DECLARATIVE AND PROCEDURAL LEARNING IN PARKINSON'S DISEASE PATIENTS HAVING TREMOR OR BRADYKINESIA AS THE PREDOMINANT SYMPTOM

Eli Vakil* and Sigal Herishanu-Naaman

(Psychology Department, Bar-Ilan University, Ramat-Gan, Israel)

ABSTRACT

The distinction between procedural and declarative memory is widely accepted in the memory literature. Converging evidence makes a strong case that the medial aspects of the temporal lobes and the diencephalon subserve the declarative memory system. However, the neuroanatomy of procedural memory is much less clear. In animal studies, damage to the basal ganglia has been found to affect procedural memory, but studies of patients suffering from degenerative diseases of the basal ganglia (e.g., Parkinson's and Huntington's disease) are less conclusive. Two groups of Parkinson's disease subtypes, with tremor (PDt) and bradykinesia (PDb) as the predominant motor symptom, were compared to controls on declarative and procedural memory tasks. The two patient groups did not differ from each other on the declarative tasks. However, in the procedural learning tasks, the PDb but not the PDt group, was significantly impaired compared to the control group. The results are discussed in terms of the differential involvement of discrete neuroanatomic loops connecting the basal ganglia and the prefrontal cortex.

Key words: procedural memory, Parkinson's disease, pre-frontal cortex

On the basis of the dissociation between preserved and affected memory tasks in amnesic patients, Cohen and Squire (1980), Cohen, Eichenbaum, Deacedo et al. (1985), and Cohen and Eichenbaum (1993) have distinguished between two types of memory – *procedural memory* and *declarative memory*. Typically, the procedural task (e.g., Tower of Hanoi puzzle - TOHP, mirror tracing or mirror reading) is presented several times, and decreased error rates or increased speed over practice reflect the extent of skill learning. Declarative memory – memory for new facts and events – is typically tested by methods of recall, recognition, or cued recall. Amnesic patients are characterized by being impaired on declarative memory tasks (Squire, 1992).

Medial temporal and diencephalic structures seem to be critical for the proper functioning of declarative memory (for review see Squire, 1992). The neuroanatomy of procedural memory is not very clear. There are reports indicating that the basal ganglia might be involved in the regulation of at least some aspects of this type of memory. Based on behavioral findings with primates, Mishkin, Malamut and Bachevalier (1984) suggested that the striatum has a major role in the acquisition of habits in primates. Support for this contention comes from results obtained from patients suffering from degenerative diseases involving the basal ganglia such as Parkinsons disease

(PD) and Huntington's disease (HD). These studies are inconclusive, even though they provide partial support for the basal ganglia hypothesis of procedural memory.

In the following review we will mostly focus on findings from PD patients, since it is questionable that HD patients represent a good model for studying the role of the basal ganglia in procedural learning (Harrington, Haaland, Yeo et al., 1990; Saint-Cyr, Taylor and Lang, 1988; Saint-Cyr and Taylor, 1992; Solivery, Brown, Jahanshahi et al., 1992).

Using procedural and declarative tasks, Saint-Cyr et al. (1988) demonstrated a double dissociation between PD and amnesic patients. PD patients performed normally in the declarative tasks but exhibited impairments in the procedural task, while amnesic patients showed the opposite pattern of results. PD patients' performance was reported to be impaired in comparison to the control group in a variety of skill learning tasks, such as complex tracking, (Frith, Bloxham and Carpenter, 1986), serial reaction time (Ferraro, Balota and Connor, 1993; Jackson, Jackson, Harrison et al., 1995), and the Tower of Toronto (Saint-Cyr et al., 1988).

However, other studies did not support the hypothesis that the basal ganglia are involved in procedural memory. Heindel, Salomon, Shults, et al. (1989) tested two groups of PD patients, one demented and the other not demented, which did not differ in terms of motor symptoms, and found that the patient's impariment on learning the pursuit-rotor task was correlated with the degree of dementia but not with the severity of motor symptoms. Harrington et al. (1990) found that PD patients were impaired on a motor (i.e., rotary pursuit) task but not on a visuoperceptual (i.e., mirror reading) task. Contrary to the findings by Saint-Cyr et al. (1988), in two other studies PD patients' performance on a Tower puzzle did not differ from normal controls (Alberoni, Della Sala, Pasetti et al., 1988; Morris, Downes, Sahakian et al., 1988).

Some of these conflicting results were resolved by Owen et al. (1992) who showed that PD performance is a function of clinical disability and precise index of performance (i.e., accuracy vs. latency). An alternative explanation for the conflicting findings in the literature is that while previously considered a homogeneous disease, PD is actually heterogeneous. The heterogeneity depends not only on the severity of the clinical symptoms but also on the predominant motor symptoms which determine the disease's course of development (Barbeau, 1986; Zetusky, Jankovic and Pirozzolo, 1985). PD patients with predominant tremor symptoms (PDt) (type *A* in Barbeau [1986] terminology) have a slower progressive clinical course compared with PD patients with predominant bradykinesia symptoms (PDb) (type *B* in Barbeau [1986] terminology). Furthermore, PDt patients are reported to be better preserved intellectually compared to PDb patients (Huber, Christy and Paulson, 1991; Huber, Paulson and Shuttleworth, 1988; Jankovic, McDermott, Carter et al., 1990; Mortimer, Pirozzolo, Hansch et al., 1982; Zetusky et al., 1985).

This study addressed the issue of whether declarative and procedural memory are differently affected in these two subtypes of PD. Since only non-demented patients in the early phase of disease were selected for the study, we anticipated that they would not significantly differ from the control group or from each

other on the declarative task. We did not have strong a priori prediction as to which group will show an advantage on procedural memory. However, since in a recent study by Leiguarda, Pramstaller, Merello et al. (1997) it was found that among PD patients, body bradykinesia was significantly related to frontal lobe-related neuropsychological tasks (e.g., TOHP), we were inclined to predict that the PDb but not the PDt patient group will be impaired on the procedural task, as compared to the control group.

Materials and Methods

Subjects

Thirty patients with Parkinson's Disease and 14 matched control subjects participated in this study. The PD patients consisted of two subgroups that were differentiated according to their most pronounced neurological signs (Barbeau, 1986; Zetusky et al., 1985). Fifteen patients with tremor as the dominant symptom (PDt), and 15 patients with bradykinesia as the dominant symptom (PDb) were identified by a senior neurologist. The PDt group consisted of 9 males and 6 females, whose ages ranged from 47 to 82 years (M = 66.87) and educational level from 7 to 17 years of schooling (M = 12.53). The PDb group consisted of 10 males and 5 females, whose ages ranged from 45 to 71 years (M = 64.20) and educational level from 8 to 19 years of schooling (M = 13.47). All patients were in the relatively early stages of the disease (Hoehn and Yahr's, 1967, stages I-III). The PDt group and the PDb group did not differ significantly (M = 2.20 and 2.33, respectively, $t(25) = .56$, $p > .05$). The number of years since onset of the disease were M = 2.97 for the PDt group and M = 4,27 for the PDb group. They did not differ significantly, $t(28) = 1.36$, $p > .05$.

All of the patients were reported to be active and alert and scored in the normal range (26-29) on the "Mini-Mental State" test (Folstein, Folstein and McHugh, 1975). They were selected from different neurology clinics in Israel. All were treated with l-DOPA and dopamine agonists. Fourteen control subjects (5 males and 9 females), matched on age and education, volunteered to participate in the study. Their ages ranged from 50 to 79 years (M = 61.43), and educational level ranged from 12 to 19 years of schooling (M = 14.36). Participants in all groups were proficient in Hebrew, had no history of mental illness, alcoholism, or drug use.

Tests and Procedure

Participants were tested individually in two session, each taking place one week apart. Two tasks were used to assess declarative memory: Visual Paired Associates (VPA) – a subtest of WMS-R (Wechsler, 1987) – and the Rey Auditory Verbal Learning Test (AVLT) (Lezak, 1983). They are standard verbal memory tests which provide measures that are parallel to those of the procedural tasks (i.e., baseline and learning rate). Two procedural memory tasks were employed as well: Tower of Hanoi Puzzle (TOHP) (Cohen et al., 1985) and Porteus' Mazes (PM) (Porteus, 1950). They were chosen because their motor load is minimal compared to other procedural tasks (e.g., serial reaction time and rotary pursuit).

Visual Paired Associates (VPA)

This test consists of a set of six different colors paired along with six nonsense shapes. Each card (10 × 14 cm) contains one pair. After each study trial, a test trial was given, in which the subject was presented with shapes only and had to select among eight alternatives the color matching each shape.

Study trials and test trials were repeated, up to a maximum of 6, if after the first 3 learning was not completed. One more matching trial was repeated half an hour after completion of the first set of trials. This task was administered in the first session.

Rey Auditory Verbal Learning Test (AVLT)

The Hebrew version of the test (Vakil and Blachstein, 1997) was administered in a standard fashion (Lezak, 1983) in the first session. Fifteen common nouns were read to the subjects for them to remember as many words as possible. Five consecutive trials (trials 1 to 5), each followed by free recall, were given in succession. In trial 6 an interference list of 15 new common nouns was presented, followed by their free recall. In trial 7, subjects were asked to recall again the first list and the same occurred 20 minutes later (trial 8). They were then asked to identify the 15 words from the first list out of 50 words presented auditorily (the list also included the 15 words of the second list and 20 new common nouns) (trial 9).

Tower of Hanoi Puzzle

The task consists of four plastic disks and three wooden pegs numbered from 1 to 3 from left to right, respectively. Initially, the disks were arranged on the left most peg (number 1) with the largest disk at the bottom and the smallest disk on the top. Participants were told that the goal was to move the disks from the left most peg (number 1) to the right most peg (number 3) in a minimum number of steps and that they had to respect the following constraints: only one disk at a time could be moved, no disk could be placed on a smaller one, and the middle peg had to be used. The optimal solution for four disks requires 15 moves. The experimenter recorded the number of moves and time required to solve the TOHP. In order to make sure that instructions were understood, a practice trial with three disks was conducted prior to the actual test with four disks. The task was administered twice in the first session, each a half an hour apart, and once in the following week. The task was repeated three times at each testing session.

Porteus Mazes

Twelve mazes of increasing difficulty were presented (Porteus, 1950). Subjects were asked to mark the pathway from the starting point to the exit with a pencil, without lifting it. They were also required not to enter a dead-end alley and to avoid crossing lines of the maze. The score was the number of mazes correctly solved. We did not use performance time and number of errors since these measures are likely affected by fine motor control, and their interpretation would have been confounded by the motor impairment of the patients. This task was administered twice, one week apart.

RESULTS

Declarative Tests

Visual Paired Associates

Table I presents the mean number of correct answers made by the three groups in the four trials of the task. Two separate analyses were conducted: the three trials as a measure of learning and the fourth trial compared with the third trial as a measure of retention over time.

Learning. Performance on the first three trials was submitted to a mixed-design ANOVA to analyze the effects of group (PDt, PDb and control) and learning trials (1 to 3). The first is a between subjects factor and the second is a within subjects factor. The learning trial effect reached significance; there was a significant overall increase in number of pairs learned from trial to trial, F (2,

TABLE I

Mean Number of Correct Answers (and Standard Deviation) by the Three Groups in the Four Trials of the VPA Task

	VPA's measures			
Group	T1	T2	T3	T4
Control (n = 14)	3.43 (1.70)	4.29 (1.77)	5.07 (1.39)	4.79 (1.72)
PDt (n = 15)	2.00 (1.31)	3.53 (1.51)	4.27 (1.71)	3.67 (1.95)
PDb (n = 15)	2.40 (1.45)	3.60 (1.88)	3.20 (2.24)	3.13 (2.03)

82) = 24.80, $p < .001$. The group effect and the Group × Learning trial interaction did not reach significance.

Retention. The groups did not significantly differ on the number of pairs correctly recognized in the third compared to the forth (i.e., delayed) trial of the task, F (2, 41) = 1.07, $p > .05$.

Rey Auditory Verbal Learning Test

Table II presents the mean number of words recalled in the eight trials of the Rey AVLT. In analogy with the VPA task, only the trials relevant to measure learning (i.e., trials 1 to 5) and retention (i.e., trials 5 and 8) were analyzed.

Learning. The number of words recalled by the three groups in the first five trials of the Rey AVLT was submitted to a mixed-design ANOVA with group and learning trials as factors. The groups significantly differed from each other on the overall number of words recalled in the first five trials, F (2, 41) = 6.30, $p < .005$. A follow-up analysis using Duncan's multiple range test indicated that the control group was significantly different (i.e., more words were recalled) in comparison to the two patient groups, PDt and PDb, which did not differ from each other. There was also a significant increase in the number of words recalled from trial to trial, F (4, 164) = 153.58, $p < .001$. The interaction between these two main effects did not reach significance, F (8, 164) = .35, $p > .05$.

Retention. The grups did not significantly differ on the number of words recalled in the fifth trial compared to the eighth (i.e., delayed) trial of the task, F (2, 41) = 1.71, $p > .05$.

TABLE II

Mean Number (and Standard Deviation) of Words Recalled in the Eight Trials of the Rey AVLT by the Three Groups

	Rey AVLT's Measures					
Group	T1	T2	T3	T4	T5	T8
Control (n = 14)	7.71 (2.76)	10.14 (2.71)	11.64 (2.74)	12.43 (2.90)	12.93 (2.34)	11.36 (3.50)
PDt (n = 15)	5.53 (1.55)	7.93 (1.58)	9.27 (2.34)	10.47 (2.90)	11.13 (1.92)	9.00 (2.65)
PDb (n = 15)	5.13 (1.85)	7.20 (2.34)	8.87 (1.89)	9.80 (2.01)	10.87 (2.62)	8.67 (2.55)

Procedural Tasks

Tower of Hanoi Puzzle

Two separate dependent measures were employed to analyze the data: The number of moves for solution and the solution time for each testing session. These scores were the median of the three repeated trials. Since patients occasionally failed to complete the test, completion time and number of moves were only calculated for completed trials.

Number of moves. Table III presents the mean number of moves required by the three groups to solve the TOHP in the three testing sessions. The results were submitted to a mixed-design ANOVA to analyze the group (PDt, PDb and control) and testing session (immediate, half an hour later, and a week later) main effects. The two main effects reached significance, but the interaction did not. The groups differed from each other significantly in the number of moves required to solve the TOHP, $F(2, 41) = 3.25$, $p < .05$. A follow-up analysis using Duncan's multiple range test indicated that the PDb group was significantly different (i.e., required more moves to solve the TOHP) from the PDt and the control groups, while the two latter did not differ from each other. Overall, there was a significant improvement from session to session, $F(2, 82) = 4.60$, $p < .02$. Notice in Table III, that the SD of scores is reduced over the testing sessins for the control and PDt groups but not for the PDb group. Such a pattern was interpreted by Saint-Cyr et al. (1988) as indication of increased stability of performance and elimination of errors in the groups with reduced SD. This observation provides additional support for the group differences found in this analysis.

TABLE III

Mean Number (and Standard Deviation) of Moves Required by the Three Groups to Solve the TOHP in the Three Testing Sessions

	Testing session		
Group	Immediate	Half hour	One week
Control (n = 14)	31.11 (10.99)	27.29 (08.92)	23.85 (07.22)
PDt (n = 15)	32.23 (12.30)	27.58 (07.77)	25.47 (10.28)
PDb (n = 15)	37.30 (15.93)	36.14 (17.41)	35.22 (15.03)

Solving time. Table IV presents the mean time, in seconds, required by the three groups to solve the TOHP, in the three testing sessions. Analysis of the same variables as above again indicates that both main effects reached significance, but the interaction between them did not. The groups differed significantly in the time needed to solve the TOHP, $F(2, 41) = 5.97$, $p < .01$. Follow-up analysis using Duncan's multiple range test indicated that while the PDb group differed significantly (i.e., required more time to solve the TOHP) from the PDt and control groups, the two latter did not differ from each other. Overall, there was a significant decrease in solving time over the three testing sessions, $F(2, 82) = 10.37$, $p < .001$. The Group $\times$ Testing session interaction did not reach significance, $F(4, 82) = .36$, $p > .05$.

TABLE IV

Mean Time, in Seconds, (and Standard Deviation) Required by the Three Groups to Solve the TOHP in the Three Testing Session

	Testing session		
Group	Immediate	Half hour	One week
Control (n = 14)	149.83 (109.77)	99.33 (069.34)	62.88 (029.41)
PDt (n = 15)	187.72 (119.53)	121.61 (098.99)	109.81 (091.42)
PDb (n = 15)	265.16 (160.99)	222.58 (171.61)	217.80 (168.92)

Porteus' Mazes

A preliminary analysis revealed that the number of mazes completed in the two sessions did not differ significantly. Therefore, the two scores were combined. The groups were significantly different in the total number of mazes completed, $F(2, 41) = 13.24$, $p < .001$. A follow-up analysis using Duncan's multiple range test showed that the PDb group solved significantly fewer mazes ($M = 16.07$) compared to the PDt group ($M = 21.43$) and the control groups ($M = 21.87$), while the two latter did not differ from each other.

Correlational Analysis

In order to asses the effect of the severity of disease on memory, Pearson product-moment correlations were calculated for the whole patient group between the Hoehn and Yahr's (1967) index and the different memory measures previously analyzed. As can be seen from Table V, the Hoehn and Yahr's index correlated significantly only with age. Age, in turn, correlated significantly with the declarative tasks but not with the procedural tasks. The two procedural tasks were highly intercorrelated and so were the two declarative tasks. Overall the correlations between the declarative and the procedural tasks were much lower than the correlations within each type of task (i.e., procedural and declarative).

TABLE V

Intercorrelations between Age, Hoehn and Yahr's Index (for the patient group only, n = 30), and the Scores of the Different Tasks (n = 44)

Measures	2	3	4	5	6	7
1. Age	.454*	–.491**	–.371*	.111	.201	–.193
2. Hoehn and Yahr's index	–	–.335	.037	–.906	.049	–.183
3. Rey AVLT (total score)		–	.522**	–.278	–.369*	.400**
4. VPA (total score)			–	–.174	–.261	.316*
5. TOHP (moves)				–	.871**	–.716**
6. TOHP (time)					–	–.747**
7. PM						–

* = $p < .05$, ** = $p < .01$. Rey AVLT (total score) = Rey Auditory Verbal Learning Test (sum of the learning trials); VPA = Visual Paired Association; TOHP = Tower of Hanoi Puzzle; PM = Porteus mazes.

DISCUSSION

The results of the present study offer a two-fold contribution: First, they confirm previous findings that basal ganglia damage affects procedural tasks,

even when they do not tax motor ability (Saint-Cyr et al., 1988). More importantly, the two subtypes of PD (i.e., PDt and PDb) differ on procedural learning. Failure to distinguish these clinically important PD subgroups may have contributed to the conflicting procedural learning results in previous researches. Further, the two patient groups do not significantly differ on the declarative memory test. The different pattern of results observed in the declarative and procedural memory tasks supports the distinction between these two types of memory. The fact that overall the correlations between the declarative and the procedural tasks were much lower than the correlations within each type of task further supports this distinction. Age correlated significantly with the declarative tasks but not with the procedural tasks (see also Vakil and Agmon-Ashkenazi, 1997).

The finding that the PDb group was consistently inferior to the PDt and control groups on the procedural tasks might be attributed to the greater impairment of their intellectual skills, as repeatedly pointed out by the literature (Huber et al., 1988; Huber et al., 1991; Jankovic et al., 1990; Mortimer et al., 1982; Zetusky et al., 1985). We believe that this interpretation is unwarranted. First, both PDt and PDb patients participating in this study were in the early stages of the disease and did not differ in terms of disease duration (i.e., Hoehn and Yahr's stages I-III). Second, only non-demented patients as determined by the "Mini-Mental State" test were included (Folstein et al., 1975). It could be argued that the "Mini-Mental State" test is not sensitive enough to subcortical dementia and that the Hoehn and Yahr's index is not an adequate measure of the motor disability. However, the fact that the two patient groups did not differ from each other on two standard memory tests (i.e., Rey AVLT and VPA) confirms that they were properly equated, at least in terms of their declarative memory. Thus, the dissociation in performance of the two patient groups between the declarative tests (equal performance) and procedural memory tasks (PDt better than PDb) is likely to be genuine.

Although the patient groups did not differ from each other on both declarative tests they were impaired in comparison to the control group on the verbal but not on the visual task. As reported above, the literature with regards to the effect of PD on declarative memory in inconsistent. It is still unclear what factors are relevant to explain the variability in the declarative memory of PD patients, but present findings indicate that they do not include the distinction between PDb and PDt.

Mortimer et al. (1982) found a relationship between the degree of bradykinesia and visuospatial deficit. This raises the possibility that the impariment observed in PDb patients in the procedural tasks is due to the visuo-spatial deficit rather than procedural learning per se. However, the fact that both patient groups differed neither from each other nor from the control group on the visual memory task (VPA) disputes this interpretation.

Overall, the findings of the present study support the basal ganglia hypothesis of procedural memory, but they suggest that not all components of the basal ganglia are equally involved. A speculative explanation of why PDb but not PDt patients demonstrated an impaired procedural learning ability is that different circuits connecting the basal ganglia with the cortex are disrupted in

these two subtypes of PD. The procedural tasks used in this study (i.e., TOHP and PM) are thought to be sensitive to frontal lobe dysfunction (Lezak, 1983). It is, therefore, reasonable to assume that in PDb patients the loops connected to the prefrontal regions are affected. This possibility is supported by Leiguarda et al's. (1997) findings showing that bradykinesia was significantly related to frontal lobe-related neurpsychological tasks, including one of those used in the present study (i.e., TOHP). While the nature of the neuropathology distinguishing bradykinesia and tremor across cortico-striatal loops remains largely unknown, there are some indications that bradykinesia is more associated than tremor to the prefrontal lobes. Alexander, DeLong and Strick (1986) identified five different loops connecting the basal ganglia with the cortex. Relevant to our discussion are the "motor", "dorsolateral prefrontal", and the "lateral orbitofrontal" loops. The motor loop mainly involves the putamen and the supplementary motor cortex. The dorsolateral prefrontal loop connects the caudate nucleus with the dorsolateral prefrontal cortex. Bernheimer, Birkmayer, Hornykiewicz et al. (1973) reported that while the severity of the tremor symptoms in PD patients was associated with homovanillic acid depletion in the pallidum, the severity of akinesia was associated with depletion of dopamine and homovanillic acid in the caudate nucleus. Based on these two pieces of evidence, it seems reasonable to suggest that the loop affected in PDb patients is that linking the caudate nucleus with the prefrontal regions.

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Eli Vakil, PhD, Psychology Department, Bar-Ilan University, Ramat-Gan 52900, Israel. E-mail: vakile@mail.biu.ac.il

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