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Motor sequence learning performance in Parkinson's disease patients depends on the stage of disease

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ABSTRACT

It is still unclear, whether patients with Parkinson's disease (PD) are impaired in the incidental learning of different motor sequences in short succession, although such a deficit might greatly impact their daily life. The aim of this study was thus to clarify the relation between disease parameters of PD and incidental motor learning of two different sequences in short succession. Results revealed that the PD patients were able to acquire two sequences in short succession but needed more time than healthy subjects. However, both the severity of axial manifestations, as assessed on a subsection of the Unified Parkinson's Disease Rating Scale III (UPDRS III) and the Hoehn and Yahr score, and the levodopa-equivalent dose (LED) were negatively correlated with the sequence learning performance. These findings indicate that, although PD patients are able to learn two sequences in short succession, they need more time and their overall sequence learning performance is strongly correlated with the stage of disease.

1. Introduction

The acquisition and optimization of movement sequences required, for example, for driving a car or brushing one's teeth is essential in daily life. It has been suggested that such action sequences are arranged into subsequences (Sakai, Kitaguchi, & Hikosaka, 2003). Progression through these subsequences might occur by a switching operation, by which, as one subsequence is completed, the representation of this sequence is inhibited and the next one activated (Hayes, Davidson, Keele, & Rafal, 1998).

In PD patients, both sequence learning and switching between different tasks has been shown to be impaired (Cools, Barker, Sahakian, & Robbins, 2001; Woodward, Bub, & Hunter, 2002). A progressive degeneration of nigrostriatal and, to a lesser extent, of mesocortical dopaminergic neurons is the main pathological feature of PD and leads to a lack of dopamine in the basal ganglia and the prefrontal cortex. This dopaminergic deficit causes not only the classical motor manifestations resting tremor, bradykinesia, rigidity, and postural instability (Grahn, Parkinson, & Owen, 2009) but also other deficits, such as in reinforcement learning, planning, sequence learning and set-switching (Carbon et al., 2003; Moustafa, Sherman, & Frank, 2008). Set-switching refers to the changing from one set of rules that guides behavior to another set and is often investigated with the "Wisconsin Card Sorting Task" (Eling, Derckx, & Maes, 2008; Hayes et al., 1998). However, Cools, van den Bercken, Horstink, van Spaendonck, and Berger (1984) found evidence for set-switching deficits in PD patients not only in sorting compound stimuli as in the Wisconsin Card Sorting Task, but also in the domain of verbal fluency and motor sequencing. Accordingly, Robertson and Flowers (1990) noted that PD patients made substantially more errors than control subjects when they had to switch between motor sequences.

On the other hand, findings regarding motor sequence learning in PD are mixed, with some studies showing profound impairment in PD patients (Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Stefanova, Kostic, Ziropadja, Markovic, & Ocic, 2000), and others showing only minor impairment (Ferraro, Balota, & Connor, 1993; Pascual-Leone et al., 1993; Sommer, Grafman, Clark, & Hallett, 1999), or none (Smith, Siegert, & McDowall, 2001). This suggests that PD patients can still learn sequences, but less efficiently than normal. It remains unclear, however, which pathophysiological factors influence the sequence learning performance of PD patients. Although it has been suggested that learning performance in PD may be related to the stage of disease, clear evidence for this association is still missing. For example, Muslimovic, Post, Speelman, and Schmand (2007) found a significant, but only weak correlation between the degree of axial disorders and implicit learning impairment by using a one-tailed Spearman's rho test. Moreover, patients with a higher Hoehn and Yahr stage of disease score showed only a trend towards worse sequence learning (Muslimovic et al., 2007).

Furthermore, in the learning paradigms of Hayes et al. (1998) and Robertson and Flowers (1990) the motor sequences were prelearned and subjects were aware of the sequence switching.

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Similarly, in common set-switching tasks such as the Wisconsin Card Sorting Task the subjects try intentionally to identify the rule for stimulus classification even though the set-switching usually occurs unbeknownst to the subjects. In contrast, it is unclear whether PD patients reveal also deficits in switching between two different motor sequences, when they learn these sequences incidentally and are not aware of the sequence switching (Grahn et al., 2009; Hayes et al., 1998; Woodward et al., 2002). Such a deficit in incidental sequence switching might have a great impact on motor function of PD patients in daily life, where many learning processes occur unconsciously and frequent switching between different action sequences is required.

The aim of this study was thus to clarify the relationship between disease parameters and motor sequence learning in PD and to test whether learning of two different motor sequences in short succession is impaired. By using the same task as in the present study, we have recently shown that healthy subjects can implicitly learn two motor sequences in short succession without significant interference between the sequences (Stephan, Meier, Orosz, Cattapan-Ludewig, & Kaelin-Lang, 2009). We hypothesized that PD patients show more impairment than healthy subjects in learning two sequences in short succession, and that their sequence learning performance correlates with the stage of disease.

2. Methods

2.1. Subjects

Thirty-nine patients with PD and 39 age-matched healthy subjects (HS) participated in the present study. The characteristics of the patient and healthy groups are listed in Table 1. The patients were recruited from the Movement Disorders Center at the Department of Neurology and diagnosed according to the criteria of the UK PD Society Brain Bank (Hughes, Daniel, Kilford, & Lees, 1992). Exclusion criteria were global cognitive deterioration, as indicated by a score below 24 on the Mini Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), and an overall attention deficit, as indicated by a score below four on the Forward Digit Span Test (Von Aster, Neubauer, & Horn, 2006). No patient had to be excluded. The study was approved by the local ethics committee, and each subject gave written informed consent.

At the time of the experiment and clinical assessments, seven patients were not being treated with any dopaminergic drug, because they had only recently received the diagnosis of PD and had not yet begun chronic dopaminergic therapy. Of the remaining patients, seven were being treated with levodopa in fixed combination with a peripheral levodopa decarboxylase inhibitor, four with a dopamine agonist only (1× ropinirol, 2× pramipexol, 1× rotigotine), and 16 with levodopa and a dopamine agonist (8× ropinirol, 5× pramipexole, 3× rotigotine), while five were receiving a combination of levodopa, dopamine agonists, anticholinergic drugs (biperiden hydrochloride) and glutamate antagonists (amantadine). To study the effect of dopaminergic medication on learning performance, the different drugs were pooled in a levodopa-equivalent dose (LED) according to the following conversion algorithm, adapted from Esselink et al. (2004): levodopa × 1 = ropinirol × 16.7 = pramipexol × 100 = rotigotine × 16.7. None of the patients had undergone deep brain stimulation. The severity of motor symptoms was assessed with the UPDRS III (Fahn & Elton, 1987) either immediately before or after the experiment. For more detailed analyses, we determined several subscores of the UPDRS III: (1) *bradykinesia* (finger taps, hand movements, rapid alternating movements of hand, leg agility, body bradykinesia and hypokinesia); (2) *rigidity*; (3) *tremor* (tremor at rest, action or postural tremor of hands); and (4) *axial symptoms* (arising from chair, posture, gait, postural stability). The stage of disease was rated on the Hoehn and Yahr scale (Hoehn & Yahr, 1967). Treatment-related complications were evaluated with the UPDRS IV (historical information relating to the past week, assessed in all but seven untreated patients). Independence in daily living was rated on the Schwab and England Activities of Daily Living (ADL) scale (Schwab & England, 1969). The duration of the disease was defined as the time interval between the occurrence of the first PD symptoms as reported by the patient and the moment of the experiment. Handedness was assessed with the Edinburgh Handedness Inventory Score (Oldfield, 1971).

Each subject was randomly assigned to either a sequence learning task or a random control task. In the PD group, 16 patients performed the random control task, 23 the sequence learning task. In the HS group, 13 subjects performed the random and 26 the sequence task.

Potential demographic and clinical intergroup differences were analysed with independent two-tailed *t*-tests or Mann–Whitney tests for ordinal data. There were no differences in age between PD patients and HS [$t(76) = 1.47$, $p = 0.15$] or between subjects performing the random task and subjects performing the sequence task [HS: $t(37) = -0.05$, $p = 0.96$; PD: $t(37) = 0.29$, $p = 0.78$]. Nor were there any differences between the PD random and the sequence groups in the UPDRS III score [$t(37) = 0.61$, $p = 0.55$], in the UPDRS IV score [$t(30) = 0.94$, $p = 0.36$], in the duration of disease [$t(37) = -1.34$, $p = 0.19$], and in the LED [$t(37) = -1.13$, $p = 0.27$], in the Hoehn and Yahr score [$U = 178.5$, $p = 0.85$], or in the ADL score [$t(37) = 0.53$, $p = 0.60$].

Table 1
Subject characteristics.

Variable	PD *n* = 39	HS *n* = 39
Age (years)	65.0 (9.0) Range: 42–82	61.0 (10.0) Range: 38–77
Sex (F/M)	14/25	23/16
Handedness (R/L/A)	36/3/0	36/2/1
Duration of PD (years)	7.6 (5.0)	
Hoehn and Yahr		
Stage 1:	2	
Stage 1.5:	0	
Stage 2:	25	
Stage 2.5:	3	
Stage 3:	9	
ADL (%)	86.8 (9.9)	
LED (mg/day)	503.1 (510.7)	
UPDRS III	24.0 (10.0)	
UPDRS IV	5.3 (4.1)	

R/L/A, right/left/ambidextrous; PD, Parkinson's disease; ADL, Schwab and England Activities of Daily Living; LED = levodopa-equivalent dose; UPDRS, Unified Parkinson's Disease Rating Scale; HS, healthy subjects; values are M (SD) or N unless otherwise specified.

2.2. Experimental procedure

We used a variant of the classic serial reaction-time task (Nissen & Bullemer, 1987), as previously described in detail (Stephan et al., 2009). Each subject was assigned to either a sequence learning condition or a separate, random control condition. Subjects had to respond with key presses corresponding to flashing-light stimuli appearing on a special Serial Response Box (SRBox, model 200a, Psychology Software Tools Inc., Pittsburgh, PA, USA). This device consists of a row of four lights above four horizontally aligned keys and is controlled by E-Prime software (Psychology Software Tools Inc., Pittsburgh, PA, USA).

The subjects were told to respond as rapidly and as accurately as possible with the more affected hand, which was the non-dominant one in 15 PD patients. The non-dominant hand was used by 7 of 39 HS as well. Each light went out after a correct key press,

and the next light went on 500 ms later. Participants were told that they would be performing a reaction-time task and were given no further information about the structure of the experiment.

The sequence learning condition consisted of eight blocks of 100 stimuli each. The stimuli appeared in random order in blocks 1–3; they appeared in two different sequences in blocks 4 and 5 (learning phase 1) and again in blocks 6 and 7 (learning phase 2). Specifically, block 4 consisted of 10 repetitions of a specific 10-trial sequence '*x*' (keys 4–3–2–4–2–3–1–2–1–3), block 5 of 10 repetitions of another sequence '*y*' (keys 2–3–2–4–3–1–3–4–2–1), block 6 again of repetitions of sequence '*x*' and block 7 again of repetitions of sequence '*y*'. The repeating sequences '*x*' and '*y*' within blocks 4–7 were presented in counterbalanced fashion, in the order *x*–*y*–*x*–*y* in half of the subjects and in the order *y*–*x*–*y*–*x* in the other half. In block 8, the stimuli again appeared in random order. The duration of each block was about 2 min. There was a 5 min resting period between the two learning phases; the other blocks were separated by 1 min resting periods. The entire experiment lasted about 30 min. The random control condition was analogous to the sequence learning condition, with the difference that the stimuli appeared randomly in all eight blocks.

After study onset (i.e., after a first pilot study phase), we decided to add additional trials to the last block 8. Therefore, in 15 PD patients and 20 HS, block 8 consisted of only 20 instead of 100 trials. These subjects were excluded from data analyses involving the whole block 8.

2.3. Data analysis

Mean error rates were below 3% in both groups (PD patients and HS) and were not further analysed. Only response times for correct responses were included in the analysis. In each block, the first key-press time was discarded. For data analysis we calculated the medians of the response times per 10 trials (=1 cycle) and then the means of these medians per block. Degrees of freedom were corrected for sphericity according to Huynh–Feldt where appropriate, and *p*-values were considered significant when below 0.05. All data are presented as mean (M) and standard deviation (SD), unless otherwise specified. Statistical analyses were performed with SPSS 16.0 (SPSS Inc., Chicago IL, USA).

2.4. Sequence learning

Sequence learning was defined as the decrease in response time due to learning the visuomotor sequences. To account for large inter-subject differences in general response velocity, the mean of the 10 cycle medians of block 3 was used as a covariate in the analyses of sequence learning in the two learning phases and as a reference for Fig. 1 (c.f., Stephan et al., 2009). We considered the mean of block 3 to be an appropriate measure of the individual baseline performance because it reflects performance before the beginning of the two sequence learning phases. To test phase 1 learning, we performed a mixed-factorial ANCOVA with blocks (4 and 5) as a within-subject factor and with conditions (random, sequence) as a between-subject factor (and the mean of block 3 as a covariate) separately for HS and PD patients. A significant effect of condition, due to shorter response times in the sequence condition, would indicate sequence learning. An interaction between block and condition would indicate interference between the two sequences. The analysis for phase 2 learning was performed accordingly with blocks 6 and 7.

To determine whether specific disease parameters could account for decreased sequence learning in PD, we conducted Spearman correlations for a calculated sequence learning parameter (the mean of cycle medians 1 and 2 of block 8 of the sequence condition minus the mean of cycle medians 9 and 10 of block 7 of the sequence condition) as well as the general response velocity (the mean of the 10 cycle medians of block 3) with several disease parameters such as PD duration, AIMS, UPDRS III, UPDRS IV, Hoehn and Yahr score, Schwab and England ADL score, and LED.

2.5. Task learning

Unspecific task learning was defined as the decrease in response time due to the learning of sequence-unrelated task requirements (e.g. moving fingers appropriately in response to visual stimuli). To check for differences in general task learning from block 1 to 8 between HS and PD patients and between subjects performing the random and the sequence tasks, we performed a mixed-factorial ANOVA with blocks (1 and 8) as a within-subject factor and with groups (HS, PD) and conditions (random, sequence) as between-subject factors. We also performed the same ANOVA separately for HS and PD patients.

Moreover, we conducted Spearman correlation analyses to examine the relationship between a calculated task learning parameter (the mean of cycle medians of block 1 minus mean of cycle medians of block 8) and several disease parameters including PD duration, AIMS, UPDRS III, UPDRS IV, Hoehn and Yahr score, Schwab and England ADL score, and LED.

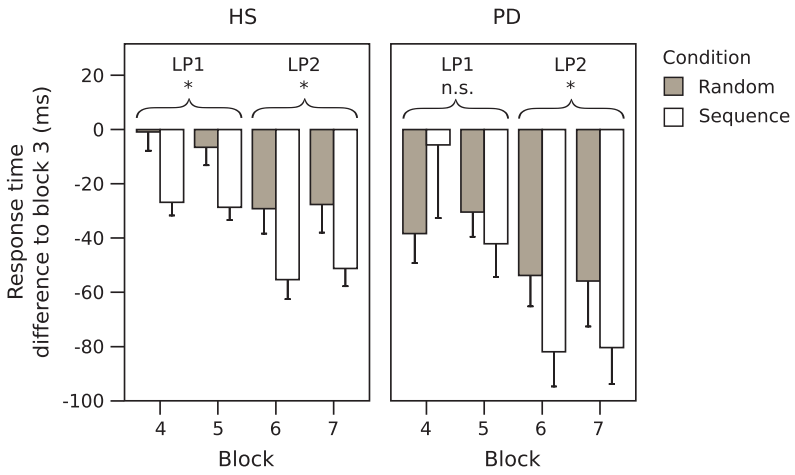

Fig. 1. Sequence learning. Averaged response time differences between each of blocks 4–7 and block 3 in the sequence condition (white bars) and in the random condition (gray bars). In the healthy subject group (HS), response times were significantly shorter in the sequence than in the random condition in both learning phases, LP1 ($^*P < 0.01$) and LP2 ($^*P < 0.01$). In contrast, PD patients showed learning only in LP2 ($^*P < 0.05$), but not in LP1 ($P = 0.54$).

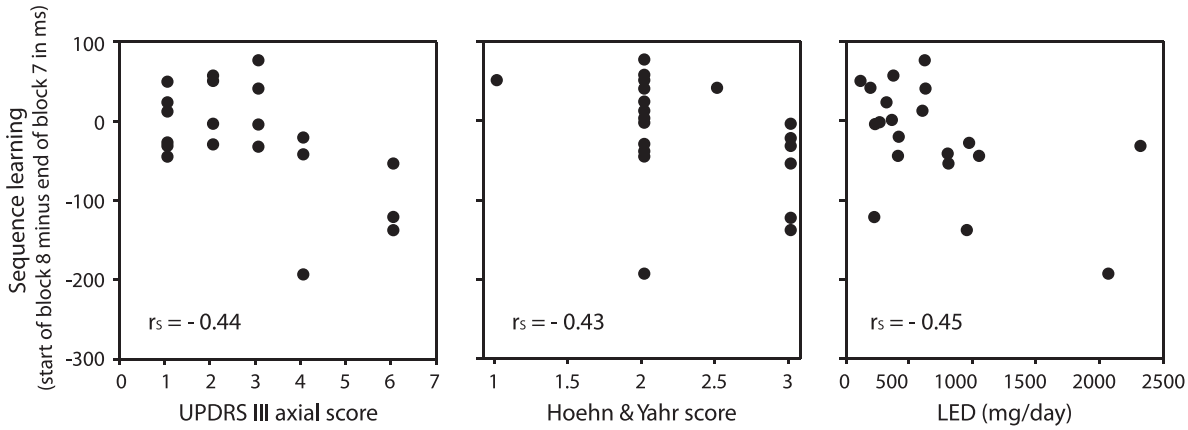

Fig. 2. Correlations between sequence learning and clinical parameters. A lower degree of sequence learning was associated with higher axial subscores on the Unified Parkinson's Disease Rating Scale III (UPDRS III, $P < 0.05$), with higher Hoehn and Yahr scores ($P < 0.05$), and with higher levodopa-equivalent doses (LED, $P < 0.05$). The sequence learning parameter was the mean of cycle medians 1 and 2 of block 8 of the sequence condition minus the mean of cycle medians 9 and 10 of block 7 of the sequence condition.

3. Results

3.1. Sequence learning

3.1.1. Early (phase 1) sequence learning

In HS, the response times in the sequence learning condition were significantly faster than in the random condition in blocks 4 and 5 (learning phase 1), indicating that sequence learning did occur [condition, $F(1, 36) = 13.59$, $P = 0.001$] (Fig. 1). Both sequences were learned to the same extent, as revealed by the absence of a significant interaction between condition and block [condition × block, $F(1, 36) = 0.22$, $P = 0.64$; block, $F(1, 36) = 0.21$, $P = 0.65$] (Fig. 1). In contrast, in PD patients, there was no significant effect of condition [$F(1, 36) = 0.39$, $P = 0.54$; block, $F(1, 36) = 3.15$, $P = 0.08$], indicating that no sequence learning occurred in learning phase 1 (Fig. 1). There was a significant interaction between condition and block [$F(1, 36) = 5.15$, $P < 0.05$], due to a slight response time increase from blocks 4 to 5 in the random condition and a decrease in the sequence condition. Nonetheless, post hoc t-tests revealed that there was no significant difference in response time between blocks 4 and 5 in either condition [random condition: $t(15) = 0.63$, $P = 0.54$; sequence condition: $t(22) = 1.84$, $P = 0.08$].

3.1.2. Later (phase 2) sequence learning

The analysis of blocks 6 and 7 revealed sequence learning in both groups [condition, HS: $F(1, 36) = 10.70$, $P < 0.01$; PD: $F(1, 36) = 4.15$, $P < 0.05$]: Response times in the sequence learning condition were significantly shorter than in the random condition (Fig. 1). Furthermore, both sequences were learned to the same extent in HS, as well as in PD patients [HS: condition × block, $F(1, 36) = 0.12$, $P = 0.73$; block, $F(1, 36) = 0.86$, $P = 0.36$; PD: condition × block, $F(1, 36) = 0.04$, $P = 0.84$; block, $F(1, 36) = 0.00$, $P = 1.00$].

Moreover, correlational analyses revealed that a higher axial subscore of the UPDRS III, a higher Hoehn and Yahr score, and a higher LED were all associated with poorer sequence learning (Fig. 2). None of the other correlations of the clinical parameters with the sequence learning parameter were significant (see Table 2). Nonetheless, the general response velocity was significantly correlated with the Schwab and England score, the total UPDRS III score, and the bradykinesia and axial subscores of the UPDRS III (see Table 2).

3.2. Task learning

Sequence-unrelated task learning led to a significant decrease in response time from blocks 1 to 8 [block, $F(1, 39) = 17.37$, $P < 0.001$], independent of group and condition [block × group, $F(1, 39) = 2.40$, $P = 0.13$; block × condition, $F(1, 39) = 0.06$, $P = 0.81$; condition, $F(1, 39) = 2.47$, $P = 0.12$; mean decrease from blocks 1 to 8 in PD patients: 109 ms, SD = 154 ms (14%, SD = 15%); in HS: 54 ms, SD = 43 ms (10%, SD = 7%)]. However, PD patients responded more slowly overall than HS [group, $F(1, 39) = 13.08$, $P = 0.001$].

Table 2
Correlations between clinical parameters and learning parameters.

Clinical parameters		Sequence learning		Task learning		General response velocity	
		r_s	p	r_s	p	r_s	p
Duration of PD		−0.28	0.19	−0.14	0.51	0.01	0.95
Hoehn and Yahr		−0.43	**0.04***	−0.32	0.13	0.32	0.05
ADL		0.21	0.34	−0.18	0.41	−0.57	**<0.001***
LED		−0.45	**0.03***	−0.12	0.57	0.08	0.61
UPDRS III	Total	0.11	0.63	−0.26	0.22	0.58	**<0.001***
	Bradykinesia	0.10	0.66	−0.10	0.65	0.61	**<0.001***
	Rigidity	0.004	0.99	−0.08	0.73	0.29	0.08
	Tremor	0.33	0.12	−0.29	0.17	0.18	0.27
	Axial	−0.44	**0.03***	−0.28	−0.19	0.48	**0.002***
UPDRS IV		−0.41	0.07	−0.45	0.07	−0.04	0.83

PD, Parkinson's disease; ADL, Schwab and England Activities of Daily Living; LED, levodopa-equivalent dose; UPDRS, Unified Parkinson's Disease Rating Scale; sequence learning parameter = (mean of cycle medians 1 and 2 of block 8 of the sequence condition) – (mean of cycle medians 9 and 10 of block 7 of the sequence condition); task learning parameter = (mean of cycle medians of block 1) – (mean of cycle medians of block 8); general response velocity = mean of the 10 cycle medians of block 3 (1 cycle = 10 trials).
* $p < 0.05$.

Also separate analyses of the response time decrease from blocks 1 to 8 in HS and PD patients revealed task learning in both groups [HS: block, $F(1, 17) = 22.77$, $P < 0.001$; block × condition $F(1, 17) = 0.18$, $P = 0.68$; condition, $F(1, 17) = 1.40$, $P = 0.25$; PD: block, $F(1, 22) = 11.25$, $P < 0.01$; block × condition $F(1, 22) = 0.18$, $P = 0.67$; condition, $F(1, 22) = 1.86$, $P = 0.19$]. None of the correlations between the clinical parameters and the task learning parameter was significant (see Table 2).

4. Discussion

Our study shows that PD patients can incidentally acquire two consecutive motor sequences in short succession although they respond significantly more slowly than healthy subjects and need more time to learn the sequences. Furthermore learning is poorer in more advanced stages of the disease.

In accordance with previous studies that suggested an association between sequence learning performance and the stage of disease (Doyon et al., 1997; Muslimovic et al., 2007), the lower performance in sequence learning in our PD group was correlated with more severe axial manifestations. Axial manifestations, as rated on the Hoehn and Yahr scale and the axial subscale of the UPDRS III, are thought to be predominantly mediated by non-dopaminergic neurotransmitter systems and to reflect the current stage of disease in patients receiving dopaminergic treatment (Burn et al., 2003). Moreover, learning was impaired with a greater amount of dopaminergic therapy. This might have resulted from a greater need of dopamine replacement in more advanced stages of disease. However, it has also been shown that while levodopa is effective to alleviate motor symptoms, it may worsen frontal lobe function, e.g., attention and working memory which are of great importance in tasks such as sequence learning tasks (Carbon et al., 2003; Ghilardi et al., 2007; Kwak, Müller, Bohnen, Dayalu, & Seidler, 2010). In contrast, neither the duration of the disease nor the functional status in daily life, as assessed by the Schwab and England ADL score, nor historical information on motor and non-motor disturbances (UPDRS IV) correlated with the extent of sequence learning. In accordance with previous studies suggesting that motor learning impairments in PD cannot be attributed to disease-related motor impairment *per se* (Laforce & Doyon, 2001; Seidler, Tuite, & Ashe, 2007), our findings revealed no association between the severity of motor manifestations affecting manual dexterity (bradykinesia, rigidity and tremor subscores of the UPDRS III) and the extent of sequence learning. Accordingly, our PD patient group performed as well as healthy subjects on sequence-unrelated task learning. Moreover, correlational analyses revealed no association of unspecific task learning with any of the clinical parameters. The general motor skill learning ability is thus not impaired in PD patients. Nonetheless, they need more training to learn motor sequences compared to healthy subjects, as they showed sequence learning only in the second learning phase. Moreover, a significant slowing of the 'general response velocity' was seen in PD patients as suggested previously (Benecke, Rothwell, Dick, Day, & Marsden, 1986, 1987; Park & Stelmach, 2009; Rand & Stelmach, 1999; Weiss, Stelmach, & Hefter, 1997) and this measure was strongly correlated with the severity of bradykinesia and axial manifestations and with poor functional status in the Schwab and England ADL scale. It is somewhat counterintuitive that the axial subscore of the UPDRS III correlates with the response time in an upper limb motor skill task, whereas the H&Y and the LED do not. However, the H&Y and LED scores are more general and imprecise measures for the overall disease progression, while axial symptoms of the UPDRS III reflect more accurately the actual state of dopaminergic and non-dopaminergic neurodegeneration. It thus makes sense that this measure correlates stronger with the general response velocity. Moreover, higher levodopa doses might speed up the general response time, compensating the slowing effect of a higher stage of disease, while specifically deteriorating sequence learning. Also, the fact that slowness in everyday life (ADL) and in specific clinical motor skill assessments (UPDRS III bradykinesia) exclusively correlated with our experimental measure of response velocity indicates that the response time in a simple motor key pressing task can be taken as a measure of the general disease-related motor slowness. This is in line with previous studies, where the movement time in sequential motor tasks correlated with the degree of clinically evaluated akinesia (Benecke et al., 1986, 1987).

However, our hypothesis that PD patients would have problems in learning two different sequences in short succession was not confirmed. PD patients were able to acquire two sequences without interference similarly to healthy subjects (Stephan et al., 2009). This was unexpected, in view of previous findings that PD patients cannot switch as well between two competing perceptual dimensions or between motor sequences and subsequences (Benecke et al., 1987; Hayes et al., 1998; Woodward et al., 2002). In contrast to such explicit switching tasks, though, subjects in our study were not even aware of the presence of the sequences, and switching between them thus occurred unconsciously. On the other hand, the overall impairment of sequence learning might also be due to balanced interference between learning the two sequences. This seems unlikely, however, as interference would be expected to impair learning of either the first introduced sequence (retrograde interference) or the second sequence (anterograde interference) (Miall, Jenkinson, & Kulkarni, 2004) and our results revealed no difference in the learning of either sequence. Thus, incidental switching between sequences during the learning process seemed not to be impaired in PD.

Our findings are thus in accord with the hypothesis that, despite the important role played by the basal ganglia in motor sequence learning, basal ganglionic dysfunction does not substantially impair sequence order learning, but rather the translation of sequence knowledge into rapid motor performance (Seidler et al., 2007).

In conclusion, procedural sequence learning performance in PD depends on the stage of disease. Overall, PD patients learn sequences less efficiently, yet they have a preserved ability to finally acquire two sequences in short succession. In addition, their performance in sequence-unrelated visuomotor task learning improves to a similar degree as that of healthy subjects.

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