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Joint principles of motor and cognitive dysfunction in Parkinson's disease

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ABSTRACT

Traditionally, the lateral premotor cortex (PM) is assigned a role in stimulus-driven rather than memory-driven motor control, whereas the opposite holds for the mesial premotor cortex (supplementary motor area, SMA). Consistently, patients with Parkinson's Disease (PD), in which a specific functional degradation of the mesial loop (i.e., SMA-Striatum) occurs, show impaired memory-driven but relatively preserved stimulus-driven motor control. However, both parts of the premotor cortex are involved in perceptual prediction tasks as well. Here we tested whether the functional bias described on the motor level (i.e., memory-driven/mesial versus stimulus-driven/lateral) can also be detected in perceptual prediction tasks thereby suggesting that PD patients exhibit the same pattern of impaired memory-driven and preserved stimulus-driven control in the cognitive domain. To this end, we investigated 20 male PD-patients "on" and "off" dopaminergic medication while performing a serial prediction task (SPT). A specific modification was implemented to the classical SPT (SPT0) that caused shifts from stimulus- to memory-based prediction (SPT+). As a result, PD patients showed a significantly impaired performance "off" compared to "on" medication for SPT+, whereas no significant "on"/"off"-effects were found for SPT0. Descriptively, the "off"-performance decreased gradually with increasing demands on memory-based prediction. Furthermore, the severity of motor deficits according to the UPDRS III correlated significantly with impaired performance in SPT0 "on" medication. Importantly, an even stronger dependency was found for UPDRS III and SPT+. These findings point to a role of the SMA-striatal loop in memory-driven serial prediction beyond the motor domain.

1. Introduction

Apart from motor deficits, cognitive impairments have a major influence on the quality of life in Parkinson's disease (PD) (Schrag, Jahanshahi, & Quinn, 2000; Ziemssen & Reichmann, 2007). Characteristic neuropsychological symptoms of PD such as deficits in attention, working-memory, concept formation, planning, and set-shifting are reminiscent of those detected in patients with prefrontal cortex lesions (Brown & Marsden, 1988; Kulisevsky, 2000; Muslimovic, Post, Speelman, & Schmand, 2005; Van Spaendonck, Berger, Horstink, Buytenhuijs, & Cools, 1996) and are therefore often subsumed under the notion of a "dysexecutive syndrome" (Martinez-Horta & Kulisevsky, 2011). In PD, frontal dysfunction is most probably caused by deficient input from the caudate nucleus (Dubois & Pillon, 1997; Saint-Cyr, Taylor, & Lang, 1988; Taylor, Saint-Cyr, & Lang, 1990) which receives no longer sufficient dopamine projections from the degenerating substantia nigra (Alexander, DeLong, & Strick, 1986; Dubois & Pillon, 1997; Taylor, Saint-Cyr, & Lang, 1986). Frontal functions may be further deteriorated due to degeneration of the dopaminergic mesocortical pathway emanating from ventral tegmental area (Javoy-Agid & Agid, 1980). In contrast to the caudate-prefrontal loops, the so-called "motor loop" (Alexander et al., 1986) that connects the putamen to the lateral premotor cortex (PM) and the supplementary motor area (SMA), is hardly ever considered as potential origin of cognitive dysfunction in PD. However, evidence has accumulated that some cognitive functions draw particularly on the premotor loops (Jeannerod, 2001; Schubotz, 2007).

In a review addressing PD-associated cognitive impairment, Brown and Marsden (1990) argued that cognitive impairment in PD is present when patients have to rely on internal strategies, whereas performance is preserved when external cues or guidance

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are provided (e.g., Dubois & Pillon, 1997; Flowers, Pearce, & Pearce, 1984; Flowers & Robertson, 1985). Notably, difficulties in internal guidance and relatively preserved external guidance of behaviour are well-known features of motor control in PD. A striking example of this bias is provided by the phenomenon of "paradoxical kinesis": Patients who suffer from hypokinesia or akinesia are able to improve their gait with help of external cues like rhythmic auditory stimulation (McIntosh, Brown, Rice, & Thaut, 1997) or visual stimuli such as transversely oriented lines on the walking surface (Azulay et al., 1999; Hanakawa, Fukuyama, Katsumi, Honda, & Shibasaki, 1999; Martin, 1967).

It has been suggested that the neurofunctional mechanisms underlying paradoxical kinesis may be related to a functional dichotomy in the (pre)motor loops: Goldberg (1985) proposed that the supplementary motor area (SMA) is associated with internally or memory guided processing, whereas the lateral premotor cortex supports externally or stimulus driven processing. This view is largely (but not always, cf. Cunnington, Windischberger, Deecke, & Moser, 2002; Weeks, Honda, Catalan, & Hallett, 2001) in keeping with imaging studies comparing internally to externally guided movements (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2003; Heuninckx, Wenderoth, & Swinnen, 2010). In Parkinson's disease, dopamine depletion is worst in the putamen (Brooks et al., 1990), whose main cortical target is the SMA (Alexander et al., 1986). Accordingly, PD patients performing motor tasks show a decreased blood flow in the SMA and putamen compared to age-matched controls (Playford et al., 1992). In contrast, they exhibit an increased blood flow of the lateral premotor cortex during motor tasks (Haslinger et al., 2001; Samuel et al., 1997). Moreover, administration of Levodopa in PD restores SMA-activation at least to a certain amount and decreases lateral hyper-activation (Haslinger et al., 2001). Lateral premotor activity is significantly higher when patients improve their motor abilities by relying on external cues (Hanakawa et al., 1999). Against the background of these observations, it has been suggested that lateral premotor activity may reflect compensatory processes for reduced SMA function in PD (Hanakawa et al., 1999).

We here aimed at investigating whether the known functional dichotomy of the lateral and mesial premotor cortex for motor tasks, i.e., lateral = stimulus–driven, mesial = memory–driven, holds also for tasks drawing on cognitive functions of the motor system. The serial prediction task (SPT) (Schubotz, 1999) has been shown to activate both the lateral premotor cortex and the SMA in the absence of motor demands (Schubotz & von Cramon, 2003). We modified the SPT in order to parametrically increase dependency on sequence memory, and hence internal guidance. Thus our motivation was to test PD patients (1) in a cognitive task that is known to engage the premotor system, which in turn is known to be particularly impaired in PD patients and (2) to vary the degree to which patients can rely on external cues. By this means we tested to what extent PD patients are able to compensate for occasional absence of prediction-triggering and prediction-confirming stimuli. Moreover, in order to uncover the direct role of dopaminergic supply, we examined the modulatory effect of dopaminergic medication on the described task by comparing the patients' performance "on" and "off" medication to that of healthy age, gender and education matched control subjects.

In the SPT, subjects monitor a repetitive stimulus sequence that accords to the structure 1-2-3-1-2-3-1-2-3; subsequently they have to indicate in a forced choice mode whether the sequence's last repetition ended orderly (1-2-3) or not (1-3-2 or 2-1-3). Note that the SPT is a purely cognitive task. In this regard, it clearly differs from otherwise related sequential paradigms such as the serial reaction time task (SRT) (Nissen & Bullemer, 1987). The parametric modification we implemented to the classical SPT (SPT+, hereafter) was a masking of a varying number of stimuli in the sequence (0–4 out of 15) during which subjects are forced to keep track of the correct stimulus order on memory basis.

We hypothesized that, due to a functional degradation of the motor system, (i) PD patients show a deficit in serial prediction when compared to healthy controls, (ii) performance correlates with PD-related motor symptoms (according to UPDRS III), and (iii) dopaminergic medication can restore performance significantly. More importantly, due to the particular detriment in the striatal-SMA-loop in PD, we furthermore expected the impairment of PD patients to be even more prominent when prediction is less regularly informed by external stimuli (i.e., in the SPT+ condition).

2. Methods

2.1. Participants

Twenty male PD patients with a mean age of 57.9 years (range 45–70 years) participated in the study. Patients were acquired from the neurologic outpatient clinic of the University Hospital of Cologne. All patients treated in the outpatient clinic and diagnosed with idiopathic Parkinson's disease according to the UK PD Society Brain Bank Criteria (Hughes, Daniel, Kilford, & Lees, 1992) were asked for participation in our study if they were less than 80 years old. No subject had undergone surgical treatment of the disease and no subject had a history of any other neurological or psychiatric diseases. Sixteen patients belonged to the rigid-akinetic and four to the equivalence type according to Spiegel et al. (2007). Symptoms of seven patients were left-dominant, and symptoms of thirteen patients were right-dominant (with onset of symptoms as criterion). All patients received dopaminergic medication (see Table 2 for levodopa equivalent daily dose [LEDD] according to Tomlinson et al. 2010) and were tested once on their regular medication and once "off" medication. "Off"-state was defined as at least 14 h of withdrawal of dopaminergic medication; long acting dopamine agonists were discontinued up to 36 h and replaced by short acting dopamine agonists until complete cessation 14 h before testing. The severity of clinical symptoms was defined according to Hoehn and Yahr (1967) and the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS III) (Fahn & Elton, 1987). UPDRS III was assessed on video tapes by a movement disorder specialist blinded for state of medication. Mean UPDRS III scores were 17.6 "on" and 26.6 "off" medication. Hoehn and Yahr ratings ranged between I and III under regular medication.

Twenty healthy male participants comparable to the patients regarding age and level of school education served as control subjects. Patients or controls with any evidence of dementia or depression were excluded from the study. All participants scored between 18 and 30 points in the Parkinson Neuropsychometric Dementia Assessment (PANDA; 18–30 points = "age adequate cognitive performance") (Kalbe et al., 2008) and lower than 16 points in the Beck depression inventory-II (BDI-II; cut-off for depression: ≥20 points) (Hautzinger, Keller, & Kühner, 2006).

All subjects gave written informed consent prior to participation. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee.

2.2. Stimuli and tasks

In the serial prediction task (SPT) a sequence of fifteen stimuli had to be monitored for any violation (Fig. 1A). Stimuli consisted of twelve concentric circles that differed in size, each composed of an outer circle and a smaller circle placed in

Table 1
Subject demographics and neuropsychological test data.

Characteristic or test	PD patients ($n=20$)	Healthy controls ($n=20$)	p value[a]
Age, y	57.85 ± 1.52	58.10 ± 1.33	.555
Education, y	10.85 ± .48	11.35 ± .43	.212
PANDA	25.65 ± .70	26.70 ± .59	.312
LPS 4	25.53 ± 1.19	25.90 ± .79	1.000
BDI-II	1.70 ± 5.40	4.75 ± 1.05	.570
TAP divided attention "on"	.055 ± .013	.029 ± .010	.085
TAP divided attention "off"	.042 ± .012	.027 ± .007	.418
TAP go/ nogo "on"	.003 ± .003	.000 ± .000	.34
TAP go/ nogo "off"	.003 ± .003	.002 ± .002	1.00

Data are shown as mean ± standard error;
PD: Parkinson's Disease; PANDA: Parkinson Neuropsychometric Dementia Assessment; LPS 4: Leistungsprüfsystem; BDI-II: Beck Depression Inventory-II; TAP: Testbatterie zur Aufmerksamkeitsprüfung.

[a] p value of paired t-tests.

Table 2
Patient's clinical and neuropsychological data "on" and "off" dopaminergic medication.

Characteristic or test	PD patients ($n=20$) "on" medication	PD patients ($n=20$) "off" medication	p value[a]
UPDRS III	17.60 ± 1.97	26.55 ± 2.03	< .001*
levodopa equivalent daily dose	639.5 ± 85.71	–	–
TAP divided attention	.055 ± .013	.042 ± .012	.459
TAP go/ nogo	.003 ± .003	.003 ± .003	1.000

Data are shown as mean ± standard error;
PD: Parkinson's Disease; UPDRS III: Unified Parkinson's Disease Rating Scale; TAP: Testbatterie zur Aufmerksamkeitsprüfung.

[a] p value of paired t-tests;
* $p < 0.05$.

its centre. All stimuli were presented on a white rectangular frame as background figure, so that the impression arose that pictures on playing cards were shown. Occurrence of the twelve different stimuli was counterbalanced across trials. One trial comprised always a sequence of three different stimuli that were shown one after the other (1-2-3). This three-stimuli-sequence was repeated five times. Each stimulus was presented 600 ms with an inter-stimulus-interval of 125 ms. Every trial was preceded by a 1 s fixation cross and followed by a forced-choice-response phase: After presentation of stimuli subjects had a period of 3.5 s to indicate whether the sequence was regular until its end or not. Therefore, two response-buttons were provided: one for answering "YES" (=sequence was correct till its end) and the other for responding "NO" (=sequential switch occurred). In 50% of the trials the sequence was violated. Here, the position of two stimuli within the last repetition was switched: instead of the previously presented sequence 1-2-3 the order 1-3-2 or 2-1-3 was shown. After subject's responses a feedback indicating either the correct or the false response was presented for 1 s. One trial lasted 18.75 s in total. The inter-trial-interval was 4 s.

The parametric modulation that aimed at enhancing internal sequencing comprised so-called "occluders", i.e., non-informative stimuli which replaced one stimulus of the sequence (Fig. 1B). This means that in case of an occluder only the white rectangular frame similar to a blank playing card appeared.

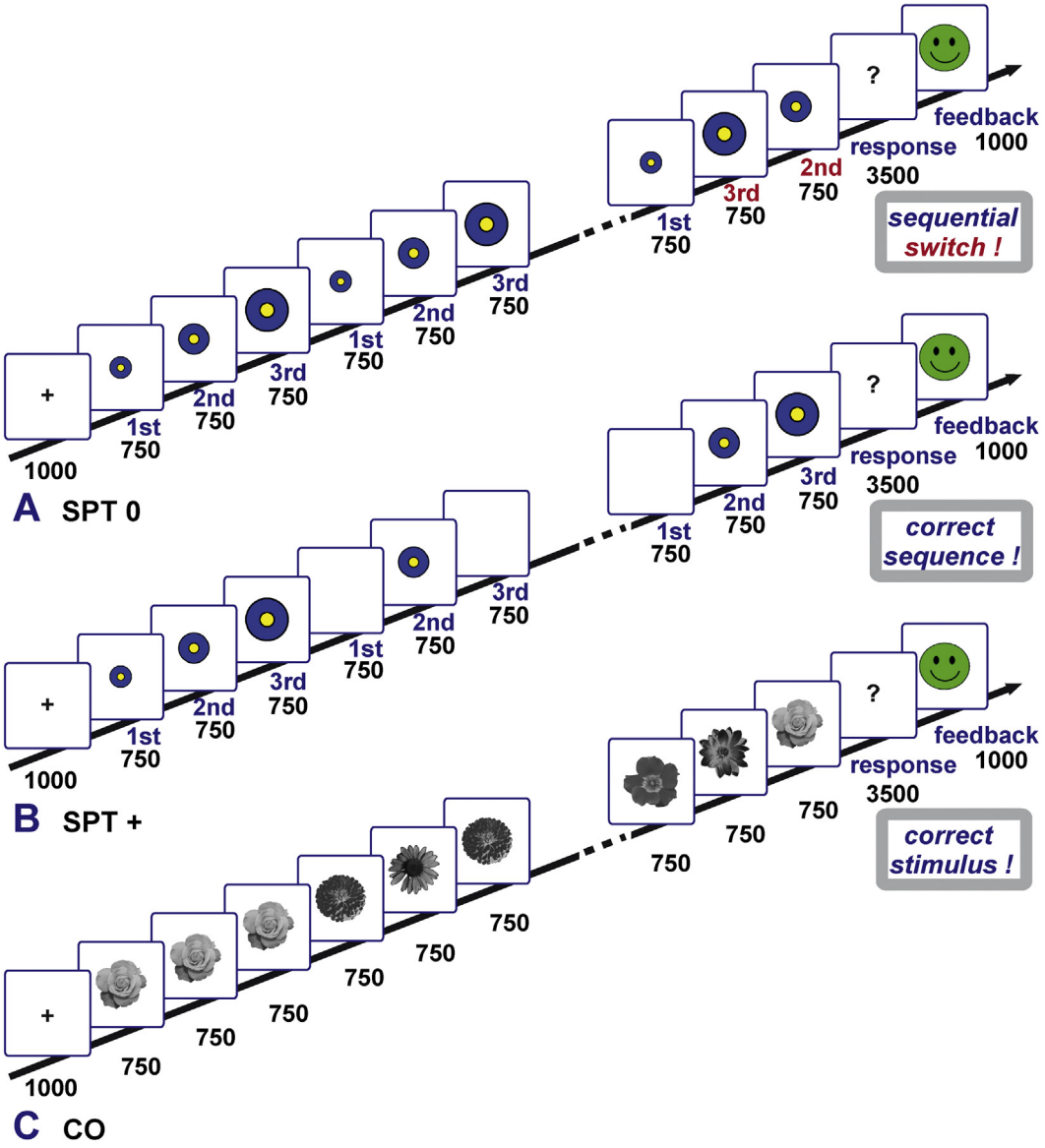

Fig. 1. Stimulus material and trial structure. Every trial was preceded by a fixation cross (1 s). Subsequently, 15 stimuli followed (note that catch trials (20%) consisted only of 12, 9, or 6 stimuli). After a forced-choice-response phase with maximum 3.5 s to deliver a response, a valid symbolic feedback was provided for 1 s. (A) SPT 0 (serial prediction task). Subjects were asked to monitor a sequence of three circles (1-2-3) that differ in size. At the end of each trial, subjects had to indicate whether the sequence ended as predicted or not (i.e., a sequential switch occurred). In 50% of all trials, the order of two of the last three stimuli in a trial was flipped (25%: 1-3-2; 25%: 2-1-3; 50%: 1-2-3). (B) SPT+(serial prediction task with occluders). Subjects had to perform in the same manner as in SPT 0, except that 1-4 stimuli of every trial were replaced by so-called occluders: instead of a circle, a blank card was shown. (C) CO (control task). Here, the first stimulus was presented three times in order to allow proper memorization. Afterwards, a random sequence of similar stimuli was presented. At the end of each trial, subjects had to indicate whether the last stimulus matched exactly the first one. Length of trials varied (15, 12, 9, or 6 stimuli) to ensure a continuous high level of attention.

In order to mark the blank card as a replacement of a standard stimulus and so to enable the subject to keep track of the sequence a flash-light signalling each stimulus (both occluder and standard stimulus) was provided. The first three stimuli were never replaced by an occluder because they were essential to define the sequence for each trial. For the following twelve stimuli 0%, 8.3%, 16.7%, 25% or 33.3% were masked by occluders. Never an occluder followed directly onto another one, and for the last three stimuli maximally one occluder occurred in order to preserve a moderate level of difficulty. Position of occluders was counterbalanced across trials. 40 trials with one to four occluders (10 trials for every occluder-condition) and 24 trials without any occluder were presented.

In addition to the SPT we applied a serial match to sample task to control for effects of no interest such as perception, attention and response (Fig. 1C). Here, also fifteen stimuli were shown consecutively with presentation parameters identical to those of the SPT. Stimuli were selected in a randomized order out of 200 different stimuli. Stimulus material consisted of 50 different monochrome photos of blossoms. Each photo was graphically modified, so that four versions with different grey values were generated, resulting in 200 different stimuli. Stimuli were also shown on the white rectangular background as in the SPT.

In this control task the first stimulus of every trial was presented three times. Subjects were instructed to memorize this stimulus. Subsequently, twelve other randomized stimuli were shown. At the end of the trial participants had to indicate whether the last stimulus was identical to the very first one. Occluders appeared also in that task in order to make the perceptual effects similar to those of the SPT, although occluders did not have any relevance for correctly answering the control task, because the last or first stimulus was never an occluder.

Twelve SPT-trials and four control task-trials that ended unexpectedly after six, nine or 12 stimuli were added in order to ensure a high level of attention. These trials had to be answered like the standard trials. All conditions were presented in a randomized order (mixed trial design). Trials were distributed across three blocks of 10.3 min with two breaks in between where subjects could take a rest for approximately 5 min. In total 99 trials were shown: 76 were SPT-trials and 23 control task trials. In each condition, 50% of the trials had to be answered with "YES" and 50% with "NO".

2.3. Study-design

Every participant attended our study on three consecutive days. The first day, every subject received training on the SPT with and without occluders and on the control task. Furthermore, each subject completed a neuropsychological test-battery including BDI-II (Hautzinger et al., 2006), PANDA (Kalbe et al., 2008) and LPS 4 (subtest 4 of the German intelligence test battery "Leistungsprüfungssystem") (Horn, 1983). BDI-II was used for assessment of depressive symptoms. LPS 4, a tool measuring reasoning, and PANDA, a screening for cognitive impairment in PD, were employed to estimate general cognitive performance. On day 1 all patients were on their regular dopaminergic medication, so that they were able to familiarize with the SPT and the control task "on" medication. The following day, 50% of patients were tested "on" medication and 50% were tested "off" medication. Healthy controls did not receive any medication. Participants first performed the two subtests "divided attention" and "go/no go" for selective attention of the TAP ("Testbatterie zur Aufmerksamkeitsprüfung") (Zimmermann & Fimm, 1992) to assess individual levels of attention that day. Subsequently, the 99 trials of the SPT and the control task were completed and the UPDRS-III was conducted for all patients. The third day was arranged in the same way as day two, except that the other 50% of patients were now tested "off" medication and vice versa.

2.4. Statistical analysis

Statistical analyses were conducted using the statistical software package SPSS (SPSS Statistic 17.0, IBM, Chicago, IL). Behavioural performance was assessed by probability of recognition (P_r=hit rate−false alarm rate) and corresponding bias index (B_r=false alarm rate/ $(1-P_r)$; Snodgrass & Corwin, 1988). The hit rate was defined as the sum of trials that were correctly answered with "YES" relative to the sum of all trials that had to be answered with "YES". The false alarm rate was defined as the sum of trials that were falsely answered with "YES" relative to the sum of trials that had to be answered with "NO". Reaction times were not included in our analysis in order to avoid any motor influence.

Paired t test for comparison of patients and controls were conducted for age, years of school education, PANDA, LPS 4 and BDI-II. Further t tests were calculated to assess differences in "on"- versus "off"-state regarding UPDRS III and performance in TAP.

We conducted an analysis of variance (ANOVA) in order to compare the performance of an increased internal and a comparatively more external sequencing and performance in the control task contrasting patients ("on" and "off" medication) with healthy controls. The analysis involved a $3 \times 2 \times 2$ design with the within-subject factors TASK (control task [CO] vs. SPT without occluders [SPT0] vs. SPT with occluders [SPT+]), GROUP (patients vs. controls) and MEDICATION ("on" vs. "off" dopaminergic medication). Healthy controls did not receive medication, but were also tested in two sessions in order to control for learning effects: session one and two were classified "on" or "off" for control subjects depending on what session was "on" or "off" medication for their matched patient.

To test whether a difference in SPT-performance was accompanied by a specific strategy, e.g., a conservative answering pattern with few positive reactions, a $2 \times 2 \times 2$ analysis of variance with factors TASK (SPT0 vs. SPT+), GROUP (patients vs. controls) and MEDICATION ("on" vs. "off") was conducted with B_r as dependent variable. B_r values greater than 0.5 indicate a liberal response bias, and values less than 0.5 indicate a conservative bias.

To estimate the effect of increasing occluders including every single occluder level we calculated a $5 \times 2 \times 2$ ANOVA with the within-subject factors TASK (SPT with zero vs. one vs. two vs. three vs. four occluders), GROUP (patients vs. controls) and MEDICATION ("on" vs. "off").

An additional analysis was carried out to assess the effect of increasing occluders in "on"- and "off"-state with respect to the individual cognitive abilities of the patients. Although patients were matched with healthy controls regarding age and level of education, this is not a very precise method to control for differences in general cognitive performance. Therefore we conducted a 2×2 AN**C**OVA for patients only using the extreme occluder values with the within-subject factors TASK (SPT0 vs. SPT with four occluders) and MEDICATION ("on" vs. "off") and included PANDA and LPS 4 as covariates to control for different cognitive abilities.

In all analyses, Greenhouse–Geisser epsilon was used where the assumption of sphericity was violated.

To further investigate the impact of severity of disease, correlation analyses for UPDRS III and performance in SPT0, SPT+, CO, PANDA and LPS 4 were carried out for "on"- and "off"-state, respectively. To examine if akinetic-rigid symptoms are more closely related to performance in SPT than tremor symptoms, UPDRS III-items were split into tremor-items and non-tremor-items according to Spiegel et al. (2007) and separately correlated with performance in SPT0 and SPT+. Note that PD patients belonged to the rigid-akinetic or equivalence type and no group comparison of tremor dominant and rigid-akinetic patients was possible. For tremor-items, the sum of UPDRS items 20 (tremor at rest) and 21 (action or postural tremor of hands) was calculated. For non-tremor-items, the sum of UPDRS items 18 (speech), 19 (facial expression), 22 (rigidity), 27 (arising from chair), 28 (posture), 29 (gait), 30 (postural stability) and 31 (body bradykinesia and hypokinesia) was calculated.

Furthermore, correlations between age and performance in SPT0, SPT+ and CO "on" and "off" medication were calculated. All correlation analyses were computed using standard Pearson's correlation coefficient and significance.

3. Results

3.1. Neuropsychological test performance and demographic data

Neuropsychological and demographic data of both patients and healthy controls are shown in Table 1. Paired t tests comparing patients and their corresponding healthy match exhibited no differences for age, education, BDI-II-scores and performance in PANDA, LPS 4, and both subtests of TAP. Table 2 provides clinical and neuropsychological data of patients "on" and "off" dopaminergic medication. Paired t tests revealed a significant difference between UPDRS III "on" medication and UPDRS III "off" medication ($p < .001$). No "on"/"off"-differences were observed for performance in both subtests of TAP (divided attention and go/nogo).

3.2. Performance and response bias in CO, SPT0 and SPT+ of patients "on" and "off" medication compared to healthy controls

The $3 \times 2 \times 2$ ANOVA examining the performance in CO, SPT0 and SPT+ for patients "on" and "off" medication and healthy controls yielded a main effect of GROUP ($F(1,19)=8.57$, $p = .009$). Healthy controls ($.74 \pm .03$; mean $\pm$ standard error) exhibited a better performance than patients ($.57 \pm .05$) independently of TASK and MEDICATION. There was also a significant main effect for TASK ($F(2,38)=49.01$, $p < .001$). Post hoc test with Bonferroni adjusted α-level indicated that performance in CO ($.84 \pm .02$) was significantly increased compared to performance in SPT0 ($.65 \pm .04$) ($p < .001$) and SPT+ ($.46 \pm .043$) ($p < .001$) and performance in SPT0 was significantly increased compared to SPT+ ($p < .001$). Furthermore, the interaction GROUP × MEDICATION × TASK was significant ($F(2,38)=3.28$, $p=.048$) (Fig. 2). Post hoc tests with Bonferroni adjusted α-level addressing the effect of medication

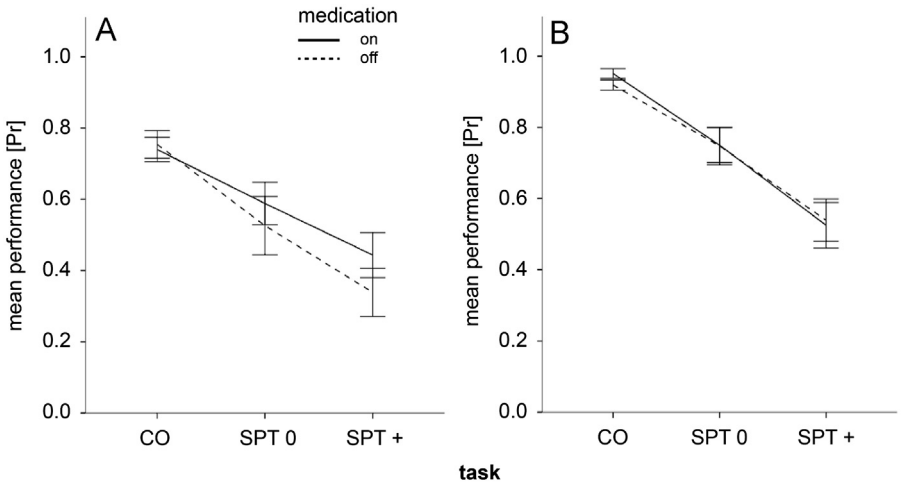

Fig. 2. Performance of patients "on" and "off" dopaminergic medication and healthy controls in the SPT with and without occluders and in the control task: ANOVA with the within-subject factors: TASK (CO vs. SPT 0 vs. SPT +) × GROUP (patients vs. healthy controls) × MEDICATION (on vs. off). Healthy controls did not receive any medication, but were classified "on" or "off" according to their matched patient. Performance was assessed by P_r (probability of recognition). CO = control task; SPT 0 = serial prediction task without occluders; SPT+ = serial prediction task with occluders. Data are shown as mean ± standard error.

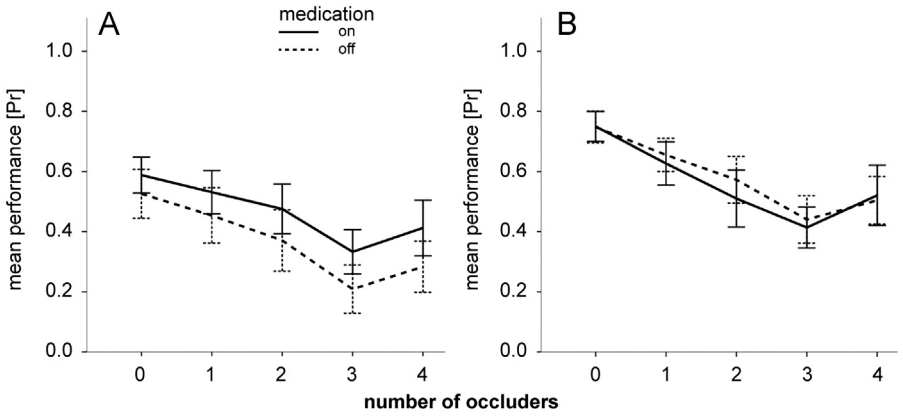

Fig. 3. Performance of patients "on" and "off" dopaminergic medication and of healthy controls for increasing levels of occluders in SPT. Note that healthy controls did not receive medication, but were classified "on" or "off" according to their matched patient. Performance was assessed by P_r (probability of recognition). Data are shown as mean ± standard error.

in patients corroborate our hypothesis: in the patient-group there was a significant decrease in performance "off" compared to "on" medication only for SPT+ ($p = .041$), whereas no significant "on"/"off"-differences for SPT0 and CO were found. Healthy controls did not exhibit a significantly different "on"/"off"-performance in any task. Note that controls did not receive any medication, but their performance on day 1 and day 2 was classified as "on" or "off" depending on whether their matched patient was "on" or "off" dopaminergic medication that day.

Because the performance of controls did not differ "on" and "off", their mean performance in SPT was calculated for comparison with patients' performance in SPT. Patients "on" medication ($.47 \pm .06$) show a trend towards poorer performance in serial prediction compared to healthy controls ($.64 \pm .05$) ($p = .054$) and patients "off" medication ($.43 \pm .07$) performed significantly worse than controls ($p = .032$). Examining both SPT-variants separately, patients "on" medication exhibited significantly poorer performance than controls in SPT0 ($p = .05$), but not in SPT+ ($p = .315$).

Regarding differences in performance in SPT+ and SPT0, t tests showed that patients "on" medication ($p = .012$), patients "off" medication ($p = .006$) and healthy controls ($p < .001$) showed better performance in SPT0 than in SPT+.

The $2 \times 2 \times 2$ ANOVA examining differences in response bias in SPT yielded no significant effects, i.e., healthy controls and patients did not show different response biases, "on" as well as "off" medication, both in SPT0 and in SPT+. Mean response bias was $.5 \pm .02$, indicating a neutral response pattern in SPT.

3.3. Performance "on" and "off" medication in SPT with increasing number of occluders

The $5 \times 2 \times 2$ ANOVA including all occluder levels and comparing performance "on" and "off" for patients and control subjects yielded a significant main effect for TASK ($F(4,76) = 17.97$, $p < .001$). Post hoc tests with Bonferroni adjusted α-level exhibited that performance in SPT0 differed significantly from performance in SPT with one occluder ($p = .041$), two occluders ($p = .015$), three occluders ($p < .001$) and four occluders ($p = .001$). Furthermore, performance in SPT with one occluder differed significantly from performance in SPT with three occluders ($p < .001$) and four occluders ($p = .030$). Controls ($.57 \pm .06$) performed better than patients ($.42 \pm .06$), though this trend was not significant ($F(1,19) = 3.57$, $p = .074$). In addition, a significant interaction GROUP × MEDICATION ($F(1,19) = 6.13$, $p = .023$) was observed. Post hoc tests revealed that performance in both groups differed significantly "off" medication ($p = .029$), but not "on" medication ($p = .248$) (Fig. 3).

The 2×2 ANCOVA comparing extreme occluder values (zero vs. four occluders) for patients "on" and "off" medication exhibited a

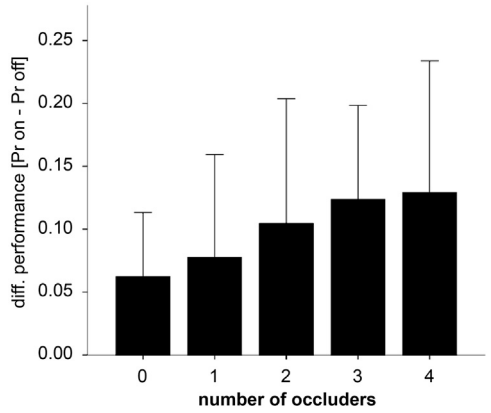

Fig. 4. Difference scores for patients' performance "on" and "off" dopaminergic medication (P_r "on"−P_r "off"). Performance was assessed by P_r (probability of recognition). SPT 0 up to SPT 4 refers to serial prediction task with 0–4 occluders. Data are shown as mean ± standard error.

main effect for TASK ($F(1,14)=5.59$, $p=.033$): Patients performed better in SPT0 ($.63 \pm .07$) than in SPT with four occluders ($.37 \pm .07$). The interaction MEDICATION × TASK shows a trend towards significance ($F(1,14)=4.16$, $p=.061$).

Descriptive patient data in Fig. 4 show the mean "on"/"off"-difference (P_r "on" medication−P_r "off" medication) of performance for all SPT trials with zero to four occluders.

3.4. Correlations of cognitive performance with UPDRS III and age

The correlation between UPDRS III "on" medication and performance in SPT0 "on" medication was significant ($r=-.514$, $p=.02$) for patients, but did not reach significance "off" medication. Also performance in SPT+ "on" correlated significantly with UPDRS III "on" ($r=-.628$, $p=.003$), while performance in SPT+ "off" and UPDRS III "off" did not correlate. There were neither correlations "on" nor "off" for UPDRS III and patients' performance in the control task, PANDA or LPS 4.

Separating UPDRS III into tremor-items and non-tremor-items the non-tremor-items "on" medication correlated significantly with performance in SPT0 ($r=-.466$, $p=.038$) and SPT+ ($r=-.601$, $p=.005$) "on" medication. In "off"-state no correlations for performance in SPT0 or SPT+ and non-tremor-items were found. The tremor-items did not correlate with performance in SPT0 or SPT+ neither "on" nor "off" medication.

Investigating the influence of age on performance in CO, SPT0 and SPT+ in patients "on" and "off" medication only a correlation of age and performance in SPT0 "off"-state was found ($r=-.487$, $p=.03$). There were also no correlations for age and performance in all tasks for healthy controls.

4. Discussion

This study was conducted to determine whether principles underlying motor dysfunction in Parkinson's disease (PD) extend to the cognitive domain. Conceptually, we focused on the phenomenon of paradoxical kinesis: Here, PD patients can improve their motor abilities with the help of external cues. This improvement is associated with the increased activation of the lateral premotor cortex, presumably reflecting a compensation of SMA-hypoactivation.

PD patients "on" and "off" medication and healthy controls were tested in a serial prediction task that does not entail motor demands and that activates both the medial and lateral premotor cortex (Schubotz & von Cramon, 2003). A parametric modulation (SPT+) that increases the memory-based load by the use of stimulus occluders was implemented to the classic SPT (SPT0). In SPT+, several stimuli of the sequence were masked by an occluder and hence had to be recalled internally to decide if the sequence was orderly repetitive or contained a sequential deviant.

We expected patients to be impaired in both SPT-variants. This hypothesis was only partly corroborated. Patients "off" medication were found to be significantly impaired in serial prediction (including all levels of occluders) compared to controls, whereas patients "on" medication performed worse than controls only in SPT0.

We further expected the impairment in SPT+ to be particularly prominent "off" dopaminergic medication. Actually the significant interaction GROUP × MEDICATION × TASK and subsequent post hoc tests revealed a significant impairment in SPT+ for patients "off"-state compared to "on"-state but no significant "on"/"off"- differences in patients' performance for SPT0 or the control task. Even though, there was a descriptive but statistically insignificant trend for "off"-patients to be also impaired in SPT0 compared to "on"-patients (see Figs. 2–4). The impairment in "off"-performance, however, descriptively enlarged when memory-based processing became more relevant with increasing number of occluders (Figs. 2–4).

Our data indicate that PD patients' cognitive deficits due to less dopaminergic supply in putamen-SMA-loop parallel their motor deficits: Impairment increases when both rely on internally initiated processing. Though patients "on" medication were not generally impaired in SPT compared to healthy subjects, but only in SPT0, our expectations were further corroborated when we compared task performance with the motor score of the UPDRS (UPDRS III). Note that UPDRS III refers to a set of motor tasks that are internally, not externally driven. Here, a significant correlation between UPDRS III and SPT0 performance was found in "on"-state, and an even stronger correlation between UPDRS III and SPT+. These results indicate that the impairment in serial prediction, particularly in internally guided serial prediction, depends upon the individual severity of PD, even though patients "on" medication did not show general deficits in SPT+ compared to controls. On the basis of an informal post-experimental survey, we suggest that patients "on" medication did not perform worse than controls in SPT+ because patients were exceptionally motivated, possibly to be able to match with healthy participants, particularly with increasing task difficulty. We therefore consider the observed medication effect within the patient group to be more meaningful and reliable than the absence of expected impairment of patients "on" medication compared to healthy controls in SPT+.

Importantly, performance in other cognitive tasks such as the control task, PANDA or LPS 4 did not correlate with the UPDRS III "on" or "off" medication, showing that our findings are not due to a general correlation of motor and cognitive abilities in our cohort of patients. Rather, our results point to a specific impairment of the premotor system (due to loss of striatal input) that affects both cognition and motor performance in a characteristic manner. This finding corroborates the assumption that the premotor system sub-serves the prediction of both re-afferent as well as afferent states (Schubotz, 2007).

When the UPDRS III was further split into tremor- and non-tremor-items, only the non-tremor-items or akinetic-rigid items correlated significantly with SPT performance. Tremor-dominant PD patients without other Parkinsonian symptoms such as balance- or gait-disturbances exhibit cognitive decline to a much lesser extent (Alves, Larsen, Emre, Wentzel-Larsen, & Aarsland, 2006; Burn et al., 2006). This suggests that tremor and cognitive impairment in PD result from different pathomechanisms. Consistent with this assumption, tremor-dominant patients show dopaminergic depletion predominantly in the lateral putamen and the caudate nucleus, whereas in akinetic-rigid PD patients

the dorsal putamen is predominantly affected (Eggers, Kahraman, Fink, Schmidt, & Timmermann, 2011). Since the dorsal putamen projects to the SMA, whereas the lateral putamen predominantly connects to the primary motor areas (Leh, Ptito, Chakravarty, & Strafella, 2007), it makes sense that akinetic-rigid symptoms correlate with performance in SPT, i.e., a task that is known to activate the SMA but not primary motor areas. Still the interpretation of correlations of tremor- and non-tremor-items with performance has to remain tentative, as no tremor-dominant PD-patients were included in the sample.

When we consider the fact that PD patients' "off"-performance was more impaired, if occluders were present in a trial, we should discuss the exact effect of these occluders in a sequence and how we believe them to increase task load. SPT in its classical version has both an internal (memory-based) and an external (stimulus-based) component: The sequence which is specified at the beginning of a trial has to be maintained in memory and participants have to match this memorized sequence to externally presented stimuli to detect possible mismatches (i.e., externally and internally guided processing takes place concurrently). Note that not three discrete stimuli have to be encoded, but only the relative changes (here: circle diameter increments or decrements) from one stimulus to the other. When occluders mask a regular stimulus in SPT+, the external validation of the current internal model is withdrawn. Participants have to fill in mentally the missing item by reference to the previous and the subsequent stimulus. In that case PD patients "off" compared to "on" medication revealed remarkable problems. For them the strategy to rely on an internally represented sequence was no longer successful.

Deficits in internal processing in contrast to the preserved performance when external guidance was provided were also detected in previous studies examining cognitive deficits in PD. As mentioned above, Brown and Marsden (1990) found that PD patients did not exhibit a general impairment in various cognitive tasks, but were only impaired when internal control was required, e. g., in spontaneous generation of task-specific planning. In contrast, their performance did not differ from controls when external guidance was present such as choosing the correct results from a number of alternatives provided.

Impairment in internal control is especially present when PD patients have to initiate a new action step or mental operation. On the motor level, PD patients with freezing of gait exhibit deficits when they have to initiate a movement by showing an inability to step or extremely short steps (Nutt et al., 2011). Also on the cognitive level patients have difficulties when they need to apply a newly generated strategy to solve a problem: PD patients were able to solve a tower of London task (Shallice, 1982) with the same number of moves as their healthy controls, but exhibited significantly longer deliberation before making the initial move (even after controlling for putatively confounding influences of motor initiation and executive times) (Morris et al., 1988).

For related reasons, PD patients are impaired in task-switching-paradigms where it is necessary to switch between two competing internal strategies and to apply one of them; this impairment is abolished when external cues indicate which strategy has to be chosen (Brown & Marsden, 1988). PD patients were not impaired in understanding the different strategies, e.g., answering an odd-man-out task, but exhibited deficits in alternating between the two competing rules on successive trials (Flowers & Robertson, 1985). In line with these findings, Werheid, Koch, Reichert, and Brass (2007) reported that PD patients in contrast to healthy controls relied to a significantly greater extent on external cues than on a learned task-sequence (schematic sequence: AABBAABB), even when the utility of the visual cue was low due to a short pre-cueing interval (100 ms).

When thinking about external and internal processing, we must not forget that switching from internal to external guidance is a behaviour that we all apply in everyday life in various situations: One example for a highly automatic or internally guided behaviour is driving a car. Especially when doing it in a familiar environment, we are able to focus our attention on something else like a conversation. But when we drive in a foreign city, we have to focus our attention on the foreign environment. Transferring this example to the behaviour of PD patients, we can say that they are generally more dependent on input from the external world. So patients would always drive as if in an unfamiliar environment and it would be very difficult for them to do something else simultaneously. Several studies investigating freezing of gait (FOG) point in this direction: Gait in PD is certainly one of the best-investigated internally controlled behaviours and FOG is a disturbance of this behaviour. Many patients with FOG have to "stop walking while talking" (SWWT) (Giladi & Hausdorff, 2006; Lundin-Olsson, Nyberg, & Gustafson, 1997). There is also broad evidence that gait is impaired when PD patients have to perform another motor task simultaneously (dual-tasking) or in cognitively challenging situations (Bond & Morris, 2000; Giladi & Hausdorff, 2006; Knobl, Kielstra, & Almeida, 2012; Rochester et al., 2005). Spildooren et al. (2010) reported that patients with FOG exhibited an impairment of gait parameters when performing a cognitive task while walking and made concurrently more errors in that cognitive task than healthy controls. Interestingly, the use of external cues or attentional strategies (e.g., a request to focus on big steps) reduces the interference effect of a dual task (Baker, Rochester, & Nieuwboer, 2007; Rochester et al., 2005). Rochester et al. (2005) suggested that this interference effect in PD patients is due to an increased competition for attention because of the inability to use automatic movement control. Cues which help initiating movements as well as maintaining initiation may potentially free up attentional resources. In other words, PD patients exhibit problems in performing two tasks simultaneously because neither of them can be performed completely, automatically or internally guided. When, however, control for one of the tasks is supported by an external source, the patients can focus their attention on the other task and both tasks can be performed adequately.

Taken together, our study revealed that a cognitive paradigm which is proven to activate the premotor system (Schubotz & von Cramon, 2004) shows a dependency on dopaminergic medication in PD patients and that task performance correlates with motor function. This stands in stark contrast to the classical view that only the non-motor loops of the five basal ganglia-thalamocortical circuits proposed by Alexander et al. (1986) contribute to cognition. Especially the role of the dorsolateral prefrontal loop (including dorsolateral prefrontal cortex and dorsolateral caudate) and that of the orbitofrontal or ventral prefrontal loop (including lateral orbitofrontal cortex and ventromedial caudate) were previously highlighted in cognitive or more precisely executive dysfunction in PD (Cools, Barker, Sahakian, & Robbins, 2001; Owen, 2004). Dopaminergic denervation of the caudate nucleus, which is involved in both loops, was proven to correlate with the degree of dementia (Rinne et al., 2000) and with cognitive decline in PD, e.g., executive dysfunction and impaired sequence learning (Bruck et al.,2001; Carbon et al., 2004; Marie et al., 1999). Additionally, cortical components of both loops, the dorsolateral and ventrolateral prefrontal cortex, were shown to serve executive functions (Owen, Evans, & Petrides, 1996). Due to the degenerative pattern of the caudate nucleus in PD, the dorsolateral prefrontal loop is affected primarily in progression of the disease (Yeterian & Pandya, 1991), and so are higher level executive functions (Owen et al., 1992). Therefore, a contribution of these two loops to cognitive dysfunction in PD seems very likely.

Our findings, however, indicate that also the so-called "motor loop" of the basal ganglia-thalamo-cortical circuits, including SMA and putamen, contributes to certain cognitive impairments in PD. Further support for this view comes from a study that found dopamine transporter (DAT) density not only of the caudate but also of the putamen to correlate significantly with performance in a prefrontal test-battery in PD patients (Muller, Wachter, Barthel, Reuter, & von Cramon, 2000). Decline in patients' "off"-performance in the present study may correspond to the SMA-hypoactivation described for motor tasks in PD patients "off" dopaminergic medication (Haslinger et al., 2001). In SPT0, the relatively preserved "off"-performance might be attributed to the continuous stimulus-based guidance, analogous to a continuous pacing signal in motor tasks. Our assumption that internal guidance is based on SMA/putamen (and external guidance on the lateral premotor loop), however, has yet to be proved in further studies including neuroimaging, because our study was not made to test a functional-neuroanatomical hypothesis. Moreover, apart from positive evidence for a functional-neuroanatomical dichotomy between the mesial and the lateral motor loop (Debaere et al., 2003; Heuninckx et al., 2010), there are also mixed findings (Ballanger et al., 2006; Cunnington et al., 2002; Weeks et al., 2001), suggesting that the neuroanatomical basis of internally and externally guided control may reflect a certain trend rather than a strict regional dichotomy (Schubotz, 2004, p. 52f; see also Jahanshahi et al., 1995).

Note that beyond dopamine denervation of the striatum, other pathologies in the brain affected by Parkinson's disease are discussed to contribute to impaired cognition in PD. Thus, the impact of disturbances of other neurotransmitter-systems (i.e., the noradrenergic, serotonergic, and cholinergic system), the direct cortical involvement as evidenced by the presence of Lewy bodies, and the degeneration of the mesocortical dopaminergic system also have to be considered (Dubois & Pillon, 1997; Kulisevsky, 2000). Future studies have to address the relevance of these different factors including the role and interaction of different basal ganglia-thalamocortical circuits influencing behaviour in both motor and cognitive function.

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