Behavioural Correlates of Cognitive Skill Learning in Parkinson's Disease

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Abstract: The impact of basal ganglia dysfunction on cognitive skill learning was explored using a learning version of the Tower of London (TOL) task, which places a heavy load on working memory and is not confounded by declarative memory, as have been previous tasks. Two subgroups of Parkinson's disease (PD) patients were assessed and also completed a selection of neuropsychological tests: the first was unmedicated (*de novo,* n=12) and the second included patients normally receiving L-DOPA, but tested off medication (n=12). Overall, neither subgroup was impaired when learning the task compared to control participants (n=22). Six patients, however, failed to improve their performance with practice. Their learning deficit could not be explained in terms of their functional status; instead, it was related to deficits on span tests. Thus, the inability to acquire a new cognitive skill in PD may not be due to learning impairments *per se*, but rather, it appears to be secondary to working memory deficits.

INTRODUCTION

It is now well established that Parkinson's disease (PD), a disorder characterized by the degeneration of dopamine neurons in the midbrain and striatum, is associated with cognitive deficits [1-3]. Such impairments occur in a variety of domains, including those involving executive functions like the generation of new concepts and mental strategies [4], problem solving [5], planning [6] and working memory [4,7]. Given their high prevalence, some investigators have suggested that PD produces a "dysexecutive syndrome" [1], similar to that seen in patients with frontal-lobe lesions [8,9]. Other cognitive deficits in visuospatial processsing [10,11] and episodic memory [12] have also been reported. However, several investigators have proposed that these impairments could also be due to the high demands the tasks used in these studies place on executive functions, and thus that they are secondary to this type of functional abnormality [3,13].

In addition to frontal lobe dysfunctions, there is increasing evidence that PD impairs procedural (non-declarative) learning, which refers to the capacity to acquire a new skill implicitly through practice of a motor, perceptual or cognitive task [14]. In PD, deficits in skill learning have been shown repeatedly using motor and perceptual paradigms such as serial reaction time [15-17], rotor pursuit [18,19], and mirror reading tasks [20-22]. Similar procedural impairments have also been observed in patients with PD using cognitive (non-motor) paradigms, but the results of such studies have been inconsistent [23,24]. One explanation for the discrepancies observed in the cognitive skill learning literature in PD is that the experimental paradigms used can differ substantially in terms of the nature of the learning process they require, as well as on the load they place on various cognitive functions.

One subset of cognitive learning paradigms that has been used is that involving tower-type tasks, such as the Tower of Hanoi (TOH) and Tower of Toronto (TOT), which have been shown to depend critically on working memory abilities because they require advanced planning and mental manipulation of information during problem solving [25,26]. Interestingly, imaging studies have shown that basal ganglia structures, such as the caudate nucleus, may specifically be recruited during the cognitive manipulation of information in working memory [27,28], hence explaining why learning using such tasks has sometimes been impaired in PD. However, even among studies using similar tower tasks, there is no clear evidence of cognitive skill learning deficits in Parkinson's disease. For instance, some investigators have observed cognitive skill learning impairments using the TOH and the TOT [5,29], while others have not been able to elicit such a deficit using the same paradigm [30]. Furthermore, the TOH and TOT tasks [5,29-31] have been criticized and sometimes rejected from the area of cognitive skill learning [32]. Indeed, the TOH and TOT are not ideal to test procedural cognitive skill learning because subjects are presented with the same problem on every trial of a particular level of difficulty, thus making learning very specific to one particular solution, and thereby limiting the ecological validity of the task in a skill learning context. Moreover, because extended practice on these tasks implies searching for a repeating strategy, this can eventually lead to explicit knowledge of that particular strategy (ex: "move disk 1 to peg 2; then move disk 2 to peg 3, etc). Once known, the strategy (or heuristic) can be used to solve subsequent problems without having to engage planning and problem solving abilities initially necessary for the task. Thus, the nature of the learning required for subjects to acquire the TOH is questioned since it may involve a combination of explicit and implicit processes. Initially, the TOH task was believed to be purely implicit because amnesic patients with declarative memory

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deficits were able to learn the task [33]. However, a subsequent study demonstrated impaired learning of the same task in amnesic patients [34]. These contradictory results again raise questions concerning the nature of the learning measured by the TOH task. Based on their own study of the TOH in amnesic patients, Winter and colleagues [35] suggest that the deficit observed is due to the fact that the information acquired on the TOH is of a declarative, rather than procedural, nature. They state that although a combination of explicit and implicit skills may be used to solve the task, it appears nonetheless possible to do so using a solution based on a purely explicit series of rules or heuristics. On the basis that the task can be solved using verbalizable rules, the authors conclude that it should not be used in the evaluation of non-declarative learning [35]. The nature of cognitive skill learning deficits in PD using tasks of executive functions is all the more elusive because the previously used tower tasks have not always been appropriate to the procedural skill learning context.

Other factors related to the heterogeneity of PD presentation may contribute to the inconsistencies described above. Indeed, disease severity [6,26,36,37], patients' age and age at disease onset [36,38,39], as well as the use of medication [26,40], have all been cited as contributing to variations in skill learning impairments and cognitive deficits in general. For example, Daum and colleagues [29] found that in comparison to patients at an early stage of the disease, those at a more advanced stage were impaired at acquiring the TOH task, suggesting that the progression of the underlying neuropathology of PD might explain the differences in skill learning abilities between these two groups. By contrast, other investigators [41-43] have failed to differentiate between PD patients and control groups performing cognitive skill learning tasks on the basis of motor severity as assessed with the Hoehn and Yahr scale [44]. The fact that some patients with severe physical disabilities have preserved cognitive functions and that motor disability correlates poorly with such functions [45], suggests that there is no simple relationship between mental and motor impairments. As an alternative to this clinical scale, the need for pharmacological treatment has also been used in some studies to characterise PD progression [46]. This clinical hallmark can be used to contrast patients who are more impaired by PD to those whose clinical features are mild enough that they still do not require symptomatic therapy such as levodopa (i.e., *de novo*). In an attempt to characterise the progression of PD on the basis of a more functional criterion than simple motor severity, we have used the latter approach by comparing *de novo* PD patients to a group of L-DOPA responders tested off medication on a task of cognitive skill learning.

In summary, the conclusions drawn from studies of cognitive skill learning in PD are limited by the use of a disease classification based solely on motor symptoms and lacking sensitivity to changes in patients' functional condition, as well as by important differences in the nature of the learning process and cognitive functions that are recruited by various tasks. In an attempt to address these two issues, we have studied cognitive skill learning in PD patients using a task which taps into working memory functions, and which is not confounded by aspects of declarative memory. Indeed, we sought to develop a problem solving task that would allow comparison with findings from previous studies, while taking into consideration the limitations mentioned above. To this end, a modified, *learning version* of the *Tower of London* (TOL) task [47] was developed to study the time course of learning. The original Tower of London has been extensively used as a measure of cognitive planning performance, but has not, until recently, been implemented as a cognitive skill learning task. Thus, while previous researchers have used the TOL to determine planning performance at a particular point in time [48,49] our group modified the TOL task and assessed cognitive skill learning in both younger and older groups of control subjects [50,51], by measuring performance on the task at different points in time, thus converting the TOL from a performance-type task to a skill learning paradigm. As mentioned, during the acquisition period subjects are presented with different problems on every trial, each of which has a different initial appearance or solution. In this sense, there is no one solution which can be applied to all problems, as can be the case in multiple trials of the TOH/TOT. This makes the learning version of the TOL primarily procedural in nature. Indeed, in accordance with the criteria for implicit learning [32,52,53] and the classification of non-declarative learning established by Squire [54,55,56], the knowledge gained through learning the modified TOL is not fully accessible to consciousness since subjects were not able to give full verbal accounts (if any) of what they had learned, as measured through a declarative knowledge questionnaire [51]. Similarly, since the subjects were not given any indication to attend to learning strategies, they did not undergo conscious hypothesis testing during learning. Also, the learning version of the Tower of London is useful for measuring implicit cognitive learning because, like most instances of problem solving, it requires a complex amalgam of different cognitive processes used in conjunction that include short-term spatial memory, working memory, planning, generation and sequencing of responses, active search of possible solutions, analysis of visuospatial information, sustained and directed attention, and visual imagery [7,26,47,49,57,58]. Thus, the information gained during learning is not the result of a single simple association or frequency count, but rather the learning process yields abstract knowledge [32]. Finally, in agreement with the guidelines for implicit learning given by Seger [32], we were able to show that, in neurologically intact adult participants, learning of the modified TOL did not rely on the hippocampal memory system associated with declarative memory. Rather, it elicited activity in a fronto-striatal circuit involving the caudate nucleus [50].

In order to assess cognitive skill acquisition on the TOL task in terms of disease severity, we followed the criteria used in the DATATOP study [46] in order to enroll two groups of patients. First, a group of non-medicated *de novo* patients (PDnon) was chosen because of their ability to function without medication. The second group consisted of patients receiving L-DOPA tested in a relatively hypodopaminergic state (12 hours off-medication) in order to eliminate the possible confounding effects acute dopaminergic stimulation can have on cognitive skills [59]. We predicted that due to deficits in working memory functions, all PD patients would display a cognitive skill learning deficit on the TOL task compared to healthy control subjects, and that PDoff patients would show a more pronounced impairment than PDnon patients.

MATERIALS AND METHODS

Participants

Twenty-four patients (14 men/10 women; mean age ± SD = 66.8 ± 9.7 years; mean education = 13.5 ± 3.7 years) who were diagnosed as having typical PD according to the criteria established by Gelb and colleagues [60] participated in this study. Their demographic and disease characteristics are presented in Table **1**. All patients were non-demented according to their performance on the Mini-Mental State examination scale (MMSE ≥ 27) [61]. They were also not depressed as indicated by their answers on the Beck Depression Inventory (BDI) [62]; patients either received a score corresponding to normal mood fluctuations (BDI: 1-10, n = 17) or "mild to moderate mood disturbance" (BDI: 11-16, n =7)[63]. Although the latter showed signs of mood disturbances, they were nevertheless included in the study because their higher scores on the inventory tended to be on items describing somatic symptoms directly related to PD. Finally, the patients were of average intelligence as determined by their global IQ scores on the Wechsler Abbreviated Scale of Intelligence (WASI, mean IQ ± SD = 101.1 ± 13.2, range: 80-126) [64]. This group of patients was compared to twenty-two right-handed healthy control participants (CT) (7 men/15 women, mean age = 66.2 ± 9.2. mean education = 13.8 ± 3.3) who had no history of depression, neurological or psychiatric diseases. Independent t-tests revealed that patients in the PD group did not differ from the CT group with respect to gender ($\chi 2 = 3.3$, $p>.05$), age ($t = 0.35$, $p = 0.73$) and level of education ($t = -0.24$, $p = 0.81$).

Performance on the cognitive skill learning task was first analysed by comparing the PD and CT groups as a whole. Then, in order to investigate the impact of disease severity, patients were divided into two subgroups: The first subgroup consisted of twelve patients (6 men) with "*de novo*" PD (PDnon), while the second subgroup included twelve patients (8 men) who were taking only Levodopa/Carbidopa as treatment for their symptoms and who did not experience motor fluctuations manifested by "on/off" phases. The latter patients were all tested 12 hours "off" medication (PDoff) to minimise any acute effects that parkinsonian medication may have on cognitive functions, and to test the nigro-striatal system in an uncompensated state. All the treated patients had a stable response (no wearing off) to levodopa. The two subgroups of patients did not differ in terms of their level of education ($t = -0.27$, $p = 0.79$), global IQ ($t = -1.16$, $p = 0.26$), scores on the BDI ($t = -1.62$, $p = 0.12$), MMSE ($t = 1.90$, $p = 0.07$) or Unified Parkinson's Disease Rating Scale (UPDRS subscales I+II+III) ($t = -1.7$, $p = 0.09$). However, significant differences between the groups were found on the measure of disease duration [$t(22) = -3.1$, $p = 0.005$], age at onset [$t(22) = -2.2$, $p = 0.04$] and on the Hoehn and Yahr scale (H&Y) [$t(22 = -3.7$, $p = 0.001$]. Specifically, nine patients in the PDnon subgroup were at stage 2 and three were at stage 2.5, whereas in the PDoff subgroup, three patients were at stage 2, one patient was at stage 2.5, and the rest were at stage 3. Given that a significant age difference was found between the PDnon and PDoff subgroups [$t(22 = -3.1$, $p = 0.005$], they were matched to two groups of twelve healthy controls (CTnon and CToff) according to their age (CTnon/PDnon: $t = 0.05$, $p = 0.96$; CToff/PDoff: $t = -0.06$, $p = 0.96$) and education level (CTnon/PDnon: $t = 0.34$, $p = 0.75$; CToff/PDoff: $t = 0.25$, $p = 0.80$) (see Table **1**). None of these participants had any history of neurological, psychological or other medical problems which may have affected their cognitive or motor performance. All subjects gave informed written consent before participating in this experiment, which was approved by the Institutional Review Board at McGill University.

Cognitive Skill Learning Paradigm

Cognitive skill learning was measured using a modified, computerised version of the Tower of London task (TOL) [47] previously used in our laboratory [50,51]. This task consists of a series of visuo-spatial problems where subjects must displace coloured balls in order to reproduce a goal-configuration. TOL problems were presented on a touch-sensitive screen, which was placed in front of the participants at an ideal distance to promote comfortable reaching towards the computer screen. Most subjects used their dominant hand to execute the task, except two patients who were more agile with their non-dominant hand because of tremor.

In this version of the TOL task, subjects were presented with two sets of coloured balls (Fig. **1**). They were told that the set at the top of the screen was the model display, while the set at the bottom corresponded to the working display. Each set was composed of three coloured balls (red, blue, green) distributed in any of three sockets, which could contain one, two or three balls. On each trial, the coloured balls appeared in predetermined locations in each of the displays. The goal of the task was to reproduce, in a minimum number of moves, the configuration of the model display by rear-

Table 1. Subjects' Demographic Information and Clinical Characteristics

Groups	N	Gender (M/F)	Age (Years)	Education (Years)	Hand. (L/R)	WASI (IQ)	Beck (Total)	MMSE (Total)	H & Y (Stage)	UPDRS (I+II+III)	Duration* (Years)	Age Onset (Years)
PD	24	14/10	66.8 ± 9.7	13.5 ± 3.7	2/22	101.1 ± 13.2	7.9 ± 5.1	28.9 ± 1.1	2.5 ± 0.6	26.1 ± 11.9	4.0 ± 4.1	63.5 ± 8.5
CT	22	7/15	66.2 ± 9.2	13.8 ± 3.3	0/22							
PDnon	12	6/6	61.6 ± 9.3	13.3 ± 4.9	0/12	98.0 ± 12.4	6.3 ± 5.2	29.3 ± 0.9	2.1 ± 0.2	22.0 ± 9.6	3.2 ± 1.3	60.0 ± 8.4
CTnon	12	3/9	61.8 ± 7.4	13.8 ± 3.9	0/12							
PDoff	12	8/4	72.1 ± 7.0	13.7 ± 2.3	2/10	104.2 ± 13.7	9.6 ± 4.5	28.7 ± 1.3	2.8 ± 0.6	30.2 ± 13.0	6.1 ± 2.4	67.0 ± 7.3
CToff	12	5/7	71.9 ± 7.7	13.9 ± 2.5	0/12							

Abbreviations: PD: Parkinson's Disease; CT: control group; M/F: male/female; Hand.: handedness (L=left, R=right); WASI: Wechsler Abbreviated Scale of Intelligence; MMSE: Mini-Mental State Examination; H&Y: Hoehn & Yahr stage; UPDRS: Unified Parkinson's Disease Rating Scale; *Years since diagnosis; MEAN ± SD.

ranging the configuration of the balls in the working display. Subjects were asked to adhere to a set of three instructions when displacing balls. They were not allowed to: (1) move a ball if another one was placed directly above it; (2) move a ball to an available position in the same column; and finally, (3) move a ball to a location that was already occupied. The program was set such that it would not respond to illegal moves. Also, the number of times participants selected and then de-selected a ball was tallied.

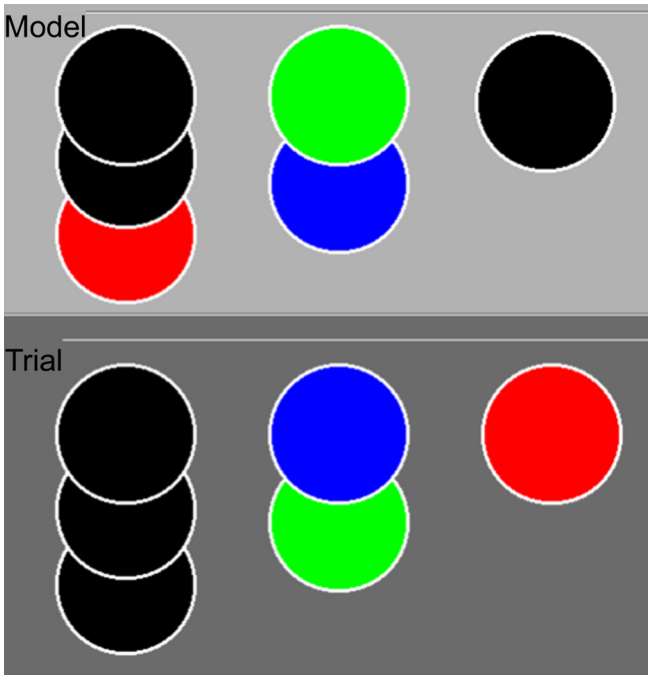

Fig. (1). Illustration showing a representative 5-move problem of the Tower of London task.

Procedure

Subjects participated in the TOL learning experiment in a single testing session, which lasted on average 52 minutes (SD = 11.2). They were first asked to complete five practice problems, each with an increasing level of difficulty (i.e. one to five moves) in order to ensure that they understood the rules governing the task. None of these problems were seen in the subsequent phase of the experiment. In total, subjects were asked to solve 9 blocks of 9 TOL problems during the learning trials. The order of administration of the blocks was randomly determined for each subject prior to the beginning of the experiment. Problems were randomly selected from all possible TOL combinations and differed in complexity relative to the number of moves required to reach the goal configuration. In this experiment, problems requiring three, four, or five moves were used. In order to structure each block and ensure an equal number of problems from each level of difficulty per block, a three-move problem was always followed by a five-move problem, which was then followed by a four-move problem, and so on. Each problem required a different solution. Thus, subjects solved a total of 81 problems, 27 at each level of complexity. Subjects were specifically instructed to plan the solution to each problem mentally before starting to displace balls. Patients were informed that initial planning and execution time would be recorded, but were advised that there would be no time limit for the problems. A maximum number of moves was, however, imposed (double the minimum number of moves required, plus four). At the end of the learning session, subjects were given a qualitative strategy knowledge questionnaire on which they were asked to describe any rules and strategies they used to solve the TOL problems. On a separate testing day, PD patients returned to the clinic for a 1.5hour testing session during which the entire neuropsychological battery of tests was administered. Patients from the PDoff group were again tested 12-hours off medication for this portion of the experiment.

Neuropsychological Tests

In addition to the use of the BDI and MMSE as screening tools, neuropsychological tests were administered to the patients to assess working memory (Spatial and Digit span subtests from the Wechsler Memory Scale (WMS-III) [65]), executive functions (64-card version of the Wisconsin Card Sorting task - WCST [66] and Stroop Color-Word interference Test [67]), and declarative memory (California Verbal Learning Test – CVLT [68]). In the WCST participants must sort cards according to three abstract rules and must modify their responses in accordance with the examiner's feedback. The WCST is a well-recognised test of executive function and is used to assess the ability to form abstract concepts, to shift and maintain set and use feedback [69]. The Stroop test is a measure of cognitive control and assesses the ease with which a person can maintain a goal in mind and suppress a habitual response in favour of a less familiar one [69]. In the incongruent condition, participants are presented with colour-words (blue, green, red) written in a conflicting colour of ink (blue, red or green). They must name the colour of the ink as quickly as possible [67]. In the CVLT, participants are asked to encode and recall a list of 16 items; it is a commonly used multiple trial list learning task that measures verbal learning and declarative memory [70].

Data Analysis

Performance and learning were determined using three indices: (1) "Initial planning time": the time subjects took to think about the solution to a problem before the first move; (2) "Execution time": the time taken to complete a problem after the first move, a measure of both execution time and subsequent planning time; (3) "Accuracy": the percentage of problems solved in the minimum number of moves, a measure of success at solving the TOL problems that is not related to motor confounds. The three types of illegal moves (described above) were recorded and grouped together for analysis. The number of times a participant selected and then de-selected a ball was also calculated and analysed separately. This type of move does not reflect illegal moves *per se*, but can be related to impulsivity, or simply a change in the problem solving/decision making process. This data was not available for one PD patient; therefore, this subject was excluded from this particular analysis.

Learning

The results obtained on all three learning indices were analysed using two-way analyses of variance for repeated measures (ANOVAs) across the nine blocks of practice. An alpha level of 0.05 was used to determine statistical significance in all analyses. In addition, cognitive skill learning was measured on an individual basis. This was done by comparing the "Accuracy" measure for the first two blocks

(Blocks 1 and 2) and the last two blocks (Blocks 8 and 9). A learning impairment was reported when an individual showed worsening of performance or no improvement in mean level of accuracy with practice and these individuals were assigned to the "no_learn" group. Participants were excluded from the analysis if they had an initial TOL performance above 80%, as this represented a ceiling effect. Since the two first blocks and the two last blocks were combined for this analysis, any improvement or worsening of performance from the beginning to the end of the learning process represented at least a 5.6% change, therefore no individual had an insignificant amount of change (e.g. 1%). Finally, in order to reduce ceiling effects, any participant starting with an initial (Block 1) performance greater than 80% and showing no improvement in performance was not considered as having a learning impairment, as the potential for improvement was limited for these individuals.

Neuropsychological Tests

The results of the PD patients on clinical neuropsychological tests were compared to published norms corrected for age [64-66,68,71]. A deficit was reported for any performance that fell below 1.5 standard deviations from the mean. This cut-off was chosen to retain specificity and maintain an acceptable level of false positive reports, while also ensuring that clinically significant deficits would be reflected in the patients' performance [72]. An impairment in executive functions was established when patients had a deficit on either the colour-word intereference trial of the Stroop test or the total number of errors made on the WCST. Likewise, an impairment in working memory was established when patients had a deficit on either the backwards portion of the Digit span or Spatial span tests (WMS-III). The number of patients in each subgroup who showed a deficit on a particular test was compared using the Chi-square test ($p < 0.05$), corrected for expected values below 5 using Fisher's exact test.

RESULTS

Cognitive Skill Learning

Two-way ANOVAs with repeated measures (Block X Group) were performed over the nine blocks of trials on all dependent measures of cognitive skill learning to assess the level of improvement in performance over the course of learning, and to establish whether patients and controls differed with respect to their ability to learn a new problem solving task.

Effect of Parkinson's Disease on Overall Performance and Learning

A significant effect of Block was found for all of the dependent measures and results are depicted in Figs. (**2**,**3**): Initial planning time [$F(8, 352) = 16.6$, $p < 0.001$], Execution time [$F(8, 352) = 22.2$, $p < 0.001$], and Accuracy [$F(8, 352) = 4.5$, $p < 0.001$]. A significant main effect of Group, suggesting a difference in performance between patients (PD) and controls (CT), was also found for the Execution time [$F(1,44) = 8.6$, $p = 0.005$] and Accuracy [$F(1,44) = 4.0$, $p = 0.05$] measures, but not for the Initial planning time [$F(1,44) = 0.02$, $p = 0.90$]. Contrary to our predictions, however, no Block X Group interaction was found for any of the dependent measures [Initial planning time: $F(8,352) = 0.9$, $p = 0.55$; Execution time: $F(8,352) = 1.1$, $p = 0.36$; Accuracy: $F(8,352) = 0.4$, $p = 0.94$], suggesting that PD patients were able to improve their performance with practice.

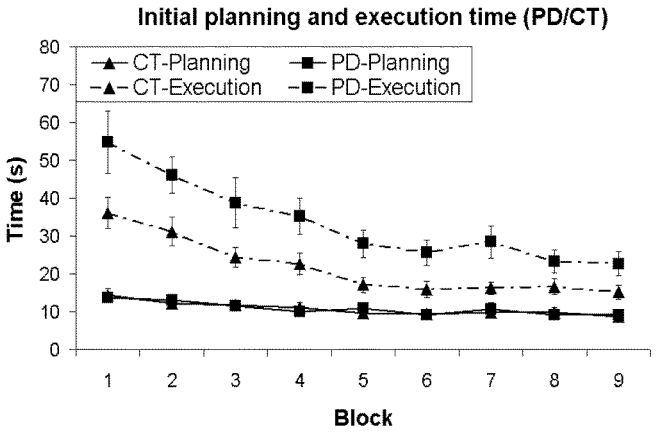

Fig. (2). Mean Planning and Execution time in seconds taken by the PD and CT groups to complete TOL problems. Error bars represent the standard error of the mean.

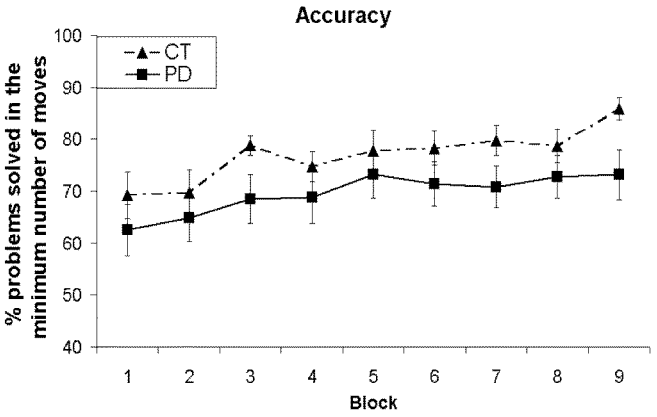

Fig. (3). Mean level of Accuracy for the PD and CT groups to complete TOL problems. Error bars represent the standard error of the mean.

When patients and controls were compared with respect to the number of illegal moves they made (types 1,2,3), significant main effects of Block [$F(8, 344) = 9.7$, $p < 0.001$] and Group were found [$F(1,43) = 4.3$, $p = 0.04$], but the Block x Group interaction was not significant [$F(8,344) = 0.9$, $p = 0.52$], suggesting that both controls and patients improved their performance over practice trials. A comparison of the number of times patients selected and then de-selected a ball revealed significant main effects of Block [$F(8, 344) = 3.0$, $p < 0.003$] and Group [$F(1, 43) = 5.2$, $p = 0.03$], as well as a significant Block x Group interaction [$F(8, 344) = 2.5$, $p = 0.01$]. When this interaction was decomposed, a significant Block effect was seen in the patient group [$F(8,176) = 3.3$; $p = 0.001$], but not in the control group [$F(8,168) = 1.0$; $p = 0.42$], probably due to the fact that the control subjects made very few selection-deselection type moves throughout the experiment.

Finally, though the analyses of the patient group as a whole revealed significant learning effects on all measures, we nevertheless sought to determine whether some individual patients had a learning impairment on this task. When the percentage of improvement in Accuracy was assessed be-

tween the beginning (Blocks 1 and 2) and the end (Blocks 8 and 9) of learning, six patients (n = 6/24, 25%) had a learning impairment on the task, but none of the control subjects failed to acquire the task. Patients with a learning impairment were assigned to the "No-Learn" subgroup, whereas the rest were assigned to the "Learn" subgroup for further analyses.

Impact of Disease Severity on Overall Performance and Learning

In order to determine whether disease severity influenced the patients' level of performance and learning on the TOL task, the PDnon and PDoff groups were compared to their respective groups of control subjects (CTnon and CToff). Separate two-way ANOVAs for repeated measures (Block X Group) were again performed over the nine blocks of trials using the same dependent measures of cognitive skill learning. The results of these analyses are presented in Figs. (**4**,**5**) for the PDnon group and Figs. (**6**,**7**) for the PDoff group.

When the PDnon and CTnon groups were compared, a main effect of Block was found on all dependent measures: Initial planning time [$F(8, 176) = 6.4$, $p < 0.001$], Execution time [$F(8, 176) = 14.2$, $p < 0.001$], and Accuracy [$F(8, 176) = 4.1$, $p < 0.001$]. However, no main effect of Group [Initial planning time: $F(1, 22) = 0.001$, $p = 0.97$; Execution time: $F(1, 22) = 3.4$, $p = 0.08$; Accuracy: $F(1, 22) = 0.59$, $p = 0.45$], or any Block X Group interaction [Initial planning time: $F(8, 176) = 1.2$, $p = 0.30$; Execution time: $F(8, 176) = 0.8$, $p = 0.0.61$; Accuracy: $F(8, 176) = 0.35$, $p = 0.94$] was found for any of the dependent measures, suggesting that the patients in the PDnon group were able to learn the TOL task and that they did not differ from their respective controls in terms of their level of performance throughout the practice trials. Similarly, significant main effects of Block were found when the two groups were compared on the number of illegal moves [$F(8, 176) = 6.1$, $p < 0.001$] and the number of time they selected and deselected a ball [$F(8, 176) = 2.2$, $p = 0.03$], with no significant main effect of Group [illegal moves: $F(1,22) = 2.1$, $p = 0.17$; deselection: $F(1,22) = 3.7$, $p = 0.07$], nor any Block X Group interaction [illegal moves: $F(8,176) = 0.9$, $p = 0.54$; deselection: $F(8,176) = 1.8$, $p = 0.07$]. These results again suggest that patients in the PDnon group significantly improved their ability to solve the TOL problems with practice.

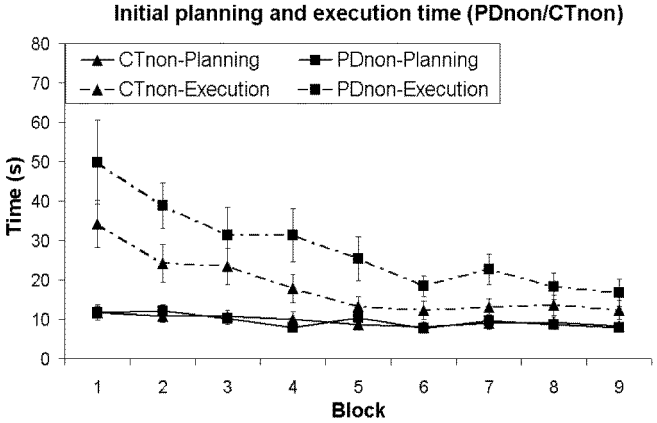

Fig. (4). Mean Planning and Execution time in seconds taken by the PDnon and CTnon groups to complete TOL problems. Error bars represent the standard error of the mean.

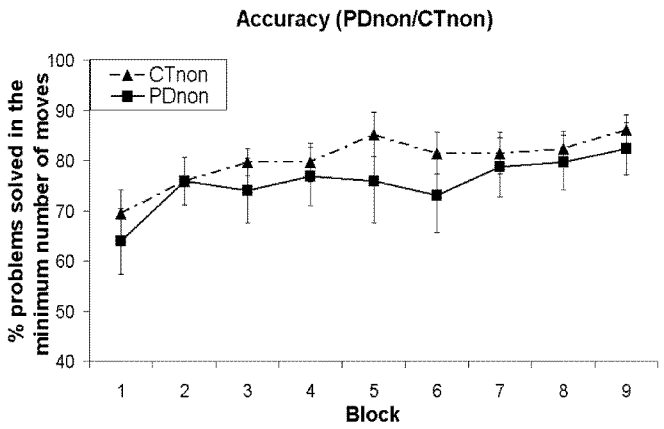

Fig. (5). Mean level of Accuracy for the PDnon and CTnon groups to complete TOL problems. Error bars represent the standard error of the mean.

When the PDoff and CToff groups were compared, a significant main effect of Block was again found on all dependent measures: Initial planning time [$F(8, 176) = 12.4$, $p < 0.001$], Execution time [$F(8, 176) = 10.7$, $p < 0.001$], and Accuracy [$F(8, 176) = 3.6$, $p = 0.001$]. Significant main effects of Group were observed for the Execution time [$F(1, 22) = 4.9$, $p = 0.04$] and Accuracy measures [$F(1, 22) = 4.5$, $p = 0.05$], but not for the measure of Initial planning time [$F(1, 22) = 0.03$, $p = 0.88$] (see Figs. (**4**,**5**)). Again, no Block X Group interaction was found for any of the dependent measures [Initial planning time: $F(8,176) = 0.4$, $p = 0.93$; Execution time: $F(8,176) = 0.7$, $p = 0.69$; Accuracy: $F(8,176) = 1.1$, $p = 0.37$]. This implies that, although less accurate and slower at solving problems, the patients in the PDoff group were able to significantly improve their performance on the TOL task over the course of the practice trials. However, despite equivalent initial planning times, they performed worse than their matched controls subjects in terms of the time taken to solve the problems, as well as on the number of problems they solved accurately. When the PDoff and CToff groups were compared on the number of illegal moves made, a significant effect of Block was found [$F(8, 176) = 4.9$, $p < 0.001$]; however, neither the main effect of Group [$F(1,21) = 2.8$, $p = 0.11$] nor the Block x Group interaction [$F(8,168] = 0.5$, $p = 0.89$] reached significance. Thus, these two groups were comparable in terms of the number of illegal moves they made, and they both significantly reduced this number over the course of practice trials. When the same analysis was performed for the number of selection-deselection moves, no significant main effect was observed for Block [$F(8,168) = 1.1$, $p = 0.35$] or Group [$F(1,21) = 2.3$, $p = 0.14$], and no Block x Group interaction [$F(1,168) = 1.1$, $p = 0.34$] was found, suggesting that neither group significantly reduced this type of move over the course of learning, and that their level of performance on this measure was equivalent. Overall, these results demonstrate significant learning effects in both PDnon and PDoff groups, though the latter patients were less accurate and took longer to actually solve the TOL problems.

Individual Assessment of Learning

Finally, when learning was investigated on an individual basis by assessing the improvement in the level of accuracy between the beginning and the end of learning, three patients

were excluded from the analysis through virtue of having an initial TOL performance of above 80% (ceiling effect), as did five control subjects. Specifically, the three patients who met the ceiling effects criterion had initial and final performances of 83%, 94% and 100%. Amongst the remaining subjects, *all* the controls showed a learning effect, while *six* patients were found to have no improvement or a worsening in performance, which represents less than the 5th percentile of the control group mean learning rate. No significant difference was found between the number of patients in the PDnon group (n = 4, 33%) and PDoff group (n = 2, 17%) who failed to improve their performance on the TOL task.

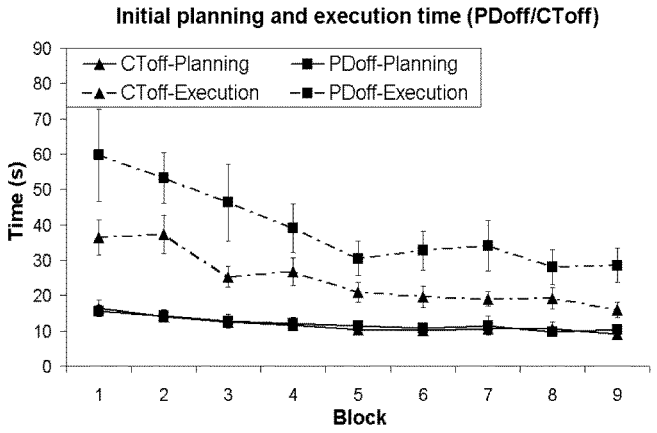

Fig. (6). Mean Planning and Execution time taken by the PDoff and CToff groups to complete TOL problems. Error bars represent the standard error of the mean.

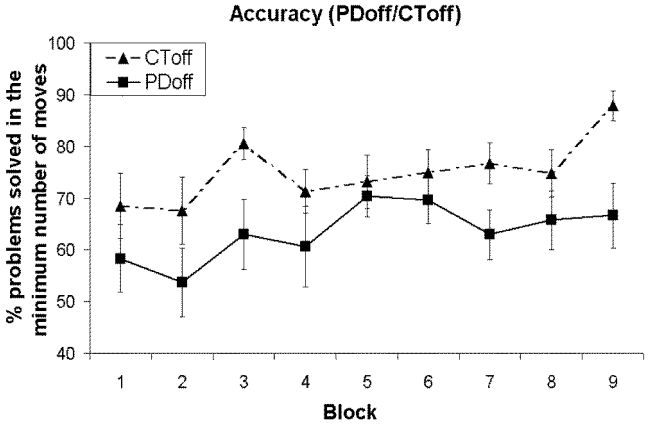

Fig. (7). Mean level of Accuracy for the PDoff and CToff groups to complete TOL problems. Error bars represent the standard error of the mean.

Neuropsychological Functions

Overall, the results revealed that a large number of patients (n=11) had deficits on executive and working memory functions (see Table **2**), whereas few patients experienced difficulties on a task of declarative memory: CVLT trials 1-5 (n=2), CVLT immediate recall (n=3), CVLT delayed recall (n=2). The number of patients from the PDnon and PDoff subgroups with deficits on executive and working memory tests did not differ significantly using Chi-square analyses, suggesting that PD patients demonstrated cognitive deficits on these tests regardless of their classification in terms of need for medication.

Finally, with the aim of identifying possible cognitive deficits that may be related to learning deficits on the TOL, the performance of the "Learn" subgroup was compared to that of the "No_learn" subgroup on neuropsychological tests. Although more patients in the "No_learn" subgroup (67%) than in the "Learn" subgroup (33%) had deficits on at least one of the executive tasks, this comparison failed to reach significance on the Chi-square analysis. However, a significant difference was found between the number of patients in the "no_learn" (83%) and "learn" (33%) subgroups who had a deficit on either the Digit span or Spatial span tasks, suggesting that working memory deficits play a role in determining the cognitive skill learning abilities of PD patients on the TOL task. In light of this observation, post-hoc Pearson's correlation analyses were carried out. TOL accuracy and total time for Block 9 were both significantly correlated with both backward digit span (B9 accuracy: $r(24) = 0.45$, $p = 0.02$; B9 total time: $r(24) = -0.45$, $p = 0.03$) and backward spatial span (B9 accuracy: $r(24) = 0.41$, $p = 0.05$; B9 total time: $r(24) = -0.48$, $p = 0.02$). No correlations were found, however, with any of the measures of declarative memory (CVLT trials 1-5: $r(24) = 0.13$, $p = 0.5$; CVLT immediate recall: $r(24)$: 0.35, $p = 0.1$; CVLT delayed recall: $r(24) = 0.36$, $p=0.09$) or executive function (Stroop: $r(24) = -1.1$, $p = 0.6$; WCST: $r(24)$: -0.34, $p = 0.1$).

Strategy Knowledge Questionnaire

The qualitative answers given on the questionnaire were compiled and analysed in order to determine whether subject had any declarative knowledge of how to solve the TOL problems and what strategies they may have used. As in our previous study [51] and in most studies of implicit skill learning [32,53] the subjects had limited access to the knowledge gained during learning and had difficulty verbalising the strategies used to solve TOL problems. Thus, both the control subjects and patients were unable to give any specific or detailed information on the strategies or algorithms used to complete TOL problems successfully. The answers given on the qualitative questionnaire were generally limited to broad and vague comments about the subjects' attempts to solve the problems, such as: "I tried to plan my solution before starting" or "I concentrated". Some subjects (n = 3) reported knowledge of a specific rule, such as "Always fill the last column first"; however, this type of rule represents information specific to only some of the TOL problems and would therefore not lead to a correct solution on all TOL problem. Only one answer given on the questionnaire appeared to relate to a specific heuristic that could be applied to the TOL problems in general: "Always place the ball that goes at the bottom of a column first". Four control subjects and five patients gave this answer on the questionnaire. Though useful in helping these subjects to solve the TOL problems correctly, knowledge of this heuristic alone could not lead to a full solution of any TOL problem, nor does it indicate declarative knowledge of the solution.

DISCUSSION

We sought to investigate cognitive skill learning in individuals with PD by comparing subgroups of patients who differed in terms of disease severity according to their overall level of functioning, and by testing them on a task that places a heavy load on working memory functions known to

Table 2. Number of Patients with Deficits on the TOL and Neuropsychological Tests

	PD Total	PDnon	PDoff	X^2	No_Learn	Learn	X^2
	n=24	n=12	n=12	p	n=6	n=18	p
No TOL learning	6	4	2	ns	6	0	NA
Stroop (colour-word)	6	4	2	ns	2	2	ns
WCST (errors)	9	6	3	ns	4	6	ns
Executive functions*	11	7	4	ns	4	6	ns
Digit Span (backwards)	9	4	5	ns	5	4	0.004
Spatial Span (backwards)	10	4	6	ns	5	5	0.007
Working memory**	11	4	7	ns	5	6	0.014

X^2 = Chi-square, significance level: $p < 0.05$; NA = not applicable; ns = not significant.
*Deficit on either the Stroop or the WCST; **Deficit on either the digit or spatial span backwards.

be related to striatal activity. Contrary to our predictions, neither the PDnon group, nor the PDoff group of patients was impaired at learning our modified version of the TOL task when considered as a whole; however, some patients were found to be impaired when their learning was assessed individually. Though unexpected, our results reflect the numerous inconsistencies that have been noted in the cognitive skill learning literature, even between studies using similar tasks [5,29-31]. They also highlight the challenge for researchers to pinpoint the exact nature and incidence of cognitive skill learning impairments in patients with PD.

In the present study, an attempt was made to control for some of the factors that might contribute to variations in the learning abilities of PD patients. First, we used a cognitive task in which the possibility of using declarative strategies for problem solving was reduced by presenting different problems to the subjects on each trial, thus increasing the implicit nature of the learning process and making it more sensitive to striatofrontal dysfunctions. Second, it was thought that using a disease severity classification based on an overall level of functioning, rather than on motor symptoms only, would reveal differences in cognitive skill acquisition among subgroups of patients. In spite of this, when the patients were divided according to their use of medication, no overall learning impairment was found on the modified TOL learning task at any level of difficulty.

Absence of Learning Impairments in PD: Neuropathology Hypothesis

Given that previous investigations have reported impairments on cognitive skill learning tasks [5,29,42,43,73], why were the PD patients tested in the present study not generally impaired at solving TOL problems? One possible interpretation is that the underlying neuropathology of the disease in our patients had not yet affected structures critical for performance and learning of the task. In fact, solving TOL problems requires a variety of executive functions, which have been shown, through imaging studies in healthy subjects, to rely heavily on intact functioning of frontal brain areas, such as the dorsolateral prefrontal cortex, and the caudate nucleus [50,58]. Cognitive abilities necessary for problem solving, such as planning and the manipulation of information in working memory, for example, have also been linked to blood flow activations in these same areas [27,28]. Finally deficits in planning and working memory functions, sometimes observed in patients at early stages of PD, have been related to dopamine dysfunction in the caudate nucleus [74-76]. Together, these findings suggest that a dysfunction of the caudate nucleus is necessary to elicit both performance and learning deficits on the TOL task in PD patients. Considering that this structure has been shown to be affected later in the progression of PD as compared to other basal ganglia structures such as the putamen [77,78], it is possible that the lack of cognitive skill impairment was due to the relative integrity of the caudate nucleus in our group of patients, as loss of function may occur only in the presence of severe dopamine depletion in this area [79]. Dopamine loss in the striatum may in turn affect frontal lobe function by disrupting activity within basal ganglia thalamocortical circuits [25,80]. Structural imaging studies using, for example, voxel-based morphometry would be necessary to further investigate this hypothesis in our group of patients. Finally, the absence of a significant difference *between* the two groups of patients could be due to the the long-duration effect of levodopa [81], since this medication can compensate for reductions in dopamine, in particular during tests of frontal-lobe function [82].

Compensation Hypothesis

Another possible interpretation for the intact performance in both groups of PD patients on the learning version of the TOL task is that they were able to compensate for their learning deficits by using alternative strategies and functions, which are known to depend on anatomical systems that differ from those used by control subjects. In support of this hypothesis, Shohamy and colleagues [83] have reported in a study of probabilistic category learning that, though PD patients adopted suboptimal strategies to perform the task, they nevertheless showed significant improvements on the weather prediction task, which has previously been shown to be sensitive to functions of the striatum [23]. Such findings suggest that the use of an alternate strategy can enable PD patients to compensate for striatal dysfunction. Note that, in light of the inability of patients and control subjects to give any specific information on the strategy knowledge questionnaire, it was not possible in this study to perform a detailed strategy analysis. The question of differential strategy use in patients and contols could be answered in a future study investigating TOL problem solving approaches in a

quantitative manner. For their part, Moody *et al.* [84] also reported significant learning effects in PD patients on the weather prediction task, but observed a different pattern of brain activity in patients compared to control subjects. Specifically, patients showed less activation in the caudate nucleus, but greater activation in the medial temporal lobe and in a region of the prefrontal cortex, both of which are associated with explicit memory processes [84]. A similar pattern of activation was also observed in PD patients performing the TOL task [80]. These results suggest that the patients activated intact learning and memory systems to compensate for impairments in dysfunctional circuits such as the basal ganglia. It is possible that a similar recruitment of alternate and intact cognitive functions may have enabled our patients to learn the TOL task. This compensation hypothesis is particularly relevant to the domain of skill learning as solving problems like those in the TOL task involves numerous cognitive functions (e.g. working memory, planning, attention, etc.) that may be affected in whole, or in part, at different stages of disease progression.

Group Differences in Performance

In spite of their ability to successfully learn to solve TOL problems, the two PD subgroups differed with respect to their overall level of performance on the task. Indeed, while the PDnon patients were comparable to their age-matched controls on all TOL dependent measures, those in the PDoff subgroup made more illegal moves and maintained longer Execution times over the course of learning. Consistent with the findings of Owen and colleagues [26], they also solved fewer problems accurately, that is, in the minimum number of moves. The latter results suggest that the PDoff patients were less efficient in performing the cognitive processes necessary for the task at hand, but not enough to impair their ability to acquire the skill. It could be argued that the increased number of illegal moves made by this subgroup of patients may have been due to fundamental difficulties in understanding or remembering the basic rules governing the task. However, given that these patients could initially solve 60% of the TOL problems correctly on average, and that very few had deficits on tasks of declarative memory, this interpretation seems unlikely. It could also be argued that the longer Execution times were related to a more general deficit in motor performance, yet the results using "Accuracy" as a dependent measure that is free of any motor components suggest that the impairment observed here is not simply a consequence of motor slowing. Instead, their performance deficit appears to be related to cognitive difficulties. Indeed, the results indicate that, though the PDoff patients had adequate initial planning times (i.e. comparable to the age-matched controls who performed better on the task), they still had poor problem solving abilities compared to the control subjects, hence suggesting that they were particularly impaired when required to carry out the solution after the initial planning phase, a process that requires information to be maintained and manipulated in working memory. Such a difficulty could explain why deficits were also seen on the measure of illegal moves, as they may have had problems in keeping all the task instructions in mind at the beginning of practice. Resource limitations, such as deficits in working memory, can contribute significantly to a person's performance of illegal moves on problem solving tasks [85,86]. Finally, it could be argued that patients were not actually engaging in any type of effortful cognitive reasoning during the "initial planning" phase or that they were being impulsive and making their first move before they had adequately planned their response. However, such behaviour would not have resulted in a significant and systematic decrease in initial planning time over the course of learning.

Individual Learning Impairments

Although learning was intact when the results of the two PD subgroups were assessed, preliminary evidence found here indicated that a small subset of patients was nonetheless impaired at learning the TOL task (No_learn subgroup). Although it could be hypothesized that fatigue was a factor in the patients' learning curve, no interaction was found on the measure of learning between the control and patient groups, suggesting that the patient group did not demonstrate a divergent learning pattern due to fatigue. The deficit in the No_learn subgroup was not related to disease severity, as defined by a need for medication, nor to the severity of motor impairment. Interestingly, however, almost all (83%) the patients in the No_learn subgroup had deficits on the Digit and Spatial span tasks, and particularly on the "backwards" portion of these tests, which has been shown to be closely related to working memory functions. This contrasted with the significantly lower percentage of patients (33%) in the "Learn" subgroup who had deficits on the same tasks, suggesting that limitations in working memory abilities, and therefore, the mental manipulation of information in short-term memory, may also be critical in determining whether PD patients are able to learn new cognitive skills. This idea is further supported by the observation that late performance on the TOL learning task correlated positively with both backward digit and spatial spans, suggesting that working memory ability was related to cognitive skill learning. Furthermore, it has also been shown that cerebral activity in the caudate nucleus is correlated with TOL task complexity, suggesting that the involvement of this structure is related to changes in the working memory demands of the task [87]. Though this finding is limited here to a small group of patients and needs to be investigated in a bigger clinical sample, the idea is also supported by previous studies in larger groups of PD patients. For instance, Filoteo *et al.* [88] found that PD patients were impaired on category learning when the working memory and selective attention requirements of the task were increased, and therefore suggest that variations in working memory demands may explain some of the discrepant findings in learning studies with PD patients. In another study of cognitive skill learning, Price [89] also found a significant correlation between working memory scores and accuracy on a category learning task. In addition, similiar observations have been made in studies of other forms of skill learning. For instance, Kennedy and colleagues [90] found an association between reduced availability of working memory and perceptual skill acquisition on a fragmented pictured paradigm and, although the involvement of working memory in implicit motor skill learning has been debated [91,92], evidence for an association between the two processes comes from the involvement of the dorsolateral prefrontal cortex, known to underly working memory, in implicit motor learning [93,94]. These observations from various fields of skill learning suggests that working memory

capacity is likely to be an important factor in determining skill learning ability and that reduced working memory underlies deficits in cognitive skill acquisition in our group of patients.

CONCLUSIONS

In sum, due to the relatively small subgroup of patients who were found to have cognitive skill learning impairments in this study, our conclusions warrant further investigation in a larger group of patients. Nonetheless, it appears that deficits in working memory play a key role in determining both performance deficits and the presence of cognitive skill learning impairments on the TOL task in some patients. Our results also suggest that failure to improve on this task may not be due to actual procedural learning impairments, but rather, it appears to be secondary to a deficit in working memory. Taken together, our findings and those of previous studies suggest that pathophysiological factors, such as dopamine depletion in the caudate nucleus, may be necessary for the appearance of impairments in some cognitive functions, and that the presence of such impairments cannot be predicted from PD patients' overall level of functioning, as assessed by their need for medication. Finally, it is possible that the lack of learning impairments in the patients tested here is due to the fact that the progression of PD has not entirely affected the networks crucial to cognitive skill learning or, that they remain able to compensate for certain deficits by recruiting alternate cognitive functions through intact brain areas. Brain imaging studies will be necessary to further investigate this hypothesis. Such studies should allow us to shed light on the complex functional neuropathology underlying cognitive skill learning in PD and, in turn, should help to identify critical functions and areas used by patients to perform normally on cognitive skill learning tasks.

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