Effects of Parkinson Disease on Two Putative Nondeclarative Learning Tasks

Probabilistic Classification and Gambling

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Objective: To assess performance on two nondeclarative (implicit) memory tasks of Parkinson disease (PD) patients without dementia in the earlier or later stages of the disease (Hoehn and Yahr Scale scores of 1–2.5 or 3–4, respectively).

Background: Different subtypes of nondeclarative memory appear to depend on different components of frontostriatal circuitry. Performance on a probabilistic classification learning (PCL) task was impaired by striatal damage (eg, in PD or Huntington disease) but not by circumscribed frontal lobe damage. On the other hand, performance on the Iowa Gambling Task (IGT) was impaired by damage to the prefrontal cortex.

Method and Results: On the PCL, the learning of the control (age- and education-matched) group (n = 19) and the early PD group (n = 16) was comparable with each other, and both groups showed better performance than the later PD group (n = 16). On the IGT, the control group learned better than both of the PD groups. The control and early PD groups were similar on measures from the Wisconsin Card Sorting Test, Stroop Test, Mini-Mental State Examination, and Beck Depression Inventory II.

Conclusions: The PCL and IGT tasks appear to rely on different parts of the frontostriatal circuitry in patients with early PD. The current finding that IGT performance was impaired in early PD implies ventromedial prefrontal cortical dysfunction early in the disease.

Key Words: gambling, nondeclarative memory, Parkinson disease, probabilistic classification

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The observation that amnesic patients learned some tasks suggested that there are different types of learning and memory.[1] Accordingly, declarative or explicit memory pertains to learning facts or events and requires conscious awareness; nondeclarative or implicit memory pertains to the gradual learning of new skills or habits and involves a sense of automaticity and lack of conscious awareness.[2]

Declarative memory (DM) and nondeclarative memory are dissociable anatomically with damage to medial temporal and medial diencephalic structures often associated with DM deficits.[3,4] Frontostriatal circuitry has been implicated in nondeclarative memory, and different nondeclarative memory tasks may depend on different parts of this circuitry.[5–7] Two nondeclarative memory tasks, probabilistic classification learning (PCL)[8,9] and the Iowa Gambling Task (IGT),[10,11] appear to depend on different regions of frontostriatal circuitry and are the focus of the current study.

One version of the PCL involves prediction of one of two outcomes (rain or shine) on a number of trials, given the particular cues provided on each trial; each cue is probabilistically associated with either outcome.[9] Learning in normal subjects occurred over 50 trials without conscious awareness, and amnesic[12] or Alzheimer patients[13] showed normal learning.[14] Patients with Parkinson disease (PD), known to experience a loss of dopaminergic innervation of the dorsal striatum,[15] showed impaired PCL learning[12,16–18]; declarative learning was intact.[12] Other groups with striatal cell loss (ie, Huntington patients)[19] or suspected striatal dysfunction (ie, Tourette patients)[20] were also impaired. Performance of the PCL task led to activation of the striatum, although other brain regions including the medial prefrontal cortex (pfc) also were involved.[21–24] However, patients with either right, left, or bilateral lesions in the dorsolateral or medial pfc were unimpaired in learning the PCL task.[12] Overall, results implicate the striatum in PCL.

The IGT involves choosing cards from four decks that have different payoffs; choices from two decks result in making money and the other two in losing money.[10,11] People shifted to choosing from the good decks before they were aware of the differential payoffs, suggesting that learning was nondeclarative.[11] One difference between the PCL and the IGT is that the IGT provides cumulative feedback in the form of net dollars earned or lost over trials. IGT learning activated the medial frontal gyrus[29] and was impaired by damage to the ventromedial pfc, implicating the pfc in the type of nondeclarative memory required by the IGT; however, the subregion(s) of the pfc that are critical for IGT learning remain the topic of debate.[10,11,25–28] Overall, results implicate the pfc in IGT learning. Coupled with the finding that patients with large uni- or bilateral frontal damage were able to learn the PCL,[12] results suggest that the PCL and IGT might assess

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different types of nondeclarative memory relying on different brain regions within frontostriatal circuitry.

PD patients have been tested on the IGT. They learned,[30] but a recent reanalysis of these data, based on a cognitive decision model, revealed that the PD group learned less well than controls.[31] Czernecki et al[32] uncovered a deficit on the IGT in a PD group on a second test administration. (Two test dates were used to examine the effects of being on or off dopaminergic medication; there was no effect.) Results suggest that IGT performance may be impaired in PD and implicate frontal cortical dysfunction in PD.[33,34]

The pfc and striatum include at least five functionally independent circuits.[35] Each is partially closed, including nonoverlapping parts of the cortex, basal ganglia, and thalamus. Damage to any one circuit has been associated with particular consequences. For example, damage to the dorsolateral prefrontal circuit is associated with executive dysfunction and damage to the orbitofrontal circuit with behavioral disinhibition and stimulus-bound behaviors.[5,6,35] Each level in a circuit contributes unique processes; thus, for example, striatally mediated tasks are not always impaired after frontal damage.[12] Overall, frontal and striatal areas are intimately connected, but they are often dissociable on cognitive tasks. The PCL and IGT may reveal this dissociation.

The purpose of the present study was to examine PCL and IGT performance in PD participants. The tasks were chosen because they are both nondeclarative and may rely on different regions within frontostriatal circuitry. For comparison, additional standard measures of executive function shown previously to be sensitive to pfc damage—the Wisconsin Card Sorting Test (WCST)[36] and the Stroop Test[37]—were used. Patients in the earlier (with scores of 1–2.5 on the Hoehn and Yahr Scale[38]) and later stages of PD (scores of 3–4) were investigated to assess the effects of PD severity. Parkinson-specific Lewy body pathology progresses with stages of the disease from hindbrain to midbrain to forebrain, with the neocortical regions only affected in the advanced stages.[39,40] These finding are consistent with the suggestion that early pathology in PD appears to be confined to the loss of striatal dopamine with sparing of the cortex, whereas there is likely to be alterations in the cortical circuitry later in the disease.[34] It was predicted that the later PD group would be more impaired on the PCL and the IGT than the early PD group.

METHODS

Participants

The 32 patients with PD were recruited from Kingston General Hospital's Movement Disorders Clinic. They were diagnosed with idiopathic PD and were prescribed medication by a neurologist. Patients were assigned to one of two groups based on their Hoehn and Yahr Scale score (using a score of <3 as early PD and ≥ 3 as later PD). Table 1 summarizes group characteristics including age, education, gender, Hoehn and Yahr scores, and levodopa dosages. They were treated with the following additional medications: ropinirole (15 patients), amantadine (7 patients), pramipexole (3 patients), pergolide (3 patients), selegeline (2 patients).

TABLE 1. Participant Characteristics (Means ± SEM)

	Control	Early PD	Later PD
No. of participants	19	16	16
Age (y)	72.6 ± 1.9	72.4 ± 2.3	77.7 ± 1.5
Education (y)	14.3 ± 0.7	14.6 ± 0.7	14.1 ± 1.1
Gender	11 M/8 F	9 M/7 F	8 M/8 F
Levodopa dosage (mg)	0	265.6 ± 33.1	350.0 ± 38.5
Hoehn and Yahr Stage score	0	2.1 ± 0.1	3.3 ± 0.1
UPDRS Motor Scale score	N/A	11.3 ± 1.1	27.2 ± 1.3

UPDRS, Unified Parkinson's Disease Rating Scale.

The control group (n = 19) was selected to match the PD groups on age, gender, and level of education, and the three groups did not differ significantly on these characteristics ($P < 0.05$). Five (26%) were spouses of the PD patients. Participants were excluded if they had ever had a stroke, head injury, learning disability, or severe psychiatric disturbance (eg, schizophrenia). Participants had to obtain a score of at least 27 out of 30 on the Mini-Mental State Examination (MMSE),[41] a screening test for dementia. Two prospective participants were excluded owing to a low MMSE score.

The General Research Ethics Board at Queen's University and Affiliated Hospitals approved this study. Participation was voluntary, and informed consent was obtained.

Dependent Measures

PCL

Knowlton et al[9] originally developed the form of the PCL task used here. It was performed on a laptop computer, with the participant responding using a metal box outfitted with two buttons: One was labeled "rain," the other "shine," and they were situated underneath a drawing of a rain cloud or the sun. Participants were informed that they were going to be a weather forecaster in this game and that they would learn to predict rain or shine using four cards depicting the following: 7 squares, 10 triangles, 9 circles, or 13 diamonds. For each trial, up to three cards appeared on the screen. Participants were not told the probabilities for one outcome (rain or shine) associated with each card (ie, 75%, 57%, 43%, and 25%). The probability associated with each card remained constant for each participant but varied across participants. After each correct response, the card(s) remained on the screen, accompanied by a high-pitched tone for 5 seconds and an icon depicting a happy face. After each incorrect response, the card(s) remained on the screen, accompanied by a low-pitched tone for 5 seconds and an icon depicting a nonsmiling face. Each 25 trials was followed by a 20-second break, with a total of 100 trials.

The dependent measure was percentage of correct responses for each block of 10 trials. A correct response was defined as selection of the highest probability outcome predicted by a single card by aggregating the card probabilities on multiple card trials. Feedback regarding the correctness of responses was determined by the probabilities assigned to each card. For the purposes of scoring, however, a response was considered to be correct if it reflected the higher probability

outcome associated with the card(s) shown on that trial. For example, if the high probability rain card was shown and the participant pressed the "rain" button, the response would be scored as correct, even if, on that occasion, the feedback to the participant indicated an incorrect response.

IGT

The IGT was modeled on the task described by Bechara et al.[10] It involved selecting one card at a time from one of four decks. Each deck had 40 cards (half with red faces and half with black faces), arranged in a fixed order. To begin, the participant was given a loan of $2000 in play money and told that the goal of this game was to try to win, or avoid losing, as much money as possible. Also, participants were told that some of the decks were worse than others. For two of the decks, the payoff was always $50, and for the other two it was always $100. However, occasional penalties for particular card selections occurred across all decks. Payoffs with no penalties were signaled by a black face card. Red face cards signaled a payoff too but were sometimes accompanied by a penalty. The $50 decks were better than the $100 decks in the long run because they had less severe penalties (ranging from $50 for one deck to $250 for the other deck). On the other hand, one of the $100 decks had penalties of up to $350 and the other had infrequent penalties of $1250. This task continued until 100 cards were drawn. The dependent measure was the number of card choices from the advantageous $50 decks for each block of 10 choices.

DM Questionnaires

Multiple-choice DM questionnaires were administered following the PCL and the IGT. For the PCL task, five questions were extrapolated from those used by Knowlton et al,[12] as used by Beninger et al.[42] A sample question was: "Where did the sun or rain cloud appear?" followed by the following choices: (a) below the cards, (b) above the cards, (c) at the right side of the screen, or (d) at the left side of the screen ("b" was correct). For the IGT, 10 questions were developed by Beninger et al[42] to mirror those from the PCL DM questionnaire.[12] A sample question was: "How much money did you start with?" followed by the choices: (a) $1500, (b) $200, (c) $1000, or (d) $2000 ("d" was correct).

Neuropsychological Tests

All participants completed the MMSE[41] to screen for evidence of dementia and the Beck Depression Inventory (2nd ed.; BDI-II)[44] to assess depressive symptoms that are often associated with PD. Participants also completed two tests purported to be sensitive to frontal lobe dysfunction: the WCST[33] and the Stroop Test.[34] In this version of the Stroop, individuals had to read a series of words (blue, tan, green, red) first and then name the colors in which a similar series of words were printed within a 2-minute limit. The dependent variable was the number of correct responses.

Procedure

Participants completed a consent form, health and demographics questionnaires, MMSE, PCL, IGT, DM questionnaires for the PCL and IGT, WCST, Stroop, BDI-II, and Unified Parkinson's Disease Rating Scale (version 3; UPDRS).[41] The bulk of the testing was conducted during a home visit. The PCL or IGT followed by their respective DM questionnaires were given in a counterbalanced order. The order of administration of all instruments was chosen because preliminary results suggested that performing the WCST first influences performance on the implicit memory tasks. The demographics questionnaire gathered information about age, gender, handedness, and educational background, and the health questionnaire gathered information about overall physical and emotional well-being, including information about current medications. Testing generally took 2.0–2.5 hours.

Participants were tested at times when they were "on" in terms of the efficacy of their medication for PD (ie, at a time when participants reported that their motor symptoms were well controlled). A separate half-hour appointment was made within 3 weeks of the test date to administer the UPDRS at Kingston General Hospital's Movement Disorders Clinic by a registered neurologist and the principal investigator of this study. The Hoehn and Yahr Scale score was derived from the UPDRS.

RESULTS

This section contains six parts. In the first two, results from repeated measures analyses of variance (ANOVA) are presented with the data from the PCL and the IGT. The within-subjects factor was trial block, with 10 trials in each block, and the between-subjects factor was group (control, early PD, and later PD). In the next two parts, results of one-way ANOVA that examined the similarities and differences between groups on the DM questionnaires (part 3) and the various neuropsychological tests (part 4) are presented. Part 5 deals with correlations among the implicit learning tasks, DM questionnaires, and neuropsychological tests for each of the groups using the Pearson product–moment correlation statistic. In the last part, potential order effects in performing the PCL and IGT are examined. Analyses were carried out using the SPSS 9.0 statistical software package.

Part 1: PCL

For the PCL task, the dependent variable was percent correct responses in blocks of 10 trials over a total of 100 trials (Fig. 1). Blocks of 10 trials were chosen because they provided less variability than smaller blocks while retaining good resolution of the learning process and because others have reported blocks of 10 trials. Performance of the control group improved from the first to second and from the third to fourth blocks; similarly, the early PD group showed its sharpest increase between the third and fourth blocks. By contrast, the later PD group showed a smaller improvement over the first five blocks, with its sharpest jump between the fifth and sixth blocks.

Results of ANOVA supported this description of the data. There was a significant effect for group ($F[2,48] = 3.73$, $P < 0.05$), trial block ($F[9,432] = 2.67$, $P < 0.01$), and interaction ($F[18,432] = 1.68$, $P < 0.05$). Simple effects ANOVA for groups at each trial block (using $\alpha = 0.01$ because of the number of comparisons) revealed a significant effect

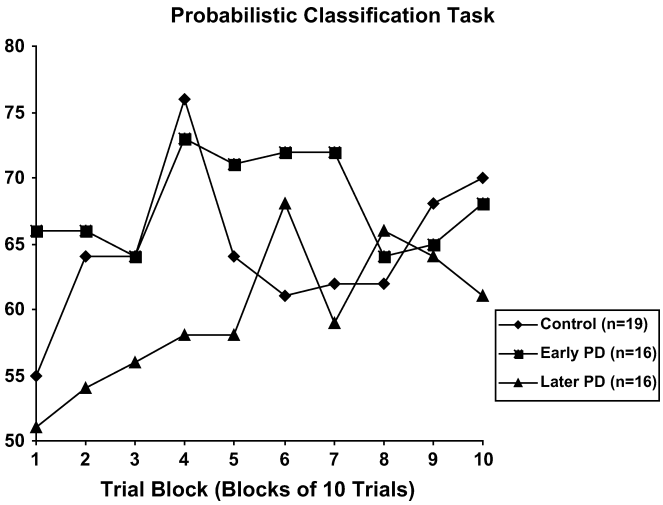

FIGURE 1. Mean percentage of correct responses on the probabilistic classification task across 100 trials in blocks of 10 for the three experimental groups.

at block 4 ($F[2,50] = 6.35$, $P < 0.01$). Bonferroni-corrected t tests showed that the control and early PD groups were significantly different from the later PD group ($P < 0.05$) and not significantly different from each other ($P > 0.05$).

Part 2: IGT

For the IGT, the dependent variable was the mean number of choices from the advantageous decks in blocks of 10 trials over a total of 100 trials (Fig. 2). All groups started selecting approximately four cards from the advantageous decks in the first block and improved over further trials. However, the control group started rising noticeably above both PD groups from blocks 5–7.

The ANOVA revealed significant effects for trial block ($F[9,432] = 5.32$, $P < 0.01$) and interaction ($F[18,432] = 2.07$, $P < 0.01$). Tests of simple effects of group for each block were conducted with $\alpha = 0.01$ to correct for the large number of analyses conducted. These tests showed the group effect to be significant at block 7 ($F[2,480] = 8.01$, $P < 0.01$). Bonferroni-corrected t tests revealed that the control group performed better than both the early and the later PD groups (all $P < 0.05$).

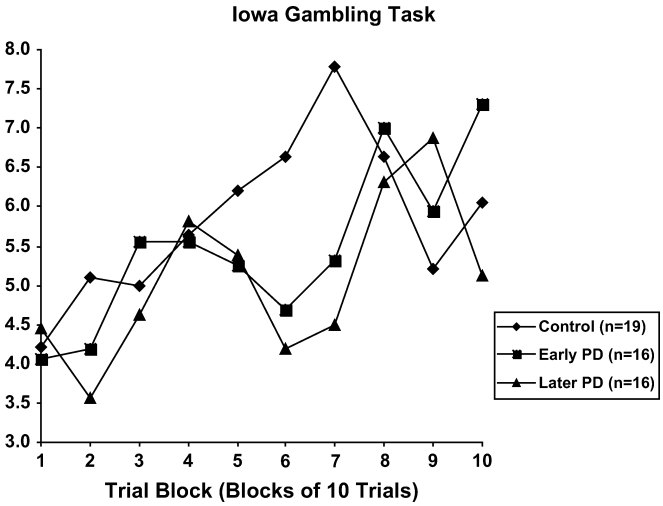

FIGURE 2. Mean number of choices from the advantageous decks on the IGT across 100 trials in blocks of 10 for the three experimental groups.

Part 3: DM Questionnaires

One-way ANOVA revealed no significant differences ($P > 0.05$) among groups on the number of correct items for the DM questionnaire for the PCL or IGT (Table 2).

Part 4: Neuropsychological Tests

Table 2 provides a summary of mean (±SEM) scores for the MMSE, WCST, Stroop, and BDI-II across groups. One-way ANOVA (Table 3) and Bonferroni-corrected t tests revealed that the control group did not significantly differ from the early PD group on any of these measures. The significant differences indicated in Table 2 (based on ANOVA and post-hoc tests) will be reported here. On the MMSE, the later PD group scored lower than the other two groups. On the WCST, the control group was better than the later PD group for categories completed and the early PD group was better than the later PD group for failure to maintain set. Thus, the later PD group had fewer categories correct than the control group and more failures to maintain set than the early PD group. On the Stroop, the later PD group made fewer correct responses than the control and early PD groups.

On the BDI-II, the later PD group was different from the control and the early PD groups. These results did not change after removing the somatic items from the BDI-II (eg, loss of energy, changes in sleep and appetite, tiredness or fatigue, and loss of interest in sex) that are often found in medical populations, regardless of the presence of co-morbid depression. Although these differences were found, it is noteworthy that all three groups were in the "minimal depression range."[43]

Part 5: Correlations Among Tests

Correlational analyses were conducted on the total number correct on the PCL and the IGT (Table 4). The PCL and IGT totals were not significantly correlated with each other for the PD groups, but they were negatively correlated for the control group ($r = -0.59$, $P < 0.01$). The PCL task was correlated with the WCST categories completed for the later PD group ($r = 0.56$, $P < 0.05$). However, when an outlier was removed, the correlation was no longer significant ($P > 0.05$); therefore, no interpretation was made for this correlation. Surprisingly, the BDI total score correlated positively with PCL score for the control group ($r = 0.59$, $P < 0.05$) and with IGT score for the early PD group ($r = 0.51$, $P < 0.05$). When the somatic items were removed from the BDI, the correlation with IGT score for the early PD group remained significant ($r = 0.53$, $P < 0.05$), and the correlation with PCL score was significant and negative ($r = -0.56$, $P < 0.05$).

Part 6: Order Effects

The presentation of the PCL and IGT was counterbalanced to control for possible order effects. The observation that performance on the two tasks was negatively correlated for the control group might reflect an order effect; for example,

TABLE 2. Mean Scores for MMSE, WCST, Stroop, BDI-II, and DM Questionnaires for PCL and IGT for PD and Control Participants

	Participant Group								
	Control			Early PD			Later PD		
Tests	Mean	SEM	n	Mean	SEM	n	Mean	SEM	n
MMSE	28.9*	0.2	19	29.0*	0.2	16	28.1	0.3	16
WCST									
Categories completed	3.8*	0.4	17	2.6	0.6	14	1.9	0.4	16
% perseverative errors	18.1	1.7	17	18.9	2.5	14	21.2	2.7	16
Failure to maintain set	1.2	0.3	17	0.9*	0.3	14	2.2	0.3	16
Stroop: total correct	88.1*	5.5	17	83.1*	5.5	14	55.1	4.1	15
BDI-II	5.2*	0.8	19	6.9*	0.7	16	12.7	1.5	16
BDI-II minus somatic items	2.3*	0.6	19	3.3*	0.6	16	7.2	1.1	16
Declarative PCL	4.4	0.1	19	4.2	0.2	16	3.9	0.2	16
Declarative IGT	7.8	0.3	19	7.6	0.4	16	6.8	0.4	16

*Different from later PD group ($P < 0.05$) by Bonferroni-corrected t test following significant ANOVA.

performance on the second task might be always worse than performance on the first. To examine this possibility, follow-up analyses compared number correct on the PCL and IGT tasks when they were presented first versus second. One-way ANOVA for each task showed no significant differences (all $P > 0.05$, data not shown).

DISCUSSION

The results can be summarized as follows: PCL performance was impaired in the later PD group but not in the early PD group. IGT performance was impaired in both PD groups. Both PD groups eventually learned both tasks. Neither PD group showed an impairment of DM. The later PD group was impaired on the WCST and Stroop.

PCL

The finding that the later PD group (with a Hoehn and Yahr score of 3–4) was impaired on the PCL replicated previous results.[12,16–18] Early PD patients (mean Hoehn and Yahr score 2.1) were not impaired in agreement with findings from a slightly more impaired group (mean Hoehn and Yahr score 2.5).[16] Perhaps the early PD group had not developed a level of dopamine cell loss sufficient to impair their learning. The degree of impairment on various cognitive tasks increases with the progression of PD.[45–47] In neuroimaging studies, performance of the PCL task led to activation of the striatum and a number of other brain regions including the pfc.[21–24] Kincess et al[48] used transcranial direct current stimulation of the pfc in humans and showed enhanced PCL; the type of stimulation (anodal) was thought to increase pfc neuronal excitability. On the other hand, patients with frontal cortical lesions were unimpaired in learning the PCL task.[12] Results generally implicate striatal dopamine in acquisition of the PCL task, but some studies suggest that the pfc may also play a role.

Schizophrenic patients treated with typical antipsychotic medications but not those treated with atypicals were impaired on the PCL task.[42] Typical antipsychotics have a high liability for producing extrapyramidal PD-like effects[49] and block dopamine receptors in the striatum.[50] Thus, the observation of impaired performance of schizophrenic patients treated with typical antipsychotics is in good agreement with the present and previous[12,16–18] findings.

Results emphasize the important role of striatal dopamine in PCL. Probabilistic classification is a form of operant conditioning, where reward (in this case, feedback concerning the correctness of the response) serves to shape appropriate responses.[7] Reward-related (ie, incentive) learning is mediated by dopamine.[51] Results are consistent with other reports of impaired incentive learning in PD patients,[52] schizophrenic patients treated with typical antipsychotic medications,[42] and animals treated with antipsychotic medications or otherwise deprived of dopaminergic neurotransmission.[51,53] The recent finding showing activation of brain regions associated with the mesencephalic dopamine system in people doing a PCL task provides further evidence for the role of dopamine.[23]

IGT

In agreement with the results of previous studies, both the early and later PD groups were impaired on the IGT. Thus, a PD group did not learn the IGT as well as the control group, and a model-fitting procedure proved to be more difficult for the PD group than for the control group owing to frequent random responses in the PD group.[31] IGT impairment was found upon a second test administration to PD participants.[32]

TABLE 3. F-Test Results for MMSE, WCST, Stroop, BDI-II, and DM Questionnaires for PCL and IGT

	Degrees of Freedom	F Ratio	*P* Value
MMSE	2, 50	3.61	0.035
WCST			
Categories completed	2, 46	4.44	0.017
% perseverative errors	2, 46	0.51	0.605
Failure to maintain set	2, 46	4.40	0.018
Stroop: total correct	2, 45	12.18	<0.001
BDI-II	2, 50	13.92	<0.001
BDI-II minus somatic items	2, 50	10.23	<0.001
Declarative PCL	2, 50	1.72	0.188
Declarative IGT	2, 50	2.08	0.136

TABLE 4. Correlations of PCL and IGT With Each Other and With MMSE, WCST, Stroop, DM, and BDI–II Scores Across Control and PD Groups

	Participant Group					
	Control		Early PD		Later PD	
	PCL	IGT	PCL	IGT	PCL	IGT
PCL	1.00	−0.59*	1.00	−0.45	1.00	0.03
IGT	−0.59*	1.00	−0.45	1.00	0.03	1.00
MMSE	−0.04	−0.04	−0.06	−0.12	0.33	0.21
WCST						
Categories completed	−0.11	0.02	−0.08	0.42	0.56†	0.03
Failure to maintain set	−0.34	0.22	−0.15	−0.17	−0.13	0.26
Stroop total correct	0.13	−0.23	0.32	0.18	0.44	0.20
Declarative PCL	−0.12	0.02	0.25	0.20	0.30	−0.08
Declarative IGT	0.05	0.12	−0.28	0.30	−0.18	0.44
BDI–II	0.59†	−0.36	−0.44	0.51†	−0.09	0.31
BDI–II minus somatic items	0.40	−0.27	−0.56†	0.53†	0.05	0.19

*$P < 0.01$; †$P < 0.05$.

The present findings are generally consistent with these results, suggesting that IGT learning is impaired in PD patients.

IGT performance was impaired by damage to the pfc.[10,11,25–28] Schizophrenic patients treated with atypical antipsychotic medications were similarly impaired on the IGT.[42] Based on animal studies of the effects of these medications on regional immediate early gene expression[50] and dopamine outflow,[54] atypical antipsychotics appear to affect frontal cortical function, possibly leading to the IGT deficit observed.[42] Neuroimaging studies showed that the medial frontal gyrus was involved in risk anticipation when performing the IGT.[29,55,56] Collectively, these findings support a critical role for frontal regions in learning of the IGT.

The groups performed at a similar level on the IGT until trial block 5 when the control group continued to improve but the PD groups did not. Our control results agree with those of Bechara et al[11] who found that their control participants started "liking" and "disliking" particular decks of cards roughly between trials 50 and 80. Bechara et al[10] reported that their participants were still not capable of articulating what was going on in the task; that is, they did not yet have declarative knowledge about the differences among the decks. Their control participants were showing anticipatory skin conductance responses (SCRs) before making risky choices during this period. Patients with pfc damage never demonstrated anticipatory SCRs, nor did they shift to the good decks. Our present results suggest that patients with (early and later) PD may lack unconscious emotional signals or be unable to use them to facilitate decision making in this task. Future studies assessing SCRs in PD patients performing the IGT task are needed.

IGT results differentiated the early PD group from the control group, even though the MMSE, WCST and Stroop did not. These other tests offer static outcome scores, whereas the IGT assesses ongoing learning performance across multiple trials. The IGT may prove to be more effective than these other tests in uncovering learning deficits in PD because of the strong rewarding properties of learning this task.

DM

DM questionnaires assessed explicit memory for training on the PCL and the IGT. PD groups were not impaired, in good agreement with previous findings.[12] One possibility is that the nondeclarative (ie, PCL and IGT) and DM tasks differed in difficulty and that the differential impairment observed in the PD patients reflected this putative difference. However, amnesics learned the PCL as well as controls but were impaired on the DM questionnaire.[12] Clearly, the DM questionnaire was sufficiently difficult to detect impairments. This result suggests that differential difficulty does not account for the observation that PD patients failed to learn the PCL but were able to answer the questions about the task correctly.

Since the pioneering work of Milner,[1] showing that some forms of memory (now termed "nondeclarative" or "implicit") were intact in amnesic patients, many studies have shown this dissociation.[57] The results of Knowlton et al[12] and the present finding that PD patients were impaired on a nondeclarative memory task but unimpaired on a DM task are among the first to show the dissociation in the reverse direction. Results strongly support the existence of multiple memory systems and implicate striatal dopamine in at least one form of nondeclarative memory; they also suggest that striatal dopamine is not necessary for DM.

Executive Functioning

The PD patients in the present study did not have dementia based on the MMSE results. Consistent with previous reports,[58,59] those in the later stages of PD showed deficits on standard measures of executive function (WCST and Stroop). It has been argued that the Stroop results may be attributable to other functions such as motor slowing.[60] Thus, PD patients with executive dysfunction were impaired on a nondeclarative memory task (mirror reading).[59] Consistent with this finding, the later PD group that performed poorly on the tests of executive function also performed poorly on both nondeclarative memory tasks. On the other hand, there were no significant correlations between PCL or IGT total score and WCST or Stroop scores for this group. Our results do not provide strong evidence that deficits in executive function are related to performance of nondeclarative memory tasks shown to rely on the striatum or pfc.

Relationships Across Tests

The negative correlation between the PCL and IGT in the control group was an unexpected finding. Previous data implicate the striatum in PCL[12,16–19] and the pfc in the IGT.[10,11,25–28] This negative correlation might suggest that some control participants approach these tasks in a more "striatal" fashion, benefiting performance on the PCL task, whereas others approach them in a more "frontal" fashion, benefiting performance on the IGT. The lack of a significant correlation in the PD groups might suggest that damage to the frontostriatal circuitry eclipses this putative bias. Further studies are needed to assess the reliability of the observed negative correlation.

Depression in PD

BDI scores were significantly higher in the later PD group compared with the control or early PD groups. However, correlational analyses revealed no significant relationships between BDI scores and performance on the other tests. BDI scores were related to PCL or IGT performance in the control and early PD groups, respectively, but these correlations were positive. A negative correlation was found between BDI score (with somatic items removed) and PCL total score for the early PD group. However, the BDI scores of this group were low and in the minimal depression range, making interpretation difficult.

Patients with PD score higher on assessments of depression[61] even when compared with other patient groups with a chronic degenerative disorder producing comparable levels of disability (eg, arthritis).[62] The present finding that later PD patients scored higher on the BDI agrees with these findings. The BDI scores of all groups were in the "minimal" range and those for the later PD group was below the "mild" depression range.[43] Therefore, the effects of depression are unlikely to account for the results of the present study.

Effects of Dopaminergic Medication

Dopaminergic medication often influences neuropsychological test performance in PD.[33,47,63,64] Cools et al[33] noted that the circuit between the dorsal striatum and the dorsolateral pfc undergoes dopamine depletion relatively early in the course of PD, leading to beneficial effects of dopaminergic medication in performing tasks thought to rely on the dorsolateral pfc (eg, switching). Consistent with this assertion, a recent positron emission tomography study demonstrated that being "on" but not "off" L-dopa was associated with blood flow changes in the right dorsolateral pfc during performance of the Tower of London Task.[65] On the other hand, the circuit between the ventral striatum and the orbitofrontal cortex remains relatively spared of dopamine depletion early in the course of PD, leading to an "overdose effect" (ie, a negative effect) of dopaminergic medication in performing tasks thought to rely on this region (eg, reversal learning).[33,47] These positive and negative effects of dopaminergic medication on neuropsychological test performance may dwindle as PD progresses.[30]

In the present study, we cannot determine if the IGT and the PCL were affected differentially by dopaminergic medication. One may speculate that dopaminergic medication could create an "overdose effect" for those in the early stages of PD on the IGT because the orbitofrontal cortex, relatively spared of dopamine loss in early PD,[33,34] was deemed to be important for IGT performance.[10,11] However, by observing more focal lesions, others[27,28] were able to show that other pfc areas are important for IGT performance. Further, an overdose effect is not likely for the IGT given that Czernecki et al[32] did not note any differences between PD patients assessed "on" and "off" L-dopa. Similarly, the present version of the PCL has been reported to be unaffected by L-dopa (D. Shohamy, personal communication). Possibly, the early PD group in the present study failed to show an impairment on the PCL (or the WCST and Stroop) due to an ameliorative effect of their dopaminergic medication. Previous studies revealed conflicting results regarding the effects of L-dopa on the WCST.[66,67] A recent study using a PCL task showed that PD patients had better learning of choices avoiding negative outcomes when off medication and better learning of choices signaling positive outcomes when on medication.[68] Results reveal the importance of medication, but more studies are needed to investigate the role of dopaminergic medication in PD-associated neuropsychological test performance.

SUMMARY AND CONCLUSIONS

The present study replicated previous findings and provided useful additional information regarding nondeclarative or implicit learning in PD. First, this study confirmed previous reports of impaired PCL learning in later PD patients and no impairment in early PD. This study showed that early and later PD patients were impaired in IGT learning. PD patients were not impaired on DM tasks. Later but not early PD patients were impaired on two tests of executive functioning, the WCST and the Stroop. Finally, the PCL and IGT were uncorrelated with each other in the PD groups. Therefore, the two tasks may target unrelated cognitive processes and areas of frontostriatal circuitry in PD. Results suggest ventromedial pfc dysfunction in early PD.

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