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Impaired sequential and partially compensated probabilistic skill learning in Parkinson's disease

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The striatal dopaminergic dysfunction in Parkinson's disease (PD) has been associated with deficits in skill learning in numerous studies, but some of the findings remain controversial. Our aim was to explore the generality of the learning deficit using two widely reported skill learning tasks in the same group of Parkinson's patients. Thirty-four patients with PD (mean age: 62.83 years, *SD*: 7.67) were compared to age-matched healthy adults. Two tasks were employed: the Serial Reaction Time Task (SRT), testing the learning of motor sequences, and the Weather Prediction (WP) task, testing non-sequential probabilistic category learning. On the SRT task, patients with PD showed no significant evidence for sequence learning. These results support and also extend previous findings, suggesting that motor skill learning is vulnerable in PD. On the WP task, the PD group showed the same amount of learning as controls, but they exploited qualitatively different strategies in predicting the target categories. While controls typically combined probabilities from multiple predicting cues, patients with PD instead focused on individual cues. We also found moderate to high correlations between the different measures of skill learning. These findings support our hypothesis that skill learning is generally impaired in PD, and can in some cases be compensated by relying on alternative learning strategies.

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects 1–3% of the population above 65 years (Hirsch, Jette, Frolkis, Steeves, & Pringsheim, 2016). The classic symptom triad of PD (tremor, bradykinesia, and rigidity) is associated with the degeneration of dopamine (DA) neurons in the substantia nigra pars compacta which causes a massive DA reduction in the basal ganglia (Kish, Shannak, & Hornykiewicz, 1988). Beside the motor symptoms, several cognitive domains are also affected. The neuropsychological profile of PD is determined by the executive dysfunction

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characterized by deficits on tasks measuring set shifting (Cools, Barker, Sahakian, & Robbins, 2001), inhibition (Gauggel, Rieger, & Feghoff, 2004), conflict resolution (Obeso *et al.*, 2011), planning (Lewis, Dove, Robbins, Barker, & Owen, 2003), dual task performance (Benecke, Rothwell, Dick, Day, & Marsden, 1986), and decision-making (Kobayakawa, Koyama, Mimura, & Kawamura, 2008). The striatal dopaminergic dysfunction in Parkinson's disease (PD) has been associated with deficits in skill learning in numerous studies, but some of the findings remain controversial. The current study focuses on PD and tests the generality of skill learning deficits in PD.

Skills are complex patterns of behaviour that are developed through continuous practice (e.g., Karni, 1996). Skill learning is an online process in which the learner repeatedly carries out the given complex behaviour to obtain better performance. This better performance can mean faster execution or more similar outcomes of the same action. Sport-related movements are the best examples for skill learning. When learning to swim, participants are aimed at carrying out the same movement repeatedly in a fast and harmonious way. However, hitting a nail with a hammer can also be considered a skill, in which learning is manifest in better hit rates. While the above examples, as well as skill learning research, are dominated by motor skills, the scope of research in the past two decades has been extended to non-motor cognitive skills, like categorization (Knowlton, Mangels, & Squire, 1996; Knowlton, Squire, & Gluck, 1994).

Skill acquisition relies mainly on procedural memory, one of two parallel memory systems that process different types of information (Squire, Knowlton, & Musen, 1993). Declarative memory supports semantic and episodic knowledge (facts and events) that can be directly recalled, while procedural memory consists of more fluid process-like information that is acquired incrementally (Squire *et al.*, 1993). Conscious access to procedural memory is difficult or impossible (Graf & Schacter, 1985). There is also evidence suggesting that different memory systems are supported by different neural bases: The declarative memory system relies on the hippocampus and other medial temporal lobe (MTL) structures (Henke, 2010), while the procedural memory system builds on frontostriatal pathways between the basal ganglia and the regions in the frontal cortex associated with movement, action planning, and motor execution (Packard & Knowlton, 2002). As the procedural memory system relies mainly on structures and networks that are dysfunctional in PD, neuropsychological studies started focusing on whether procedural memory functions are in fact deficient in PD. These studies often used different skill learning tasks and are overviewed in the following section.

Most studies of skill learning in PD focusing on motor sequence learning used the Serial Reaction Time Task (SRT, Nissen & Bullemer, 1987) in which participants have to respond to the location of a target stimulus appearing at one of four possible locations. Unknown to the participants, the locations follow a deterministic sequence. As long as the sequence is present, reaction times (RTs) decrease, while in the absence of the sequence, RTs increase. Studies found deficient learning on the SRT in PD, especially in terms of sequence-specific learning (Siegert, Taylor, Weatherall, & Abernethy, 2006; but see Kwak, Müller, Bohnen, Dayalu, & Seidler, 2012), but the degree and nature of the impairment varies greatly across studies. Some studies found no evidence of sequence learning (Jackson, Jackson, Harrison, Henderson, & Kennard, 1995), while others showed present but decreased learning performance compared to healthy control (HC) subjects (Ferraro, Balota, & Connor, 1993; Pascual-Leone *et al.*, 1993). Others argue that the sequence learning deficit is only observed due to the required motor response. With verbal instead of motor responses, some studies showed normal performance (Smith, Siegert, &

McDowall, 2001), while others observed decreased sequence learning (Westwater, McDowall, Siegert, Mossman, & Abernethy, 1998).

The above-described inconsistencies are partially explained by a recent review suggesting that the generality of the motor skill learning deficit relies on task and patient characteristics (Ruitenberg, Duthoo, Santens, Notebaert, & Abrahamse, 2015). Task characteristics include the length of training, or specific stimulus features, whereas patient characteristics are related to medication status, disease severity, and sequence awareness. Medication also seems to have an effect: Results show that sequence learning can be even more vulnerable in participants on medication than in patients off medication (Kwak, Müller, Bohnen, Dayalu, & Seidler, 2010; Kwak *et al.*, 2012; Ruitenberg *et al.*, 2015). Studies of disease severity suggest a larger sequence learning deficit in patients experiencing freezing of gait (Vandenbossche *et al.*, 2013) or less dopaminergic denervation (Kwak, Bohnen, Müller, Dayalu, & Seidler, 2013; for an overview, see Ruitenberg *et al.*, 2015). Ruitenberg *et al.* (2015) also argue that the deficient effect of medication might be expressed through decreased explicit awareness to the sequential regularities.

The previous section described motor skill learning, but deficits have also been found outside this domain in PD. Feedback-based probabilistic category learning (i.e., category learning where cues and categories have a probabilistic association) was expected to be vulnerable in PD for several reasons: because of (1) the importance of DA in feedback-based learning and the dopaminergic dysfunction in PD (Grahn, Parkinson, & Owen, 2008; Kehagia, Barker, & Robbins, 2013) and (2) the importance of striatal structures in category learning (Filoteo & Maddox, 2007). In many studies, the Weather Prediction (WP) task is used as a model of probabilistic category learning (Knowlton *et al.*, 1994). In the WP task, participants see one, two, or three of four possible cues and have to decide whether there would be sunshine or rain. Unknown to the participants, the different cues and outcomes have a probabilistic relationship. Immediate feedback after each decision helps the identification of the cue-outcome contingencies (Knowlton *et al.*, 1994). In accordance with the above-described predictions, the acquisition of non-sequential probabilistic associations was found to be vulnerable in PD as evidenced by impaired learning on the WP task (Shohamy, Myers, Onlaor, & Gluck, 2004). Results, however, are not conclusive on which aspect of learning is deficient. Comparison of feedback-based (feedback provided after each decision) and observation-based (cue-outcome pairs are shown without required actions) versions of the WP task showed either a selective deficit in feedback-based learning (Shohamy, Myers, Grossman, *et al.*, 2004), or a selective deficit in observation-based learning (Schmitt-Eliassen, Ferstl, Wiesner, Deuschl, & Witt, 2007). Other studies identified practice or strategy-based deficits in PD. One study suggested that the deficit only emerges at later stages of training (Shohamy, Myers, Grossman, *et al.*, 2004), while others argue that patients with PD are unable to develop an optimal strategy for solving the task (Shohamy, Myers, Onlaor, *et al.*, 2004). There is also a study that failed to find a probabilistic category learning impairment in PD (e.g., Price, 2005).

Although skill learning is often regarded as a prototypically procedural function, skill learning in real life (together with tasks that model skill learning) relies on multiple memory systems: Depending on the nature of the task, it taxes procedural, declarative, and working memory and involves implicit and explicit processes to different degrees. There is evidence that working memory deficits are associated with diminished efficiency of learning on the SRT task (Gómez Beldarrain, Grafman, Pascual-Leone, & Garcia-Monco, 1999). The WP task has been found to rely on explicit processes by a number of experimental studies (Kemény, 2014; Kemény & Lukács, 2013a; Price, 2009). Reliance on such processes can be more pronounced in the face of striatal dysfunction in PD, as shown by stronger reliance on single-cue strategies (Shohamy, Myers, Onlaor, *et al.*, 2004) and by imaging results of increased MTL activation and decreased striatal activation in patients with PD during the WP task (Moody, Bookheimer, Vanek, & Knowlton, 2004).

As reviewed above, the striatal dopaminergic dysfunction in PD has been associated with deficits in skill learning in a number of studies using both the SRT and the WP tasks, but the results are inconclusive so far. Our primary aim in this study was to test different forms of skill learning in the same group of patients with PD. Are both sequential and non-sequential forms of learning similarly impaired, when cross-study differences potentially caused by the heterogeneity of different PD groups or other factors (regarding, e.g., severity of symptoms) are controlled for? As we also wanted to relate our findings to previous results on skill learning in PD, we chose the SRT task to test the learning of motor sequences and the WP task to test probabilistic category learning in a non-sequential task because they (1) have been extensively used in the literature and (2) measure different aspects of skill learning. Both tasks are argued to be implicit and procedural (although see Destrebecqz & Cleeremans, 2001; and Lagnado, Newell, Kahan, & Shanks, 2006; Newell, Lagnado, & Shanks, 2007), but they differ in several regards. Learning on the SRT task (1) involves sequence learning, (2) involves motor learning, (3) is deterministic, and (4) is non-feedback based, while learning on the WP task is (1) non-sequential, (2) non-motor, (3) probabilistic, and (4) feedback based.

In both the WP (Poldrack *et al.*, 2001) and SRT tasks (Dennis & Cabeza, 2011), the competitive nature of implicit and explicit systems is characterized by the negative correlation between striatal and MTL activation. Based on the established basal ganglia deficits in PD and on earlier findings, we expect impaired performance in PD on both the SRT and WP tasks, although predictions for the WP task are less straightforward. Detailed strategy analyses of learning on the WP task also allow us to compare learning qualitatively between the groups. As far as we know, our study is the first to focus on different types of skill learning in the same group of patients with PD. We expect our results to provide a step forward in understanding what types of skills rely on the fronto-striatal loops that are deficient in PD.

Methods

Participants

Altogether, 34 patients with L-dopa responsive idiopathic PD (13 female, 21 male; age 62.83 ± 7.9 years, range: 48–78; Hoehn-Yahr stage, 3.7 ± 0.5; duration of PD symptoms 9.0 ± 3.8 years) were involved in the study. Parkinsonian motor symptoms and signs were rated using the motor part III of the Unified Parkinson's Disease Rating Scale (UPDRS: Goetz *et al.*, 1995). The UPDRS-III motor score in 'medication off' state was 47.5 ± 7.5, and in 'medication on' state was 27.1 ± 8.1, showing a 42.9% improvement after antiparkinsonian medication. Daily doses of medications were standardized by the use of a formula for L-dopa-equivalent doses (LED: Wüllner *et al.*, 2010). The mean daily LED was 778.6 ± 313.3 mg. All PD participants were tested under medication.

Severity of depression in the PD sample was assessed using the Beck Depression Inventory (4.15 ± 6.91, min: 0, max: 15), anxiety by the Spielberger State and Trait Anxiety Inventory (STAI-S, 20.79 ± 12.32, min: 2, max: 48; STAI-T, 24.5 ± 9.6, min: 6, max: 48), and cognitive impairment by the Mini-Mental State Examination (MMSE, 28.06 ± 1.5, min: 25, max: 30). The PD group was in the normal range regarding depression and anxiety severity, and based on the MMSE scores, none of the patients showed cognitive impairment.

Performance of the PD group was compared to that of a group of age-matched HC individuals. Their mean age was 62.76 ± 7.86 years (14 female, 20 male, age range: 48–78). Data of HC participants were collected from a previous cross-sectional study on skill learning (Lukács & Kemény, 2015). All participants provided a written informed consent, in accordance with the principles set out in the Declaration of Helsinki and the stipulations of the local Institutional Review Board. Sample characteristics are provided in Table 1.

Stimuli and design

Participants completed two skill learning tasks: the SRT and WP tasks. Both tasks were presented on a 640 × 480 display, on a computer using E-prime 1.2 (Psychology Software Tools Inc., Pittsburgh, PA, USA).

The SRT task

The SRT task was an adaptation of Meulemans, Van der Linden, and Perruchet (1998). Four horizontally aligned circles appeared on the screen (diameter approximately 55 pixels). One circle was black (target stimulus), while the other three were white with a black contour. The distances between the circles were equal.

The task for participants was to press the button corresponding to the location of the target. The response buttons were Y, C, B, and M. On a standard Hungarian QWERTZ keyboard, these buttons are arranged horizontally in the bottom line of the keyboard with one button between each. A special keyboard was used, in which all keys other than the response keys were removed. Each target item was on screen until response. In the case of

Table 1. Sample characteristics and results on clinical scales

	PD group (n = 34)		HC group (n = 34)	
Characteristics	Mean	*SD*	Mean	*SD*
Age (years)	62.83	7.90	62.76	7.86
Sex (M/F)	21/13		20/14	
Hoehn-Yahr stage	3.7	0.5		
Medication in LED	778.6	313.03		
Duration of illness (years)	9	3.8		
UPDRS-III motor score off	47.5	7.5		
UPDRS-III motor score on	27.1	8.1		
BDI	6.91	4.15		
STAI-S	20.79	12.32		
STAI-T	24.5	9.6		
MMSE	28.06	1.5		

Note. BDI = Beck Depression Inventory; HC = healthy control group; LED = levodopa equivalent units; MMSE = Mini-Mental State Examination; PD = Parkinson's disease; STAI-S = State and Trait Anxiety Inventory, State Subscale; STAI-T = State and Trait Anxiety Inventory, Trait Subscale; UPDRS = Unified Parkinson's Disease Rating Scale.

an incorrect response, a 560 ms tone was played.[1] The response-stimulus interval was 250 ms. Participants were asked to use the middle and index fingers of both their hands, and keep them on the keyboard all the time.

The task was composed of 12 blocks, each block including 60 stimuli. The target stimulus appeared in accordance with a 12-element sequence in blocks 1–11. The sequence was a second order conditional sequence, in which adjacent (first-order) elements carry no predictive information (i.e., a stimulus may be followed by any of the three other possible stimuli with equal probability), but two consecutive elements together determine what the next element will be: 121,423,413,243, where the numbers represent the position of the black circle. In Block 12, the sequence was replaced by pseudorandom appearance of the target stimuli. No immediate repetitions were allowed, and the frequency of the different elements was equal within the block.

The WP task

The WP task was the adaptation of Knowlton *et al.* (1994), and identical to the one used by previous studies (Kemény & Lukács, 2013b). Each experimental item was a combination of one, two, or three of four possible cues appearing simultaneously. Cue1 was a square, Cue2 was a triangle, Cue3 was a pentagon, and Cue4 was a rhombus. Cues appeared 144 pixels from the top. Each cue was fit into a 125 × 125 pixel square. The displays of single cues or cue combinations appeared in the horizontal centre line. In combinations, Cue1 was always preceding all other cues, Cue2 was always preceding Cue3 and Cue4, and Cue3 was always left from Cue4 if presented together.

Participants were asked to guess, based on the cues, whether there will be sunshine or rain, and press ENTER or SPACE, respectively. The response keys were marked by a weather icon of the outcome. Each prediction was followed by a feedback revealing the correct answer. Feedback was provided in the form of an 83 × 86 pixel icon of a sun or a cloud with rain. The icon appeared in the horizontal centre line 343 pixels from the top along with the cue or cue combination.

There were four blocks of 50 items. The order of the items was pseudorandom. No two consecutive items used the same cues. That is, the combination of cues 1 and 3 could not appear twice in a row, while this combination could be followed by, for example, the combination of cues 1, 3, and 4.

Unknown to the participants, each cue had a preset predictive value. Two cues predicted each outcome: Cues 1 and 2 predicted sunshine, while cues 3 and 4 predicted rain. For each outcome, there was a strong and a weak cue, the strong cues were associated with sunshine (Cue1) or rain (Cue4) in 85.7% of their appearances, while Cue2 (sunshine) and Cue3 (rain) predicted their outcome with 70%. Table 2 summarizes the design.

This experiment was part of a larger project in which participants were tested in several cognitive domains. Testing consisted of a single session that ran for approximately 4 hr including self-paced breaks between the tasks. Tasks had a fixed order throughout the session: The SRT task was administered first, and the WP task later.

[1] *This tone was used to maintain the attention of participants. The feedback appeared only in case of incorrect responses, which were very few in number, and was related to local stimulus-response contingencies. No feedback was provided on the global, sequence level.*

Table 2. Types and occurrences of cues or cue combinations per blocks of 50 trials. Column 1 (Cues) identifies cues and combinations. Column 2 (Frequency) shows the number of appearances within a block of 50 trials. Column 3 provides the probability with which the given cue or combination is associated with sunshine (which equals 1 minus the probability of rain)

Cues	Frequency	*p*(SUN)
1	8	.875
2	4	.75
3	4	.25
4	8	.125
1,2	8	.875
1,3	1	1
2,3	2	.5
2,4	1	0
3,4	8	.125
1,2,3	2	1
1,2,4	1	1
1,3,4	1	0
2,3,4	2	0

Data analysis

Due to technical problems, data of three patients with PD were not registered: one in the SRT task and two in the WP task. One additional patient had accuracy below 80% on the SRT task. Data of these participants were excluded task-wise: Their data from the other task were included in the analyses. Their age-matched controls were also excluded from the respective analyses. After the exclusion, the mean accuracy of participants was 98.17% on the SRT task. As this value is close to ceiling, we did not analyse accuracy further.

For the SRT task, only RTs of correct answers were considered. RTs deviating more than two standard deviations from the mean were excluded at the participant level (which lead to the exclusion of 3.57% of the items overall, 3.56% in the PD, and 3.59% in the HC group). We computed a raw learning score for sequence learning by subtracting the mean RTs of the last sequenced block from the mean RTs of the random block (Block 12–Block 11).

As previous studies have pointed out the importance of differences in the baseline RTs between clinical and control groups, we applied individual *Z*-transformations on RTs. Individual mean and standard deviation were calculated for each participant. Each RT was transformed by subtracting the participant's individual mean from the RT and dividing the difference by the participant's individual standard deviation (Christ, White, Mandernach, & Keys, 2001). *Z*-transformed learning scores were calculated by subtracting Block11 ZRTs from Block12 ZRTs.

Two types of analyses were conducted for the SRT task. First, we compared overall group means of RTs. Second, based on an earlier study of children with Specific Language Impairment (Lukács & Kemény, 2014), we categorized each participant as a 'learner' or a 'non-learner'. To classify participants as 'learners' and 'non-learners', we defined a threshold based on our data. Excluding the first six items (due to being block initial), we split items of the random block (Block 12) into odd and even items. We compared the median RTs for correct responses for odd versus even items. As the items do not differ in experimental settings, the mean difference was not expected to deviate from 0. The prediction of a lack of difference was borne out by a paired sample *t*-test, $t(63) = 1.230, p = .223$. The observed mean difference was 13.4 ms with the confidence intervals of −8.37 and 35.17. The upper bound of the confidence interval (35.17 ms) was used as a threshold for 0 effect (i.e., no learning). All participants having an RT difference (Block 12 minus Block 11) smaller than 35.17 ms were classified as 'non-learners', whereas all participants above the threshold of 35.17 ms were classified as 'learners'. This method is based on a previous study of visual cueing in reading and spelling deficit (Banfi *et al.*, 2017). After categorizing participants, chi-squared tests were applied to determine whether the number of learners differed by group (PD vs. HC).

In the case of the WP task, we calculated a categorization score following previous publications (e.g., Knowlton *et al.*, 1994). One, two, or three cues can appear in each item. Each cue has its own predictive value, which is its strength of association with the outcome of 'sun'. For each item, we averaged the predictive values of the presented cues. If the average predictive value is above 50%, we expect sun as an outcome, and if the value is below 50%, we expect rain as a correct answer. As the expected correct answer is only probabilistically related to the final outcome, the feedback could show a correct or an incorrect prediction. Percentages of correct predictions were averaged by block.

Three types of analyses were conducted on WP results. First, the performance levels of the two groups and then the rate of 'learners' versus 'non-learners' were compared. In the case of the WP task, learners were participants with performance above 55% on block 4 (where 50% is chance level). The third analysis compared strategies used by the two groups.

Previous studies have identified three different strategies for solving the WP task (Gluck, Shohamy, & Myers, 2002). Participants using the One-cue strategy focus on one of the cues and give a systematic answer only if that specific cue is present. Singleton strategy-users provide systematic responses if only 1 cue is present at a time; when combinations are present, they respond randomly. Multi-cue strategy-users provide answers based on all cues by averaging predictive values. Previous theories suggested that participants using the Multi-cue strategy rely on procedural memory, while Singleton and One-cue strategy-users rely on declarative memory (Gluck *et al.*, 2002). Others argue against the memory system-based distinction (Kemény & Lukács, 2013a). Although the results on the foundations of strategy use are not conclusive, we still expect to see whether possible performance differences are due to different strategies or quantitative differences in learning by the same strategy. We calculated the best fitting strategy for each participant in each block following the procedure described in previous studies (Gluck *et al.*, 2002). Each strategy predicts a certain response to cues or combinations. For each block of each participant, we calculated a model score for all types of strategies. This model score is a quantitative measure of how the participants' responses fit with the predictions of the given strategy.

To compute the model scores, for each cue and cue combination, we summed up the difference of the expected and actual 'sun' answers and divided them with the sums of squares of the number of presentations of each cue or cue combination. The computation of the model score is provided in Equation (1). If the model score of the Multi-cue strategy was lower than 0.1, the participant was assumed to use the Multi-cue strategy. If the model score for the Multi-cue strategy was above 0.1, but any of the other model scores were below 0.1, the participant was assumed to use a single strategy. If no model scores were below 0.1, no strategy use was assumed (criteria identical to Gluck *et al.*, 2002).

$$\text{ModelScore}_M = \frac{\sum_P (\#\,\text{sun\_expected}_{P,M} - \#\,\text{sun\_actual}_P)^2}{\sum_P (\#\,\text{presentations}_P)^2}. \quad (1)$$

The Multi-cue strategy is the most optimal strategy for the WP task, while the Singleton and One-cue strategies are suboptimal. Strategies are fit to each block separately. Healthy participants are expected to show one of the suboptimal strategies early in the task, and switch to Multi-cue strategy later (Gluck *et al.*, 2002). Using χ^2 tests, we compared the number of participants in the two groups, who managed to develop a Multi-cue strategy.

To see whether learning on the two different skill learning task is related, and whether patients who are impaired on one task are also likely to be impaired on the other, we also analysed the associations between performance measures on the two tasks. First, we analysed correlations between the task indices separately for each group. Then, we compared the rate of learners and non-learners among the tasks within each group using χ^2 tests. Finally, on cognitive functions, we tested the correlations between performance on the two tasks and medication and UPDRS measures. There is a growing literature (Kehagia *et al.*, 2013; Kudlicka, Clare, & Hindle, 2011; Ruitenberg *et al.*, 2015, 2016) on the effect of medication and symptom severity on different cognitive functions in PD, and our aim with this analysis was to see how our main results are modulated by these factors. This latter analysis was only performed on PD patients' results (as controls do not have LEDs and UPDRS scores). As two measures of the same SRT task were used, the alpha-level was decreased to .025.

Results

Serial Reaction Times task

Comparison of overall group performance levels

We conducted a univariate ANOVA to test whether raw learning scores differ by group. Raw learning scores in the HC group were significantly higher than those in the PD group (64.46 ms for the HC, −5.83 ms for the PD group), as revealed by a significant main effect of Group, $F(1, 62) = 6.170$, $p = .016$, $\eta_p^2 = .091$. To test whether the individual groups showed evidence of learning (above chance results), their average raw learning score was compared to 0 with a one-sample *t*-test. Mean scores were significantly above 0 in the HC, $t(31) = 2.685$, $p = .012$, but not in the PD group, $t(31) = -0.393$, $p = .697$. Reaction times by Block and by Group are provided in Figure 1.

A similar result was obtained for *Z*-transformed data. The ANOVA revealed that the *Z*-transformed learning scores of the HC group were significantly higher than those of the PD group (0.384 for the HC and 0.034 for the PD group), $F(1, 62) = 8.261$, $p = .006$, $\eta_p^2 = .118$. One-sample *t*-tests showed a mean learning score above 0 in the HC group, $t(31) = 3.668$, $p = .001$, but not in the PD group, $t(31) = 0.546$, $p = .589$. Figure 2 depicts *Z*-transformed RTs by Block and by Group.

Comparison of the ratio of learners

A χ^2 test was applied on the number of participants in the two learning categories (Learners vs. Non-learners) by Group (PD vs. HC). The numbers of learners are provided in Table 3. Results revealed that the distribution of category membership differed by group,

$\chi^2(N = 64, df = 1) = 6.349, p = .012$, with a significantly higher rate of learners in the HC group on the SRT task.

Weather Prediction task

Comparison of overall group performance levels

In the case of the WP task, we compared categorization performance by Block (Block 1–4) and by Group (PD vs. HC) using a mixed-model ANOVA. The Huynh-Feldt corrected ANOVA[2] revealed a significant main effect of Block, $F(2.613, 161.976) = 12.432$, $p < .001$, $\eta_p^2 = .167$ (55.6% on Block1, 59.0% on Block2, 62.1% on Block3, and 64.4% on Block4). No other effects were significant (both $ps > .517$, both $Fs < 0.425$). Figure 3 provides categorization performance by Block and by Group. Performance shows a linear increase, as suggested by a significant linear contrast, $F(1, 62) = 31.427$, $p < .001$, $\eta_p^2 = .336$.

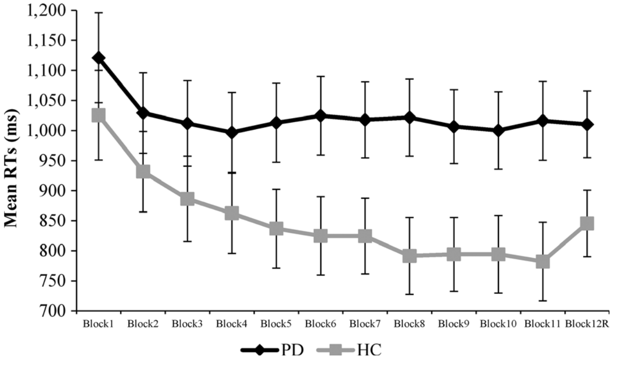

Figure 1. Reaction times in milliseconds by Block and by Group in the SRT task. Error bars indicate *SEM*.

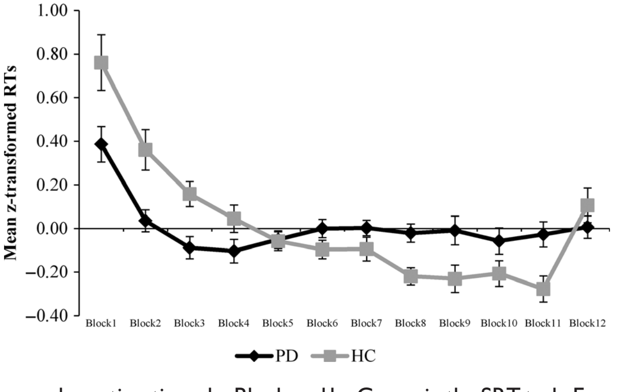

Figure 2. *Z*-transformed reaction times by Block and by Group in the SRT task. Error bars indicate *SEM*.

[2] *Correction was made due to violation of sphericity as indicated by a significant Mauchly's test of sphericity.*

Table 3. The percentage and number of participants in each category by group in the tasks

		N (%)	
Task	Group	Learners	Non-learners
SRT	PD	9 (28.13)	23 (71.87)
	HC	19 (59.38)	13 (40.62)
WP	PD	26 (81.25)	6 (18.75)
	HC	21 (65.62)	11 (34.38)

Note. SRT = Serial Reaction Time task; WP = Weather Prediction task.

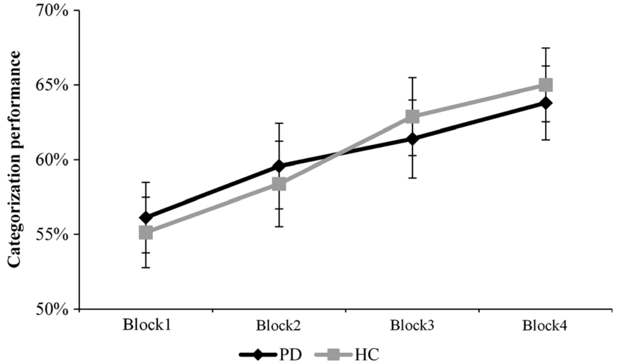

Figure 3. Categorization performance on the WP task by Block and by Group. Error bars indicate *SEM*.

Comparison of the ratio of learners

The number of learners and non-learners of the WP task was compared by group membership (PD vs. HC). Results revealed no significant difference in the ratio of learners versus non-learners on the WP task, $\chi^2(N = 64, df = 1) = 2.003, p = .157$, see Table 3 for the distributions.

Strategy analysis in the WP task

Responses of one participant in the PD group did not match any of the three strategies throughout the four blocks; hence, this patient was excluded from strategy analysis along with the matching control participant. Of the 31 patients with PD, 11 were able to use the Multi-cue strategy, and 20 used one of the single strategies. In the control group, 20 Multi-cue strategy-users and 11 Single strategy-users were identified. A χ^2 test was computed to compare the distribution of Multi-cue strategy-users and Single strategy-users across the two groups. The test showed that the proportion of Multi-cue strategy-users was higher in the control group, χ^2 $(N = 62, df = 1) = 5.226, p = .022$.

Associations between performance on the SRT and WP tasks

Correlations between performance measures of the two tasks

Associations between performance measures of the two tasks were tested using Pearson's correlations. Correlations were examined separately in the PD and HC groups, and also in the entire group of participants (collapsed over PD and HC). Both raw and *Z*-transformed learning scores were used from the SRT task, and their associations were tested with overall performance on the WP task. As two SRT measures were used, alpha-level was corrected to .025. In the case of HC participants, the correlation between WP performance and raw SRT learning scores just fell short of significance after Bonferroni correction, $r(n = 30) = .405$, $p = .026$. All other correlations were significant in both groups separately, and in the entire group as well (correlations were between .360 and .443, and all ps $< .025$). Table 4 provides the between-task correlations in each group, as well as the two groups collapsed.

Comparing the ratio of learners and non-learners across the two tasks

Using χ^2 tests, we compared the number of learners and non-learners on the SRT task and WP task in each group. The χ^2 test revealed that the ratio of learners was larger on the WP task than on the SRT task in the PD group, χ^2 $(N = 34, df = 1) = 33.356, p < .001$, but the distribution was comparable across the two tasks in the HC group, χ^2 $(N = 34, df = 1) = 1.602, p = .206$.

Correlations between performance and medication and symptom severity

Correlations were tested between LED and UPDRS-III ‘medication off’ and ‘medication on’ scores on the one hand, and SRT raw and Z-transformed learning scores, as well as WP performance on the other. This analysis was only carried out for patients with PD. Pearson’s correlations were used with an alpha-level corrected to .025 because of the use of two SRT measures. Results showed that in the case of the SRT task ($n = 30$), LED was not significantly correlated with either raw learning scores, $r = .308$, $p = .098$, or Z-transformed learning scores, $r = .299$, $p = .109$. Similarly, no significant correlations were observed between LED and overall WP performance ($n = 30$), $r = .147$, $p = .437$. UPDRS-III motor scores in ‘medication off’ or ‘medication on’ status did not show significant correlations with performance measures either ($-.354 <$ all rs $< -.130$, all ps $> .055$). Table 5 provides the correlation coefficients between UPDRS and LED measures and performance indices.

Summary and discussion

This study tested the vulnerability of different forms of skill learning associated with the impairments of frontostriatal circuits in patients with PD using a SRT, testing the learning

Table 4. Pearson’s correlations between WP and SRT performance measures

Groups	Raw learning scores	*Z* learning scores
WP performance		
PD group	.436*	.428*
HC group	.405	.443*
Groups collapsed	.360**	.360**

Notes. Number of participants is 30 for each group, and 60 for the collapsed analysis.
HC = healthy controls; PD = Parkinson’s disease; SRT = Serial Reaction Time task; WP = Weather Prediction task.
$^*p < .025$; $^{**}p < .005$.

Table 5. The associations (Pearson's correlation) between LED and UPDRS motor scale scores and skill learning performance

	LED	UPDRS 'medication off'	UPDRS 'medication on'
Raw learning scores	.308	−.169	−.251
Z learning scores	.299	−.179	−.130
WP overall performance	.147	−.144	−.354

Notes. No correlations reached significance with alpha = .025 (Bonferroni-corrected).
LED = levodopa equivalent units; UPDRS = Unified Parkinson's Disease Rating Scale; WP = Weather Prediction task.

of motor sequences and a WP task, testing non-sequential probabilistic category learning. In the case of the SRT task, no evidence of sequence learning was observed in the PD group, while the control group showed a significant sequence learning effect. Controlling for baseline RT differences using *Z*-transformed RTs yielded the same pattern of results and confirmed the lack of a sequence-specific learning effect in patients with PD on the SRT task. Taken together, these SRT results argue that, in line with previous findings (Kwak *et al.*, 2012), sequence learning is deficient in PD, and this impairment is not only related to a general motor learning deficit, but is shown by missing or smaller sequence-specific learning (i.e., RT increase at the removal of the sequence in Block 12) in patients with PD.

Probabilistic categorization, however, seemed to be intact in PD at the first glance: Performance levels of the clinical and control groups were not statistically different, and both groups improved significantly across blocks resulting in a quantitatively similar performance. In spite of similar levels of performance, qualitative differences in strategies were observed: While the majority of control participants relied on the optimal Multi-cue strategy, responses of participants in the clinical group reflected the use of one of the suboptimal strategies.

Findings also showed that the sequence learning deficit observed on the SRT task in the PD group is evident from the lower proportion of participants who showed evidence of sequence learning in the PD than in the HC group. Within-group comparisons of the number of learners and non-learners on the SRT versus WP tasks also showed that motor sequence learning is more challenging in PD than probabilistic categorization: In PD, a larger number of participants learnt on the WP than on the SRT task. In the HC group, there was no statistically significant difference between the ratio of learners versus non-learners across the two tasks (showing that PD differences in distributions do not stem from, for example, differences in task difficulty between the SRT and WP tasks).

Our choice of tasks was motivated by earlier findings in the literature and their controversial nature. We hoped to gain new insight into the generality of the skill learning deficit in PD on these two well-established tasks by testing the same group of patients with PD, avoiding potential confounds stemming from differences in patient characteristics across studies. While our results demonstrate the differential vulnerability of different aspects of skill learning, the observed learning efficiency differences can stem from factors outside the sequential–non-sequential divide, as pointed out by our reviewers. As discussed in the Introduction, the two tasks differ on multiple other levels: involving motor versus non-motor learning, feedback based versus non-feedback based and depending on deterministic versus probabilistic information. As several of these dimensions can be affected by the dopaminergic dysfunction in PD, the task effect could reflect problems in these areas as well. These concerns cannot be addressed by the current paper and call for further studies comparing, for example, sequential versus non-sequential motor learning, or other task conditions minimally differing in being feedback based or not, or deterministic and probabilistic. Such designs could further elucidate the generality of the impairment in PD.

A more detailed look at the lack of a group difference in probabilistic categorization showed that on the WP task, the distribution of learners versus non-learners was comparable in the two groups. Strategy analysis, however, revealed that this comparable performance is reached using qualitatively different approaches. HC participants are expected to identify the individual cue-outcome contingencies, combine the contingencies, and base their decision on such a complex process. Patients with PD on the other hand simplified the task, and only focused on one cue at a time. While previous studies (Gluck *et al.*, 2002) identified this strategy as 'suboptimal', in this study final performance levels were comparable to those achieved by the 'optimal' Multi-cue strategy. The reason for this might stem from differences in predictive values of cues between the studies. Predictive values in this study were much higher than those in the Gluck *et al.* (2002) study, which might explain why even suboptimal PD strategies yielded good performance. With lower probabilities, single-cue strategies are expected to be less successful, and group differences between patients with PD and HCs might become evident in performance levels as well. It is also important to note, that despite being generally considered a suboptimal strategy, it is more readily available for patients with PD, and with the current predictive values, it successfully compensates categorization performance to a normal level.

Strategy-based differences have been associated with different memory systems. Previous studies suggested that single strategies rely on the declarative memory system, while the Multi-cue strategy is procedural (Gluck *et al.*, 2002; Poldrack *et al.*, 2001). Based on the declarative-procedural dissociation, we could argue that the procedural deficit in PD is compensated by declarative strategies. A similar compensation ('seesaw' effect, Ullman & Pullman, 2015) has already been described in developmental dyslexia (Hedenius, Ullman, Alm, Jennische, & Persson, 2013) and specific language impairment (Lukács, Kemény, Lum, & Ullman, 2017). Note, however, that experimental psychological studies question whether the different strategies can be mapped onto the procedural-declarative memory distinction (see Kemény, 2014; Kemény & Lukács, 2013a for detailed discussion).

Performance on the WP task has been described as a result of competition between the different memory systems. In healthy adult participants, the mediotemporal lobe was found to be activated early on in the task, but this activation was followed by a rapid deactivation (Poldrack *et al.*, 2001). This deactivation was accompanied by a later activation of the basal ganglia, which correlated with learning performance. Shohamy, Myers, Onlaor, *et al.* (2004) argue that this later activation might be indicative of the integration of information, which is related to the use of the Multi-cue strategy. Using Multi-cue strategy has been found to be deficient in Parkinson's syndrome by both previous papers (e.g., Shohamy, Myers, Onlaor, *et al.*, 2004), and by the current results. Our study, however, was not designed to examine declarative compensation of procedural dysfunctions.

The novelty of this study is that it tests two different forms of skill learning within the same group of participants, eliminating possible differences in patient characteristics this way. The sequence learning deficit together with qualitatively different learning on the

WP task in patients with PD is suggestive of a general deficit in skill learning. The generality of the deficit is further supported by the finding that performance measures of the WP and SRT tasks are positively correlated, showing that patients who are impaired on one type of skill learning are also likely to be impaired on the other type (the association was also present in the HC group).

As discussed in the Introduction, skill learning performance has been hypothesized to be closely associated with medication status (Ruitenberg *et al.*, 2015). Previous work has shown that DA depletion is associated with cognitive impairment in PD (e.g., Grahn *et al.*, 2008; Lewis *et al.*, 2003). In the early stage of the disease, DA depletion is restricted to the putamen and the dorsal caudate nucleus, sparing more ventral parts of the striatum (Cools *et al.*, 2001; Kish *et al.*, 1988). This pattern could explain the differential effect of dopaminergic replacement therapy on various cognitive functions. According to the 'dopamine overdose hypothesis', while DA medication increases the low DA level in the putamen and dorsal striatum, it over-stimulates the ventral striatum. This hypothesis is supported by observations that patients with PD manifest improved cognitive performance after DA therapy on planning and set shifting tasks mediated by the dorsolateral frontostriatal circuit (Cools *et al.*, 2001; Lange *et al.*, 1992) and impaired performance on those that involve the ventral striatum and its ventrolateral prefrontal connections, such as reversal learning (Swainson *et al.*, 2000), reward learning (Cools, Altamirano, & D'Esposito, 2006), and risk-taking paradigms (Cools *et al.*, 2001; Voon & Fox, 2007). Taking these results into consideration, a possible explanation for somewhat controversial findings in studies on motor sequence learning in PD could be that some of these studies included DA medication in the analysis of results while others have not. Kwak *et al.* (2010, 2012), for example, argue that DA medication has a differential effect on early and later phases of sequence learning. A significant impairment associated with medication was observed only in the early phase of learning compared to PD patients OFF their medication and HCs (Kwak *et al.*, 2010). The early phase of sequence learning is reliant on the ventral and anterior striatum, while learning in the later phase is more related to the dorsal and posterior striatum (Lehéricy *et al.*, 2005; Miyachi, Hikosaka, & Lu, 2002). This is in line with Kwak *et al.* (2012)'s other findings, demonstrating that patients ON medication show no activity in the ventral striatum in the early phase of sequence learning, whereas activity is observed in this area OFF medication. In another study, Ruitenberg *et al.* (2016) found evidence that DA medication impairs planning processes but enhances execution processes of movement sequence learning. Regarding the performance on the WP task, most of the results point towards a negative effect of DA medication on learning (e.g., Jahanshahi *et al.*, 2010; Wilkinson, Lagnado, Quallo, & Jahanshahi, 2008).

While the current experiment was not designed to test the role of medication in skill learning, we did have information on the medication doses and motor effects. We therefore analysed the correlations between LED and learning scores on both tasks. We also tested the relationship between symptom severity assessed by the UPDRS-III motor subscale ('medication off' and 'on' state, respectively) and task performance measures. No significant correlations were found between performance measures and UPDRS-III scores (either 'medication on' or 'medication off'). Targeted studies should explore how medication and symptom severity affects cognitive functions.

Conclusions

We investigated the generality of the skill learning deficit by testing two different forms of skill learning in the same group of Parkinson's patients with a basal ganglia deficit. We found a severe deficit in motor sequence learning on the SRT task. Patients with PD, on the other hand, showed probabilistic category learning performance comparable to HCs on the WP task. This typical performance was due to successful compensatory mechanisms. These findings, together with associations between performance measures on the two tasks, suggest a general deficit of skill learning in PD.

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