to support our assumption that PD patients' deficits in the prediction of serial stimuli are due to motor loop dysfunction and that PM hyperactivity provides a compensational mechanism that is limited by disease progression.

To conclude, our results point to a contribution of premotor functions to some cognitive abilities of PD patients. Thus, cognitive deficits in PD are not exclusively caused by affected prefrontal loops but can be more appropriately explained by the interplay of multiple mechanisms including motor loop dysfunction. An impairment in perceptual sequence processing, as measured in the serial prediction task, may produce deficits in various cognitive tasks that require the processing of serial information and the prediction of future events. Therefore, it is worth considering to which degree premotor engagement can be advantageous in other cognitive tasks not only as a motor component, but as an interface with other frontal areas.

Acknowledgements

Klara Hagelweide and Anna Schönberger share the first authorship. We thank Carmen Selbach for experimental assistance. We are grateful to all participants, in particular to our patients, who enabled this study. This study was supported by the German Research Foundation, Clinical Research Group 219: KFO 219 TP4 (GZ SCHU 1439/3-1) (R.I.S., G.R.F.). The authors report no disclosures or conflicts of interest.

References

Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9 (1), 357–381.

Alhourani, A., McDowell, M.M., Randazzo, M., Wozny, T., Kondylis, E., Lipski, W.J., Richardson, R.M., 2015. Network effects of deep brain stimulation. J. Neurophysiol (jn-00275).

Boertien, T., Zrinzo, L., Kahan, J., Jahanshahi, M., Hariz, M., Mancini, L., Foltynie, T., 2011. Functional imaging of subthalamic nucleus deep brain stimulation in Parkinson's disease. Mov. Disord. 26 (10), 1835–1843.

Bronstein, J.M., Tagliati, M., Alterman, R.L., Lozano, A.M., Volkmann, J., Stefani, A., Pahwa, R., 2011. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch. Neurol. 68 (2) (165-165).

Brück, A., Portin, R., Lindell, A., Laihinen, A., Bergman, J., Haaparanta, M., Rinne, J.O., 2001. Positron emission tomography shows that impaired frontal lobe functioning in Parkinson's disease is related to dopaminergic hypofunction in the caudate nucleus. Neurosci. Lett. 311 (2), 81–84.

Carbon, M., Ghilardi, M.F., Feigin, A., Fukuda, M., Silvestri, G., Mentis, M.J., Eidelberg, D., 2003. Learning networks in health and Parkinson's disease: reproducibility and treatment effects. Hum. Brain Mapp. 19 (3), 197–211.

Carbon, M., Reetz, K., Ghilardi, M.F., Dhawan, V., Eidelberg, D., 2010. Early Parkinson's disease: longitudinal changes in brain activity during sequence learning. Neurobiol. Dis. 37 (2), 455–460.

Ceballos-Baumann, A.O., Boecker, H., Bartenstein, P., von Falkenhayn, I., Riescher, H., Conrad, B., Alesch, F., 1999. A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson disease: enhanced movement-related activity of motor-association cortex and decreased motor cortex resting activity. Arch. Neurol. 56 (8), 997–1003.

Chiken, S., Nambu, A., 2016. Mechanism of deep brain stimulation: inhibition, excitation, or disruption? Neuroscientist 22 (3), 313–322.

Cooper, J.A., Sagar, H.J., Jordan, N., Harvey, N.S., Sullivan, E.V., 1991. Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. Brain 114 (5), 2095–2122.

Davis, K.D., Taub, E., Houle, S., Lang, A.E., Dostrovsky, J.O., Tasker, R.R., Lozano, A.M., 1997. Globus pallidus stimulation activates the cortical motor system during alleviation of parkinsonian symptoms. Nat. Med. 3 (6), 671–674.

De Hemptinne, C., Ryapolova-Webb, E.S., Air, E.L., Garcia, P.A., Miller, K.J., Ojemann, J.G., Starr, P.A., 2013. Exaggerated phase–amplitude coupling in the primary motor cortex in Parkinson disease. Proc. Natl. Acad. Sci. USA 110 (12), 4780–4785.

Dirnberger, G., Jahanshahi, M., 2013. Executive dysfunction in Parkinson's disease: a review. J. Neuropsychol. 7 (2), 193–224.

Elgh, E., Domellöf, M., Linder, J., Edström, M., Stenlund, H., Forsgren, L., 2009. Cognitive function in early Parkinson's disease: a population-based study. Eur. J. Neurol. 16 (12), 1278–1284.

Evans, A.H., Pavese, N., Lawrence, A.D., Tai, Y.F., Appel, S., Doder, M., Piccini, P., 2006. Compulsive drug use linked to sensitized ventral striatal dopamine transmission. Ann. Neurol. 59 (5), 852–858.

Fahn, S., Elton, R., 1987. Members of the UPDRS Development Committee: Unified Parkinson's Disease Rating Scale. Florham Park, New York.

Finelli, D.A., Rezai, A.R., Ruggieri, P.M., Tkach, J.A., Nyenhuis, J.A., Hrdlicka, G., Shellock, F.G., 2002. MR imaging-related heating of deep brain stimulation electrodes: in vitro study. Am. J. Neuroradiol. 23 (10), 1795–1802.

Friston, K.J., Frith, C.D., Liddle, P.F., Dolan, R.J., Lammertsma, A.A., Frackowiak, R.S.J., 1990. The relationship between global and local changes in PET scans. J. Cereb. Blood Flow Metab. 10 (4), 458–466.

Friston, K., Ashburner, J., Frith, C.D., Poline, J.B., Heather, J.D., Frackowiak, R.S., 1995. Spatial registration and normalization of images. Hum. Brain Mapp. 3 (3), 165–189.

Friston, K.J., Rotshtein, P., Geng, J.J., Sterzer, P., Henson, R.N., 2006. A critique of functional localisers. Neuroimage 30 (4), 1077–1087.

Fukuda, M., Barnes, A., Simon, E.S., Holmes, A., Dhawan, V., Giladi, N., Eidelberg, D., 2004. Thalamic stimulation for parkinsonian tremor: correlation between regional cerebral blood flow and physiological tremor characteristics. Neuroimage 21 (2), 608–615.

Gawrys, L., Falkiewicz, M., Pilacinski, A., Riegel, M., Piatkowska-Janko, E., Bogorodzki, P., Koziorowski, D., 2014. The neural correlates of specific executive dysfunctions in Parkinson's disease. Acta Neurobiol. Exp. 74, 465–478.

Georgi, J.C., Stippich, C., Tronnier, V.M., Heiland, S., 2004. Active deep brain stimulation during MRI: a feasibility study. Magn. Reson. Med. 51 (2), 380–388.

Goldberg, G., 1985. Supplementary motor area structure and function: review and hypotheses. Behav. Brain Sci. 8 (04), 567–588.

Grafton, S.T., Turner, R.S., Desmurget, M., Bakay, R., Delong, M., Vitek, J., Crutcher, M., 2006. Normalizing motor-related brain activity Subthalamic nucleus stimulation in Parkinson disease. Neurology 66 (8), 1192–1199.

Hanakawa, T., Fukuyama, H., Katsumi, Y., Honda, M., Shibasaki, H., 1999. Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. Ann. Neurol. 45 (3), 329–336.

Haslinger, B., Erhard, P., Kämpfe, N., Boecker, H., Rummeny, E., Schwaiger, M., Ceballos-Baumann, A.O., 2001. Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. Brain 124 (3), 558–570.

Heo, J.H., Lee, K.M., Paek, S.H., Kim, M.J., Lee, J.Y., Kim, J.Y., Jeon, B.S., 2008. The effects of bilateral subthalamic nucleus deep brain stimulation (STN DBS) on cognition in Parkinson disease. J. Neurol. Sci. 273 (1), 19–24.

Hoehn, M.M., Yahr, M.D., 1967. Parkinsonism: onset, progression, and mortality. Neurology 50 (2) (318-318).

Hughes, A.J., Daniel, S.E., Kilford, L., Lees, A.J., 1992. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J. Neurol. Neurosurg. Psychiatry 55 (3), 181–184.

Jahanshahi, M., Ardouin, C.M.A., Brown, R.G., Rothwell, J.C., Obeso, J., Albanese, A., Limousin-Dowsey, P., 2000. The impact of deep brain stimulation on executive function in Parkinson's disease. Brain 123 (6), 1142–1154.

Kalbe, E., Calabrese, P., Kohn, N., Hilker, R., Riedel, O., Wittchen, H.U., Kessler, J., 2008. Screening for cognitive deficits in Parkinson's disease with the Parkinson neuropsychometric dementia assessment (PANDA) instrument. Park. Relat. Disord. 14 (2), 93–101.

Lewis, S.J., Dove, A., Robbins, T.W., Barker, R.A., Owen, A.M., 2003. Cognitive

impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. J. Neurosci. 23 (15), 6351–6356.
Limousin, P., Greene, J., Pollak, P., Rothwell, J., Benabid, A.L., Frackowiak, R., 1997. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. Ann. Neurol. 42 (3), 283–291.
Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19 (3), 1233–1239.
Mallol, R., Barrós-Loscertales, A., López, M., Belloch, V., Parcet, M.A., Ávila, C., 2007. Compensatory cortical mechanisms in Parkinson's disease evidenced with fMRI during the performance of pre-learned sequential movements. Brain Res. 1147, 265–271.
Mentis, M.J., Dhawan, V., Nakamura, T., Ghilardi, M.F., Feigin, A., Edwards, C., Eidelberg, D., 2003a. Enhancement of brain activation during trial-and-error sequence learning in early PD. Neurology 60 (4), 612–619.
Mentis, M.J., Dhawan, V., Feigin, A., Delalot, D., Zgaljardic, D., Edwards, C., Eidelberg, D., 2003b. Early stage Parkinson's disease patients and normal volunteers: comparative mechanisms of sequence learning. Hum. Brain Mapp. 20 (4), 246–258.
Michely, J., Volz, L.J., Barbe, M.T., Hoffstaedter, F., Viswanathan, S., Timmermann, L., Grefkes, C., 2015. Dopaminergic modulation of motor network dynamics in Parkinson's disease. Brain 138 (3), 664–678.
Mortimer, J.A., Pirozzolo, F.J., Hansch, E.C., Webster, D.D., 1982. Relationship of motor symptoms to intellectual deficits in Parkinson disease. Neurology 32, 133–137.
Mure, H., Hirano, S., Tang, C.C., Isaias, I.U., Antonini, A., Ma, Y., Eidelberg, D., 2011. Parkinson's disease tremor-related metabolic network: characterization, progression, and treatment effects. Neuroimage 54 (2), 1244–1253.
Muslimović, D., Post, B., Speelman, J.D., Schmand, B., 2005. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 65 (8), 1239–1245.
Nagano-Saito, A., Habak, C., Mejía-Constaín, B., Degroot, C., Monetta, L., Jubault, T., Ptito, A., 2014. Effect of mild cognitive impairment on the patterns of neural activity in early Parkinson's disease. Neurobiol. Aging 35 (1), 223–231.
Oswal, A., Brown, P., Litvak, V., 2013. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr. Opin. Neurol. 26 (6), 662–670.
Oswal, A., Beudel, M., Zrinzo, L., Limousin, P., Hariz, M., Foltynie, T., Brown, P., 2016. Deep brain stimulation modulates synchrony within spatially and spectrally distinct resting state networks in Parkinson's disease. Brain 139 (5), 1482–1496.
Owen, A.M., 2004. Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. Neuroscientist 10 (6), 525–537.
Park, D.C., Reuter-Lorenz, P., 2009. The adaptive brain: aging and neurocognitive scaffolding. Annu. Rev. Psychol. 60, 173–196.
Perestelo-Pérez, L., Rivero-Santana, A., Pérez-Ramos, J., Serrano-Pérez, P., Panetta, J., Hilarion, P., 2014. Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials. J. Neurol. 261 (11), 2051–2060.
Poletti, M., Frosini, D., Pagni, C., Baldacci, F., Nicoletti, V., Tognoni, G., Bonuccelli, U., 2012. Mild cognitive impairment and cognitive-motor relationships in newly diagnosed drug-naive patients with Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 83, 601–606.
Polito, C., Berti, V., Ramat, S., Vanzi, E., De Cristofaro, M.T., Pellicanò, G., Pupi, A., 2012. Interaction of caudate dopamine depletion and brain metabolic changes with cognitive dysfunction in early Parkinson's disease. Neurobiol. Aging 33 (1) (206-e29).
Rinne, J.O., Portin, R., Ruottinen, H., Nurmi, E., Bergman, J., Haaparanta, M., Solin, O., 2000. Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F] fluorodopa positron emission tomographic study. Arch. Neurol. 57 (4), 470–475.
Reuter-Lorenz, P.A., 2002. New visions of the aging mind and brain. Trends Cogn. Sci. 6 (9), 394–400.
Rodriguez-Oroz, M.C., Jahanshahi, M., Krack, P., Litvan, I., Macias, R., Bezard, E., Obeso, J.A., 2009. Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms. Lancet Neurol. 8 (12), 1128–1139.
Sabatini, U., Boulanouar, K., Fabre, N., Martin, F., Carel, C., Colonnese, C., Rascol, O., 2000. Cortical motor reorganization in akinetic patients with Parkinson's disease. Brain 123 (2), 394–403.
Saint-Cyr, J.A., Taylor, A.E., Lang, A.E., 1988. Procedural learning and neostyrial dysfunction in man. Brain 111 (4), 941–960.
Samuel, M., Ceballos-Baumann, A.O., Blin, J., Uema, T., Boecker, H., Passingham, R.E., Brooks, D.J., 1997. Evidence for lateral premotor and parietal overactivity in Parkinson's disease during sequential and bimanual movements. A PET study. Brain 120 (6), 963–976.
Sawamoto, N., Piccini, P., Hotton, G., Pavese, N., Thielemans, K., Brooks, D.J., 2008. Cognitive deficits and striato-frontal dopamine release in Parkinson's disease. Brain 131 (5), 1294–1302.
Schönberger, A.R., Barbe, M.T., Hagelweide, K., Kühn, A.B., Fink, G.R., Schubotz, R.I., 2013. Joint principles of motor and cognitive dysfunction in Parkinson's disease. Neuropsychologia 51 (8), 1417–1425.
Schönberger, A.R., Hagelweide, K., Pelzer, E.A., Fink, G.R., Schubotz, R.I., 2015. Motor loop dysfunction causes impaired cognitive sequencing in patients suffering from Parkinson's disease. Neuropsychologia 77, 409–420.
Schubotz, R.I., von Cramon, D.Y., 2003. Functional–anatomical concepts of human premotor cortex: evidence from fMRI and PET studies. Neuroimage 20, S120–S131.
Schubotz, R.I., von Cramon, D.Y., 2004. Anterior-posterior functional gradient within premotor fields: fMRI on memory-driven versus stimulus-driven sequencing. In: Proceedings of the 10th Annual Meeting of the Organization for Human Brain Mapping, Budapest, Hungary.
Schubotz, R.I., 2007. Prediction of external events with our motor system: towards a new framework. Trends Cogn. Sci. 11 (5), 211–218.
Shrivastava, D., Abosch, A., Hughes, J., Goerke, U., DelaBarre, L., Visaria, R., Vaughan, J.T., 2012. Heating induced near deep brain stimulation lead electrodes during magnetic resonance imaging with a 3 T transceive volume head coil. Phys. Med. Biol. 57 (17), 5651.
Silberstein, P., Pogosyan, A., Kühn, A.A., Hotton, G., Tisch, S., Kupsch, A., Brown, P., 2005. Cortico-cortical coupling in Parkinson's disease and its modulation by therapy. Brain 128 (6), 1277–1291.
Snodgrass, J.G., Corwin, J., 1988. Pragmatics of measuring recognition memory: applications to dementia and amnesia. J. Exp. Psychol.: Gen. 117 (1), 34.
Steffener, J., Brickman, A.M., Rakitin, B.C., Gazes, Y., Stern, Y., 2009. The impact of age-related changes on working memory functional activity. Brain Imaging Behav. 3 (2), 142–153.
Strafella, A.P., Dagher, A., Sadikot, A.F., 2003. Cerebral blood flow changes induced by subthalamic stimulation in Parkinson's disease. Neurology 60 (6), 1039–1042.
Thobois, S., Mertens, P., Guenot, M., Hermier, M., Mollion, H., Bouvard, M., Sindou, M., 2002. Subthalamic nucleus stimulation in Parkinson's disease. J. Neurol. 249 (5), 529–534.
Tomlinson, C.L., Stowe, R., Patel, S., Rick, C., Gray, R., Clarke, C.E., 2010. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov. Disord. 25 (15), 2649–2653.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15 (1), 273–289.
Udupa, K., Chen, R., 2015. The mechanisms of action of deep brain stimulation and ideas for the future development. Progress. Neurobiol. 133, 27–49.
Weaver, F.M., Follett, K., Stern, M., Hur, K., Harris, C., Marks, W.J., Pahwa, R., 2009. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. Jama 301 (1), 63–73.
Weinberger, M., Mahant, N., Hutchison, W.D., Lozano, A.M., Moro, E., Hodaie, M., Dostrovsky, J.O., 2006. Beta oscillatory activity in the subthalamic nucleus and its relation to dopaminergic response in Parkinson's disease. J. Neurophysiol. 96 (6), 3248–3256.
Wienhard, K., Schmand, M., Casey, M.E., Baker, B., Bao, J., Eriksson, L., ... Nutt, R., 2002. The ECAT HRRT: performance and first clinical application of new high resolution research tomograph. IEEE Trans. Nucl. Sci. 40 (1), 104–110.
Williams, L.N., Seignourel, P., Crucian, P.G., Okun, M.S., Rodriguez, R.I., Skidmore, F.M., Fernandez, H.H., 2007. Laterality, region, and type of motor dysfunction correlate with cognitive impairment in Parkinson's disease. Mov. Disord. 22 (1), 141–145.
Zgaljardic, D.J., Borod, J.C., Foldi, N.S., Mattis, P.J., Gordon, M.F., Feigin, A., Eidelberg, D., 2006. An examination of executive dysfunction associated with frontostriatal circuitry in Parkinson's disease. J. Clin. Exp. Neuropsychol. 28 (7) (1127-11).