Does implicit learning in non-demented Parkinson’s disease depend on the level of cognitive functioning?

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Abstract


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1. Introduction

Parkinson’s disease (PD) is a movement disorder characterized by a loss of motor control, with important symptoms of postural instability, rigidity, bradykinesia and tremor (Waters, 1999). These primary symptoms of PD originate from the loss of dopaminergic cells in the region of the substantia nigra. Dopaminergic neurons project to the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement (Tolosa, Wenning, & Poewe, 2006). As the disease evolves, psychiatric problems like depression become more prominent. Beside motor and affective symptoms, PD patients often complain of fatigue, memory and attention problems (Bosboom, Stoffers, & Wolters, 2004).

In the present study, we examined the relationship between the implicit acquisition of movement sequences and the general level of cognition in PD. Implicit learning is commonly defined as acquiring new information without intending to do so, and in such a way that the resulting knowledge is hard to express (Cleeremans, Destrebecqz, & Boyer, 1998). Several studies have indicated that the implicit acquisition of sequential behavior is impaired in PD patients (e.g., Shin & Ivry, 2003; Smith & McDowell, 2006). This suggests that the basal ganglia structures are crucially involved in implicit learning of movement sequences, although there is evidence that frontal areas may also play a critical role in implicit learning (Gomez-Beldarrain, Garcia-Monco, Rubio, & Pascual-Leone, 1998). Other authors propose that implicit learning is achieved by a distributed network of cortical and subcortical structures (Exner, Koschack, & Irle, 2002).

Implicit learning of movement sequences in PD patients was investigated in the current study by means of the serial reaction time (SRT) task, developed by Nissen and Bullemer (1987). In a typical SRT task, participants respond as fast as possible to a stimulus presented in one of four horizontal locations. Responses are made by pressing a key corresponding to the spatial position of the stimulus. However, participants do not know that the location of the stimulus follows a repeating sequence. Typical results are that reaction times (RTs) decrease progressively over training (practice effect), and increase significantly when the location sequence 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. Numerous studies have shown that the SRT task can be seen as an appropriate tool to study learning of sequence movements (Bischoff-Grethe, Goedert, Willingham, & Grafton, 2004; Deroost & Soetens,
Studies investigating sequence-specific learning in PD have yielded mixed results. Some authors found severe sequence learning deficits (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; Sommer, Grafton, Clark, & Hallett, 1999) or even reported no impairment at all (e.g., Smith, Siegert, & McDowall, 2001). Recently Siegert, Taylor, Weatherall, and Abernethy (2006) conducted a meta-analysis and concluded that implicit learning in PD is impaired as compared to a healthy control group.

Explanations for these mixed results could lay either in motor or cognitive features of the disease. An explanation in motor terms entails the use of heterogeneous samples, meaning they consist of patients differing in severity of the disease, measured by the Hoehn and Yahr (1967) scale. If implicit learning relates to damage of the basal ganglia, patients in a more severe stage of the disease might experience more problems with sequence acquisition. The studies cited above did not give information about the classification of their participants or they used a mixed group containing patients who belonged to different stages. This hampers a general conclusion of the obtained SRT results. To overcome this problem, we used a homogeneous sample in the present study: all participants were classified as being in Stage 3 of the Hoehn and Yahr scale (early impairment of equilibrium, along with significant slowing of body movements).

A second explanation, covering cognitive features, is that the loss of motor control in PD is accompanied with cognitive deficits. Hence, it is possible that differences in level of cognitive functioning can explain the contrasting results of sequence learning in PD. According to several studies cognitive deficits become more prominent in Stage 3 of the Hoehn and Yahr (1967) scale (e.g., Braak, Rüb, & Del Tredici, 2006; Riepe, Kassubek, Tracik, & Ebersbach, 2006). Consequently, differences in implicit learning performance may be observed even in PD patients classified within the same stage of the disease.

Preliminary evidence for an association between cognitive functioning and implicit learning in PD was found in a recent study conducted by Deroot, Kerckhofs, Coene, Wijnants, and Soetens (2006). Sequence learning in this study was investigated in PD by means of the SRT task using a sample of PD patients that all belonged to the same stage of the disease (Stage 3). The PD group could clearly be divided into two distinct subgroups based on their overall performance on the SRT task: a fast and accurate subgroup and a slow and less accurate subgroup. Sequence learning in faster PD patients was highly comparable to the group of controls, whereas sequence learning was severely impaired in slower PD patients. In addition, cognitive functioning, motor learning and disease duration proved to be correlated. To obtain more insight in these correlations, additional post hoc analysis were carried out, indicating that the PD fast group obtained higher scores on the SCOPA-COG (Marinus et al., 2003) than the PD slow group. The SCOPA-COG consists of 10 items, including ‘memory’ (replicating the order in which cubes were pointed out, digit span backward, immediate and delayed word recall), ‘attention’ (counting down by threes and months backward), ‘executive functioning’ (successive repetitions of fist-edge-palm movements, set shifting with dices and fluency animals), and ‘visuospatial functioning’ (mental reconstruction of figures).

The present study was carried out in order to gain more direct support for the relationship between SRT performance and the level of cognitive functioning, as suggested by Deroot et al. (2006). As the disease progresses, dopaminergic dysregulation of the fronto-striatal circuits occur, playing a great role in the development of cognitive problems and executive dysfunction in PD (Piatt, Fields, Paolo, & Troster, 1999). If we add this to the knowledge that subcortical striatal deterioration can be held responsible for impaired implicit learning in PD, an association between implicit learning and global cognitive level can be argued.

To this end, we included measures of both motor and cognitive aspects of PD in a homogeneous sample consisting of patients classified in Stage 3 of the Hoehn and Yahr scale. This is a major improvement compared to previous studies, in the sense that motor and cognitive factors were kept under control as much as is possible in a clinical population. To classify the patients’ cognitive level, we constructed three subgroups with respect to the scores obtained on the SCOPA-COG (Marinus et al., 2003): the low, average and high cognitive group. Based on the results of Deroot et al. (2006), we hypothesized a significant difference in implicit sequence learning between these three cognitive groups.

## 2. Method

### 2.1. Participants

Twenty-five PD patients participated in the study. All participants had normal to corrected-to-normal vision, and had no orthopedic or additional neurological disorders. Participation in the experiment was voluntarily with informed consent in accordance with the Ethics Committee of the Vrije Universiteit Brussel (VUB).

All PD patients were diagnosed by a trained neurologist and 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). Disease duration ranged from 2 to 19 years, with an average of 8.56 years ($SE = 0.88$). At the time of testing, all patients were in the on-phase of anti-Parkinson medication. This is a stable period after taking their medication with no to mild motor constraints. Medications used by subjects in the present study could be divided into two groups, namely dopamine precursor levodopa (Prolopa, Stalevo, Madopar, and Sinemet Control) and dopamine agonists (Mirapexin, ReQuip, Permax, Amantan, Eldepryl, Comtan, and Azilect). Medication statistics were implemented in Table 1.

On the basis of the analysis of SCOPA-COG scores, we divided the sample of patients into three groups. This was accomplished by calculating the mean SCOPA-COG score ($M = 25.76$, $SE = 0.94$) of all participants. Patients scoring more than two $SE$’s below average ($score = 0 < x < 23.87$) were included in the low scoring (LS) group. Patients scoring more than two $SE$’s above average ($score = 27.65 < x < 43$) were included in the high scoring (HS) group. The average scoring (AS) group consisted of patients scoring within two $SE$’s around the mean ($score = 23.87 < x < 27.65$).

The LS group ($M = 19.5$, $SE = 1.31$) included six participants, two women and four men with an average age of 68.1 years ($SE = 2.79$), ranging from 57.5 to 74.9 years. The AS group ($M = 25.6$, $SE = 0.34$) consisted of 11 patients, six women and five men with an average age of 67.2 years ($SE = 1.56$), ranging from 58.5 to 75.5 years. The HS group ($M = 30.8$, $SE = 0.80$) included one woman and seven men with an average age of 58.9 years ($SE = 2.81$), ranging from 50.2 to 69.9 years. The average years of education for the LS, AS and HS groups were 15.0 years ($SE = 0.86$), 15.5 years ($SE = 0.79$), and 18 years ($SE = 1.07$), respectively.

All participants scored above the standard cut-off score of 24 on the Mini Mental State Examination (MMSE, Folstein, Folstein, & McHugh, 1975). The MMSE was used as a screening instrument for intellectual functioning [LS ($M = 27.5$, $SE = 0.76$); AS ($M = 27.9$, $SE = 0.44$); HS ($M = 28.5$, $SE = 0.62$)].
In addition, we employed the Geriatric Depression Scale (GDS, Yesavage et al., 1983) to track down major clinical depression in patients. Participants scoring above the cut-off of 11 points were excluded from this study. The average GDS score amounted to 5.0 (SE = 0.97) for the LS group, 3.7 (SE = 0.69) for the AS group, and for the HS group the average GDS score was 3.4 (SE = 0.87). For important differences between these variables, see Section 3.

### 2.2. Design and procedure

The study was conducted in the psychological laboratory of the VUB. The experiment began with the administration of the MMSE and the GDS. In addition, the scales for outcomes in Parkinson's disease-cognition (SCOPA-COG, Marinus et al., 2003) was used to assess: (1) memory and learning; the LS group scored lower than the AS group, (2) attention, (3) executive functions, and (4) visuospatial functions.

After screening, all patients 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. Four horizontally aligned white squares of side 1.5 cm (or 1.4° visual angle) functioned as location markers, against a light gray background. The squares remained on screen throughout a block of trials. Gaps between two squares measured 2.5 cm (or 2.4° visual angle) with a viewing distance of approximately 60 cm. On each trial of the SRT task, a black dot of 8 mm diameter (or 0.8° visual angle) appeared in one of four squares. 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 10% 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, patients completed a practice block of 50 trials in random order to train the stimulus–response mapping. After practicing the mapping, participants executed 15 experimental blocks of 50 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. Participants were instructed to make less than five errors per block. In case of an incorrect response, the word “Error” was presented for 750 ms. No error corrections were possible. After each block of trials, patients received feedback about their error rates and RTs for that particular block. A break of 30 s was imposed before the next block started.

In the SRT session, implicit learning of a first-order conditional (FOC) sequence was tested: 13242134124, the numbers 1–4 denote the leftmost, left, right and rightmost target position, respectively. Several studies indicate that FOC sequences are more sensitive to assess impaired sequence learning in PD than second-order conditional (SOC) sequences (e.g., Derooit et al., 2006; Kelly, Jahanshahi, & Dirnberger, 2004). The FOC sequence was continuously repeated over the experimental Blocks 1–15. During Block 7 and Block 14, however, the sequence turned to a random order to assess sequence learning during early and later stage of training. This was done (1) to assess whether the experimental groups acquired sequence knowledge equally fast and (2) to not overlook potential learning effects disappearing in later stages because of fatigue or lack of concentration. The random sequence introduced in Blocks 7 and 14 was generated on the basis of a random seed that differed between patients. The four stimulus alternatives occurred equally often in all structured and random sequences.

At the end of the experiment, we administered a standardized questionnaire to assess whether the patient became aware of the sequence. These questions start on a general level as whether participants noticed something special about the task and gradually turn more specific with sequence-related questions.

### 2.3. Statistical analysis

Group comparisons and comparisons between conditions were carried out using an analysis of variance (ANOVA) with repeated measures. In addition an analysis of covariance (ANCOVA) was performed to rule out that differences observed on the SRT task were due to differences in disease severity. A significance level of .05 was used.

### 3. Results

#### 3.1. Clinical and demographic differences between groups

With respect to the level of cognitive functioning, we observed significant differences between groups (see Table 1) for the global SCOPA-COG score and for the subtests ‘executive functions’ and ‘memory and learning’; the LS group scored lower than the AS,
group and both groups scored lower than the HS group. Patients in the LS group performed significantly worse than patients in both the AS and HS groups on the subtest 'visuospatial functions'. For the subtest 'attention' the patients in the HS group performed significantly better than patients in the AS group.

For the variables 'age' and 'disease duration', patients in the HS group were significantly younger and less long diagnosed than patients in both the LS and AS group.

3.2.2. RT: Practice effects

We investigated general practice effects for all groups, indicated by the decrease in RTs across experimental Blocks 1–6, 8–13, and 15. Random Blocks 7 and 14 were not included in this analysis because they are used to assess sequence-specific learning. Overall practice effects do not only provide information about the general level of performance, but can offer a preliminary indication for sequence learning.

To estimate practice effects, we carried out a repeated measures ANOVA with group (LS, AS, and HS) as between-subjects factor and block (all experimental blocks, with the exclusion of random Blocks 7 and 14) as within-subjects factor. A main effect of group showed that RT levels differed between groups, $F(2,22) = 7.84$, $p < .01$, (see Fig. 1). A Bonferroni post hoc test confirmed that the HS group ($M = 484$ ms, $SE = 17$ ms) was performing faster than both the AS group ($M = 667$ ms, $SE = 55$ ms) and the LS group ($M = 744$ ms, $SE = 23$ ms), respectively, $p < .05$ and $p < .01$. Differences in RTs between the AS and LS group were not significant, $p < 1$.

Furthermore, the main effect of block was significant, implying a decrease in RTs because of a general practice effect or training, $F(2,47) = 11.92$, $p < .001$. No significant group $\times$ block interaction could be found, meaning there was no difference in practice effects between the three PD groups, $F(4,47) = 1.47$, ns.

3.2.3. RT: Sequence learning

We first examined a possible difference between groups in sequence-specific learning in early stages of training by comparing random Block 7 with the mean of surrounding Blocks 6 and 8. Slower RTs in the random block imply that patients have acquired sequence-specific knowledge in the structured blocks. A repeated measures ANOVA was carried out with group (LS, AS, and HS) as between-subjects factor and sequence learning (random Block 7 versus the mean of Blocks 6 and 8) as within-subjects factor. A main effect of group indicated that the RT level differed between groups, $F(2,22) = 5.56$, $p < .05$ (see practice effect). More important is that we did not find a significant main effect for sequence learning, neither a significant group $\times$ sequence learning interaction, respectively, $F(1,22) = 2.07$, ns and $F(2,22) = 0.27$, ns. This means that none of the three groups acquired sequence-specific knowledge during early stages of training, see Fig. 2.

We subsequently estimated sequence-specific learning effects in later stages of training for each group by comparing RTs in random Block 14 with the mean of the adjacent sequenced Blocks 13 and 15.

![Fig. 1. Mean reaction times per block for the high, average and low scoring PD groups (HS, AS, and LS). All blocks are sequenced, except for random Block 7 and 14.](image-url)
A second repeated measures ANOVA was carried out with group (LS, AS, and HS) as between-subjects factor and sequence learning (random Block 14 versus the mean of Blocks 13 and 15) as within-subjects factor. Again, a main effect of group indicated that the RT level differed between groups, $F(2,22) = 5.28, p < .05$. Importantly both sequence learning, $F(1,22) = 13.87, p = .001$, and the interaction sequence learning $\times$ group was significant, $F(2,22) = 5.90, p < .01$. A post hoc Bonferroni test showed that both AS ($M = 53 \text{ ms}, SE = 14 \text{ ms}$) and HS ($M = 32 \text{ ms}, SE = 5 \text{ ms}$) differed significantly in the amount of sequence learning with the LS ($M = 7 \text{ ms}, SE = 10 \text{ ms}$) group, respectively, $p < .05$ and $p < .01$. The difference between the AS and HS group was not significant, $p > 1$.

A possible concern is that sequence learning and disease duration are confounded ($r = -.44, p < .05$). Therefore, we carried out an ANCOVA with group (LS, AS, and HS) as between-subjects factor, sequence learning (random Block 14 versus the mean of Blocks 13 and 15) as within-subjects factor and disease duration as covariate. Opposed to our ANOVA results we did no longer find a main effect of group, indicating that the RT level was not significantly different between groups, $F(2,19) = 0.85$, ns. However, more important was that both sequence learning, $F(1,19) = 8.22, p = .01$, and the interaction sequence learning $\times$ group stayed significant, $F(2,19) = 3.95, p < .05$. These results indicate that even after controlling for disease duration, an impact of cognition on SRT task performance remains.

### 3.3. Explicit knowledge of the sequence

Since FOC sequences are built up of less complex, first-order associations, it could be argued that explicit awareness is more likely to occur. To address this issue we assessed explicit knowledge using a standardized awareness questionnaire, consisting of both general and more specific questions about the used sequence. Scores on the post-test questionnaire, reflected in percentages, were based on how good subjects could reproduce the sequence correctly. A high percentage means a high chance that subjects are aware of the sequence. The LS group ($M = 2.83\%, SE = 2.83\%$), AS group ($M = 1.55\%, SE = 1.55\%$), and HS group ($M = 4.25\%, SE = 2.78\%$) did not differ significantly on the explicit awareness task. Moreover, correlations between the questionnaire and learning on the SRT task were not significant, indicating that patients learned implicitly.

### 4. Discussion

In the present study we investigated the impact of cognitive functioning on implicit sequence learning in PD. Previous studies conducted with PD patients have led to mixed results, ranging from (severely) impaired (e.g. Ferraro et al., 1993; Jackson et al., 1995; Pascual-Leone et al., 1993; Sommer et al., 1999; Westwater et al., 1998) to intact sequence learning (Smith et al., 2001). In the present study, we took into account both motor and cognitive aspects in order to a possible explanation for the inconsistent results. We assessed sequence learning in the SRT task in patients all classified in Stage 3 of the Hoehn and Yahr (1967), whose level of cognitive functioning was determined using the SCOPA-COG (Marinus et al., 2003).

Error rate analysis showed that error rates were significantly lower in the HS group as compared to the AS and LS group. No speed-accuracy trade-offs were found in groups. The results of the SRT task showed significant practice effects for all groups, albeit not differing significantly between groups. Nevertheless, no sequence learning effects could be observed in early training (Block 7). Possibly, subjects were not trained sufficiently to already display implicit sequence learning during early stages of training. During later stages of training (Block 14), however, we found significant sequence learning in both the AS and HS group, but not in the LS group. These significant results remain after controlling for disease duration.

In the line of these findings we can conclude that low scoring cognitive patients systematically fail in learning sequence-specific information and perform worse than average and high scoring patients. These results are in agreement with the previous findings of Deroost et al. (2006) and can be considered as support for the relationship between implicit learning and cognitive level. The association between cognitive functioning and implicit sequence learning could be explained through striatal deterioration as the disease progresses. The striatum does not only play a crucial role in implicit learning (Exner et al., 2002), dopaminergic dysregulation of the fronto-striatal circuits can also occur in PD, leading to cognitive decline and executive dysfunction (Piatt et al., 1999). This means that decreased cognitive functioning could be associated with impaired implicit learning. This can provide an explanation for the mixed results in studies with PD patients. However, there are several issues, discussed below, needed to be clarified in future research before any strong conclusions can be drawn.

Dividing PD patients into subgroups based on their cognitive abilities was rather difficult to do. We decided to use the SCOPA-COG to assess cognitive functioning in PD because it is assumed to be a reliable and valid screening tool. A disadvantage, however, lays in the fact that the test does not include norms, making it difficult to determine whether a score is high or low. Verbaan et al. (2007) conducted a longitudinal cohort study (PROPARK study) to screen PD patients with assessment instruments that have been found to be valid and reliable. They evaluated cognition in 400 patients with PD by means of the SCOPA-COG. Results showed that patients with normal cognition scored a mean of 28.0 ($SD = 4.6$) and patients with impaired cognition scoring 17.6 ($SD = 3.7$). With respect to these recent findings we can argue that the classification of our groups is fairly accurate.

The different clinical and demographical variables showed that the high cognitive group was significantly younger and less long diagnosed with PD than patients in the average and low cognitive group. Nevertheless, an analysis of covariance showed that disease duration did not influence the obtained sequence learning results (age and education could not be analyzed because the statistical assumption for linearity was violated). Future studies should match for these variables to reduce possible confounding factors.
In recruiting patients motor screening was solely based on the Hoen and Yahr scale. However, in future research a more sensitive instrument such as the Unified Parkinson's Disease Rating Scale (UPDRS) should be used along with relevant subscales that have been developed to examine specific symptom types. More information on the motor symptoms could provide further insight into the impact of motor impairment on sequence-specific learning behavior.

Another point of improvement for future research could be to exclude the average scoring cognitive group and compare more high and low cognitive patients. This polarization could help find more support for differences in implicit learning between low and high cognitive patients. In addition, comparing PD subgroups with healthy controls would be helpful in order to see whether high scoring patients acquire sequence-specific learning in a similar way than control subjects.

In conclusion, the present study demonstrated that implicit sequence learning is associated with cognitive functioning in PD. Patients obtaining higher scores on the SCOPA-COG score systematically performed better on the SRT task: the low scoring cognitive group was significantly worse in acquiring sequence-specific information than average and high cognitive scorers. This shows that the SRT task is an adequate instrument to assess cognitive decline in PD dependently or not in order to account their level of cognitive functioning.

More research is required to investigate whether motor and cognitive decline in PD develop dependently or not in order to improve diagnosis and treatment in PD.

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References


