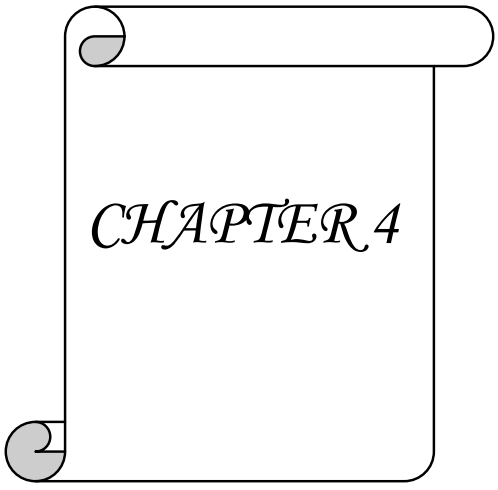
Cognitive sequelae of Parkinson's disease : nature, course, risk factors and functional impact

Muslimović, D.

Publication date
2009



Motor procedural learning in Parkinson's disease

Dino Muslimović, Bart Post, Johannes D. Speelman, Ben Schmand

Brain 2007; 130:2887-2897

Summary

Functional neuroimaging research has repeatedly implicated the striatum in motor procedural learning, but attempts to explore this relation in patients with Parkinson's disease (PD) have yielded inconsistent results. Furthermore, the functional impact of procedural learning impairment is unknown. The present study sought to examine the effects of PD on procedural learning and to determine whether impaired procedural learning affects functional status. The performance of 95 non-demented PD patients on the Serial Reaction Time Task (SRTT) was compared with that of 44 demographically matched control subjects. The SRTT is a four-choice reaction time task in which visual stimuli are presented in six blocks of 100 trials either in a repeating sequence of 10 stimuli or randomly. Learning was inferred from the reduction of response times over five successive blocks of repeating sequence trials and from the increase in response times in the sixth random block. In addition, neuropsychological tests of declarative memory, executive and visuospatial functions were administered to all participants. Patients also received quantitative ratings of functional outcome. The two groups did not differ in the learning rate across blocks of repeating sequence trials. However, PD patients were significantly less efficient than controls in acquiring sequence-specific knowledge, although this impairment was relatively small ($d = 0.38$). Patients with more advanced clinical symptoms tended to show worse performance. Separate analyses of a subgroup of 24 non-medicated patients in the early stages of PD revealed no differences in SRTT performance relative to controls. Neuropsychological testing showed impairments in attention and executive functions, immediate and delayed explicit memory, and visuospatial skills in the PD group, but none of the cognitive measures were related to procedural learning. Reduced motor sequence learning in PD patients did not influence their functional status. These findings indicate that procedural learning impairment is not an early feature of PD, but is likely to emerge with progression of the disease, independently of cognitive dysfunction or dopaminergic medication.

Introduction

Procedural learning is a form of non-declarative or implicit memory, which refers to the ability to acquire motor or cognitive skills gradually through practice.[10] Acquisition of such skills is manifested by increased accuracy or speed of performance as a result of repeated exposure to a specific procedure, without conscious recollection of the prior learning episode or the rules underlying the task. Procedural learning is generally contrasted with declarative or explicit memory, which involves the acquisition of facts and events accompanied by conscious awareness of the learned information. It is commonly assessed with recall and recognition tests for verbal or visuospatial material, such as word list learning, story recall and visual reproduction tasks. These two memory systems are dissociable in several clinical populations and presumably rely on distinct neural circuits.[63] While declarative memory is clearly associated with the medial temporal lobes and diencephalic brain structures,[62] the neuroanatomical substrates underlying procedural learning are still not fully understood. The observations that patients with Huntington's disease[40] or Parkinson's disease[51] are impaired on various skill acquisition tasks even in the context of relatively intact declarative memory have been viewed as important evidence for the involvement of the basal ganglia in procedural learning. In addition, the cerebellum and the frontal cortex have also been implicated as components of the neural network that supports the acquisition of new skills.[71] However, specific contributions of each of these structures seem to vary depending on the motor or cognitive processes underlying the specific task, as evidenced by distinct patterns of deficits on different skill acquisition tasks within the same group of patients.[23, 24, 32] These clinical observations are consistent with the view that procedural learning is not a unitary construct, but rather an aggregate of heterogeneous skill learning processes which are likely to be dissociable both functionally and neuroanatomically.[62]

In research on motor skill learning, the most frequently employed experimental paradigm has been the serial reaction time task (SRTT).[44] The SRTT is a choice reaction time task, in which participants are required to respond as quickly as possible to the presentation of a visual stimulus appearing at one of several different spatial locations. Unknown to the participants, the location of the stimulus follows a repeating sequence. Two types of learning are thought to occur in this test. One is 'sequence-specific learning', that is the improve-

ment of responding due to the repetition of the sequence of stimuli. The other is a more general, non-specific type of learning related to other aspects of the task, which is evident from a gradually increasing response speed (or accuracy) over the course of the performance. An important argument for the use of the SRTT as a measure of procedural learning is that the performance does not seem to depend on explicit memory processes since patients with impaired declarative memory, such as Korsakoff's syndrome,[44] Alzheimer's disease,[30] or subjects given scopolamine to produce transient amnesia,[44] typically show improvement on the task, although they are unaware of the sequential nature of the stimuli.

Functional neuroimaging studies with healthy subjects have demonstrated that SRTT performance is associated with striatal activation, often in combination with cortical activation in areas involved in motor circuitry,[1] including the premotor cortex and the supplementary motor area.[12, 21, 27, 46] The role of the striatum in motor skill acquisition has been supported by neuropsychological investigations of patients with Huntington's disease[31, 72] in which marked impairments have been observed in implicit sequence learning, although such results have not been consistently reported.[6] However, the interpretation of these results is problematic because Huntington's disease is frequently associated with structural and metabolic changes that extend beyond the basal ganglia.[50] Thus, the impairment in this population of patients may also be due to dysfunction in other structures than the basal ganglia. Research focusing on Parkinson's disease (PD) as the best available model of regional basal ganglia dysfunction is even less conclusive. While some studies have reported that non-demented PD patients are profoundly impaired in SRTT learning,[26, 64] others have found only minor decrease in learning,[17, 45, 61] or even normal performance.[60] Similarly, conflicting results have also been reported in studies examining SRTT learning in patients with focal basal ganglia lesions.[15, 56, 66]

The discrepant findings in the literature on procedural sequence learning in PD may be explained in part by differences in disease severity across patient samples, since SRTT performance appears to be related to the degree of clinical disability.[13] Other reasons that could account for these discrepancies involve the differences in treatment regimens, methodological variations of the SRTT employed, and the possible role of frontal/executive dysfunction. With regard to the latter possibility, PD patients with evidence of executive dys-

function have been reported to exhibit more prominent procedural learning impairment,[26] suggesting the involvement of the prefrontal cortex in the observed deficit in this type of learning. A recent meta-analysis of SRTT studies in PD pointed to a number of methodological shortcomings in this area of research, including the use of small patient samples, the lack of information regarding both the clinical characteristics of the patients assessed and matching methods of the patient and control groups, and inadequate reporting of experimental data.[57] Furthermore, although acquisition of motor skills is assumed to play a significant role in adaptive behavior, to our knowledge, no study to date has addressed the functional relevance of impaired motor procedural learning in patients with PD.

The primary aim of the present study was therefore to further examine the effects of PD on motor procedural learning by comparing SRTT performance of a relatively large sample of non-demented PD patients with that of healthy control subjects. In addition, to control for the potentially confounding effects of medication, we evaluated SRTT performance in a subgroup of newly diagnosed, untreated PD patients. Furthermore, we investigated the relationship between procedural learning and executive functions, declarative memory, and visuospatial skills. In light of previous findings, it was expected that procedural learning would be related to executive functions, but not to explicit memory or visuospatial functions. Finally, we sought to assess whether procedural learning contributes to functional status in patients with PD. We anticipated that impairment in procedural learning would interfere with activities of daily living.

Methods

Subjects

Ninety-five patients with PD participated in the study. These patients were part of a larger sample of PD patients (n = 190) who participated in the baseline assessment of an ongoing longitudinal research project investigating the course of functional and cognitive decline in PD. Details of the case-finding procedure have been published elsewhere.[42] In brief, consecutive patients with newly diagnosed PD recruited from the neurology outpatient clinics of six general hospitals in Amsterdam and surrounding area, were included (n = 58). In addition, patients were identified from the medical records and from the Dutch Parkinson's

Disease Association (n = 37). A diagnosis of PD was confirmed by the project neurologist, based on standard clinical criteria.[19] Exclusion criteria were age of 85 years or older, insufficient command of the Dutch language, global cognitive deterioration as indicated by performance below the standard cutoff of 24 points on the Mini Mental State Examination (MMSE),[18] and the presence of somatic illness with a life expectancy of less than a year.

At the time of the examination, 24 patients were not receiving any medication. Of the remaining 71 patients, 28 were treated with levodopa plus a peripheral levodopa-decarboxylase inhibitor, 15 with a dopamine agonist (pergolide [n = 9], pramipexol [n = 4], ropinirol [n = 2]), 19 with levodopa in combination with a dopamine agonist (pergolide [n = 16], pramipexol [n = 2], ropinirol [n = 1]), two with amantadine, one with amantadine plus an anticholinergic drug (orfenadrine), and six with levodopa in combination with either amantadine (n = 1), entacapone (n = 3), orfenadrine (n = 1), or pergolide and entacapone (n = 1). To calculate levodopa dose, different drugs were pooled in a levodopa equivalent dose.[14] Except for two patients who were using amitriptyline or diazepam, none of the patients received antidepressants, benzodiazepines or antipsychotics. None of the patients had undergone neurosurgery for relief of motor symptoms.

As a part of neurological examination, all patients received quantitative assessments of clinical disability. The severity of extrapyramidal symptoms was rated using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS).[16] The stage of disease was determined with the Hoehn and Yahr rating scale.[25] The duration of disease was defined as the time between the appearance of the first symptom of PD as reported by the patient and the moment of assessment.

The control group (n = 44) consisted of spouses, friends or relatives of PD patients. Exclusion criteria for control subjects were a history of major psychiatric disorders, head injury with loss of consciousness, cerebrovascular disorders, alcohol or substance abuse, psychoactive medication, and other central nervous system diseases that could influence cognitive performance. Written informed consent was obtained from all subjects after the nature of the study was fully explained. The study was approved by the local ethics committee of the participating hospitals.

Table 1. *Demographic and clinical characteristics of the total PD group, a sample of newly diagnosed, non-medicated PD patients (NMPD) and healthy controls (HC)*

	Total PD (n = 95)		NMPD (n = 24)		HC (n = 44)	
Variable	M	SD	M	SD	M	SD
Age	64.9	8.9	60.7	10.8	64.1	8.3
Education (years)	11.5	2.4	11.7	1.8	12.1	2.4
Gender (M/F)	58/37		13/11		23/21	
Handedness (R/L/A)	81/10/4		20/2/2		38/5/1	
DART-IQ	100.0	19.6	103.8	19.2	105.1	16.0
MMSE	27.9	1.7	28.4	1.7	28.4	1.4
HADS	9.7*	6.2	9.5	6.8	7.0	4.3
HADS-Anxiety	5.0	3.5	5.5	4.1	4.3	2.5
HADS-Depression	4.7†	3.4	4.0	3.3	2.7	2.4
Duration of PD (years)	3.1	2.6	1.2	0.5		
UPDRS motor section	18.2	9.2	14.4	7.5		
Hoehn and Yahr scale	1.9	0.7	1.5	0.6		
stage 1	27		12			
stage 1.5	6		3			
stage 2	33		7			
stage 2.5	15		1			
stage 3	14		1			
Barthel ADL Index	19.7	0.8	19.8	0.5		
SE-ADL (%)	90.2	4.6	91.7	4.8		
FIM	122.3	5.0	124.1	3.1		
FIM-motor scale	87.5	4.7	89.3	3.0		
FIM-cognitive scale	34.8	0.5	34.9	0.3		
LED (mg/day)	291.3	286.7				

Handedness (R/L/A) = right, left, ambidexter; DART = Dutch Adult Reading Test; MMSE = Mini Mental State Examination; HADS = Hospital Anxiety and Depression Scale; UPDRS = Unified Parkinson's disease Rating Scale; SE-ADL: Schwab and England Activities of Daily Living scale; FIM = Functional Independence Measure; LED = Levodopa equivalent dose.
* $p < 0.05$, compared to controls.
† $p < 0.001$, compared to controls.

As can be seen in Table 1, control subjects were matched to the PD patients in age, gender distribution, educational level, premorbid intellectual ability (National Adult Reading Test, Dutch version; [DART-IQ]),[53] MMSE score, and handedness as assessed by a modification of Annet's inventory.[34] The PD group exhibited greater affective changes as reflected by a higher total score on the Hospital Anxiety and Depression scale (HADS),[75] which was primarily due to increased level of depression (HADS-Depression subscale), whereas no group differences were observed on HADS-Anxiety subscale. It is worth noting that only three patients would be classified as having probable affective disturbances based on the originally proposed cut-off values. Since correlational analyses did not indicate significant association between affective symptomatology and any of the dependent variables on the procedural learning task, patients exhibiting signs of depression were not excluded

from the present study. The average disease duration in the PD sample was 3.1 years (range 0.5 – 11 years). Assessment of functional status revealed that patients viewed themselves as independent in most daily activities.

Demographic and clinical characteristics of newly diagnosed, non-medicated PD patients are also shown in Table 1. There were no differences between non-medicated PD patients and controls with respect to age, gender, education, handedness, premorbid intelligence, global cognitive status or the prevalence of affective symptoms.

Neuropsychological assessment

A comprehensive neuropsychological test battery was administered to all participants to evaluate several cognitive domains. *Attention and psychomotor speed* were assessed with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit symbol test,[67] the Trail Making Test parts A en B,[47] the Stroop Color Word test,[65] and an adapted version of WAIS-R forward and backward digit span, in which three trials were administered per length of digit strings, with the maximum score of 21.[35] *Declarative memory* was examined using the Rey Auditory Verbal Learning Test (RAVLT),[48] the Rivermead Behavioral Memory Test (RBMT) Logical Memory subtest,[73] the Wechsler Memory Scale-III (WMS-III) Faces recognition test,[69] and the Visual Association Test.[36] Different aspects of *executive function* were assessed with the Modified Wisconsin Card Sorting Test (MWCST),[44] Controlled Oral Word Association Test (COWAT),[3] Category fluency (animals and supermarket items),[37, 41] the Tower of London-Drexel test (TOL^{DX}),[11] and the WAIS–III Similarities.[68] Tests measuring *visuospatial and constructive abilities* included the Judgment of Line Orientation (JOLO),[4] the Clock Drawing Test,[49] and the subtest Visuo-spatial reasoning of the Groningen Intelligence Test (GIT).[37] This latter test is a tangram-like task in which subjects are instructed to select the figures, which they think are needed to fill up a geometric design. One point is awarded for each correct response (range 0 - 20). The validity of this test classification was found to be satisfactory (Cronbach's $\alpha > 0.6$ for each cognitive domain).

Procedural learning: Serial Reaction Time Task (SRTT)

The SRTT was administered using a response box that had five horizontally aligned lights (red light-emitting diodes) and five buttons (1.5 cm X 1.5 cm), one immediately below each light. The distance between adjacent buttons was 2.5 cm. The light located in a rightmost position on the response box was never lit and was distinguished by its grey color. The subjects were instructed to rest their middle and index fingers of each hand on the response buttons and to press as quickly and as accurately as possible one of the four buttons that corresponded to the position where a red light had appeared. The response box was connected to a laptop computer that used the E-prime software version 1.0 to run the SRTT.[54]

Before starting the SRTT experiment, two practice blocks of 20 random sequence trials each were administered to ensure that participants understood the instructions. Following practice, each subject completed seven blocks of 100 trials. A trial consisted of a light signal and a button press. The first block (where stimuli were presented in random order) was a baseline condition and was discarded from the analysis. In blocks 2 to 6 a sequence of 10 light positions was repeated 10 times. Designating the four stimuli positions as 1, 2, 3, and 4 from left to right, the repeating sequence was 1-2-4-3-4-2-1-4-1-3. The sequence used in the present study was of second-order conditional type, which implies that in order to predict the next position of a stimulus, knowledge of the previous two positions is required since the immediately preceding position alone does not provide sufficient information. The subjects were not informed about the repeating pattern. In the seventh block, the sequence of the light positions was presented in a random order, with the constraint that stimuli never appeared in the same location on two consecutive trials. After each block of 100 trials, participants were allowed to rest for one minute. No feedback on performance was provided during these breaks. The interval between the subject's response and the appearance of the next stimulus was 500 milliseconds. If the subject did not respond within 3 seconds, the next stimulus appeared. Response time (RT) was defined as the interval between the appearance of the stimulus and the moment the subject pressed the response button. Incorrect responses or failure to respond within the 3 seconds were recorded as errors. The computer controlled stimulus presentation and recorded the subject's RT and accuracy on each trial. RTs were recorded in milliseconds.

For each block of trials, we calculated the median RT. The rationale for using the median rather than the mean was to minimize the impact of skewness of the RT distribution and outlier RTs. For each block we calculated the mean and standard deviation of individual median RTs. In addition, the mean number of errors was recorded for each block.

The following two variables were computed as a measure of procedural learning: (i) learning rate, defined as the reduction of RT in the repeating sequence blocks 2-6, reflecting both proficiency in execution of the reaction time task ('reaction-time task learning') and sequence-specific learning; and (ii) sequence-specific learning, which is a rebound increase in RT between blocks 6 (the last repeating sequence block) and 7 (random block), reflecting sequence-specific learning only. If subjects acquired knowledge about the repeating sequence, it should have facilitated their performance on the last repeating sequence block but it would be of no advantage on the last random sequence block. Hence, RT in the last random block should be longer than in the last repeating sequence block. Accordingly, a greater difference in RTs between blocks 6 and 7 corresponds to better sequence-specific learning.

Assessment of functional status

Three scales were used to assess functional status in PD patients: the Barthel Activities of Daily Living Index,[38] the Schwab and England Activities of Daily Living scale (SE-ADL),[55] and the Functional Independence Measure (FIM).[28] Higher score on all scales indicate better functional capacity. The FIM is divided in motor (13 items, range 13 - 91) and cognitive (5 items, range 5 - 35) subscales. The motor subscale contains items that measure self-care, sphincter control, mobility and locomotion, whereas the cognitive subscale evaluates communication and social cognition (i.e. social interaction, problem-solving and memory). All functional scales were administered by the project neurologist.

Statistical analysis

Differences in demographic and clinical characteristics between the PD and control groups were analyzed with independent two-tailed t-tests. Mann-Whitney test was used to analyze ordinal data, while frequencies were compared with chi-square test.

Because RTs in the PD group violated normal distribution, analyses were based on log-transformed data. Analysis of variance (ANOVA) was performed to analyze the RT data. Repeated measures ANOVA were used with group as the between-subject factor and block as the within-subject factor. Comparisons of RTs in individual blocks between the PD and control groups were carried out using t-test.

Correlational analyses revealed that age and premorbid intellectual ability were strongly associated with performance on the majority of the neuropsychological tests in both PD and control groups. These variables were therefore selected as covariates in multivariate analysis of covariance (MANCOVA) to examine relative differences between the PD and control groups within each domain of cognitive functioning. When multivariate comparisons revealed significant results, Bonferroni corrected univariate ANCOVAs with age and premorbid IQ as covariates were conducted to examine single neuropsychological measures.

A multiple regression analysis was conducted to examine the relationship between procedural learning and executive functions, declarative memory and visuospatial skills. The dependent variable in the linear regression analysis was sequence-specific learning on the SRTT, whereas the independent variables were the neuropsychological tests.

The measures of functional outcome are ordinal and do not confirm to a normal distribution. Therefore, the non-parametric Spearman rho statistic was used to explore the relationship between functional status and sequence-specific learning.

All analyses were carried out using SPSS statistical package version 11.0. The level of significance was set at $p < 0.05$, unless otherwise indicated.

Results

Serial Reaction Time Task

Figure 1 displays the mean of median RT as a function of blocks for the PD and control groups. Analysis of baseline performance in block 1 (random presentation of stimuli) revealed that PD patients responded somewhat slower to stimuli than controls, although the difference in RT was not significant [$t(137) = 1.30$, $p = 0.20$].

Learning rate blocks 2-6: Response time

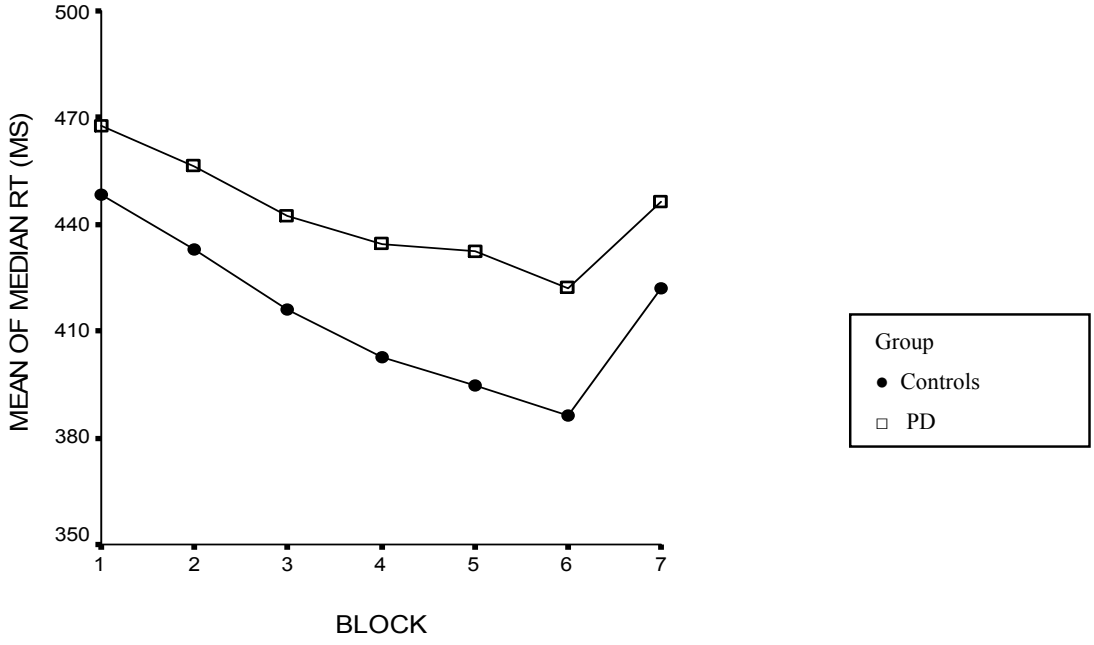
A 2 (Group) X 5 (Block) ANOVA with repeated measures on the block factor revealed a main effect of Group [$F(1, 137) = 5.50$, $p < 0.05$], indicating that the control group was faster than the PD group. There was also a main effect of Block [$F(4, 134) = 41.44$, $p < 0.0001$], suggesting that both groups demonstrated a reduction in RT to repeating sequence of stimulus presentation. The Group X Block interaction did not reach significance, but there was a trend for PD patients to show somewhat less improvement in general reaction time learning than controls [$F(4, 134) = 2.28$, $p = 0.07$].

Sequence-specific learning (block 6 versus block 7): Response time

To investigate group differences in sequence-specific learning, a 2 (Group) X 2 (Block) repeated measures ANOVA was performed. The analysis revealed a main effect of Group [$F(1, 137) = 6.26$, $p < 0.05$], as well as a main effect of Block [$F(1, 137) = 125.05$, $p < 0.0001$]. In addition, a significant interaction of Group and Block was observed [$F(1, 137) = 6.28$, $p < 0.05$], indicating that, overall, the PD group exhibited a lower increase in RT than control subjects when switch was made from the last sequential block to a random block. The interaction effect remained significant when the HADS-score was used as a coviariate in the analysis.

For the control group, the switch from a repeating sequence block to a random block resulted in a RT increase of 36 ms (SD = 36), and in the PD group an average increase of 24 ms (SD = 27). Within group comparisons using t-test for paired samples revealed significant differences in RT between blocks 6 and 7 in the control group [$t (43) = -6.34$, $p < 0.0001$] as well as in the PD group [$t (94)= -9.37$, $p < 0.0001$], indicating that both groups demonstrated procedural sequence learning. The effect size[9] for sequence-specific learning was 0.38, suggesting a relatively small difference in amount of learning between PD patients and controls. Moreover, analysis of the individual data revealed that the majority of participants in both the control (89%) and PD (86%) groups showed an increase in RT when the switch was made to a random presentation of stimuli.

Figure 1. *The mean of the median RT of the PD and control groups in the seven blocks of trials on the SRT*



Accuracy

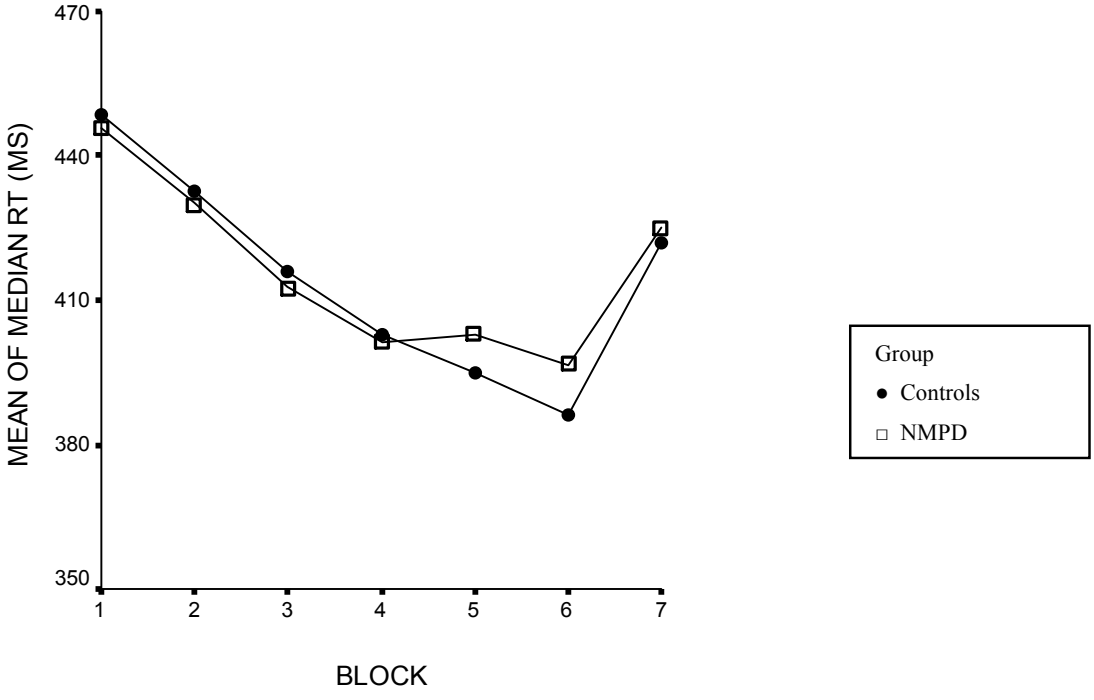
Accuracy for both groups was very high and remained stable across the blocks. Since both groups showed almost negligible number of errors (mean percentage of errors per block PD < 1.5%, controls < 0.6%), a statistical comparison would have little sense and was not performed.

SRTT performance in non-medicated PD patients

To examine the impact of PD on procedural learning removed from the effects of medication, SRTT performance of a subgroup of 24 newly diagnosed, untreated patients with PD was compared to all control subjects. A Group (non-medicated PD *vs.* controls) X Block (2-6) repeated measures ANOVA revealed a main effect of Block [$F(4, 63) = 26.34$, $p < 0.0001$]. The effects of Group ($F < 1$) and Group X Block interaction [$F(4, 63) = 1.60$, $p = 0.19$] were not significant. To examine sequence-specific learning, blocks 6 and 7 were entered in another ANOVA. This analysis showed a main effect of Block [$F(1, 66) = 60.05$, $p < 0.0001$], but no effect of Group ($F < 1$). Of importance, the interaction effect of Group and Block was not significant ($F < 1$), indicating that non-medicated PD patients showed a

similar increase in RT from the last repeating sequence block to the random block as did control subjects (Figure 2).

Figure 2. *The mean of the median RT of the subgroups of non-medicated PD patients (NMPD; n = 24) and control subjects in the seven blocks of trials on the SRTT*



Neuropsychological performance of PD patients and control subjects

One-way MANCOVAs with age and premorbid IQ as covariates showed differences between PD patients and control subjects across all cognitive domains (Table 2). Within the domain of attention and psychomotor speed, univariate differences on Digit symbol test and Trail Making test B accounted for multivariate results. Within the memory domain, PD patients performed consistently worse than controls on all tests except on measures of delayed word recognition and visual associative learning. Univariate differences on the TOL^{DX} test and supermarket fluency accounted for the multivariate differences in executive functions. Multivariate difference between the PD and control groups in the visuospatial domain was due to JOLO and GIT Visuo-spatial reasoning task. The pattern of performance remained essentially the same when the HADS-score was used as a covariate in addition

Table 2. *Neuropsychological test results (raw scores) in PD patients and healthy controls (HC)*

Measure	PD (n = 95) M	PD (n = 95) SD	HC (n = 44) M	HC (n = 44) SD	F	p-value
Attention and Psychomotor speed – MANCOVA: F = 5.92; p < 0.001						
WAIS-R Digit symbol test	38.8	11.3	50.1	11.8	36.80	< 0.001†
Trail Making Test A	50.2	19.6	39.7	15.4	7.91	0.01
Trail Making Test B	121.4	63.6	87.0	35.2	9.02	0.003†
Stroop test (word reading)	47.6	10.5	44.2	8.0	1.83	0.18
Stroop test (color naming)	63.4	14.2	58.3	10.9	2.81	0.10
Stroop interference test	122.2	44.7	100.9	25.0	6.29	0.01
Digit span forward	12.6	2.8	12.3	3.3	2.46	0.12
Digit span backward	8.4	2.5	9.6	2.8	3.95	0.05
Memory – MANCOVA: F = 4.32; p < 0.001						
RAVLT trial 1-5	39.2	10.8	46.9	9.2	14.94	< 0.001†
RAVLT delayed recall	7.9	3.1	10.1	3.1	12.22	0.001†
RAVLT recognition	27.6	2.3	28.6	2.1	3.40	0.07
RBMT LM immediate recall	14.5	5.6	18.7	5.6	14.91	< 0.001†
RBMT LM delayed recall	10.9	5.5	15.0	5.5	14.60	< 0.001†
WMS-III Faces immediate	31.5	4.6	34.6	3.6	12.95	< 0.001†
WMS-III Faces delayed	34.5	4.5	37.3	4.1	11.28	0.001†
Visual Association Test	11.6	1.0	11.9	0.3	3.45	0.07
Executive functions – MANCOVA: F = 3.72; p = 0.001						
MWCST categories	4.0	1.7	4.8	1.4	6.26	0.01
MWCST perseverations	6.0	6.1	3.2	3.4	5.83	0.02
Animal fluency	18.8	5.1	20.8	4.8	2.21	0.14
Supermarket fluency	18.8	5.2	21.6	3.9	8.08	0.005†
COWAT Letter fluency	30.3	9.5	34.6	10.4	2.99	0.09
Tower of London test	5.5	2.1	7.1	2.0	15.36	< 0.001†
WAIS-III Similarities	21.9	5.9	24.2	5.5	2.09	0.15
Visuospatial/constructive skills – MANCOVA: F = 3.43; p = 0.02						
JOLO	22.9	4.4	25.6	4.2	8.34	0.005†
GIT Visuo-spatial task	9.3	3.1	11.1	3.6	6.07	0.02†
Clock Drawing Test	12.5	1.7	12.9	1.2	1.31	0.25

MANCOVA = multivariate analysis of variance with age and premorbid IQ as covariates.
WAIS = Wechsler Adult Intelligence Scale; RAVLT = Rey Auditory Verbal Learning Test; RBMT LM = Rivermead Behavioral Memory Test Logical Memory; WMS = Wechsler Memory Scale; COWAT = Controlled Oral Word Association Test; MWCST = Modified Wisconsin Card Sorting Test; JOLO = Judgment of Line Orientation; GIT = Groningen Intelligence Test.
† Significant with Bonferroni correction.

to age and premorbid IQ. The changes were observed only on Trail Making test B and supermarket fluency, which were no longer significantly different between the groups.

Compared with controls, non-medicated PD patients showed mildly impaired performance on the Digit symbol test, WMS-III Faces immediate recognition test and TOL^{DX} test. There were no significant differences between the two groups on the remaining measures of

cognitive functioning.

Cognitive correlates of procedural learning

To determine whether cognitive abilities could account for decreased sequence-specific learning in the PD group, we conducted a linear regression analysis (method enter) in which the dependent variable was the difference in RT between block 7 (random block) and block 6 (the last repeating sequence block) on the SRTT. Given a rather large number of neuropsychological tests employed in the present study, composite z scores for the domains of attention and psychomotor speed, declarative memory, executive functions, and visuospatial abilities were included in the analysis as the independent variables. All measures from the test battery were transformed into z scores using the means and standard deviations from the control group. Subsequently, composite scores were computed for each cognitive domain by summing the z scores from the individual tests that contributed to the particular domain and computing the mean.

The cognitive variables accounted for only 2% of the variance associated with sequence-specific learning in the PD group ($F < 1$, $p = 0.78$). None of the four cognitive domains assessed in this study contributed significantly to the multiple regression equation (attention/psychomotor speed: $\beta = 0.06$, $t = 0.36$, $p = 0.72$; declarative memory: $\beta = 0.03$, $t = 0.19$, $p = 0.85$; executive function: $\beta = -0.08$, $t = -0.47$, $p = 0.64$; visuospatial skills: $\beta = 0.13$, $t = 0.99$, $p = 0.33$). Similar results were observed for the control group (9% of the variance accounted by the model, $F < 1$, $p = 0.44$).

When regression analysis was repeated using the raw score on the test in each domain that best discriminated between PD patients and controls (i.e. Digit symbol test, RAVLT trial 1-5, TOL^{DX} test, JOLO) instead of the composite scores, the same negative results were obtained.

Relationship between procedural learning and clinical disability and functional outcome

To examine whether the severity of motor symptoms or disease duration affected sequence-specific learning in PD patients, a series of correlational analyses were carried out using Spearman's rho test. A weak, but significant correlation was observed between the degree

of axial disorders and learning impairment (rho = -0.17, p = 0.05, one-tailed test). Furthermore, the patients with more severe motor symptoms, as evaluated with Hoehn and Yahr scale and the UPDRS motor section, showed a trend towards worse sequence-specific learning (rho = -0.15, p = 0.08). Disease duration and the severity of tremor, bradykinesia or rigidity were not significantly related to learning impairment (rho < |0.14|). There was no association between procedural learning impairment and levodopa dosage (n = 95; rho = -0.13, p = 0.22).

To assess whether procedural learning contributed to functional status in PD, Spearman correlation coefficients were calculated and significance was assessed using a one-tailed test. No significant relationship was found between sequence-specific learning impairment and any of the three functional scales employed in this study (rho < |0.11|).

Discussion

The present study examined motor procedural learning in the largest sample of PD patients reported to date and is the first to assess the ability of newly diagnosed, not previously treated patients to acquire a motor sequence using the SRTT. The results indicate that PD patients were less efficient than control subjects in acquiring sequence-specific knowledge. Procedural learning impairment appeared to be independent of executive dysfunction, and it did not affect patients' functional status. This impairment was found to be rather small (d = 0.38). The novel finding of this study is that non-medicated PD patients were not impaired in this type of motor skill learning; the impairment was limited to medicated patients with more advanced clinical symptoms. As a group, the PD patients were able to achieve sequence-specific knowledge, albeit to a lesser degree than control subjects. These results are largely consistent with previous reports in the literature, demonstrating an attenuation rather than abolition of procedural sequence learning in patients with PD.[7, 17, 45, 61]

The degree of sequence-specific learning impairment in our PD sample is smaller than in a recently published meta-analysis of six SRTT studies of 67 PD patients and 87 healthy control subjects, which yielded a mean effect size of 0.73.[57] It is likely that this discrepancy is due to procedural differences between studies. For example, while the present study used a 10-item sequence, the length of the sequence in the articles included in the meta-analysis

varied from 8 to 12-element sequences. Notably, the largest effect size was obtained from a study that used a 12-item sequence.[58] Furthermore, in two articles that used the same length of the sequence as in the present study, the learning impairment was either somewhat smaller (d = 0.16)[61] or similar (d = 0.32)[7] to that observed in our patient sample.

In contrast to sequence-specific learning, the results on the other measure of procedural learning derived from the SRTT (i.e. learning rate over blocks 2 to 6) indicate that PD patients exhibited similar improvement as controls in general reaction-time task learning. It is important to note that the mean response time of the PD group on the baseline condition of the SRTT (block 1 in Figures 1 and 2) was comparable with that of the control group. Therefore, it is unlikely that the lack of a significant difference in general reaction time learning is due to the fact that PD patients had more room than controls to improve their performance. In addition, comparable performance levels of the two groups at the baseline condition and the overall high accuracy of responding suggest that the patients did not simply have difficulty in performing the task, which could have interfered with their ability to acquire a motor sequence.

Current knowledge about procedural learning in PD is primarily obtained from studies of medicated patients. Although in some studies attempts have been made to address the possible role of dopaminergic medication by studying patients during withdrawal of levodopa treatment, the results of these studies may be difficult to interpret in light of the potentially chronic effects of pharmacologic treatment on dopamine receptors.[39] The present study is the first to evaluate SRTT performance in untreated, newly diagnosed patients with PD. The results showed that non-medicated PD patients were as able as control subjects to demonstrate both general improvement with the reaction-time task and to acquire sequence-specific knowledge. It is important to note, however, that no significant association between SRTT performance and levodopa dosage was found in the total PD sample. Therefore, it is unlikely that procedural learning impairment observed in the present study can be explained by drug treatment effects. The presence of the learning impairment in the total PD sample but not in a subgroup of untreated patients may reflect the effects of disease severity. This possibility is supported by the finding that patients with more advanced clinical symptoms tended to show worse performance in sequence-specific learning. This finding is consistent

with several earlier studies, showing that motor learning impairments predominantly occur in PD patients in more advanced stages of the disease.[13, 23]

PD patients in the present study exhibited impairments on neuropsychological measures of attention and psychomotor speed, executive functions, declarative memory and visuospatial skills. These findings are in accordance with previous observations concerning the cognitive profile in non-demented PD patients.[5, 33] None of the cognitive measures were found to be associated with procedural learning, however. This finding indicates that other types of cognitive dysfunction cannot account for procedural learning impairment observed in our PD sample. The lack of a significant association between executive dysfunction and procedural learning was not predicted, and it is in contrast with a previous study, in which PD patients with impaired performance on the Wisconsin Card Sorting Test (WCST) were found to exhibit the most severe impairments in SRTT learning.[26] While the same test was also used in the present study, the contribution of executive function to procedural learning was assessed with a composite domain score based on a number of measures purported to assess executive abilities rather than the score on individual tests. When performance on the WCST was analyzed separately, it appeared that neither the number of categories achieved nor persereverative errors in our PD sample were associated with sequence-specific learning impairment. Furthermore, the finding that newly diagnosed, untreated PD patients showed impairments in planning (i.e. Tower of London test) and certain aspects of attention (i.e. Digit symbol test), but demonstrated an otherwise normal performance on the procedural learning task adds support for the independence of motor sequence learning and executive functions. Although there is some evidence that executive dysfunction may interfere with procedural learning,[20, 52] several studies, consistent with the present report, failed to observe such an effect in patients with frontal lobe lesions[13] or PD patients using either the SRTT,[59] rotary pursuit task,[22] or artificial grammar learning task.[74]

The lack of significant association between measures of declarative memory and procedural learning implies independence of these memory systems in PD. It is worth noting that declarative memory impairments were far more prominent than impairments in procedural learning. This finding is consistent with previous reports in the literature, showing that deficits in the memory domain in patients with PD are particularly prominent on those

tests that involve effortful and controlled processes, such as free recall measures, rather than tests focusing on automatic aspects of cognitive processing.[2, 70]

The finding that procedural learning impairment does not seem to influence functional capacity of PD patients may be due to the characteristics of our patient sample. Functional assessment revealed that the majority of patients viewed themselves as independent in most daily activities (see Table 1). The restricted range of scores on the functional scales employed in the present study may have limited the likelihood of obtaining a statistically significant relationship.

Non-medicated PD patients, most of whom were in Hoehn and Yahr stage 1 or 2, were found to perform normally on the SRTT. This finding asks for some, admittedly speculative, interpretation. The primary neuropathological changes in PD involve degeneration of nigrostriatal dopaminergic neurons, which leads initially to depletion of dopamine in the putamen and areas involved in the motor loop, and later in the course of the disease, to impairment in the caudate nucleus.[29] Evidence for the role of the putamen in the acquisition of motor skills comes from a functional magnetic resonance imaging (fMRI) study in healthy subjects by Rauch et al. (1997),[46] who reported a significant relationship between the magnitude of the signal intensity change in the putamen and implicit sequence learning derived from the SRTT. The pattern of SRTT performance observed in our PD sample seems in conflict with the results of this study. The finding that procedural sequence learning was normal in non-medicated patients early in the course of PD and that impairment became evident with disease progression might imply that the critical striatal substrate for this type of learning lies outside the putamen and its associated circuits. Alternatively, putaminal pathology in our sample of untreated patients with mild clinical disability may not have reached a critical level sufficient to produce impairments in skill learning. Furthermore, if the putamen and its associated cortical areas of the motor loop are important for motor skill learning, as Rauch et al.[46] study suggests, one would expect to find a strong relationship between procedural learning impairment and the degree of the core motor symptoms of the disease. In the present study, however, there were no significant associations between motor learning and the severity of any of the cardinal motor symptom triad of bradykinesia, tremor or rigidity in the total PD group. In contrast, procedural learning impairment in PD

patients was found to be related to the severity of axial symptoms (disorders of gait and posture), which are believed to be predominantly mediated by nondopaminergic systems, in particular the cholinergic system.[8] Taken together, these findings argue against the primary role of the dopaminergic putaminal system in procedural learning.

Strengths of the present study are the large PD sample, the careful evaluation of the patient's clinical state, the comparison of medicated and unmedicated patients, the extensiveness of the neuropsychological examination and the fact that we attempted to investigate the clinical relevance of the motor learning impairment. However, some methodological limitations of the study should also be recognized. First, the SRTT was administered as a part of a comprehensive neuropsychological test battery. Due to time limitation the SRTT could not be administered to some patients. These were often patients who had more severe motor dysfunction and were likely to experience more problems in performing the task. This may have introduced a selection bias in our analyses. Therefore, it remains uncertain whether the present results can be generalized to PD patients in advanced stages of the disease. Second, the mean disease duration in our patient sample was relatively short (3.1 years; Table 1). Most of the patients have recently been diagnosed. This may have limited the likelihood of finding significant correlations with motor symptom severity and cognitive impairments in other domains than skill learning. However, the range of disease durations varied from 0.5 to 11 years, and almost a third of the patient sample had a Hoehn and Yahr score higher than 2 (Table 1). Moreover, neuropsychological evaluation revealed cognitive impairments in all domains (Table 2), some of which were present even in early, non-medicated patients. Thus, there seems to be enough variance in our data set. It is unlikely that the modest relations of procedural learning with motor symptom severity, and the absence of any association between skill learning and cognitive impairments can be explained by restriction of range effects. Third, we did not check whether the participants had acquired explicit knowledge of the repeating sequence. However, with the second-order conditional sequence used in the present study it is unlikely that subjects became aware of the sequence, although it is possible that some subjects may have acquired at least partial explicit sequence knowledge. Furthermore, one may argue that the reduced sequence-specific learning in our PD sample is an artifact of the better ability to acquire explicit

knowledge on the part of the control group. However, with the exception of one study,[45] studies that used a similar 10-item sequence did not observe differences in explicit knowledge of the repeating sequence between control subjects and patients with PD,[7, 13, 64] Huntington's disease,[6, 31] or focal basal ganglia lesions.[66]

In summary, the present findings indicate that PD patients are able to acquire procedural knowledge of a motor sequence, but they learn it somewhat less efficiently than control subjects. This impairment is likely to occur mainly in patients with moderately severe clinical symptoms, and it cannot be attributed to dopaminergic medication or cognitive dysfunction. Impaired procedural motor learning in PD patients does not seem to affect their functional status.

References

1. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986; 9:357-381.
2. Appolonio I, Grafman J, Clark K, Nichelli P, Zeffiro T, Hallet M. Implicit and explicit memory in patients with Parkinson's disease with and without dementia. *Arch Neurol* 1994; 51:359-367.
3. Benton AL, Hamsher KDS. *Multilingual Aphasia Examination: Manual.* Iowa City: University of Iowa, 1976.
4. Benton A, Hamsher K, Varney N, Spreen O. *Contributions to neuropsychological assessment – a clinical manual.* New York: Oxford University Press, 1983.
5. Brown RG, Marsden CD. Cognitive function in Parkinson's disease: from description to theory. *Trends Neurosci* 1990; 13:21-28.
6. Brown RG, Redondo-Verge L, Chacon JR, Lucas ML, Channon S. Dissociation between intentional and incidental sequence learning in Huntington's disease. *Brain* 2001; 124:2188-2202.
7. Brown RG, Jahanshahi M, Limousin-Dowsey P, Thomas D, Quinn NP, Rothwell JC. Pallidotomy and incidental sequence learning in Parkinson's disease. *NeuroReport* 2003; 14:21-24.
8. Burn DJ, Rowan DN, Minett T, et al. Extrapyramidal features in Parkinson's disease with and without dementia and dementia with Lewy bodies: a cross-sectional comparative study. *Mov Disord* 2003; 18:884-889.
9. Cohen J. *Statistical power analysis for the behavioral sciences* (2nd ed.). New York: Academic Press, 1988.
10. Cohen NJ, Squire LR. Preserved learning and retention of pattern analyzing skills in amnesia: dissociation of knowing how and knowing that. *Science* 1980; 210:207-210.
11. Culbertson WC, Zilmer E. *The Tower of London^{DX} (TOL^{DX}): Manual.* North Tonawanda, New York: Multi-Health Systems, 2001.
12. Doyon J, Owen AM, Petrides M, Sziklas V, Evans AC. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. *Eur J Neurosci* 1996; 8:637-648.
13. Doyon J, Gaudreu D, Laforce R, et al. Role of the striatum, cerebellum, and frontal lobes in the learning of a visuomotor sequence. *Brain Cogn* 1997; 34:218-245.
14. Esselink RAJ, de Bie RMA, de Haan RJ, et al. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD. A randomized trial. *Neurology* 2004; 62:201-207.
15. Exner C, Koschack J, Irle E. The differential role of premotor frontal cortex and basal ganglia in motor sequence learning: evidence from focal basal ganglia lesions. *Learn Mem* 2006; 9:376-386.
16. Fahn S, Elton RI, and members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. *Recent development in Parkinson's disease*. Vol. 2. New York: Macmillan Health Care Information, 1987: 153-164.
17. Ferraro FR, Balota DA, Connor LT. Implicit memory and the formation of new associations in nondemented Parkinson's disease individuals and individuals with senile dementia of the Alzheimer type: a Serial Reaction Time (SRT) investigation. *Brain Cogn* 1993; 21:163-180.

18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-198.
19. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol* 1999; 56:33-39.
20. Gomez-Beldarrain M, Grafman J, Pascual-Leone A, Garcia-Monco JC. Procedural learning is impaired in patients with prefrontal lesions. *Neurology* 1999; 52:1853-1860.
21. Grafton ST, Hazeltine E, Ivry R. Functional mapping of sequence learning in normal humans. *J Cogn Neurosci* 1995; 7:497-510.
22. Haaland KY, Harrington DL, O'Brien S, Hermanowicz N. Cognitive-motor learning in Parkinson's disease. *Neuropsychology* 1997; 11:180-186.
23. Harrington DL, Haaland KY, Yeo RA, Marder E. Procedural memory in Parkinson's disease: impaired motor but not visuoperceptual learning. *J Clin Exp Neuropsychol* 1990; 12:323-339.
24. Heindel WC, Salmon DP, Shults CW, Walicke PA, Butters N. Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington's and Parkinson's disease patients. *J Neurosci* 1989; 9:582-587.
25. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; 17:427-442.
26. Jackson GM, Jackson SR, Harrison J, Henderson L, Kennard C. Serial reaction time learning and Parkinson's disease: evidence for a procedural learning deficit. *Neuropsychologia* 1995; 33:577-593.
27. Jenkins IH, Tarazona FJ, Pascual-Leone A, Brooks DJ. The functional anatomy of explicit and implicit motor learning. *Neurology* 1997; 48 (Suppl 2):A305.
28. Keith RA, Granger CV, Hamilton BB, Sherwin FS. The Functional Independence Measure: a new tool for rehabilitation. In: Eisenberg MG, Grzesiak RC, eds. *Advances in clinical rehabilitation*. New York: Springer, 1987: 6-18.
29. Kish SJ, Shannak K, Hornykiewicz O. Uneven patterns of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathofysiologic and clinical implications. *N Engl J Med* 1988; 318:876-880.
30. Knopman DS, Nissen MJ. Implicit learning in patients with probable Alzheimer's disease. *Neurology* 1987; 37:784-788.
31. Knopman D, Nissen MJ. Procedural learning is impaired in Huntington's disease: evidence from the Serial Reaction Time task. *Neuropsychologia* 1991; 29:245-254.
32. Knowlton BJ, Squire LR, Paulsen JS, Swerdlow NR, Swenson M, Butters N. Dissociations within non-declarative memory in Huntington's disease. *Neuropsychology* 1996; 10:538-548.
33. Levin BE, Tomer R, Rey GJ. Cognitive impairments in Parkinson's disease. *Neurologic Clinics* 1992; 10: 471-485.
34. Lezak MD, Howieson DB, Loring DW. *Neuropsychological assessment* (4th ed.). New York: Oxford University Press, 2004.
35. Lindeboom J, Matto D. [Digit series and Knox cubes as concentration tests for elderly subjects]. *Tijdschr Gerontol Geriatr* 1994; 25:63-66.
36. Lindeboom J, Schmand B, Tulner L, Walstra G, Jonker C. Visual association test to detect early dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry* 2002; 73:126-133.

37. Luteijn F, Barelds DPH. *Groningen Intelligence Test 2 (GIT-2): Manual.* Amsterdam, The Netherlands: Harcourt Assessment BV, 2004.
38. Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. *Md State Med J* 1965; 14:61-65.
39. Marsden CD, Jenner P. L-dopa's action in Parkinson's disease. *Trends Neurosci* 1981; 4:148-150.
40. Martone M, Butters N, Payne M, Becker JT, Sax DS. Dissociations between skill learning and verbal recognition in amnesia and dementia. *Arch Neurol* 1984; 41:965-970.
41. Mattis S. *Dementia Rating Scale (Professional Manual)*. Odessa, Florida: Psychological Assessment Resources, 1973.
42. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology* 2005; 65:1239-1245.
43. Nelson HE. A modified card sorting test sensitive to frontal lobe defects. *Cortex* 1976; 12:313-324.
44. Nissen MJ, Bullemer P. Attentional requirements of learning: evidence from performance measures. *Cognit Psychol* 1987; 19:1-32.
45. Pascual-Leone A, Grafman J, Clark K, et al. Procedural learning in Parkinson's disease and cerebellar degeneration. *Ann Neurol* 1993; 34:594-602.
46. Rauch SL, Whalen PJ, Savage CR, et al. Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. *Hum Brain Mapp* 1997; 5:124-132.
47. Reitan RM. *Trail making test.* Manual for administration and scoring. Tucson, AZ: Reitan Neuropsychological Laboratory, 1992.
48. Rey A. *L'examen clinique en psychologie*. Paris: Presses Universitaires de France, 1964.
49. Royall DR, Cordes JA, Polk M. CLOX: an executive clock drawing task. *J Neurol Neurosurg Psychiatry* 1998; 64:588-594.
50. Rosas HD, Koroshetz WJ, Chen YI, et al. Evidence for more widespread cerebral pathology in early HD: An MRI-based morphometric analysis. *Neurology* 2003; 60:1615-1620.
51. Saint-Cyr JA, Taylor AE, Lang AE. Procedural learning and neostriatal dysfunction in man. *Brain* 1988; 111:941-959.
52. Sarazin M, Deweer B, Merkl A, Von Poser N, Pillon B, Dubois B. Procedural learning and striatofrontal dysfunction in Parkinson's disease. *Mov Disord* 2002; 17:265-273.
53. Schmand B, Lindeboom J, van Harskamp F. [*Dutch Adult Reading Test*]. Lisse, The Netherlands: Swets and Zeitlinger, 1992.
54. Schneider W, Eschman A, Zuccolotto A. *E-prime version 1.0 User's guide*. Pittsburgh: Psychology Software Tools Inc, 2002.
55. Schwab JF, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson MC, eds. *Third symposium on Parkinson's disease*. Edinburgh: E&S Livingstone, 1969:152-157.
56. Shin JC, Aparicio P, Ivry R. Multidimensional sequence learning in patients with focal basal ganglia lesions. *Brain Cogn* 2005; 58:75-83.

57. Siegert RJ, Taylor KD, Weatherall M, Abernethy DA. Is implicit sequence learning impaired in Parkinson's disease? A meta-analysis. *Neuropsychology* 2006; 20:490-495.
58. Smith JG, McDowall J. Impaired higher order implicit sequence learning on the verbal version of the Serial Reaction Time task in patients with Parkinson's disease. *Neuropsychology* 2004; 18:679-691.
59. Smith JG, McDowall J. The implicit sequence learning deficit in patients with Parkinson's disease: a matter of impaired sequence integration? *Neuropsychologia* 2006; 44:275-288.
60. Smith J, Siegert RJ, McDowall J. Preserved implicit learning on both Serial Reaction Time task and artificial grammar in patients with Parkinson's disease. *Brain Cogn* 2001; 45:378-391.
61. Sommer M, Grafman J, Clark K, Hallet M. Learning in Parkinson's disease: eyeblink conditioning, declarative learning and procedural learning. *J Neurol Neurosurg Psychiatry* 1999; 67:27-34.
62. Squire LR. *Memory and brain*. New York: Oxford University Press, 1987.
63. Squire LR. Declarative and nondeclarative memory: multiple brain systems supporting learning and memory. *J Cogn Neurosci* 1992; 4:232-243.
64. Stefanova E, Kostic VS, Ziropadja Lj, Markovic M, Ocic GG. Visuomotor skill learning on Serial Reaction Time task in patients with early Parkinson's disease. *Mov Disord* 2000; 15:1095-1103.
65. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol* 1935; 18:643-662.
66. Vakil E, Kahan S, Huberman M, Osimani A. Motor and non-motor sequence learning in patients with basal ganglia lesions: the case of serial reaction time (SRT). *Neuropsychologia* 2000; 38:1-10.
67. Wechsler D. *Wechsler Adult Intelligence Scale-Revised (WAIS-R): Test Manual.* New York: Psychological Corporation, 1981.
68. Wechsler D. *Wechsler Adult Intelligence Scale 3rd edition (WAIS-III): Test Manual.* New York: Psychological Corporation, 1997.
69. Wechsler D. *Wechsler Memory Scale 3rd edition (WMS-III): Test Manual.* New York: Psychological Corporation, 1997.
70. Weingartner H, Burns S, Diebel R, LeWitt P. Cognitive impairment in Parkinson's disease: distinguishing between effort demanding and automatic cognitive processes. *Psychiatry Res* 1984; 11:223-235.
71. Willingham DB. A neuropsychological theory of motor skill learning. *Psychol Rev* 1998; 105:558-584.
72. Willingham DB, Koroshetz WJ. Evidence for dissociable motor skills in Huntington's disease patients. *Psychobiology* 1993; 21:173-182.
73. Wilson B, Cockburn J, Baddeley A. *Rivermead behavioural memory test*. Reading, UK: Thames Valley Test Company, 1985.
74. Witt K, Nühsman A, Deuschl G. Intact artificial grammar learning in patients with cerebellar degeneration and advanced Parkinson's disease. *Neuropsychologia* 2002; 40:1534-1540.
75. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-370.