Depression Impairs Learning Whereas Anticholinergics Impair Transfer Generalization in Parkinson Patients Tested on Dopaminergic Medications

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Abstract: In a study of acquired equivalence in Parkinson disease (PD), in which patients were tested on normal dopaminergic medication, we found that comorbid clinical depression impairs initial acquisition, whereas the use of anticholinergic therapy impairs subsequent transfer generalization. In addition, this study provides a replication of the basic finding of Myers et al (2003) that patients with PD on dopaminergic therapy are impaired at initial acquisition, but normal at subsequent transfer generalization, generalizing these results to an Arabic-speaking population including many participants with no formal education. These results are consistent with our past computational modeling, which argues that acquisition of incrementally acquired, feedback-based learning tasks is dependent on cortico-striatal circuits, whereas transfer generalization is dependent on medial temporal (MT) structures. They are also consistent with prior computational modeling, and with empiric work in humans and animals, suggesting that anticholinergic drugs may particularly impair cognitive abilities that depend on the MT lobe.

Key Words: Parkinson disease, depression in Parkinson disease, anticholinergics, learning and transfer

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Parkinson disease (PD) is a neurodegenerative disorder that is associated with degeneration of dopaminergic neurons in the nigro-striatal pathway of the basal ganglia.[1] A variety of other neuronal systems, such as the prefrontal cortex, are affected in PD, causing dysfunction in multiple neuromediator systems. This accounts for the complex pattern of functional deficits seen in patients with PD.[2] These deficits include motor symptoms (tremor, bradykinesia, rigidity) and nonmotor symptoms (depression, hallucination), and subtle cognitive impairments even in the early disease stages. For purposes of symptom alleviation, patients receive a variety of medications, such as dopaminergic medications (eg, L-dopa and dopamine agonists), anticholinergics (eg, trihexyphenidyl), and neurostimulants (eg, amantadine).

Dopaminergic medications, such as L-dopa, are usually prescribed for patients with PD to ameliorate motor deficits. However, L-dopa affects cognitive function in a more complicated way, including both beneficial and detrimental outcomes.[3,4] For example, patients with PD tested on L-dopa show impairment in learning an incrementally acquired concurrent discrimination task, with no effect on generalization; a comparable group tested on overnight withdrawal from L-dopa were not impaired at acquisition, relative to matched healthy controls.[4] These findings are consistent with past computational models that suggest that cortico-striatal circuits play a critical role in stimulus-response-based habit learning,[5,6] and with observations from animal studies suggesting that dopaminergic modulation of cognitive function adheres to an inverted "U" function whereby excessive, and insufficient, dopamine receptor stimulation impairs cognitive function.[7–9]

In contrast, anticholinergic medications, such as trihexyphenidyl, may provide substantial alleviation of motor symptoms in PD. Trihexyphenidyl acts as an M1 muscarinic antagonist.[10,11] Immunologic localization shows that the hippocampus has a high concentration of muscarinic acetylcholine receptors M1-M5.[12] Studies have shown that the use of drugs with anticholinergic properties is associated with cognitive decline in PD.[13–15] These results are consistent with computational models that argue that anticholinergic drugs might disrupt learning by selectively reducing the ability of the hippocampus to store new information.[16,17] The hippocampus also plays a pivotal role in some types of complex learning, such as the ability to transfer when familiar responses are presented in novel recombinations, that is, to use already acquired generalizations to make decision about equivalent stimuli.[18,19] Hence, antimuscarinic anticholinergics alleviate motor symptoms in PD, but may cause cognitive dysfunctions.

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Although motor disturbances in PD do not present clinically until approximately 70% to 80% of striatal dopamine has already been lost, nonmotor symptoms are evident sometimes years before the onset of motor disturbances.[20] These include hyposmia/anosmia, gastrointestinal (GI) disturbances, sleep abnormalities, autonomic dysfunction, anxiety, depression, and, at later stages, impaired cognition.[21–25] It is well recognized that the incidence of depression among patients with PD is much higher than among age matched healthy participants.[26,27] Furthermore, depression in Parkinson disease patients is frequently associated with cognitive impairment.[28,29] Imaging studies showed that patients with PD who develop depression show structural changes that reflect dysfunction at the level of the substantia nigra.[30] Conversely, patients with major depression (and no PD) have basal ganglia abnormalities,[31] and structural changes in the substantia nigra visible on structural neuroimaging.[32] It has also been shown that depression has an impact on cognitive and learning processes that involve the striatal system.[33] On the basis of these findings, depression in PD and major depression may both affect striatal-dependent cognitive functions.

To test both striatal-based and hippocampal-based cognitive functions, we used an acquired equivalence task,[18] (Table 1) that was earlier shown to rely on these neural systems. Accordingly, we use this task to investigate the effects of L-dopa, anticholinergics, and depression on these brain structures. In this task, there are 3 acquisition stages, in which antecedent stimuli are represented on the screen as cartoon faces, and consequents are represented as different colored cartoon fish. Two antecedent stimuli A1 and A2 are associated with the same consequent stimulus X1, whereas 2 antecedent stimuli B1 and B2 are associated with consequent Y1. Next, A1 is associated with a new consequent X2, whereas B1 is associated with a new consequent Y2. Finally, a transfer phase tests whether patients would show acquired equivalence and associate A2 with X2 and B2 with Y2, even though these particular stimulus pairings had never been trained.

We administered the acquired equivalence task to a group of individuals with PD and matched healthy controls (HC). In addition to comparing the performance of patients versus controls, data within the PD group were analyzed as a function of depressive state and by whether or not patients were on anticholinergics (trihexyphenidyl).

METHODS

Participants

Parkinson Disease

Fourteen individuals (5 females, 9 males) with PD were recruited from neurologic clinics in the West Bank including Ramallah, Hebron, and Bethlehem and from clinics in East Jerusalem. Ages of patients with PD ranged from 47 to 77 years (M = 60.28, SD = 9.19). Degree of Parkinsonism, as assessed by the[34] scale, ranged from 1.0 to 3.0; (M = 2.14, SD 0.86). Motor symptoms were assessed using the Unified Parkinson Disease Rating Scale (UPDRS), and ranged from 6 to 54; (M = 24.2, SD 13.98). Duration as initial diagnosis of the disease ranged from 1 to 15 years (M = 5.5, SD 4.64). All patients with PD were on dopaminergic medications at the time of testing (13 on L-Dopa/Carbidopa, 1 on the dopamine agonist pramipexole). Seven of the patients were also on anticholinergic medications at the time of testing. Six patients were on low doses of amantadine (an antiviral and antiparkinsonian drug that enhances dopamine release from nerve endings) and were tested at least 18 hours after the last dose. All patients completed the Mini-Mental Status Exam (MMSE)[35]; (M = 25.5, SD 4.92), Brookdale Cognitive Screening Test (BCST) (was developed at the Brookdale Institute of Gerontology, Jerusalem for use in populations with high illiteracy rates,[36] and includes items on orientation, language, memory, attention, naming, abstraction, concept formation, attention, praxis, calculation, right left orientation, and visuospatial orientation, with a maximum score of 26)[37,38]; (M = 24.28, SD 2.84). Patients were also screened for depression (BDI-II; Beck, 1987); (M = 18.85, SD 12.19). The referring neurologist also screened patients for absence of dementia and other neurologic or psychiatric disorders other than PD.

Healthy Controls

Sixteen HC participants (10 females, 6 males) were recruited from multiple cities and towns in the West Bank. These individuals ranged in age from 49 to 73 years (M = 58.43, SD 6.86). These participants were screened for dementia, depression, or other neurologic or psychiatric conditions that could contribute to memory impairment. The control group averaged 26.75 (SD 4.29) on MMSE, 24.75 (SD 2.51) on BCST, and 11.75 (SD 9.39) on BDI-II.

TABLE 1. Acquired Equivalence Paradigm in Humans

Acquisition Stage 1: Shaping	Acquisition Stage 2: Equivalence Training	Acquisition Stage 3: New Consequents	Transfer Phase: Equivalence Testing
A1→X1	A1→X1	A1→X1	
	A2→X1	A2→X1	A2→X2?
		A1→X2	
B1→Y1	B1→Y1	B1→Y1	
	B2→Y1	B2→Y1	B2→Y2?
		B1→Y2	

Note that transfer phase interleaved trials with the earlier learned information and the novel pairs.

Group Comparisons and Correlations

We used Wilcoxon-Mann-Whitney (WMW) nonparametric statistical test to investigate for differences between the PD group and HC participants on the demographic or neuropsychologic measures mentioned above. We also analyzed these data looking for possible correlations of these measures with behavior.

We did not find any statistically significant differences between the PD and HC groups on any demographic or neuropsychologic measures using WMW test, a nonparametric statistical test, except for BDI II scores (Age: Mann–Whitney $U = 98$, $n_1 = 16$, $n_2 = 14$, $P = 0.56$ 2-tailed; Years of education: Mann–Whitney $U = 102.5$, $n_1 = 16$, $n_2 = 14$, $P = 0.692$ 2-tailed; MMSE: Mann–Whitney $U = 92.5$, $n_1 = 16$, $n_2 = 14$, $P = 0.411$ 2-tailed; BCST: Mann–Whitney $U = 107.5$, $n_1 = 16$, $n_2 = 14$, $P = 0.854$ 2-tailed; BDI-II: Mann–Whitney $U = 63.5$, $n_1 = 16$, $n_2 = 14$, $P = 0.043$ 2-tailed).

We used Kruskal Wallis (KW) nonparametric statistical test to compare demographic and neuropsychologic measures of subgroups of the PD group, according to their depression status (measured by BDI-II) and the use of anticholinergics, with HC participants. KW test revealed no difference between the PD group on anticholinergics (7 patients with PD), the PD group not on anticholinergics (7 patients with PD), and the HC group in any of the demographic or neuropsychologic measures (Age: χ^2 (2, $N = 30$) = 2.382, $P = 0.304$; Years of education: χ^2 (2, $N = 30$) = 2.526, $P = 0.283$; MMSE: χ^2 (2, $N = 30$) = 0.688, $P = 0.709$; BCST: χ^2 (2, $N = 30$) = 0.426, $P = 0.808$; BDI-II: χ^2 (2, $N = 30$) = 5.389, $P = 0.068$). WMW test revealed no effect of use of anticholinergics on UPDRS (Mann–Whitney $U = 24.5$, $n_1 = 7$, $n_2 = 7$, $P = 1.0$ 2-tailed) or H&Y scores (Mann–Whitney $U = 17.5$, $n_1 = 7$, $n_2 = 7$, $P = 0.343$ 2-tailed).

When we compared results from PD subgroups according to their depression status using WMW test, we found no significant effect of depression status on the above mentioned measures (Age: Mann–Whitney $U = 20.5$, $n_1 = 8$, $n_2 = 6$, $P = 0.651$ 2-tailed; Years of education: Mann–Whitney $U = 14.5$, $n_1 = 8$, $n_2 = 6$, $P = 0.215$ 2-tailed; MMSE: Mann–Whitney $U = 16$, $n_1 = 8$, $n_2 = 6$, $P = 0.296$ 2-tailed; BCST: Mann–Whitney $U = 22$, $n_1 = 8$, $n_2 = 6$, $P = 0.763$ 2-tailed; H&Y: Mann–Whitney $U = 17.5$, $n_1 = 8$, $n_2 = 6$, $P = 0.374$ 2-tailed) except for UPDRS (Mann–Whitney $U = 6.5$, $n_1 = 8$, $n_2 = 6$, $P = 0.023$ 2-tailed), which was significantly greater among depressed PD subgroup (8 patients with PD) than the nondepressed PD subgroup (6 patients with PD). We also found no significant effect of depression status (measured by BDI-II) among HC participants (Age: Mann–Whitney $U = 13.5$, $n_1 = 12$, $n_2 = 4$, $P = 0.201$ 2-tailed; Years of education: Mann–Whitney $U = 9$, $n_1 = 12$, $n_2 = 4$, $P = 0.068$ 2-tailed; BCST: Mann–Whitney $U = 19$, $n_1 = 12$, $n_2 = 4$, $P = 0.484$ 2-tailed) except for MMSE (Mann–Whitney $U = 7$, $n_1 = 12$, $n_2 = 4$, $P = 0.034$ 2-tailed). When we compared data from the 4 earlier groups using KW test [PD with depression, PD without depression, HC with depression (4 HCs), HC without depression (12 HCs)], we found no significant effect of group [Age: χ^2 (3, $N = 30$) = 2.564, $P = 0.464$; Years of education: χ^2 (3, $N = 30$) = 5.99, $P = 0.112$; MMSE: χ^2 (3, $N = 30$) = 6.189, $P = 0.103$; BCST: χ^2 (3, $N = 30$) = 0.615, $P = 0.893$]. WMW test revealed no difference between PD subgroups according to the use of amantadine (6 patients with PD were receiving amantadine, and 8 were not) on the above mentioned demographic and neuropsychologic measures (Age: Mann–Whitney $U = 19.5$, $n_1 = 8$, $n_2 = 6$, $P = 0.56$ 2-tailed; Years of education: Mann–Whitney $U = 20.5$, $n_1 = 8$, $n_2 = 6$, $P = 0.648$ 2-tailed; MMSE: Mann–Whitney $U = 22.5$, $n_1 = 8$, $n_2 = 6$, $P = 0.845$ 2-tailed; BCST: Mann–Whitney $U = 15$, $n_1 = 8$, $n_2 = 6$, $P = 0.176$ 2-tailed; BDI-II: Mann–Whitney $U = 21.5$, $n_1 = 8$, $n_2 = 6$, $P = 0.746$ 2-tailed; H&Y: Mann–Whitney $U = 17$, $n_1 = 8$, $n_2 = 6$, $P = 0.338$ 2-tailed; UPDRS: Mann–Whitney $U = 9.5$, $n_1 = 8$, $n_2 = 6$, $P = 0.06$ 2-tailed).

As for correlational analyses, MMSE scores decreased significantly as age increased in PD (Spearman rho; $r = -0.631$, $P = 0.015$), but fell short of significance in HC (Spearman rho; $r = -0.41$, $P = 0.115$). BCST scores were also negatively correlated with age, significantly in PD (Spearman rho; HC $r = -0.383$, $P = 0.143$; PD $r = -0.693$, $P = 0.006$). MMSE and BCST scores were significantly higher for more educated HC participants (Spearman rho; MMSE with education, HC: $r = 0.819$, $P = 0.000$; BCST with education, HC: $r = 0.584$, $P = 0.018$). For patients with PD, MMSE scores correlate significantly with years of education (Spearman rho; $r = 0.742$, $P = 0.002$). However, BCST scores of patients with PD do not show the same significant correlation (Spearman rho; $r = 0.437$: $P = 0.118$).

Behavioral Testing

As described below in more detail, the acquired equivalence task administered was identical to that described in,[18] except for the use of Arabic-translated instructions.

Apparatus

Behavioral testing was automated on a Macintosh ibook G3 or G4 laptop computer with a color screen, using software programmed in the SuperCard language. Testing took place in a quiet room, with the participant seated in front of the computer at a comfortable viewing distance. The keyboard was masked except for 2 keys, labeled "LEFT" and "RIGHT," which the participant could press to record a response.

Stimuli

Four drawings of faces (man, woman, girl, boy) served as the antecedent stimuli. The boy and woman had blonde hair, whereas the girl and man had brown hair. Thus, each antecedent had 3 obvious, binary-valued features: age (adult vs. child), gender (male vs. female), and hair color (blond vs. brunette); each antecedent shared exactly 1 feature with each other antecedent. For each participant, the 4 face drawings were randomly assigned to be antecedents A1, A2, B1, and B2. The consequents were 4 drawings of a fish colored red, orange,

pink, and purple. For each participant, the colored fish were randomly assigned to be the consequents X1, X2, Y1, Y2. The antecedents and consequents all seemed about 1 inch tall on the computer screen, with the participant seated at a comfortable viewing distance. The phases and pairings in the task are shown in Table 1.

Procedure

All participants signed statements of informed consent before the initiation of any behavioral testing. All research procedures conformed to the regulations established by the research ethical committee at Al-Quds University and conducted in accordance with the Declaration of Helsinki.

At the start of the experiment, these instructions seemed on the screen (translated into Arabic): "Welcome to the experiment. You will see drawings of people who each have some pet fish. Different people have different kinds of fish. Your job is to learn which kinds of fish each person has. At first, you will have to guess." The experimenter read these instructions aloud to the participant and then clicked the computer mouse button to begin the acquisition phase. On each trial, the screen showed an antecedent (face) and 2 consequents (fish), as shown in Figure 1-A along with the prompt: "Which fish does this person have? Use the LEFT or RIGHT key to choose." The participant responded by pressing 1 of the 2 labeled keys. The selected consequent (fish) was circled, and corrective feedback was given (Fig. 1B). In the case of an incorrect response, an alert beep also sounded. There were 3 stages of acquisition, each with increasing numbers of trial types. As the consequents could seem in either left–right ordering, there were 4 trial types in Acquisition Stage 1, 8 in Acquisition Stage 2, and 12 in Acquisition Stage 3. Each stage consisted of a maximum of 8 blocks, each consisting of 1 instance of each trial type in random order. Acquisition Stages 1 and 2 terminated early if the participant reached criterion performance of 8 consecutive correct responses; Acquisition Stage 3 terminated early if the participant reached criterion performance of 12 consecutive correct responses. The start of a new training stage was not signaled to the participant.

At the conclusion of Acquisition Stage 3, these instructions seemed (translated into Arabic): "Good! In this part of the experiment, you will need to remember what you have learned so far. You will NOT be shown the correct answers. At the end of the experiment, the computer will tell you how many you got right. Good luck!" The transfer phase followed. There were 16 trials: all 6 trial types from the acquisition phase plus the 2 new test trial types: face A2 presented along with the 2 fish X2 and Y2 for the participant to choose between, and face B2 presented along with the 2 fish X2 and Y2 for the participant to choose between, with the consequents in each possible left–right ordering. On each trial, the screen showed 1 face and 2 fishes; the fish chosen by the participant was circled, but no corrective feedback was given. Trial order was random for each participant.

RESULTS

Behavioral Testing

As described above, the acquired equivalence task has 2 phases: acquisition and transfer. Besides replicating earlier results of,[18] the aim of this study was to study the effects of anticholinergics and depression on learning and transfer performance in patients with PD.

Below, we present the results in each task phase separately.

Acquisition Phase

Four healthy controls and 2 patients with PD failed to reach criterion for learning the task in phases 1 and two. So, we excluded these results (controls: N = 12, patients with PD: N = 12). We conducted a WMW test with group and number of errors in acquisition phase as test variable. Patients with PD on dopaminergic medications made significantly more errors than HC participants (Mann–Whitney $U = 35.5$, $n_1 = 12$, $n_2 = 12$, $P = 0.035$ 2-tailed) (Fig. 2A). This is qualitatively similar to the results of (Fig. 2B).[18]

Among patients with PD, depression status affects performance on acquisition, as patients with PD BDI-II scores significantly correlated with the number of errors in the acquisition phase (Spearman rho; $r = 0.73$,

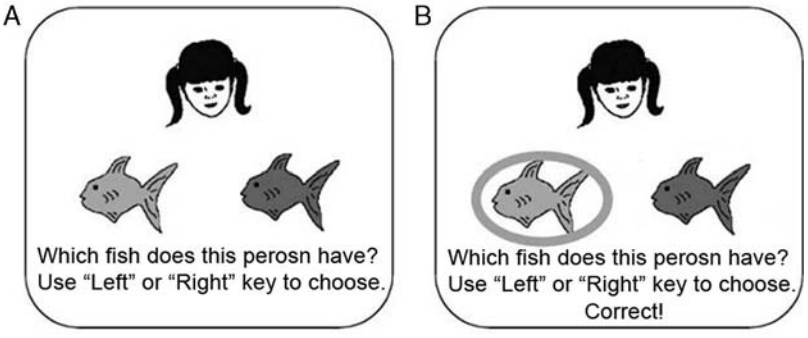

FIGURE 1. Example screen events during 1 trial. A, Stimuli appear B, Participant responds and corrective feedback is given.

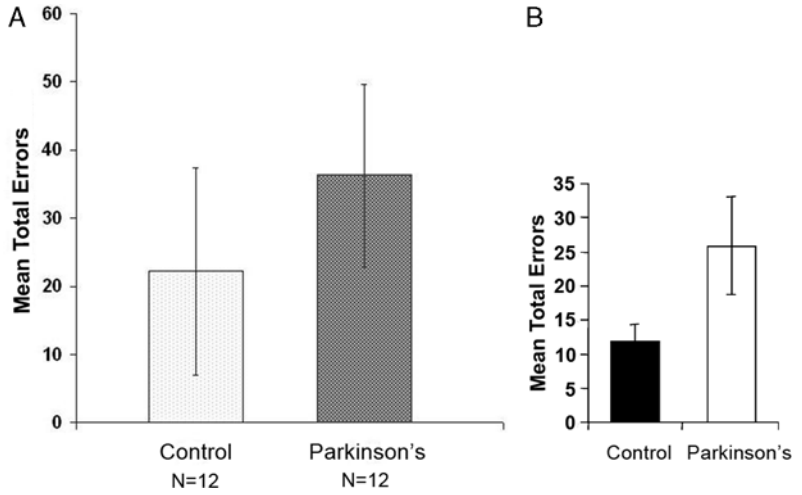

FIGURE 2. A, Total errors to criterion (± SEM) in the acquisition phase (stages 1 to 3). B, Adapted with permission from *J Cogn Neurosci.* 2003;15:185–193. Figure 1; Total errors to criterion (± SEM) in the acquisition phase (stages 1 to 3).

$P = 0.007$) (Fig. 3A). However, HC participants' BDI-II scores and acquisition number of errors did not show the same significant correlation (Fig. 3B, Spearman rho; $r = 0.31$, $P = 0.327$). The correlation between depression status (BDI-II score) and the severity of symptoms (UPDRS) fell short of statistical significance (Spearman rho; $r = 0.548$, $P = 0.065$). KW test revealed a significant effect of group, defined according to BDI II scores (nondepressed HCs, depressed HCs, nondepressed PD, depressed PD), on performance on acquisition [$\chi 2(3, N = 24) = 8.603$, $P = 0.035$]. Overall, 7 of the 12 patients with PD were classed as having depression, defined as BDI-II score greater than 13. This subgroup of depressed patients with PD made significantly more errors on acquisition than the nondepressed patients with PD (Fig. 4A, WMW test; Mann–Whitney $U = 4$, $n_1 = 7$, $n_2 = 5$, $P = 0.028$ 2-tailed). Two of the 12 HC participants also scored above 13 on the BDI-II; when the performance of the depressed control participants was compared with that of nondepressed control participants, no difference was detected (WMW test; Mann–Whitney $U = 5$, $n_1 = 2$, $n_2 = 10$, $P = 0.282$ 2-tailed). In addition, when performance of the remaining nondepressed control participants was compared against the nondepressed PD subgroup, there was no group difference in acquisition (WMW test; Mann–Whitney $U = 19$, $n_1 = 5$, $n_2 = 10$, $P = 0.462$ 2-tailed).

There was no effect of group, defined according to the use of anticholinergics (HCs, on anticholinergics PD, not on anticholinergics PD), on performance on acquisition [KW test; χ^2 (2, $N = 24$) = 4.459, $P = 0.108$). Patients with PD who were on anticholinergics (7 patients with PD) did not carry out differently from those who did not receive anticholinergics (5 patients with PD) (WMW test; Mann–Whitney $U = 15$, $n_1 = 7$, $n_2 = 5$, $P = 0.685$ 2-tailed). In addition, there was no effect of group (HCs, on amantadine PD, not on amantadine PD) on performance on acquisition [KW test; χ^2 (2, $N = 24$) = 4.459, $P = 0.108$). Performance on acquisition of the PD subgroup who received amantadine (6 patients with PD)

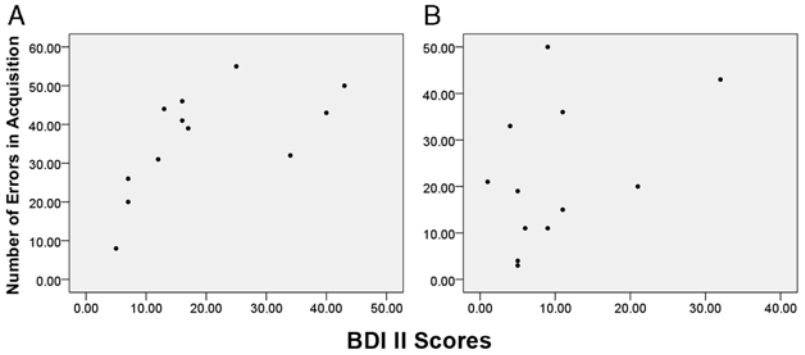

FIGURE 3. A correlation between BDI II scores and number of errors in the acquisition phase for: (A) patients with PD (N = 12) (Spearmen rho; r = 0.73, $P = 0.007$), (B) Healthy control participants (N = 12) (Spearman rho; r = 0.31, $P = 0.327$).

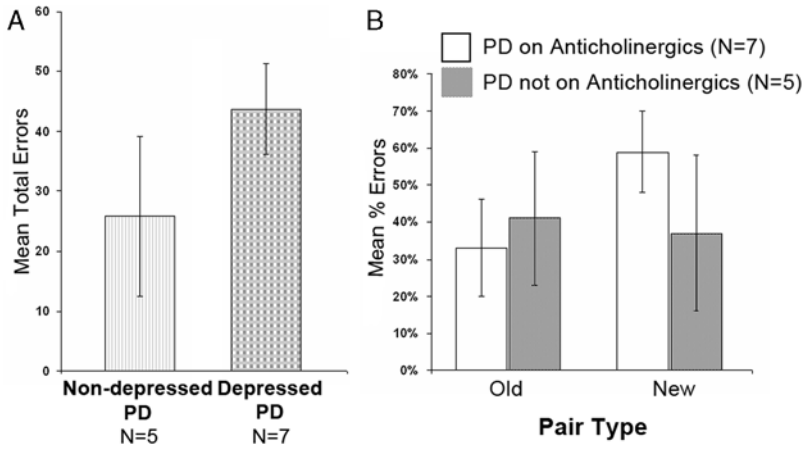

FIGURE 4. A, Total errors to criterion (± SEM) in the acquisition phase for depressed and nondepressed PD. B, Transfer error performance, mean percent errors (± SEM) on the old (earlier trained) and new pairs for PD who receive anticholinergics and those who do not.

was the same as those who did not (6 patients with PD) (WMW test; Mann–Whitney $U = 17$, $n_1 = 6$, $n_2 = 6$, $P = 0.873$ 2-tailed).

Transfer Phase

Old Pairs: In the transfer phase, WMW test revealed no group difference between patients with PD on dopaminergic medications and HC participants in performance on testing of the already acquired pairs (old pairs) (Mann–Whitney $U = 47.5$, $n_1 = 12$, $n_2 = 12$, $P = 0.156$ 2-tailed). This finding is similar to the results of Myers et al.[18]

There was no effect of group on performance on testing of the old pairs (KW test; groups according to BDI II scores: χ^2 (3, $N = 24$) = 4.177, $P = 0.243$; groups according to use of anticholinergics: χ^2 (2, $N = 24$) = 2.604, $P = 0.272$; groups according to use of amantadine: χ^2 (2, $N = 24$) = 2.02, $P = 0.364$). There were no significant differences among PD subgroups on testing of the old pairs. Depression status among patients with PD showed no effect on performance (WMW test; Mann–Whitney $U = 7$, $n_1 = 7$, $n_2 = 5$, $P = 0.086$ 2-tailed), neither did the use of anticholinergics (WMW test; Mann–Whitney $U = 11$, $n_1 = 7$, $n_2 = 5$, $P = 0.289$ 2-tailed) nor the use of amantadine (WMW test; Mann–Whitney $U = 16.5$, $n_1 = 6$, $n_2 = 6$, $P = 0.809$ 2-tailed).

New Pairs: The PD on dopaminergic medications and the HC groups did not differ significantly in transfer to the new pairs (WMW test; Mann–Whitney $U = 43.5$, $n_1 = 12$, $n_2 = 12$, $P = 0.097$ 2-tailed), which replicates findings.[18]

KW test showed no effect of group according to BDII II scores and use of amantadine on transfer to the new pair [groups according to BDI II scores: χ^2 (3, $N = 24$) = 4.241, $P = 0.237$; groups according to use of amantadine: χ^2 (2, $N = 24$) = 2.856, $P = 0.24$]. However, there was a significant effect of group, according to the use of anticholinergics on transfer to the new pair [KW test; χ^2 (2, $N = 24$) = 6.26, $P = 0.044$]. Among patients with PD, depressed and nondepressed subgroups showed no effect on performance on transfer of the new pair (WMW test; Mann–Whitney $U = 16.5$, $n_1 = 7$, $n_2 = 5$, $P = 0.869$ 2-tailed). In contrast, patients with PD who received anticholinergics made significantly more errors than those who did not receive anticholinergics (Fig. 4B, WMW test; Mann–Whitney $U = 5.5$, $n_1 = 7$, $n_2 = 5$, $P = 0.048$ 2-tailed). However, the use of amantadine had no effect on the PD subgroups on transfer of the new pair (WMW test; Mann–Whitney $U = 16.5$, $n_1 = 6$, $n_2 = 6$, $P = 0.808$ 2-tailed).

DISCUSSION

In this study, we used an acquired equivalence task to compare behavioral function in medicated patients with PD and HC participants, depressed and non depressed patients with PD, and patients with PD receiving anticholinergic medications (trihexyphenidyl) and those who do not. This study was conducted in an Arabic speaking population with participants who had less formal education than those in the original study of Myers et al.[18] Overall, the current results replicate those of the earlier study: patients with PD tested on dopaminergic medication made significantly more errors than HC during the acquisition phase, but not during the transfer phase.

Among the PD group, depressed patients were significantly more impaired on acquisition than nondepressed patients. We also found that BDI-II scores correlated with the performance on the acquisition phase of the task. Our finding of impairment in stimulus-response learning (in the acquisition phase) among depressed patients is in agreement with existing data showing that depression is associated with nigral dysfunction[32] and with cognitive impairment in tasks that test striatal function.[33] It is probably the case that depression further exacerbates dopamine dysfunction in patients

with PD.[30] Alternatively, a dysfunctional dopaminergic system might lead to the development of depression.

Animal models of depression show decreased dopaminergic activity in the mesolimbic system rather than the nigrostriatal system.[39–41] Other studies show that tricyclic antidepressants facilitate dopamine release in the nucleus accumbens in animal models of depression.[39,42] Studies also show that dopamine receptor stimulation plays an important role in the mechanism of action of antidepressants.[43,44] These findings raise more questions about the possible interaction between the mesolimbic and the nigrostriatal dopaminergic systems and interaction with other neurotransmitter systems that are implicated in the pathogenesis of depression, namely the serotonergic system.

Many studies suggest that psychiatric manifestations in PD might be caused by ventral striatum dopaminergic deficit and depletion of serotonin and norepinephrine.[45] For example, postmortem studies in PD suggest that the serotonergic dorsal raphe show some degenerative changes.[46] Therefore, depression in PD might be a reflection of serotonergic system dysfunction. However, computational models point to dopaminergic system dysfunction as the cause of impairment on acquisition of incrementally acquired feedback-based learning,[5,6] but this does not rule out a possible role of serotonin.

Now we turn to how anticholinergics affected cognitive performance. In trials that include transfer to a new pair of stimuli, patients with PD on anticholinergics (trihexyphenidyl) were significantly more impaired than patients with PD who did not receive anticholinergics, suggesting that the use of trihexyphenidyl may detrimentally affect hippocampal function. This is consistent with prior studies in humans showing that transfer performance is selectively disrupted, in nondemented elderly humans with hippocampal atrophy[19] and in amnesic patients with bilateral MT damage.[47] In addition, animal studies of acquired equivalence implicate the entorhinal cortex in the transfer phase.[48]

Earlier studies showed that the use of the anticholinergic trihexyphenidyl for treatment of PD causes confusion and impairment of memory.[15,49,50] In addition, the use of other antimuscarinic agents, such as scopolamine, has a detrimental effect on hippocampal function.[51–53] Nonetheless, other studies show that the cholinergic system is already dysfunctional in PD.[2,54] Studies conducted on animal models show that systemic injection of scopolamine significantly increases the number of active dopaminergic neurons in the substantia nigra.[55] It is perhaps the case that anticholinergic treatment enhances basal function sufficiently to remediate dopamine reductions in affected structures (eg, striatum) but produces a hyperdopaminergic state in otherwise intact brain structures (eg, hippocampus). Even though dopamine and acetylcholine are colocalized in the central nervous system,[56–58] this study did not investigate their interaction.

BDI-II scores significantly correlated with the number of errors during acquisition in patients with PD. This finding points out nigral/striatal involvement in depression in PD, and may be in depression per se. But, the correlation between BDI-II scores and acquisition errors in HC participants was short of significance; thus, we cannot make a generalization about the effect of subclinical depression on striatal function in individuals without PD. Conversely, recent imaging studies suggest that some patients with depression who show structural abnormalities at the level of the substantia nigra are possibly at an elevated risk of later developing definite PD.[32] But, nonmotor manifestations of PD (such as depression) are the earliest to appear.[59] This early neurotransmitter imbalance in the basal ganglia might disrupt other systems that have been indicated in the pathogenesis of depression.

To our knowledge, this is the first study to investigate the effects of depression and the use of anticholinergic medications on cognitive function in PD within a single task. Depression and anticholinergic effects on cognitive function are dissociable. Further study of depression in PD is required to outline the associated cognitive deficits and develop a better understanding of the mechanisms and systems involved. Anticholinergic use for the treatment of Parkinson disease should be further addressed to beneficial and detrimental effects of anticholinergic therapy on the brain areas that these drugs affect.

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