

## Nonverbal deficits in explicit and implicit memory of Parkinson's disease patients

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This study examined verbal and nonverbal aspects of explicit and implicit memory in a sample of 19 Parkinson's disease (PD) patients and 21 control subjects. For implicit memory evaluation, we used a Mirror Reading (MR) task employing verbal material as well as a nonverbal Serial Reaction Time (SRT) task. For explicit memory measurement we applied a word pairs task (verbal) and pairs of a Japanese ideograms task (nonverbal). The PD patients displayed impairments in the nonverbal tasks only, namely, in the SRT task and the pairs of Japanese ideograms task. No correlation between Wisconsin Card Sorting Test (WCST) scores and the results of tasks in which PD patients displayed deficits (SRT and pairs of Japanese ideograms) were discovered. Interestingly, such a correlation was found in the case of MR and words pairs tasks, which did not distinguish PD patients from control group.

Key words: Parkinson's disease, implicit memory, explicit memory, Serial Reaction Time, Mirror Reading

### INTRODUCTION

Contemporary memory theories distinguish between explicit and implicit learning processes (Gabrieli 1998, Squire 2004). The explicit (declarative) learning system is responsible for conscious acquisition and retrieval of facts and events, and apparently depends mainly on the integrity of the temporal lobe and diencephalic brain structures. Implicit (nondeclarative) learning and memory involve acquisition and recollection not accompanied by awareness. Most of the data points out to the role of basal ganglia in at least some forms of implicit learning (Squire and Zola 1996, Packard and Knowlton 2002).

Parkinson's disease (PD) manifests itself in a triad of motor symptoms: tremor, bradykinesia and rigidity. PD depends on the progressive death of neurons in substantia nigra, what results in a loss of striatal dopamine and the subsequent dysfunction of basal

ganglia. Besides motor symptoms, neurocognitive abnormalities were repeatedly described in PD, among which those regarding executive functions and memory appear to be predominant (Owen 2004, Muslimovic et al. 2005). Deficits in executive functions emerge since basal ganglia dysfunction also affects the frontal lobes, including the prefrontal cortex, which is postulated to be pivotal for executive processing (Heyder et al. 2004). Previous studies have shown that PD patients suffer from both the implicit and explicit memory deficits. However, the obtained data are often contradictory (see, e.g., Bondi and Kaszniak 1991, Yamadori et al. 1996, Witt et al. 2002, Smith and McDowall 2006b).

One source of discrepancies in memory studies of PD is the possibility that verbal and nonverbal aspects are differentially affected. Unfortunately, concurrent evaluations of both verbal and nonverbal aspects of memory of PD patients have been not only rare but limited to explicit memory and furthermore, they have produced often contradictory results, either showing comparable impairments (Farina et al. 2000, Vingerhoets et al. 2005, Whittington et al. 2006) or

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indicated selective deficits in the verbal tasks (Vakil and Herishanu-Naaman 1998).

Notably, in the case of implicit memory, task classification into verbal and nonverbal tasks is less utilized. However, studies employing mirror reading (MR), a classical nondeclarative task with verbal characteristic often pointed to a deficit in PD patients (Roncacci et al. 1996, Yamadori et al. 1996, Koenig et al. 1999, Sarazin et al. 2002; please note, however, also contradictory results by Harrington et al. 1990, Bondi and Kaszniak 1991). Nonetheless, it can be considered that most implicit tasks involve the processing of nonverbal (motor or perceptual) information (e.g. rotor pursuit, mirror tracing or Serial Reaction Time).

PD patients' deficits in implicit and explicit memory have repeatedly been described in scientific literature, however, the exact pattern of the impairments is still unknown. The aim of the present study was to explore both verbal and nonverbal aspects of PD patients' memory in both implicit as well as explicit variants. Therefore we choose two implicit tasks tapping visuospatial functions: in particular, nonverbal Serial Reaction Time task (SRT) (Nissen and Bullemer 1987) and verbal MR task. MR and SRT tasks are classic paradigms of implicit memory examination. Notably, to our best knowledge, none of them has been used for studying Polish PD patients before. In the case of explicit memory assessment we developed two parallel versions of the task: one employed learning pairs of words and other one used Japanese ideograms instead (which were completely nonverbal for Polish participants). The Wisconsin Card Sorting Test (WCST) was also employed as a measure of executive functions with the purpose of testing frontal dysfunction involvement in memory performance.

## METHODS

### Participants

Nineteen patients with idiopathic PD and 21 healthy control subjects matched for age and education participated in the study (Table I). All participants (both patients and control subjects) scored above the cutoff of 24 points on the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) indicating absence of dementia. There were no significant group differences for performance on the MMSE, as well as the score for the Beck Depression Inventory (BDI) (Beck et al. 1961) (Table I). According to the Hoehn and Yahr (1967) degree of clinical disability scale of severity of PD, 4 patients belonged to Stage I, 14 to Stage II and 2 to Stage III. Twelve patients were with left body side motor symptom onset and seven with right side onset. Time since diagnosis ranged from 6 months to 10 years with the mean of 4.45 years ( $SD = 0.5$ ). All patients were treated with levodopa medication, none of them received anticholinergic drugs. Two patients were taking antidepressive drugs (fluoxetine and sertraline).

### Wisconsin Card Sorting Test (WCST)

A standard tool to assess executive function level, the Wisconsin Card Sorting Test (WCST) (Heaton et al. 1993) in Polish adaptation (Jaworowska 2002) was employed. The test requires a subject to sort response cards to four stimulus card according to the color, number, or form. The subject is asked to match successive response cards to cue cards, although the rule of sorting is not provided. The only information is the feedback, whether the answer is right or wrong, which is given after each card match. When the subject discovers and

Table I

Sociodemographic and clinical characteristics of PD and healthy control participants				
Measure	PD ( $n=19$ )[Mean (SD)]	Control ( $n=21$ )[Mean (SD)]	$t/Z$	$P$
Age (years)	57.00 (10.70)	55.69 (9.12)	0.42	ns
Education (years)	15.05 (2.17)	16.24 (1.61)	-1.90	ns
MMSE	29.16 (1.07)	29.43 (0.75)	0.53	ns
BDI	11.79 (8.38)	10.43 (8.24)	0.52	ns

(MMSE) Mini-Mental State Examination; (BDI) Beck Depression Inventory

maintains over 10 consecutive answers, the principle is changed unexpectedly and the subject has to find the new sorting strategy. The WCST is considered an assessment of abstract concept formation, shift and maintenance in response to feedback (Spreen and Strauss 1998).

### Serial Reaction Time task

The SRT task used in this study was the version of a paradigm introduced by Nissen and Bullemer (1987). In a typical SRT task subjects are presented with a stimulus displayed in four spatially arranged positions. The participants are instructed to respond as quickly as possible to the appearance of the stimulus by pressing the key corresponding to its spatial position. Unbeknownst to the subjects, the stimulus is presented in repeated sequence. Learning is measured as a shortening of the reaction times (RTs) with practice of the sequence and a lengthening when the presentation of the stimulus is switched to random. In the current study we employed the second-order conditional (SOC) sequence (A-B-A-D-B-C-D-A-C-B-D-C)<sup>1</sup> from the study of Smith and McDowall (2004). In this kind of sequence each spatial position is equally probable and only two successive positions can be a base for predicting the next one. The procedure of the SRT task used was very similar to that described by Smith and McDowall (2004) was used. The stimulus was an asterisk that appeared in one of four quadrants allocated on the computer screen. Each participant was instructed to press the key corresponding to the position of the stimulus as quickly as possible. After a subject pressed the appropriate key, the stimulus disappeared and was presented in the next position from the sequence. The interval between the subject's response and the next stimulus presentation was 500 ms. The procedure of this task consisted of 60 trial blocks. Each PD patient participated in three sessions of SRT task. The first session (training) consisted of six blocks. The second performed after an hour (test 1 h), and the third session completed on the next day (test 24 h) were composed of four blocks each. In the first and in the last block of each session the stimulus was presented in a random manner (however it never appeared in the same position on two consecutive trials). In the middle blocks (four in the training session; two in the tests sessions), the stimulus appeared according to the sequence order. Each nonrandom block consisted of 5 repetition of the SOC sequence.

### Serial Reaction Time task – explicit measures

We provided very cautious measurement of sequence explicit knowledge as Smith and McDowall (2004) did: multiple choice question, two recognition measures and recall task. Nevertheless, we applied a cued recall task instead of the free generation procedure used by Smith and McDowall (2004). The cued recall task consisted of the prediction of the next position of the stimulus appearance and is more relevant to the information acquired in SRT task.

After completing the last SRT session, participants were given a questionnaire and were asked to choose one of five statements concerning the task: (a) I think that the asterisk was appearing in a random manner and I did not notice any kind of sequence; (b) I suppose that the asterisk was appearing according to a sequence but it is also possible that it was appearing in random manner; (c) I am certain that the asterisk was appearing in a sequence, but I am not sure what that sequence was; (d) I am certain that the asterisk was appearing in a sequence and I think I know what the sequence was; (e) I am sure that the asterisk was appearing according to a sequence and I know exactly what the sequence was (the questionnaire as well as all the instructions were in Polish). Statements were scored from 1 to 5 points, with higher numbers representing increasing explicit knowledge of the sequence.

After the questionnaire all participants were informed about the presence of the repeating sequence in the SRT task. In the next stage, subjects performed two recognition tests: whole sequence recognition and fragment recognition. The target and distractor sequences were presented on a computer screen. In the case of the full recognition task, one target, the SOC sequence and the 5 distraction patterns, were presented. The fragment recognition test consisted of 4 SOC sequence fragments and 4 distractor sequences, each 4 elements long. In both recognition tasks, subjects were supposed to watch the sequence carefully and subsequently assess the probability that the pattern just seen was the sequence from the SRT task. The participants were asked to rank their subjective certainty on a scale ranging from 0 to 100, presented in a graphic form. A choice of 100 indicated absolute certainty that the sequence just presented was the target sequence from the SRT task. A rating of 0 signified a strong conviction that the sequence just seen

<sup>1</sup> The four letters denote four spatial positions of the stimulus presentation

was not the repeated pattern from the SRT task. A selection of 50 expressed complete uncertainty and no ability to decide in either direction.

The last explicit measure conducted was a cued recall task. The stimulus was presented according to the SOC sequence, and participants were asked to predict the next position of the stimulus and press the corresponding key. When the answer was made, the asterisk disappeared and occurred in the next position from the sequence (independent of the answer given by the participant, correct or not). Thus the previous position of the stimulus was always displayed and the subject had to predict the consecutive one. Three repetitions of the sequence were performed during the recall task.

### **Mirror Reading task**

The task consisted of reading words inverted along horizontal axis (upside down). Words used as stimuli were 360 common Polish nouns, 5 or 6 letters long. The subjects were asked to read aloud the word presented on the screen as quickly as possible. When the answer was correct the experimentator pressed a key, and the time measured from the moment of the display was recorded. After 500 ms the next word was presented on the screen. If the subject was unable to read the word or made a mistake, the answer was recorded as error. The task was conducted in three sessions (training, testing after one hour, and again on the next day). Each session consisted of 120 words except the training, which was preceded with 10 word instructions. Since there were three independent groups of words, the order of their administration was counter-balanced, and the order of presentation of words within a session was random and different for each participant.

### **Declarative Memory tasks – word pairs and pairs of Japanese ideograms**

In this task participants were supposed to learn six pairs of Polish words (training), and memory of the learned material was checked 3 times: the first immediately after the training (test 0), the second after about an hour (test 1 h), and the third on the next day (test 24 h).

The training material consisted in three words (A1, A2, A3) forming pairs with two sets of three words

(B1, B2, B3 and C1, C2, C3). The procedure was as follows: on the top of the screen one word was displayed (A1 or A2 or A3), after 1 000 ms three words at the bottom of the screen were also presented (B1 and B2 and B3 or C1 and C2 and C3). The subject had to choose one of the bottom words and point it with the computer mouse. When the choice was made the feedback (“correct” or “wrong”) was displayed. Training was composed of three parts: initial practice of the first set of pairs (A1 and B1, A2 and B2, A3 and B3), thereafter acquisition of the second group of three pairs (A1 and C1, A2 and C2, A3 and C3) and the last was practice of all six pairs together. Each part of the training was performed until the subject achieved 75% of correct answers (calculated independently for each pair). When the training was accomplished the test was performed. The procedure of the test was similar to training, with the exception that no feedback after the subject’s answer was provided. The test consisted of 24 trials, and each word pair checked 4 times.

The procedure (the training of six pairs and three memory tests) of the nonverbal version of this task was exactly the same; only six Japanese ideograms were used instead of words.

## **RESULTS**

### **Serial Reaction Time task – explicit measures**

The SRT task was chosen as an implicit memory measure, however the procedure of the tasks does not guarantee, that the explicit learning does not occur. Results of explicit measures do not concern main hypothesis, however are crucial part of SRT paradigm if it is employed as an implicit measure.

For analysis of implicit sequence learning in the SRT task, the results of subjects who acquired explicit knowledge about the sequence had to be excluded. Thus we used 4 methods estimating this knowledge: questionnaire, two recognition measures (fragment and full sequence) and cued recall task. Table II presents means and standard deviations for explicit measures of PD patients and control subjects divided into “implicit” and “explicit” groups. For each task measuring awareness a specific cut-off point was employed, scoring above which qualified the person to group supposed to have some degree of explicit knowledge about the sequence.

In the questionnaire, the choice of the response scored as 3 (“I am certain that the asterisk was appearing in a sequence, but I am not sure what that sequence was”) was interpreted as a manifestation of possible awareness of the sequence. There were 5 PD patients and 3 control subjects who chose this answer and none of the participants in the study chose the higher scoring statements.

In the recognition score, the criterion of explicit knowledge was fixed as greater than 40. In the whole sequence recognition 3 PD patients and 1 control subject reached the criterion. In the case of fragment recognition only one control subject performed above the criterion.

In the recall of the sequence, a score 0.45 (45% of correct predictions) was set as a cutoff point indicating explicit knowledge. Eight PD patients and 6 control

subjects scored above 0.45. Further analysis of explicit knowledge of the sequence revealed that only 2 patients and 1 control subject scored above the explicit criterion in more than a single measure, in all three cases of questionnaire and recall of the sequence. Only the results of those 3 participants were excluded from implicit learning analysis. In the case of other subjects, when only one measure indicated sequence awareness, the premises seemed insufficient to make statements about their explicit knowledge of the sequence.

### Serial Reaction Time task – implicit measures

Based on the results of the explicit measures 2 PD patients and 1 control subject were not included in the implicit learning analysis. All the statistics were conducted for 20 control subjects and 16 patients (1 patient was not able to perform the task because of intensification of motor symptoms). In the SRT task the primary dependent measure was the median reaction time for responses on 12 consecutive trials. The mean reaction times (RTs) for each block were derived from 5 medians (each block of SRT task consisted in 60 trials). Figure 1 represents the mean for each of six training blocks in the PD and control groups.

To examine the general performance of both groups in SRT training, an ANOVA with repeated measures was carried out with Group (PD and control) as the

Table II

Explicit knowledge of the sequence on the Serial Reaction Time task				
Measure	PD patients ( <i>n</i> =18)		Control group ( <i>n</i> =21)	
	implicit	explicit	implicit	explicit
Questionnaire*				
<i>n</i>	13	5	18	3
Mean	1.53	3	1.78	3
SD	0.51	-	0.43	-
Recognition score – whole of the sequence				
<i>n</i>	15	3	20	1
Mean	7.86	42.66	0.6	44
SD	20.81	5.03	17.52	-
Recognition score – fragments of the sequence				
<i>n</i>	18	-	20	1
Mean	1.11	-	-2.08	50
SD	12.22	-	25.10	-
Sequence recall score (initial 24 trials)				
<i>n</i>	10	8	15	6
Mean	0.35	0.53	0.34	0.49
SD	0.06	0.05	0.07	0.03

\*The table shows mean responses for questionnaire statements concerning the pattern of the asterisk occurrence in SRT task. Statements were scored from 1 to 5 points, with higher numbers indicating increasing explicit knowledge of the sequence.

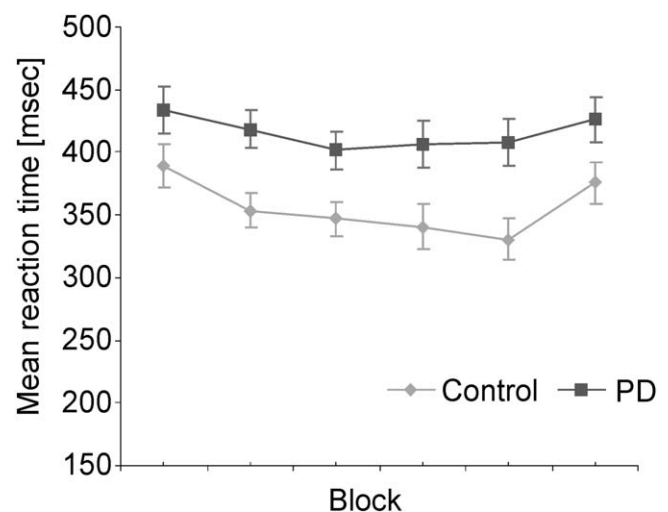


Fig. 1. Serial Reaction Time task performance on the training session: Parkinson's disease (PD) group and control subjects group. Error bars represent standard error of the mean. Stimulus in blocks 2–4 were presented in repeating sequence, in blocks 1 and 6 it was presented in a random way.



between-subjects factor and Block (4 successive sequence blocks of SRT training) as the within-subjects factor. This analysis revealed the main effect for Group:  $F_{1,34}=6.12$ ;  $P=0.018$ . It can be therefore stated, that PD patients' RTs (Mean = 404 ms) were elevated compared to the control group (Mean = 345 ms). The effect of Block factor also reached significance ( $F_{3,102}=4.01$ ;  $P<0.01$ ) indicating changes in RTs across consecutive blocks of trials. Importantly, there was no significant Group  $\times$  Block interaction:  $F_{3,102}=1.67$ ;  $P=0.179$ , pointing out to similar trends of RTs shortening in both groups (apart from general slowness of PD patients).

In order to assess sequence-specific learning, analysis for RTs in the random block 6 and in the preceding sequence block 5 was performed. An ANOVA with repeated measures was conducted with Group (PD and control) as the between-subjects factor and Sequence (block 5 – with sequence and block 6 – random) as within-subject factor. As expected the effect for Group factor was significant:  $F_{1,34}=4.96$ ,  $P=0.033$ , which confirms generally longer RTs of PD patients. The significant main effect for the Sequence factor ( $F_{1,34}=4.77$ ,  $P<0.001$ ) indicated an impact on RTs from the manner in which the stimulus was presented. Importantly, the Group  $\times$  Sequence interaction reached significance:  $F_{1,34}=6.27$ ,  $P=0.017$ ; verifying the difference between PD and control groups in the cost in RTs, when switching from sequence to random block. On average, the PD patients had RTs in the random block compared to the sequence block longer by 20 ms. In the control group this differences amounted to 46 ms.

To attenuate the impact of general slowness on observed RTs and more precisely to assess sequence-specific effects, the measure of learning proportional to baseline RT (from Smith and McDowall 2004) was employed. This sequence-specific learning score was calculated as follows: block 5 (sequence score) was subtracted from block 6 (random) and divided by the sum of them. The one-way ANOVA (with Group factor: PD and control) performed on this score approached significance:  $F_{1,34}=7.17$ ,  $P=0.01$ . This analysis confirmed a lesser degree of sequence-specific learning in SRT training exhibited by PD patients compared to the control group.

In the case of SRT test sessions, in order to minimize the additional learning effects and assess mainly the retention of the skill, only four blocks were per-

formed. ANOVA with repeated measures was conducted on sequence-specific learning scores calculated from the last block (with random stimulus presentation) and the second to the last (with sequence) in SRT training, test 1 h and test 24 h. This analysis revealed the main effect for Group factor:  $F_{2,34}=9.44$ ,  $P=0.004$ . The SRT session factor did not approach significance ( $F_{2,68}=0.35$ ,  $P=0.76$ ), nor did the Group  $\times$  SRT session interaction:  $F_{2,68}=0.57$ ;  $P=0.56$ . Those results permitted a conclusion about retention of the acquired skill, but no learning benefits in test sessions of SRT task in both groups.

### Mirror Reading task

The MR task was performed by 19 PD patients and 21 control subjects, however the results of 3 patients and 3 control subjects were excluded from analysis of reading times, because of the high error scores (more than 10% of failure responses). Figure 2 presents the mean reading times in successive sessions of the MR task. Performance on the MR task was submitted to ANOVA with repeated measures with Group (PD and control) as a between-subject factor and Session (training, test 1 h and test 24 h) as within-subject factor. Results showed the main effect for the Session

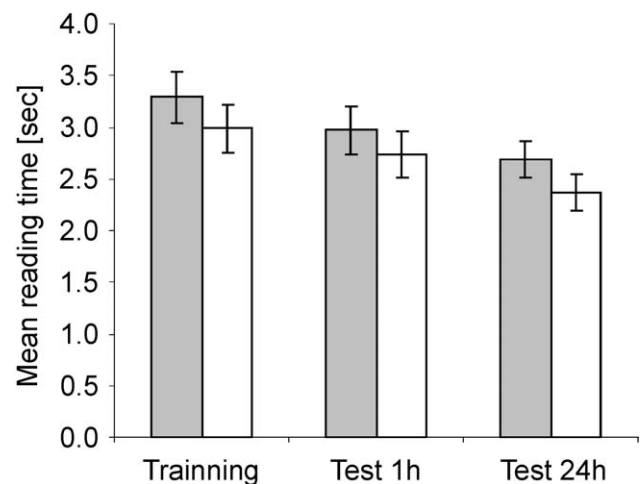


Fig. 2. Average reading times in successive sessions of Mirror Reading Task. Results of control group ( $n=18$ ) are represented in grey and PD patients – in white ( $n=16$ ). PD patients were a little bit slower than the subjects from control group but this difference was not significant  $F_{1,32}=0.05$ ;  $P=0.82$ . Both groups were improving their performance across MR sessions  $F_{2,64}=23.69$ ;  $P<0.00$ . Vertical bars indicate standard error of the mean.

factor ( $F_{2,64}=23.69$ ,  $P<0.01$ ), indicating significant overall shortening in reading times of inverted words. Even though PD patients read slower than control subjects, the effect for the Group factor did not reach significance ( $F_{1,32}=0.05$ ;  $P=0.82$ ), what means no divergence between both groups' general performance (mean reading time across the entire task). The Group  $\times$  Session interaction was also not significant:  $F_{2,64}=0.25$ ;  $P=0.78$ . This result clearly shows that there were no differences between groups in both the rate and the extent of learning of reading mirror words.

### Association of implicit tasks results with the progression of the disease

An ANOVA with repeated measures was conducted in order to assess, if the MR consecutive sessions results differed in the control subjects and groups of patients at various phases of the disease (according to the Hoehn and Yahr scale). Because only two patients in the third phase of the disease participated in the study, the second and the third phase patients were merged into one group for this analysis. No patients were excluded from this analysis. No significant differences were revealed between groups (control sub-

jects, patients from Stage 1 and merged patients from Stage 2 and 3).

In the case of the SRT results analysis in relation to the progression of the disease, subjects were also divided into three groups: control participants, patients from Stage 1 and merged patients from Stage 2 and 3. A one-way ANOVA performed for these three groups revealed a significant effect for group factor ( $F_{2,33}=4.5$ ,  $P<0.05$ ) indicating that those groups were different in the range of sequence learning. *Post-hoc* Tukey Test for different N result indicated significant difference only between merged Stage 2 and 3 PD patients group and the control group ( $P<0.05$ ) (Fig. 3).

### Executive functions and their relation to implicit learning

The results of the WCST revealed significant differences in performance between PD patients and control subjects. The results of the comparison of both groups are shown in Table III. PD patients were making significantly more errors, more perseverative answers and perseverative errors than the control group. They were also accomplishing fewer sorting categories than control subjects and were making fewer conceptual-level responses.

The correlational analysis between the sequence specific learning measure from SRT training, test 1 h, test 24 h and WCST scores yielded no significance, thus no relation between measures of executive dysfunction and implicit sequence learning level was found.

In the case of the MR results, the correlational analysis revealed (performed for all participants except those with more than 10% of failure response in MR task,  $n=34$ ) significant relationships between three WCST scores namely: number of errors, perseverative answers and perseverative errors. This pattern recurred pattern for all MR sessions. Significant Spearman  $r$  coefficients for MR results and WCST scores are presented in Table IV.

For further examination of the relationship between WCST and MR results, PD patients were divided by taking into account 5 measures of WCST (perseverative answers, perseverative errors, total errors, number of categories completed and percent of conceptual-level answers) into group with no executive dysfunction (PD-nonEXF;  $n=8$ ) and with executive

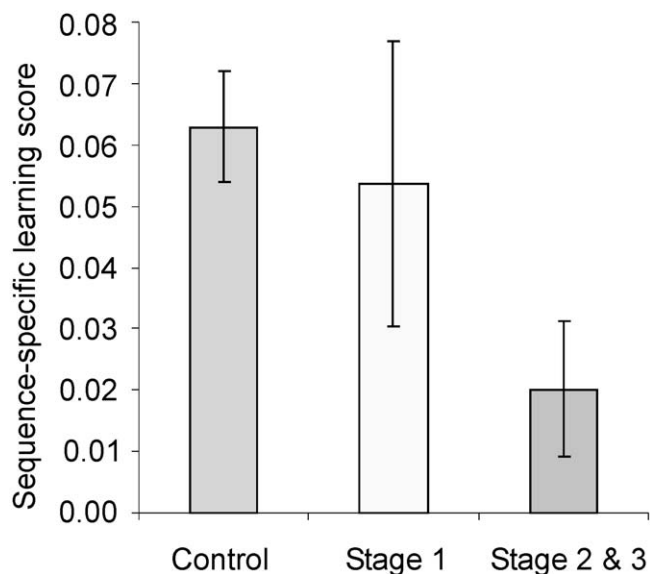


Fig. 3. Mean sequence-specific learning score in SRT training in control group and in PD patients divided into groups according to Hoehn and Yahr scale (control:  $n=20$ ; PD stage 1 H and Y:  $n=3$ ; PD stage 2 and 3 H and Y:  $n=13$ ). Vertical bars indicate standard error of the mean.

Table III

WCST results for Parkinson’s disease patients (PD) and control subjects						
Variable	PD		Control		<i>t</i> (df=38)	<i>P</i>
	Mean	SD	Mean	SD		
Percent of conceptual-level response	53.08	16.60	67.54	15.20	2.88	0.007
	Median		Median		<i>Z</i>	<i>P</i>
Total errors	47		16		−2.78	0.005
Perseverative answers	28		9		−2.66	0.008
Perseverative errors	25		9		−2.76	0.006
Number of categories correctly sorted	5.0		6.0		1.99	0.046

dysfunction (PD-EXF;  $n=8$ ) and subsequently comparing these with control subjects in MR performance. An ANOVA with repeated measures (with consecutive sessions of MR as intrafactor) revealed no significant differences between the control group, PD-nonEXF and PD-EXF groups ( $F_{2,31}=0.27$ ,  $P=0.76$ ) and no interaction between the group and session factors ( $F_{4,62}=0.36$ ,  $P=0.82$ ).

### Declarative Memory tasks

Due to the fatigue of participants and the limited time of examination, the data from declarative memory tasks are not complete. In addition, the data of two

subjects (pairs of words task) were lost as a result of technical difficulties.

### Declarative Memory tasks – training

Declarative tasks used in the present study were constructed in an attempt to measure retrieval apart from acquisition. In our method subjects trained until they reached the criterion of 3 correct answers in 4 on the same trials. This arbitrary criterion was set to ensure that all subjects had learned the material to the same extent independently from efficacy and speed of learning. This aim was achieved in the training of the word pairs task: the PD and control groups gave similar numbers of correct answers in the last session of the training:  $Z=-1.06$ ,  $P=0.28$ . Furthermore both groups did not differ in the efficacy of learning measured as the number of trials needed to accomplish training (PD patients:  $M = 181$   $SD = 106$ ; control group:  $M = 138$   $SD = 83$ ). However in the training of Japanese ideograms the conception of the training was not fully met even though all participants achieved the same criterion in training (no less than 75% correct answers), the PD patients finished learning with significantly fewer correct answers:  $Z=-2.26$ ,  $P=0.02$ . Interestingly, when the total number of trials to complete the training of Japanese ideograms was compared, there were no significant differences between groups:  $t_{22}=0.192$ ,  $P=0.84$  (PD patients:  $M = 179$ ,  $SD = 68$ ; control group:  $M = 173$ ,  $SD = 89$ ). The

Table IV

Spearman <i>r</i> correlation coefficient between WCST score and Mirror Reading results ( $n=34$ )			
WCST measures	Mirror Reading Training	Mirror Reading Test 1 h	Mirror Reading Test 24 h
Total errors	0.37*	0.43*	0.41*
Perseverative answers	0.38*	0.40*	0.41*
Perseverative errors	0.34*	0.36*	0.37*

\*  $P<0.05$



Table V

Pairs of words memory results of PD patients and control group (Test 0, Test 1 h and Test 24 h)								
	PD patients ( <i>n</i> =18) Median	lower quartile	upper quartile	Control group ( <i>n</i> =17) Median	lower quartile	upper quartile	<i>Z</i>	<i>P</i>
Test 0	23.0	21.0	24.0	24.0	23.0	24.0	−1.90	0.058
Test 1 h	22.0	20.0	24.0	23.0	21.0	24.0	−1.65	0.099
Test 24 h	20.5	16.0	23.0	23.0	19.0	24.0	−1.35	0.190

difference in the extent to which PD patients and control group learned the pairs of Japanese ideograms was an unexpected artifact of the method and had to be considered in the analysis of memory test.

#### Declarative Memory tasks – memory tests

Three test sessions followed training: the first was administered immediately after completion of training, the second after an hour, and the third on the next day. The results of the declarative memory assessment for PD patients and control subjects are shown in Table V (word pairs task), and in Table VI (Japanese ideograms). Mann-Whitney *U*-test yielded no significant differences between groups in the number of correct answers on all three tests of memory of word pairs. However, in the task measuring memory of Japanese ideograms, PD patients scored significantly worse than the control group. Mann-Whitney *U*-test revealed that in Test 0 and Test 24 h, the PD patients gave significantly fewer correct answers.

The obtained results indicate that PD patients and control subjects displayed similar level of learning and preservation in time of verbal material measured in the word pairs task. On the other hand PD patients seem to

have some deficits in nonverbal information retention (pairs of Japanese ideograms task). Nevertheless, it has to be stressed that nonverbal declarative memory data were collected only from 11 patients and 13 control subjects, while word pairs data were collected from 18 PD patients and 17 control subjects, thus the outcome of these two tasks is not exactly comparable.

Since PD patients scored worse than control subjects on Test 0 and test 24 h in Japanese ideograms task, and they performed to a less extent during training, we wanted to check whether those events were somehow connected. Accordingly, a correlational analysis was performed for the number of correct answers in the last training session and for the test results (Test 0, Test 1 h and Test 24 h). Spearman *r* correlation coefficients did not reach significance level in any case, indicating that the end result of training was not a sensitive predictor of the memory performance.

#### Executive functions and their relation to explicit learning

The Spearman Rank Order Correlation between declarative tasks results and WCST scores was employed in order to find out if the executive functions

Table VI

Pairs of Japanese ideograms memory results of PD patients and control group (Test 0, Test 1 h and Test 24 h)								
	PD patients ( <i>n</i> =11) Median	lower quartile	upper quartile	Control group ( <i>n</i> =13) Median	lower quartile	upper quartile	<i>Z</i>	<i>P</i>
Test 0	23.0	20.0	24.0	24.0	24.0	24.0	−2.374	0.018
Test 1 h	23.0	20.0	24.0	24.0	23.0	24.0	−1.243	0.214
Test 24 h	20.0	16.0	23.0	24.0	23.0	24.0	−2.533	0.011

level was associated with explicit memory. Significant correlations were revealed for results in Test 0 of word pairs task and three WCST scores: errors ( $R_{35}=-0.34$ ,  $P=0.046$ ), perseverative answers ( $R_{35}=-0.45$ ,  $P=0.007$ ) and perseverative errors ( $R_{35}=-0.40$ ,  $P=0.017$ ). Other declarative memory measures were not found to be associated with WCST performance.

### Lateralization of motor symptoms onset and memory tests results

MR tasks performance (in training, test 1 h and test 24 h) was compared among three groups: control subjects, PD patients with right side onset of motor symptoms and patients with left side onset of motor symptoms. An ANOVA with repeated measures revealed no significant effects for group factor ( $F_{2,31}=0.26$ ,  $P=0.76$ ) and for the interaction factor of group and repeated measures ( $F_{4,62}=1.44$ ,  $P=0.22$ ). Thus, it can be stated that the level of performance of the MR task in both groups of PD patients was similar to that displayed by control group.

In the case of SRT task, an ANOVA with repeated measures on sequence-specific learning scores reached the significance for the interfactor of Group:  $F_{2,33}=5.06$ ,  $P=0.01$ . Nevertheless, *post-hoc* tests revealed that only the control group differed from both left and right side body onset patients. The two groups of patients did not differ significantly.

Regarding the declarative words pairs task no significant differences were revealed when three groups: left side onset patients, right side onset patient and control group were compared (Kruskal-Wallis An ANOVA by rank for Training: Kruskal-Wallis for Test 0:  $H=3.69$ ,  $P=0.15$ ; for Test 1 h:  $H=2.88$ ,  $P=0.23$  and for Test 24 h:  $H=2.2$ ,  $P=0.33$ ). Furthermore, the comparison (Mann-Whitney *U* Test) between the left and right side patients as well as each of these groups with the control did not yield any significant differences.

Another situation came out in the pairs of Japanese ideograms task: Kruskal-Wallis ANOVA by rank revealed significant differences between control and both groups of patients in Test 0 ( $H=6.05$ ,  $P=0.04$  and Test 24 h ( $H=10.86$ ,  $P<0.01$ ). A Mann-Whitney *U* test carried out for left side body onset patients and the control group turned out to be significant for results in Test 0 ( $Z=2.32$ ,  $P=0.01$ ) and Test 24 h ( $Z=3.11$ ,  $P<0.01$ ). In the case of right side body onset patients no significant differences in comparison with the con-

trol group was found. The difference between both patients groups turned out to be significant in Test 24 h:  $Z=2.18$ ,  $P=0.024$ .

## DISCUSSION

### Nondeclarative memory results

The main result of the present study is that the PD patients, as compared with control subjects, displayed lower levels of acquisition in the case of procedural task (SRT) and decreased retrieval in case of declarative memory task (pairs of Japanese ideograms). Notably, both tasks were of nonverbal character, whereas no deficits were noted for the verbal tasks: explicit words pairs task and implicit MR task.

In the current study we have shown PD patients' deficit in implicit sequence learning and this result is in agreement with previous findings (Jackson et al. 1995, Westwater et al. 1998, Vakil et al. 2000, Smith and McDowall 2004). However, our result is not fully congruent with some other studies which revealed only minor deficits (Sommer et al. 1999, Werheid et al. 2003b) or even completely intact SRT performance in PD patients (Smith et al. 2001). Nevertheless, in some of the studies, which did not report SRT deficits, explicit knowledge was assessed only by a free recall method (Sommer et al. 1999, Smith et al. 2001, Werheid et al. 2003b) that could not exclude all participants with a high level of awareness of the sequence. In order to address this problem in the present study, the level of explicit knowledge was assessed by cued recall and two recognition measures, thus excluding of participants with explicit knowledge of the sequence, which could be more accurate and enable detection of implicit learning deficits.

Another factor that should be considered in the analysis of SRT deficit is the clinical characteristic of PD patients who participated at the present study. *Post-hoc* tests revealed that only patients at the more advanced stages of the illness (namely 2<sup>nd</sup> and 3<sup>rd</sup> stage) differed from the control subjects' results. Hence, we assume that impairment in sequence learning appears when motor symptoms are present bilaterally (Stage 2). Until now, the issue of relationship between progression of the disease and SRT performance was not thoroughly investigated. However, the study of Deroost and coworkers (2006) that examined a homogenous group of PD patients in the 3<sup>rd</sup> stage of the disease revealed

SRT impairments. Our results seem to indicate that this impairment emerge even at the earlier stage of the disease.

Our SRT data are also congruent with neuroimaging studies of healthy subjects, which repeatedly described striatum (and its cortical projections) involvement in implicit sequence learning (see, e.g., Willingham et al. 2002, Destrebecqz et al. 2005, Reiss et al. 2005, Seidler et al. 2005). Furthermore, a fMRI study of PD patients' SRT performance (Werheid et al. 2003a) did not find right putamen activation in PD patients group (during sequence blocks), which was present in healthy control subjects. It is possible that our behavioral data (and others from previous studies) reflect the changed function of the striatum observed in the neuroimaging experiment.

The second task used in our study to examine PD patients' implicit memory was MR, which revealed no significant difference between patients and control group. This finding is opposite to that of most MR studies in PD, which usually described patients' impairment (Roncacci et al. 1996, Yamadori et al. 1996, Koenig et al. 1999, Sarazin et al. 2002). In our study we used horizontal transformation of words, contrary to most of the aforementioned studies that employed words inverted along vertical axis. Vertical transformation obliges "right to left visual scanning", which was shown to be specifically impaired in PD (Koenig et al. 1999). On the other hand, the type of transformation seems not to determine the presence of the deficit; since Harrington and coworkers (1990) did not find PD patient' impairment in MR, even though they employed vertical transformation.

In the study of Sarazin and coauthors (2002) PD patients as a whole did not exhibit MR task deficit, however those with dysexecutive syndrome were severely impaired. Furthermore, the relationship between WCST defined executive dysfunction and impaired learning in MR was more evident in the second experiment, when a more demanding version of the task was used: each word included ambiguous letters: b, d, p, q, u and n. The MR task from the present study was probably less difficult (fewer ambiguous letters and no requirement of right to left visual processing) and probably less sensitive in the detection of MR learning deficits. In reappraising our version of the MR task, other characteristics (such as: number of words used, their length and frequency in everyday language), could also be pointed out as possibly signifi-

cant and differentiating from the material used in the previous studies. It seems reasonable to examine other versions of mirror reading, to conclude further about PD patients' acquisition of the MR skill.

Another factor that may account for the results obtained in the MR task is the stage of disease of PD patients who participated in the study. In the study of Poldrack and Gabrieli (2001) MR learning was shown to be associated with the activation in the tail of the caudate nucleus, which participates in a visual loop (*via* reciprocal connection with temporal cortex) and its dysfunction emerges in later stages of PD (the putamen is affected first) (Morrish et al. 1996). Most of the PD subjects who performed MR task in present study were in stage 1 ( $n=4$ ) or stage 2 ( $n=13$ ). It is conceivable that deficits in acquisition of MR skill are more pronounced in further progression of the disease (e.g. in 3<sup>rd</sup> Stage) especially when the procedure of the task used is not very demanding.

### Declarative memory results

Together with implicit learning, examination of declarative memory assessment was conducted. Generally, in the training phase, PD patients did not exhibit significant differences comparing to the control group indicating normal declarative learning. Contrary to the training, the declarative memory tests disclosed differences between PD patients and control group. In the case of the nonverbal version of the task, PD patients exhibited significantly lower scores in immediate and the 24 h memory tests. The lack of difference in test after 1 h does not rule out the general conclusion about worse retention capacity of PD patients, which emerged in nonverbal version of the task.

In the case of the word pairs task, it is noticeable that PD patients scored lower than control subjects in all three memory tests however these difference only approached statistical significance. Whittington and colleagues (2000) point out that many studies concerning recognition memory in PD have too low statistical power (due to the limited number of PD participants) to detect small or medium size effects. This may be the case in our declarative memory results, which were obtained from fewer groups, therefore we can suppose that a verbal memory deficit was present, however in a much lesser degree than in the case of nonverbal material. On the other hand verbal and visual memory function may be differentially affected in some

instance. Singh and Behari (2006) revealed PD patients' separate visual memory deterioration (with relatively spared verbal memory) that was associated with initiation of levodopa therapy.

Declarative assessment employed in the current study is not a standard type, but the procedure of memory tests is more comparable to recognition and cued recall measures than those addressing free recall. Some studies reported PD patients' impairments restricted to free recall measures and accompanied by normal levels of recognition (Flowers et al. 1984, Breen 1993, Ivory et al. 1999). Our results support findings that PD patients are impaired in recognition measures too (Owen et al. 1993, Stebbins et al. 1999, Davidson et al. 2006, Whittington et al. 2006).

### WCST correlations

The next important issue is verification of the apparent correlation between memory results and WCST scores. Such associations may reflect prefrontal cortex projection to caudate nucleus (executive loop) involvement in processing a particular memory task (Seeger 2006). In the case of the SRT task neuroimaging data revealed participation of the caudate nucleus as well as prefrontal and posterior cortex in implicit sequence learning (Rauch et al. 1997, Peigneux et al. 2000, Whilingham et al. 2007). Nevertheless in our study no significant correlation between the SRT results and WCST scores was found. This result is in agreement with other studies (Smith and McDowall 2004, 2006a) but in opposition to findings of Jackson and others (1995) that PD patients with executive dysfunction were more severely impaired in SRT performance, than those with normal WCST scores. There are also several findings indicating that tests measuring working memory capacity results are related to SRT performance (Howard and Howard 1997, Schwartz et al. 2003, Smith and McDowall 2006a). It is proposed that explicit and implicit memory systems interact with each other during information processing (Poldrack and Rodriguez 2004, Destrebecqz et al. 2005) and some of the data suggest a role of the prefrontal cortex in mediating this interaction (Poldrack and Rodriguez 2004). This suggestion could be the explanation of our SRT data, since we excluded all participants with emerging explicit knowledge about the sequence. In consequence we also did not observe the correlation between SRT and executive function level measured

by WCST. Such a relationship could emerge during switching between implicit and explicit processing.

Contrary to SRT results, the MR performance turned out to be significantly correlated with some WCST scores: namely perseverative answers, perseverative errors and total errors. As was mentioned before, Sarazin and colleagues (2002) reported the relationship between mirror reading performance and the WCST score: the deficit in the acquisition of the skill was found only in the subgroup with decreased executive functions level. The correlation found in the present study is in partial parallel with findings of Sarazin and coworkers (2002). However, subsequent analysis did not revealed significant difference in MR performance between those PD subjects who scored higher and those who scored lower in WCST test. One explanation for this discrepancy is that participants of our study could be less impaired in the area of executive functions than those examined by Sarazin and others (2002). However, it is hard to conclude whether our PD subjects displayed executive dysfunction to a smaller degree, because in the study of Sarazin and colleagues (2002) a less complicated version of WCST (Nelson 1976) was employed. The other explanation for no strong evidence of the linkage between MR results and WCST scores is the possibly lower sensitivity of our version of MR tasks, which is discussed above.

In the case of declarative memory tests, only the results of Test 0 of words pairs task correlated with WCST measures. This single correlation is quite difficult to interpret. A partial explanation is that in the case of initial measurement of verbal memory (Test 0) revealed a difference closest to statistical significance level. Nevertheless, it does not enlighten, why such a correlation did not appear for Japanese ideograms results. A speculative explanation for this pattern is that in performance of verbal tasks, executive functions were more engaged. Interestingly, corresponding findings emerged, as discussed above, in the implicit tasks: the correlation with WCST scores was present only for MR task, which however did not distinguish PD patients from the control group.

In summary we would like to point out the double dissociation found in our study: implicit deficit was restricted to the nonverbal SRT task, at the same time correlation between WCST scores was noticeable only in the case of the MR task consisting in processing of verbal information. A similar pattern is noticeable for declarative tasks: the verbal version of the task



revealed some association with WCST results, however the deficit in task results was present only for nonverbal assessment. This pattern may indicate that executive functions are more engaged in processing verbal tasks (at least those used in the present study) than those with nonverbal material. This involvement emerged as a correlation (for the entire group of subjects, control and patients), nevertheless the influence was not strong enough to differentiate levels of performance across groups.

### Double dissociation – trying to explain

One possible explanation of nonverbal deficits obtained in present study could be the predominance of PD subjects with left side body onset of motor symptoms (twelve from all nineteen, although in particular tasks this ratio slightly differed with left side body onset patients always in a majority). Left-side dysfunction points to primary degeneration of right hemisphere, which is known from the prevailing role in nonverbal functions (Lezak 1995). In the case of the SRT task several neuroimaging studies showed right lateralized activation of striatum (Whilingham et al. 2002, Werheid et al. 2003a) however Rauch and coauthors (1997) point to “interindividual variability with respect to the laterality and striatal subterritories involved”. We compared right and left body side onset patients in nondeclarative SRT and MR tasks, and we did not found any significant differences in their performance. Hence we did not find evidence that different results in nonverbal and verbal nondeclarative tasks were the effect of prevalence of left side onset patients with inferred right hemisphere dysfunction.

Interestingly, such a significant difference was found in case of Japanese ideograms task: left body side onset patients were worse than right body side onset patients in the test after 24 h. When we compared only left side onset PD patients’ results with control group we found significant differences in test 0 and test 24 h. Such a difference was not revealed between right side onset patients and control subjects. All these results indicate that the deficit in memory of Japanese ideograms was demonstrated solely by left side body onset patients. Then, the nonverbal declarative deficit revealed in the present study seems to be coupled to the primary dysfunction of the right hemisphere. Our results correspond to the study of Amick and coworkers (2006), who described the association of body side

motor symptoms onset in PD with asymmetrical memory dysfunction. Patients with left body side motor symptoms onset (greater right hemisphere dysfunction) were worse in visual than verbal memory tasks. The opposite pattern of performance (poorer verbal than visual memory) was displayed by right body side onset patients (inferred left hemisphere dysfunction).

### CONCLUSIONS

First of all, we found PD patients’ impairment in implicit sequence acquisition and demonstrated distinct declarative deficit in retention of pairs of the Japanese ideograms task. We found that in the case of declarative memory tasks, this asymmetry was produced by left side-body onset patients with probably greater right hemisphere dysfunction. The obtained results point to the nonverbal tasks as more sensitive in detecting memory deficits in PD patients, at least at the early-stage of the disease. Moreover our data demonstrated that nonverbal memory deficits were independent from executive dysfunction, which suggests a distinct neuronal basis for these aspects of cognitive impairment in PD.

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