Learning sequence movements in a homogenous sample of patients with Parkinson’s disease

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Abstract

We investigated the acquisition of sequence movements in Parkinson’s disease (PD) by means of the serial reaction time (SRT) task. To this end, we used a sample of PD patients that fell within the same stage of the disease. Sixteen PD patients and 16 age-, sex- and education-matched control subjects performed the SRT task with a first-order conditional (FOC) sequence and with a second-order conditional (SOC) sequence. The results showed that the group of PD patients could be divided into two distinct subgroups: a fast PD patient subgroup ($n=11$) and a slow PD patient subgroup ($n=5$). FOC and SOC sequence learning in faster PD patients proved to be highly comparable to the group of controls. In contrast, learning of FOC and SOC sequences was severely impaired in slower PD patients. Since slow PD patients also scored lower on measures of cognitive functioning than faster PD patients, we assume that the deficits in SRT learning of the former reflect some more general cognitive impairment. This indicates that SRT performance can provide additional information about the cognitive abilities of PD patients, and accordingly may contribute to disease screening.

Keywords: Sequence learning; Parkinson; SRT task; Motor learning

Parkinson’s disease (PD) is a movement disorder that is characterized by a general loss of motor control, resulting in primary symptoms of tremor, rigidity, postural instability and bradykinesia (e.g. Tarsy, 2005). The disease is caused by the degeneration of the dopamine-producing cells in the substantia nigra, which leads to the dysfunction of the basal ganglia (e.g. Riederer, Gerlach, & Foley, 2002). As the basal ganglia structures are assumed to play a central role in the acquisition of skills in general and learning of sequence movements in particular (e.g. Gabrieli, 1995), many studies have been conducted with PD patients in order to get more insight in the processes underlying the acquisition of sequential behaviour.

In the present study, learning of sequence movements in PD patients is investigated by means of the serial reaction time (SRT) task, developed by Nissen and Bullemer (1987). In a typical SRT task, participants respond as quickly as possible to a stimulus presented in one of four horizontal locations. Responses are made by pressing a key that is assigned to the spatial position of the stimulus. Unbeknown to the participants, the location of the stimulus follows a repeating sequence. Typical results are that reaction times (RTs) decrease progressively over training, and increase significantly when the sequence of locations turns to a random order. The increase in RT with the insertion of the random sequence is ascribed to the acquisition of sequence-specific knowledge.

As participants’ execution of sequence movements is in response to a sequence of perceived objects, both motor and perceptual components contribute to sequence learning (e.g. Deroost & Soetens, in press; Deroost & Soetens, 2006; Goschke, 1998; Koch & Hoffmann, 2000; Mayr, 1996; Remillard, 2003). However, ample research has demonstrated that knowledge acquired during sequence learning is predominantly motor in nature (e.g. Deroost & Soetens, in press; Nattkemper & Prinz, 1997; Willingham, 1999; Willingham, Nissen, & Bullemer, 1989), so that the SRT task can be considered as an appropriate tool to investigate learning of sequence movements.

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To gain insight in the brain structures involved in sequence learning, many studies have addressed SRT learning in PD patients, leading, however, to mixed results. Whereas some authors found severe sequence learning deficits in PD patients as compared to healthy controls (e.g. Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Westwater, McDowall, Siegert, Mossman, & Abernethy, 1998), other studies only found relatively minor impairment (e.g. Ferraro, Balota, & Connor, 1993; Pascual-Leone et al., 1993) or even reported intact sequence learning (e.g. Smith, Siegert, & McDowall, 2000).

A possible explanation for these inconsistent findings is that the studies cited above used PD patients that differed with respect to the severity of the disease, as measured by the Hoehn and Yahr (1967) scale. Even within a single study, patients classified as being in different stages of the Hoehn and Yahr scale are included. This makes general interpretation of the SRT results problematic, as it seems likely that differences in learning performance are related to the degree of the severity of the disease. If the basal ganglia truly play a central role in the acquisition of sequence movements, SRT learning should become more impaired as the disease progresses. In order to enhance the comparison of SRT performance across PD patients, we used a homogeneous patient sample, in the present study: only patients with a moderate degree of severity of PD were included. All PD patients were classified as being in Stage 3 of the Hoehn and Yahr scale (early impairment of equilibrium, along with significant slowing of body movements).

Another factor that could contribute to the heterogeneity of results of SRT studies, involving PD patients, concerns the statistical structure of the sequences. As demonstrated repeatedly, a sequence can contain many kinds of information, which all have a specific influence on SRT performance (e.g. Cohen, Ivry, & Keele, 1990; Reed & Johnson, 1994). In a sequence containing first-order associations (called first-order conditional sequence or FOC sequence; Reed & Johnson, 1994), an upcoming target position can be predicted by the previous position. For instance, in the FOC sequence used in the present study, 1232413412 (with the numbers 1–4 denoting the leftmost, left, right and rightmost target position), Position 1 is two times more likely to be followed by Position 3 than by Position 4, but never by Position 2 (repetitions are excluded). In contrast, learning a sequence composed of second-order conditionals (called second-order conditional sequence or SOC sequence) requires knowledge of the previous two positions in order to predict the next position, as the previous position alone provides insufficient information. For instance, for the presently used SOC sequence, 12134213424, Position 1 is equally often followed by Positions 2–4. However, since each pair of target positions has only one unique successor in the sequence, knowing the previous two Positions 1–2 facilitates prediction of the upcoming Position 1.

Because SOC sequences are built up of more complex, higher-order associations, SOC sequence learning tends to be reduced as compared to FOC sequence learning in normal populations (e.g. Deroost & Soetens, in press; Reed & Johnson, 1994; Remillard & Clark, 2001; Soetens, Melis, & Notebaert, 2004). However, if statistical structure affects learning in PD patients in a similar way, then differences in statistical structure of the sequential material may to some extent account for the conflicting findings in sequence learning studies with PD patients. Unfortunately, previous research with PD patients that attempted to control for statistical structure of the sequences has yielded mixed results. For instance, Kelly, Jahanshahi, and Dirnberger (2004) compared PD patients and healthy control subjects on learning of hybrid and ambiguous sequences (Cohen et al., 1990). Whereas ambiguous sequences are composed entirely of second-order conditionals, hybrid sequences contain a mixture of first- and second-order conditionals. The results showed that, in concurrence with tone-counting, PD patients and controls performed the SRT task equally well with hybrid sequences, but ambiguous sequence learning was absent in both groups. The authors concluded that hybrid and ambiguous sequence learning are differentially affected by attentional load, imposed by the tone-counting task, but that, nevertheless, sequence learning of first-order conditionals is preserved in PD patients.

This observation is in disagreement with the results reported by Smith and McDowall (2004), who used a verbal version of the SRT task to overcome patients’ motor deficits. In this study, a group of PD patients and control participants performed the SRT task with both a FOC sequence and a SOC sequence. The results showed that PD patients demonstrated learning of both the FOC and SOC sequence. However, as compared to the group of controls, learning of both sequences was less pronounced in PD patients. This indicates that PD patients are impaired in the acquisition of both first- and second-order conditionals, at least on the verbal SRT task.

In the present study, we compared FOC and SOC sequence learning effects in PD patients by using the standard motor version of the SRT task. After all, it is possible that the results obtained by Kelly et al. differ from those of Smith and McDowall because in the latter study a verbal version of the SRT task was used. By controlling for statistical structure, in combination with a homogeneous sample of PD patients, we tried to surmount a number of important difficulties that complicate the interpretation of SRT data in PD patients.

1. Method

1.1. Participants

Sixteen patients with PD and 16 healthy control subjects, matched for age, sex and education, participated in the study. All subjects had normal to corrected-to-normal vision and participated as volunteers with informed consent in accordance with the Ethics Committee of the Vrije Universiteit Brussel (VUB). Both groups consisted of 10 women and six men. The average age of the control group was 65.9 years (S.D. = 6.04 years), ranging from 55 to 74 years. For the PD group, the average age was 66.6 years (S.D. = 5.73 years), range 55–72 years. The control group’s average years of education amounted to 12.3 years (S.D. = 1.88 years), whereas the patients’ average years of education amounted to 12.6 years (S.D. = 2.53 years).

All PD patients were classified as being in Stage 3 of the Hoehn and Yahr scale (moderate impairment: early impairment of equilibrium, along with significant slowing of body movements). The time since diagnosis ranged from 4 to 22 years, with an average of 11.5 years (S.D. = 5.13 years). At the time of testing, all patients were in the on-phase of anti-Parkinsonian medication.
Both PD patients (M = 27.3, S.D. = 1.54) and control participants (M = 28.8, S.D. = 1.17) scored above the standard cut-off of 24 on the mini mental state examination (MMSE, Folstein, Folstein, & McHugh, 1975), which was used as a screening instrument for intellectual functioning. In addition, a major clinical depression was an exclusion criterion for participation: only participants scoring below the cut-off of 11 points on the geriatric depression scale (GDS, Yesavage et al., 1983) were included in the study group. For the PD patients, the average GDS score amounted to 4.3 (S.D. = 3.26), for the group of controls the average GDS score was 1.1 (S.D. = 1.20).

1.2. Design and procedure

The study was conducted in the psychological laboratory of the VUB. The experiment started with the administration of the MMSE and the GDS, to screen intellectual abilities and mental status, respectively. The PD patients had to complete two additional measures. The first measure was the scales for outcomes in Parkinson’s disease-cognition (SCOPA-COG, Marinus et al., 2003) which was used to assess: (1) memory and learning, (2) attention, (3) executive functions, and (4) visuospatial functions. Secondly, the unified Parkinson disease rating scale (UPDRS, Fahn, Elton, & the UPDRS Development Committee, 1987) was administered, in order to rate the degree of clinical severity of PD. The UPDRS consists of the subscales: (1) mentation, behaviour, and mood, (2) activities of daily living, and (3) motor exam.

After screening, all participants performed the SRT task, which was run on a Pentium 4 personal computer with 17-in. screen, using E-prime Version 1.1 software (Schneider, Eschman, & Zuccolotto, 2002). SRT testing occurred individually under the supervision of the experimenter. On each trial of the SRT task, a black dot of 8 mm diameter (or 0.8° visual angle with a viewing distance of approximately 60 cm) appeared in one of four horizontally aligned white squares of side 1.5 cm (or 1.4° visual angle), against a light grey background. The squares functioned as location markers and remained on screen throughout a block of trials. Gaps between two squares measured 2.5 cm (or 2.4° visual angle). Participants were instructed to react as fast as possible to the location of the target dot, while restricting the error rate to a maximum of 5% per block. The ‘c’, ‘v’, ‘b’, and ‘n’ keys, situated on the bottom row of a standard keyboard, corresponded to a leftmost, left, right, and rightmost target and had to be pressed with the left middle finger, left index finger, right index finger and right middle finger, respectively.

Before starting the SRT experiment, participants completed a practice block of 50 random trials to train the stimulus-response mapping. After practicing the mapping, participants executed 11 SRT blocks of 75 trials. At the start of a block, a warning for the upcoming trials appeared, urging participants to rest their fingers lightly on the four response keys. The target was presented until the response was made. Subsequently, after a response-stimulus interval of 50 ms, the next target appeared on screen. RTs and accuracy were recorded on each trial. In case of an incorrect response, the word “Error” was presented for 750 ms. No error corrections were possible. After each block of trials, participants received feedback about their error rates and RTs for that particular block. A break of 30 s was imposed before the start of the next block.

All participants completed two sessions of the SRT task, with sessions being separated by 1 week. The two SRT sessions differed with respect to the statistical structure of the sequence that was used. In one SRT session, FOC sequence learning was tested (132342134142, the numbers 1–4 denote the leftmost, left, right and rightmost target position, respectively), whereas the other session assessed learning of a SOC sequence (121342314324). The FOC and SOC sequences were continuously repeated over the experimental Blocks 1–9 and 11 in their respective session. In Block 10 of each session, the sequence turned to a random order to assess sequence-specific learning. The random sequence was always generated on the basis of a random seed that differed between participants. The four stimulus alternatives occurred equally often in all structured and random sequences.

The order of FOC and SOC learning sessions was counterbalanced over participants in both the PD group and the group of controls, so that half of the participants of each group started with the FOC learning session, whereas the other half started with SOC learning. The rest of the participants were assigned to the reverse order.

2. Results

2.1. Matching

Both the group of PD patients and healthy controls consisted of 10 women and six men. The two groups did not differ significantly in terms of age, nor in average years of education (see Table 1).

However, PD patients performed poorer on the MMSE than the control subjects. The group of PD patients also obtained higher scores on the GDS than the group of controls. This was due to PD patients scoring higher on items rating general physical immobility (there was no difference with control subjects on items that specifically assessed mental symptoms of depression). Analyzing the demographic and clinical characteristics in terms of gender did not reveal any significant difference.

2.2. SRT task

The performance on the SRT task was derived from both the mean error rates and mean RTs. The correlation between error rates and RTs showed no indication for speed-accuracy trade off in the PD group (r = 0.16, ns and r = 0.18, ns for FOC and SOC sequence learning, respectively), nor in the group of controls (r = −0.06, ns and r = −0.25, ns for FOC and SOC sequence learning, respectively).

Subsequently, we determined general practice effects in each group, inferred from a decrease in errors/RTs over the experimental Blocks 1–9 and 11. Random Block 10 is not included in this analysis since it is inserted to assess sequence-specific learning. Overall practice effects do not only provide information about the general level of performance, but also include sequence-specific learning effects. Accordingly, a decrease in errors/RTs over practice can offer a preliminary indication for sequence learning.

Then we estimated sequence-specific learning effects for each group by comparing errors/RTs in random Block 10 with the mean of the adjacent sequenced Blocks 9 and 11. Higher error rates/RTs in the random block imply that participants have acquired sequence-specific knowledge.

2.2.1. Practice effects

2.2.1.1. Errors. To estimate practice effects, we conducted a repeated measures ANOVA on the mean error rates with group (PD versus controls) as between-subjects factor and sequence order (FOC versus SOC) and block (all the exper-

### Table 1: Demographic and clinical characteristics of the PD patients and healthy controls.

<table>
<thead>
<tr>
<th>Measure</th>
<th>PD patients (n = 16)</th>
<th>Controls (n = 16)</th>
<th>t (30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M = 10.26/6.32</td>
<td>M = 10.26/6.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.6 ± 5.73</td>
<td>65.9 ± 6.04</td>
<td>0.33</td>
<td>0.74</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.6 ± 2.53</td>
<td>12.3 ± 1.88</td>
<td>0.48</td>
<td>0.64</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.3 ± 1.54</td>
<td>28.8 ± 1.17</td>
<td>3.11</td>
<td>0.004</td>
</tr>
<tr>
<td>GDS</td>
<td>4.3 ± 3.26</td>
<td>1.1 ± 1.20</td>
<td>3.67</td>
<td>0.002</td>
</tr>
</tbody>
</table>
... within-subjects factors. This analysis showed that the PD group (M = 6.8%, S.D. = 1.40%) made more errors than the group of controls (M = 1.3%, S.D. = 1.3%), F(1, 30) = 7.49, p < 0.05, partial \( \eta^2 = 0.20 \). In addition, there was a tendency for errors to fluctuate more over blocks in the group of PD patients, than in the group of controls, F(9, 270) = 1.73, p < 0.10, partial \( \eta^2 = 0.05 \). Other main and interaction effects were not significant.

2.2.2.1. Errors. Sequence-specific learning was determined by performing a repeated measures ANOVA on the mean error rates, with group (PD versus controls) as between-subjects factor and sequence order (FOC versus SOC) and block (all the experimental blocks, with the exclusion of random Block 10) as within-subjects factors. The analysis demonstrated a main effect of group, indicating that the mean RT level in the PD group (M = 739 ms, S.D. = 309 ms) was higher than in the group of controls (M = 512 ms, S.D. = 132 ms), F(1, 30) = 8.01, p < 0.01, partial \( \eta^2 = 0.21 \) (see Fig. 1).

The main effect of block was also significant, showing a decrease in RT over training or a general practice effect, F(9, 270) = 7.86, p < 0.001, partial \( \eta^2 = 0.21 \). Other main and interaction effects were not significant.

2.2.2. Sequence learning

2.2.2.1. Errors. Sequence-specific learning was determined by performing a repeated measures ANOVA on the mean error rates, with group (PD versus controls) as between-subjects factor and sequence order (FOC versus SOC) and sequence learning (random Block 10 versus the mean of Blocks 9 and 11) as within-subjects factors. This analysis mainly confirmed that error rates were higher in the PD group than in the group of controls, F(1, 30) = 7.04, p < 0.05, partial \( \eta^2 = 0.19 \). Other main and interaction effects were not significant, which indicates that sequence learning was not reflected in the error rates.

2.2.2.2. RTs. For the RT analysis, we compared the RTs in random Block 10 with the mean of the adjacent sequenced Blocks 9 and 11. A repeated measures ANOVA was carried out with group (PD versus controls) as between-subjects factor and sequence order (FOC versus SOC) and sequence learning (random Block 10 versus the mean of Blocks 9 and 11) as within-subjects factors. This analysis indicated that the RT level in the PD group was elevated as compared to the group of controls, F(1, 30) = 9.55, p < 0.01, partial \( \eta^2 = 0.24 \).

Furthermore, higher RTs in random Block 10 as compared to the mean of Blocks 9 and 11 indicated the presence of sequence learning, F(1, 30) = 22.19, p < 0.001, partial \( \eta^2 = 0.43 \). Importantly, there was a significant group \( \times \) sequence order \( \times \) sequence learning interaction, F(1, 30) = 9.97, p < 0.01, partial \( \eta^2 = 0.25 \) (see Fig. 2). These interactions were further analyzed with a priori planned comparison tests, which are used to test specific hypothesis about group differences, without inflating the type I error rate. The results of the planned comparison tests showed that there was a difference in FOC sequence learning between the group of controls and the group of PD patients, F(1, 30) = 4.99, p < 0.05. Whereas FOC sequence learning took place in the group of controls (M = 74 ms, S.D. = 34 ms), F(1, 30) = 21.67, p < 0.001, learning was not significant in the group of PD patients (M = 24 ms, S.D. = 83 ms), F(1, 30) = 2.24, ns.

In contrast to FOC sequence learning, there was no difference in SOC sequence learning between the two groups, F(1, 30) = 0.30, ns. Learning proved to be as good in the group of controls (M = 30 ms, S.D. = 41 ms), F(1, 30) = 4.69, p < 0.05, as in the group of PD patients (M = 45 ms, S.D. = 67 ms), F(1, 30) = 10.66, p < 0.01.

Comparing FOC with SOC sequence learning showed that control subjects displayed more learning with the FOC sequence than with the SOC sequence, F(1, 30) = 8.99, p < 0.01. For the
PD patients, on the other hand, the difference between FOC and SOC sequence learning was not significant, \( F (1, 30) = 2.14, \text{ns.} \)

In sum, practice effects and sequence learning effects were only reflected in the RTs. The results of the RT analysis showed that the control subjects and the group of PD patients demonstrated similar practice effects. With respect to sequence-specific learning, the results indicated that, whereas SOC sequence learning was preserved in PD patients, FOC sequence learning proved to be impaired as compared to healthy control subjects.

### 2.3. Subgroups

The analysis of SRT performance revealed a large variance in general RT level and error rates, in particular within the group of PD patients. Closer inspection showed that 5 out of 16 PD patients executed the SRT task at a significantly slower pace than the rest of the group. Their average mean RT level on the sequenced experimental blocks (Blocks 1–9, 11) amounted to \( M = 1084 \text{ ms} \) (S.D. = 303 ms), whereas the average mean RT level of the remaining patients amounted to \( M = 582 \text{ ms} \) (S.D. = 132 ms). At the same time, these five patients exhibited a remarkably large number of errors (\( M = 16.9\% \), S.D. = 1.20%), whereas the error rate of the remaining patients was much lower (\( M = 2.2\% \), S.D. = 0.81%). In the group of controls, only one participant had a higher average RT level (\( M = 1000 \text{ ms} \)) than the rest of the controls (\( M = 485 \text{ ms} \), S.D. = 77 ms), albeit in combination with a normal average error rate (\( M = 0.5\% \)).

On the basis of these observations, we decided to divide the total group of participants into three subgroups: PD fast (\( n = 11 \)), PD slow (\( n = 5 \)) and controls (\( n = 15 \)), the one participant performing slower than 2500 ms was considered an outlier and was discarded from statistical analysis [(1) outliers PD fast subgroup: \( M = 0.1\% \), S.D. = 0.19\% for the FOC sequence and \( M = 0.1\% \), S.D. = 0.10\% for the SOC sequence; (2) PD slow subgroup: \( M = 1.9\% \), S.D. = 2.3\% for FOC sequence learning and \( M = 4.0\% \), S.D. = 1.59\% for SOC sequence learning; (3) controls: \( M = 0.0\% \), S.D. = 0.1\% for FOC sequence learning and \( M = 0.0\% \), S.D. = 0.0\% for SOC sequence learning].

To assess practice effects, we carried out a repeated measures ANOVA with subgroup (PD fast, PD slow and controls) as between-subjects factor and sequence order (FOC versus SOC) and block (all the experimental blocks, with the exclusion of random Block 10) as within-subjects factors. A main effect of subgroup showed that RT levels differed between subgroups, \( F (2, 28) = 37.84, p < 0.001 \), partial \( \eta^2 = 0.73 \). A Bonferroni post hoc test indicated that the PD fast patients (\( M = 582 \text{ ms} \), S.D. = 132 ms) and the controls (\( M = 485 \text{ ms} \), S.D. = 77 ms) were both faster than the PD slow subgroup (\( M = 1084 \text{ ms} \), S.D. = 303 ms), both \( p < 0.001 \). The difference between the fast PD patients and the control subjects, on the other hand, was not significant.

Furthermore, also the main effect of sequence order was significant, \( F (1, 28) = 7.54, p < 0.05 \), partial \( \eta^2 = 0.21 \), as was the interaction between subgroup and sequence order, \( F (2, 28) = 4.20, p < 0.05 \), partial \( \eta^2 = 0.23 \). A Bonferroni post hoc test showed that this was attributable to the PD slow group performing faster on the FOC SRT session than on the SOC SRT session, \( p < 0.05 \).

There was also a tendency for subgroup to interact with block, \( F (18, 252) = 1.62, p < 0.10 \), partial \( \eta^2 = 0.10 \). In addition, significant interactions were found between sequence order and block, \( F (9, 252) = 3.67, p < 0.001 \), partial \( \eta^2 = 0.12 \), as well as between subgroup, sequence order and block, \( F (18, 252) = 3.02, p < 0.001 \), partial \( \eta^2 = 0.18 \). Bonferroni post hoc tests of these interactions showed that practice effects differed between FOC sequence and SOC sequence learning in the PD slow subgroup, \( p < 0.05 \), indicating a decrease in RT over blocks for the former sequence, but not for the latter sequence (see Fig. 3a and b). For the other two subgroups, however, there was no difference in the RT decrease over blocks between the two sequences, ns. Other differences were also not significant.

### 2.3.2. Sequence learning

#### 2.3.2.1. Errors

To determine sequence-specific learning based on the error rate, we performed a repeated measures ANOVA, with subgroup (PD fast, PD slow and controls) as between-
subjects factor and sequence order (FOC versus SOC) and sequence learning (random Block 10 versus the mean of Blocks 9 and 11) as within-subjects factors. This analysis confirmed the main effect of subgroup, $F(2, 28) = 65.51, p < 0.001$, partial $\eta^2 = 0.82$ (see practice effect). In addition, subgroup interacted with sequence learning, $F(2, 28) = 6.11, p < 0.01$, partial $\eta^2 = 0.30$. This could be explained by PD slow patients making more errors on the mean of Blocks 9 and 11 ($M = 15.8\%$, S.D. = 1.01%) than on random Block 10 ($M = 17.7\%, S.D. = 1.37$), $F(1, 28) = 7.87, p < 0.01$, thus showing an opposite pattern as might be expected for sequence learning. Other main and interaction effects were not significant. In conclusion, no indications for sequence learning could be inferred from the error analysis.

2.3.2.2. RTs. Sequence-specific learning was inferred from an increase in RT in random Block 10 as compared to the mean of the surrounding sequenced Blocks 9 and 11. A repeated measures ANOVA was performed, with subgroup (PD fast, PD slow and controls) as between-subjects factor and sequence order (FOC versus SOC) and sequence learning (random Block 10 versus the mean of Blocks 9 and 11) as within-subjects factors. This analysis showed a main effect of subgroup, $F(2, 28) = 39.15, p < 0.001$, partial $\eta^2 = 0.74$. Sequence order, $F(1, 28) = 9.03, p < 0.01$, partial $\eta^2 = 0.24$, as well an interaction effect between subgroup and sequence order, $F(2, 28) = 7.59, p < 0.01$, partial $\eta^2 = 0.35$, demonstrated and explained in the analysis of practice effects.

Furthermore, sequence learning was significant, $F(1, 28) = 11.89, p < 0.01$, partial $\eta^2 = 0.30$, and differed between the three subgroups, $F(2, 28) = 11.32, p < 0.001$, partial $\eta^2 = 0.45$. Most important, the subgroup $\times$ sequence order $\times$ sequence learning interaction proved to be significant, $F(2, 28) = 7.70, p < 0.01$, partial $\eta^2 = 0.35$. Planned comparison tests showed that FOC sequence learning was significant in the PD fast group ($M = 66\text{ ms}, S.D. = 14\text{ ms}$), $F(1, 28) = 23.11, p < 0.001$, and in the group of controls ($M = 73\text{ ms}, S.D. = 12\text{ ms}$), $F(1, 28) = 38.29, p < 0.001$ (see Fig. 4). However, no learning of the FOC sequence occurred in the group of PD slow patients. The learning effect was even significant in the negative direction ($M = -69\text{ ms}, S.D. = 20\text{ ms}$), $F(1, 28) = 11.52, p < 0.01$. Consequently, both the PD fast group and the control group displayed better FOC sequence learning than the PD slow group, $F(1, 28) = 30.26, p < 0.001$ and $F(1, 28) = 3.64, p < 0.01$, respectively. The difference in FOC sequence learning between the fast PD patients and controls, on the other hand, was not significant, $F(1, 28) = 0.14,\text{ ns}$.

SOC sequence learning was again significant in the PD fast group ($M = 66\text{ ms}, S.D. = 16\text{ ms}$), $F(1, 28) = 17.55, p < 0.001$, and in the group of controls ($M = 32\text{ ms}, S.D. = 13\text{ ms}$), $F(1, 28) = 5.63, p < 0.05$. In the PD slow group, on the other hand, sequence learning was once more absent ($M = 0\text{ ms}, S.D. = 23\text{ ms}$), $F(1, 28) = 0.01,\text{ ns}$, however, unlike FOC sequence learning, only the difference between the PD fast and PD slow group was significant, $F(1, 28) = 5.52, p < 0.05$. Other differences in SOC sequence learning between subgroups were not significant.

Comparing FOC with SOC sequence learning showed that control subjects displayed better learning with the FOC sequence, $F(1, 30) = 8.29, p < 0.01$. For the PD fast patients, the difference between FOC and SOC sequence learning was not significant, $F(1, 30) = 0.01,\text{ ns}$. Because of the negative FOC sequence learning effect, FOC sequence learning differed significantly from SOC sequence learning, for the PD slow patients, $F(1, 30) = 7.88, p < 0.01$. 

Fig. 4. Sequence learning (difference between random Block 10 and the mean of the adjacent Blocks 9 and 11) per sequence order for the subgroups PD fast, PD slow and controls.
To summarize, differences in SRT learning between the subgroups could mainly be derived from the RT analysis. PD slow patients only displayed a practice effect on the FOC sequence learning session, whereas PD fast patients and controls displayed a practice effect on both FOC sequence and SOC sequence learning sessions. In addition, sequence learning could only be established in the PD fast subgroup and in the group of controls, who demonstrated similar learning effects with both the FOC sequence and the SOC sequence. The subgroup of PD slow patients did not demonstrate any sequence-specific learning effects. This was the case on both FOC sequence and SOC sequence learning sessions, although learning effects for the SOC sequence did not differ significantly from the control subjects. In sum, sequence learning was impaired in PD slow patients, and this effect was most obvious for FOC sequence learning.

The observation that learning deficits in PD slow patients were more apparent with the FOC sequence, is likely to be attributed to the fact that sequence learning for controls subjects was better for FOC than for SOC sequences. Consequently, differences with controls were more pronounced with the FOC sequence than with the SOC sequence. Strangely, PD fast patients performed equally well with both sequences.

Possibly, there is an alternative explanation than can account for the specific learning impairment with the FOC sequence of the PD slow patients, namely differences in explicit awareness between FOC and SOC sequence learning. In the present study, we did not include measurements of explicit knowledge acquisition, like is often done in SRT research, as it was not our aim to find support for the implicit nature of SRT learning, which is still a highly controversial issue (for reviews, see e.g. Cleeremans, Destrebecqz, & Boyer, 1998; Frensch, 1998; Shanks & John, 1994). However, if we assume that explicit awareness is more likely with FOC sequences than with SOC sequences, and will also become more apparent in the second session than in the first session, explicit awareness could potentially confound our conclusions with respect to learning deficits depending on sequence order. More specifically, if PD slow patients received the FOC sequence always in the second session, their specific learning impairment with the FOC sequence could be attributed to a more general deficit in explicit sequence learning. Therefore, we looked at differences in the order of session assignment (FOC-SOC versus SOC-FOC) between the three subgroups (due to the division in odd subgroups, sequence order was no longer counterbalanced over sessions). In the PD fast subgroup 7 out of 11 patients received the FOC sequence learning session first, whereas the remaining four patients started with the SOC sequence learning session. In the PD slow subgroup, four out of five patients first completed the FOC sequence learning session, so that only one patient started with the SOC sequence learning session. For the controls subgroup, seven subjects started with FOC sequence learning, and eight subjects with SOC sequence learning.

Subsequently, in order to determine the effects of session order on RT sequence learning estimates, we conducted a repeated measures ANOVA with subgroup (PD fast, PD slow and controls) and session order (FOC-SOC versus SOC-FOC) as between-subjects factors and sequence order (FOC versus SOC) and sequence learning (random Block 10 versus the mean of Blocks 9 and 11) as within-subjects factors. This analysis indicated that session order had no effect on sequence learning: there was no interaction with sequence learning, \( F(1, 25) = 0.99, \) ns, partial \( \eta^2 = 0.04, \) nor with subgroup \( \times \) sequence learning, \( F(2, 25) = 1.36, \) ns, partial \( \eta^2 = 0.09, \) nor with sequence order \( \times \) sequence learning, \( F(1, 25) = 0.99, \) ns, partial \( \eta^2 = 0.004, \) nor with subgroup \( \times \) sequence order \( \times \) sequence learning, \( F(2, 25) = 1.91, \) ns, partial \( \eta^2 = 0.13. \) Consequently, contrary to what might be expected when explicit learning is more likely with FOC sequences and more likely in the second session, session order did not affect sequence learning in any way. This suggests that, even if explicit awareness contributed to sequence learning, this did not have an influence on the learning estimates of the different subgroups. Accordingly, it seems unlikely that the specific learning deficit with the FOC sequence in the PD slow subgroup can be explained by a more general impairment of explicit sequence knowledge acquisition.

### 2.4. Demographic and clinical differences between the PD fast and PD slow subgroups

In order to gain more insight in the learning impairments of the PD slow group, as compared to the PD fast subgroup, we determined to what extent the two subgroups differed in terms of demographic and clinical characteristics. As shown in Table 2, age, years of education, GDS score as well as disease duration did not differ between the two subgroups. In contrast, there was a significant difference in the degree of severity of the disease, as derived from the general UPDRS. The two groups also clearly differed in gender composition. Whereas the PD slow group consisted entirely of men, 10 out of 11 participants in the PD fast group were women.

With respect to the other variables, the PD fast group obtained higher scores on the SCOPA-COG than the PD slow group. In particular, on the subscale ‘memory and learning’ of the SCOPA-COG, PD fast patients performed significantly better than the PD slow patients. The difference in MMSE score as well as the subscale motor exam of the UPDRS just failed to show a tendency towards significance.

Correlational analysis furthermore indicated that learning effects in RTs, collapsed across FOC and SOC sequence learning, correlated positively with gender \( (r = 0.70, p < 0.05). \) In addition, scores on the SCOPA-COG \( (r = 0.62, p < 0.05), \) and in particular scores on the subscales ‘memory and learning’ \( (r = 0.68, p < 0.05) \) and ‘executive functions’ \( (r = 0.50, p < 0.05) \) of the SCOPA-COG correlated positively with SRT performance, although the two subgroups obtained similar scores on the latter subscale. Other variables did not correlate significantly with learning effects in RTs. With respect to learning effects in error rates, collapsed across FOC and SOC sequence learning, errors only correlated with gender \( (r = 0.54, p < 0.05). \)

In conclusion, the two subgroups of PD patients differed most significantly in terms of disease severity, gender composition, and the scores obtained on the SCOPA-COG, in particular the subscale ‘memory and learning’.
In the present study, we investigated sequence learning in the SRT task in PD patients and matched controls. Previous SRT studies involving PD patients have yielded mixed results, ranging from (severely) impaired (e.g. Ferraro et al., 1993; Jackson et al., 1995; Pascual-Leone et al., 1993; Westwater et al., 1998) to preserved sequence learning (e.g. Smith et al., 2000). However, all these studies used samples of PD patients that fell within different stages of the disease. Hence, it is possible that conflicting findings result from differences in disease severity between PD patients. Another factor that could contribute to the contradictory results is the sequential material that is used to assess sequence learning in the SRT task, in particular the statistical structure of the sequences.

In the current study, we tried to diminish the influence of these potentially confounding factors by assessing SRT learning in a homogeneous sample of PD patients: all were diagnosed as having PD in a moderately severe degree (Stage 3 of the Hoehn and Yahr scale). In addition, we controlled for the statistical structure of the sequences by comparing FOC and SOC sequence learning (Reed & Johnson, 1994). Our results for the slow PD patient subgroup are in agreement with the findings of Smith and McDowall (2004), who also demonstrated impaired FOC and SOC sequence learning in PD patients, using a verbal version of the SRT task. The present study extents their results to the standard motor version of the SRT task, at least in slower PD patients. On the other hand Kelly et al. (2004) reported preserved learning of first-order associations in PD patients. The patients included in the study of Smith and McDowall were, however, diagnosed as being in a more advanced stage of the disease, (PD patients fell within Stages 2–4 of the Hoehn and Yahr scale) than the patient sample used by Kelly et al. (PD patients fell within Stages 1–3 of the Hoehn and Yahr scale), which could suggest that learning of first-order conditionals and second-order conditionals is related to disease severity. This could explain why PD slow patients, who obtained lower scores on the UPDRS than PD fast patients, failed to demonstrate sequence-specific learning.

In order to gain further insight in the differences between the two subgroups of PD patients, we compared the demographic and clinical variables. The results showed that slower PD patients performed worse on the SCOPA-COG than faster PD patients, in particular on the subscale ‘memory and learning’. Another apparent difference was that the slow PD subgroup con-

### Table 2
Demographic and clinical characteristics of the PD fast subgroup and the PD slow subgroup

<table>
<thead>
<tr>
<th>Measure</th>
<th>PD fast (n = 11)</th>
<th>PD slow (n = 5)</th>
<th>t (14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M</td>
<td>S.D.</td>
<td>M</td>
<td>S.D.</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.8</td>
<td>6.32</td>
<td>68.4</td>
<td>4.16</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.9</td>
<td>2.74</td>
<td>12.0</td>
<td>2.12</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>10.5</td>
<td>5.56</td>
<td>13.8</td>
<td>3.42</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.7</td>
<td>1.49</td>
<td>26.4</td>
<td>1.34</td>
</tr>
<tr>
<td>GDS</td>
<td>4.4</td>
<td>3.04</td>
<td>4.2</td>
<td>4.09</td>
</tr>
<tr>
<td>SCOPA-COG</td>
<td>27.2</td>
<td>4.81</td>
<td>21.6</td>
<td>2.41</td>
</tr>
<tr>
<td>Memory and learning</td>
<td>10.2</td>
<td>2.82</td>
<td>6.2</td>
<td>2.17</td>
</tr>
<tr>
<td>Attention</td>
<td>3.5</td>
<td>0.82</td>
<td>3.8</td>
<td>0.45</td>
</tr>
<tr>
<td>Executive functions</td>
<td>9.3</td>
<td>2.00</td>
<td>7.8</td>
<td>1.30</td>
</tr>
<tr>
<td>Visuospatial functions</td>
<td>4.8</td>
<td>0.87</td>
<td>3.8</td>
<td>1.30</td>
</tr>
<tr>
<td>UPDRS</td>
<td>48.0</td>
<td>10.96</td>
<td>56.4</td>
<td>3.58</td>
</tr>
<tr>
<td>Mentation, behaviour, and mood</td>
<td>2.6</td>
<td>2.16</td>
<td>2.4</td>
<td>0.55</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>15.3</td>
<td>4.34</td>
<td>17.8</td>
<td>2.77</td>
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<tr>
<td>Motor exam</td>
<td>29.9</td>
<td>7.30</td>
<td>36.2</td>
<td>4.49</td>
</tr>
</tbody>
</table>

3. General discussion

In addition, we found no evidence for the acquisition of sequence-specific knowledge in slower PD patients for the FOC sequence, nor for the SOC sequence. The sequence learning deficit was most obvious for the FOC sequence; that is, the difference with controls was larger for the FOC than for the SOC sequence. This is probably attributable to the fact that controls displayed better sequence learning with the FOC than with the SOC sequence, like is generally observed in normal populations (e.g. Deroost & Soetens, in press; Reed & Johnson, 1994; Remillard & Clark, 2001; Soetens et al., 2004). Hence, as differences with controls increase with FOC sequences as compared to SOC sequences, it seems that FOC sequence learning is a particular sensitive measure to assess sequence learning impairments in PD patients.

The results showed that there was a large variability in the SRT data of the PD patients, although all were classified as being in the same stage of the disease. Further analysis indicated that the group of PD patients could be divided into two distinct subgroups: one subgroup executed the SRT task at a much slower rate than the second subgroup. In addition, the slower subgroup made more errors than the fast subgroup. In view of that, SRT performance of both subgroups was compared to the group of controls. The results indicated that the fast PD subgroup and the group of controls performed the SRT task in a highly comparable way. Both groups displayed similar training patterns and demonstrated equal amounts of FOC and SOC sequence learning. In contrast, SRT performance of the slow PD subgroup was severely impaired, as compared to both the control group and the subgroup of fast PD patients. General practice effects were visible for the FOC sequence, but absent for the SOC sequence.
sisted entirely of men, whereas the fast PD patients were almost exclusively women (one man).

At present, there is no evidence that sequence learning is affected by gender, nor in normal populations, nor in PD patients. More research will have to determine whether the observed gender difference in the PD patient subgroups is due to coincidence or whether there is truly a systematic relationship between gender and SRT performance in PD patients.

We presume that the differences in SRT performance between the two subgroups of PD patients are related to other factors. In particular, we conjecture that the lower scores on the SCOPA-COG in the slower PD patient subgroup are an indication for specific deficits of cognitive functioning, which become reflected in the impaired SRT performance. Although the exact nature of these cognitive deficits cannot be determined on the basis of our study, the differences between the two PD subgroups were most obvious at the level of learning measures: slower PD patients performed worse on both the SRT task and on the subscale ‘memory and learning’ of the SCOPA-COG.

Interestingly, these two tasks rely on different types of acquisition processes. For the SCOPA-COG subscale ‘memory and learning’ participants receive instructions about the learning goals, making learning an intentional process. In contrast, SRT learning takes place without participants’ being informed about the structured nature of the task, so that learning occurs incidentally. Since the group of slow PD patients was particularly impaired on the SRT task and on the SCOPA-COG subscale ‘memory and learning’, this suggests that their learning deficit is more general in nature, extending over both intentional and incidental learning processes.

In conclusion, the results of the present study indicate that there is a large variability in SRT performance even within PD patients diagnosed as falling within the same stage of the disease. Therefore, it is not surprising that SRT research, using PD patients of different disease stages, has yielded such conflicting results. Although the sample sizes of both PD subgroups were too small to draw general conclusions, the present findings suggest that the score on the SCOPA-COG is a good predictor for SRT performance: PD patients scoring lower on the SCOPA-COG also displayed less sequence learning in the SRT task. This could indicate that SRT deficits reflect a more general cognitive impairment. A possible way to obtain more interpretable SRT results could therefore be to divide PD patients in different experimental groups on the basis of their cognitive abilities, as measured for example by the SCOPA-COG. Future research with larger sample sizes can determine whether PD patients scoring similarly on measures of cognitive functioning will display more comparable learning patterns in the SRT task. Perhaps, in the end, the SRT task can be added to the diagnostic tools for screening PD patients’ cognitive abilities and accordingly contribute to the fine-tuning of treatment.

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