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Spatial and Object Working Memory Deficits in Parkinson's Disease are Due to Impairment in Different Underlying Processes

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Abstract

Working memory maintenance processes for visual-spatial and visual-object information were evaluated in patients with Parkinson's disease (PD). PD patients and controls performed a working memory task with two conditions that differed only in the aspect of the stimuli that the participant was instructed to remember: their locations or shapes. Maintenance processes were investigated by measuring accuracy over 1 s, 5 s, and 10 s delays. Results indicated that patients were impaired in maintaining object information over the delay. In contrast, the patients showed impairment on the spatial condition only when the to-be-remembered stimulus was highly similar in location to the probe, but this impairment was equivalent across the delays, suggesting that this deficit was not due to maintenance impairment. These results suggest that deficits in working memory for spatial and object information are mediated by distinct cognitive processes in nondemented patients with PD and may differ in their pathophysiological basis.

Keywords

Parkinson's disease; working memory; caudate nucleus; striatum; dopamine

Working memory is a limited capacity information processing system responsible for encoding and transiently maintaining perceptual representations so that they are available in the absence of information from the environment (Jolicoeur & Dell'Acqua, 1998; Ranganath, DeGutis, & D'Esposito, 2004; Woodman & Vogel, 2005). More specifically, *encoding* processes are thought to bring transient perceptual representations into a more durable working memory store, and *maintenance* processes hold them there so that the information can be used to guide cognition and behavior over brief delays. Prefrontal cortex is widely understood to play a critical role in working memory (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster, 1973, 1998; Goldberg, Berman, Randolph, Gold, & Weinberger, 1996; Quintana, Yajeya, & Fuster, 1988; Wager & Smith, 2003), and the caudate nucleus also appears to plays a role either directly or through its functional and anatomical connections with prefrontal cortex. This latter assertion is based on studies showing non-human primates with caudate lesions (Levy, Friedman, Davachi, & Goldman-Rakic, 1997; Niki, Sakai, & Kubota, 1972) and patients with caudate dysfunction due to Parkinson's disease (PD) (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Gilbert et al., 2005; Lewis et al., 2003; Lewis, Dove, Robbins, Barker, & Owen,

2004; Owen, Iddon, Hodges, Summers, & Robbins, 1997) to be impaired on working memory tasks.

Although a deficit in working memory is common in patients with PD, spatial and object working memory may be differentially impaired. A few studies show similar spatial and object working memory deficits in patients with PD (Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000; Pillon et al., 1998), but a number of others indicate that there is greater spatial than object working memory impairment, and this pattern is most frequently observed in patients who are in mild to moderate disease stages (Bradley et al., 1989; Owen et al., 1993, 1997; Postle, Jonides, Smith, Corkin, & Growdon, 1997; Postle, Locascio, Corkin, & Growdon, 1997; Swainson et al., 2000; Taylor, Saint-Cyr, & Lang, 1986). This behavioral dissociation is consistent with evidence that PD may selectively impact brain structures that support spatial working memory as compared to object working memory. Dopamine depletion appears to be greatest in the anterodorsal extent of the head of the caudate nucleus (Kish, Shannak, & Hornykiewicz, 1988), and dopamine uptake sites in the head and body are reduced more dorsally than ventrally (Joyce, 1993; Kaufman & Madras, 1991; Piggott et al., 1999)[1]. In the normal brain, cortical regions implicated in visual-spatial and visual-object processing have remarkable segregation in their connections to the caudate nucleus, such that visual-spatial processing areas (e.g., posterior parietal cortex) project preferentially to the dorsal and lateral sections of the head, and visual-object processing areas (e.g., inferior temporal cortex) project most strongly to the tail and the ventral genu (Baizer, Desimone, & Ungerleider, 1993; Ungerleider & Mishkin, 1982; Yeterian & Pandya, 1991, 1993, 1995). Functional segregation within the caudate nucleus is also apparent with the dorsal head of the caudate involved in spatial working memory and more caudal or ventral regions involved in object working memory (Cohen, 1972; Divac, Rosvold, & Szwarcbart, 1967; Iverson, 1979; Levy et al., 1997; Postle & D'Esposito, 1999). Taken together, these findings suggest that a selective deficit in spatial working memory in mild to moderate PD could be explained by greater disruption of visual-spatial processing circuits that involve anterodorsal regions of the caudate nucleus.

A second major issue surrounding the nature of the working memory deficit in PD concerns whether the deficit is specific to maintenance processes. The integrity of working memory maintenance processes in PD has been examined by varying the length of the delay between presentation and recall of the memoranda with the assumption that maintenance deficits would be greater at the longer delays. Although some studies showed a greater working memory deficit with increasing delays (Marie, Lozza, Chavoix, Defer, & Baron, 2007; Perbal et al., 2005; Sullivan, Sagar, Cooper, & Jordan, 1993), most studies have found no effect of delay length on the working memory performance of PD patients with either verbal stimuli (Fournet et al., 2000; Graceffa, Carlesimo, Peppe, & Caltagirone, 1999; Marie et al., 1995; Sullivan et al., 1993), spatial stimuli (Fournet et al., 2000; Ketcham, Hodgson, Kennard, & Stelmach, 2003; Le Heron, MacAskill, & Anderson, 2005), or visual pattern stimuli that likely require both object and spatial processing (Owen et al., 1993; Sahakian et al. 1988). These results suggest that working memory impairment in patients with PD is not due to an underlying deficit in maintenance processes under most conditions; however, to our knowledge, whether working memory deficits are related to maintenance processes in PD has not been separately examined for both spatial and object information within the same study.

The purpose of the present study was to further investigate whether PD is associated with a selective impairment in spatial working memory as compared to object working memory, and to investigate whether the nature of any observed impairment is consistent with a maintenance deficit. This was carried out by comparing patients with PD and normal control subjects on

[1]It should be noted that these neuropathological studies in PD did not examine the tail of the caudate, so it is unknown whether this pattern of dopamine loss extends to the most posterior regions of this structure.

object and spatial working memory tasks that manipulated the delay period. In addition, the degree of similarity between the to-be-remembered stimuli and the probe stimuli was manipulated in order to determine whether the patients would show an impairment related to the grain of resolution[2] of representations in their working memory stores. In other words, it may be that PD patients can encode generalized representations of object or spatial stimuli but not their precise parameters. Although not a direct manipulation of encoding processes per se, the similarity manipulation could have an impact on the early stage encoding processes that bring perceptual representations into working memory stores.

Current Experiment

Although there is evidence that patients with PD are selectively impaired in spatial working memory compared to object working memory (e.g., Postle, Jonides, et al., 1997), this dissociation and its relationship to maintenance processes remains open to question. To address this issue, patients with PD and normal control subjects were compared on an adaptation of Postle and colleagues' (1997) delayed response task that was composed of analogous spatial working memory and object working memory conditions. The two conditions differed only in task instructions (i.e., what the participant should attend to, location or shape). In the current adaptation, participants viewed two abstract 'target' shapes for 2 seconds on a computer screen, and after a variable delay (1, 5, or 10 s) were asked to judge if a third 'probe' shape matched either of the first two shapes in location (spatial condition) or shape (object condition). The distance and shape similarity between the probe and targets were systematically varied to examine whether requiring a more precise representation in working memory might differentially impact spatial and object working memory in patients with PD. Delay period was manipulated to examine whether different maintenance requirements might differentially impact spatial and object working memory. A short delay of 1 s was included because previous studies showed that encoding of 1 to 3 visually presented stimuli (letters or symbols) continue after offset of the stimuli but are complete by about 1 s (Jolicoeur & Dell'Acqua, 1998). Thus, performance at this delay was expected to reflect the integrity of perceptual and attentional encoding processes required to bring perceptual representations into working memory stores. Performance at the longer 5 and 10 s delays was expected to reflect the ability to maintain visual-spatial and visual-object information in working memory.

Method

Participants

Eighteen nondemented patients with PD (10 men and 8 women) and 18 normal controls (10 men and 8 women) participated in the study. The patients with PD were recruited from the Movement Disorders Clinics at the San Diego VA Health Care System and the University of California, San Diego. All patients were diagnosed by a board-certified neurologist with specialty training in movement disorders. The diagnosis of PD was based on the presence of at least two of the following symptoms: (1) resting tremor, (2) rigidity, or (3) bradykinesia, the absence of atypical symptoms, and a positive response to dopaminergic medication. The patients had been diagnosed an average of 6.1 years (range = 1 – 20, SD = 4.7) prior to their participation in the study. Patients exhibited mild to moderate motor impairments as rated by Hoehn and Yahr's (1967) scale (M = 2.0, range = 1 – 2.5, SD = 0.5). The mean score on the motor examination section of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn, Elton, & the UPDRS Development Committee, 1987) was 21 (range = 1 – 45, SD = 11.5). Using a clinical classification method proposed by Kang et al. (2005) and based on specific UPDRS items, 8 patients were classified as tremor-dominant, 7 were akinetic-rigid, and 3 were

[2]We would like to thank an anonymous reviewer for suggesting this term.

mixed (features of tremor and akinetic-rigid). The patients were treated with their normal regimen of dopaminergic agents at the time of testing (see Table 1). None were taking anticholinergic or antipsychotic medications. One patient was taking Citalopram Hydrobromide 20mg daily, one patient was taking Fluoxetine, 40mg daily, and no patients were taking anxiolytic medications. No controls were taking antidepressants or anxiolytics. Patients were tested when on their usual medications and at the time of day when they felt most cognitively alert.

Normal control participants were recruited from relatives of patients or by newspaper advertisement. All participants were screened for a history of significant neurological disease (other than PD), serious psychiatric illness (major affective disorder or schizophrenia), and substance abuse. In addition, participants were excluded if they scored below 132 on the Dementia Rating Scale (DRS; Mattis, 1976) or worse than 20/50 on the Rosenbaum Pocket Vision Screener.

The demographic characteristics of the patients and controls are presented in Table 2. The PD patients and controls did not differ significantly in age, $t(34) = 0.02$, $p = .98$, $d < .01$, years of education, $t(34) = 0.33$, $p = .74$, $d = .11$, Rosenbaum acuity scores, $t(31) = 0.51$, $p = .61$, $d = .17$, or DRS scores, $t(33) = 1.66$, $p = .11$, $d = 0.47$. [3] The range of DRS scores for the controls was 136 to 144, and the range for the PD patients was 133 to 144. The PD patients scored higher than the controls on the Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986), $t(32) = 3.02$, $p < .01$, $d = 1.04$. The range of GDS scores was 0 to 8 for controls 0 to 11 for the PD patients.[4]

Apparatus and stimuli

Stimuli were presented on a 50.8 cm monitor. Randomization and presentation of stimuli, and recording of response accuracy and reaction time, were executed by Eprime software, version 1.1. Participants responded via two keys on a standard computer keyboard, which were designated by colored stickers and labeled with a sign behind the keys. The sign read “match” behind the “z” key, which was colored blue, and “different” behind the “/” key, which was colored red.

The sixty-one shapes used as stimuli were created using a method developed by Attneave and Arnoult (1956). Briefly, this method involves randomly selecting six coordinate pairs on a 10 × 10 matrix. The peripheral points are connected to form a convex polygon and any remaining interior points are each connected to a randomly determined side. Lines that define sides to which interior points are connected are removed. The height and width of the shapes each subtended approximately 1.1° × 1.1° of visual angle (there was some slight variability in the size of the shapes). The shapes were solid white and presented against a black background.

The perceptual similarity of the shapes was established in a preliminary study. Shapes were presented to seven healthy control participants (mean age = 26.0) in a series of pairs that were either non-matched pairs (i.e., 2 different shapes), or matched pairs (i.e., 2 of the same shape). For non-match pairs, each shape was paired with every other shape twice to comprise 3660 non-match trials. The same number of match trials was also presented. All trials were presented randomly. Participants were instructed to press the match key with their left hand if the two shapes presented on the screen were the same and the different key with their right hand if they

[3]Due to time limitations, the Rosenbaum, GDS, and DRS were not given to 1, 2, and 3 controls, respectively. All patients completed all measures.

[4]Despite the significant difference in GDS scores between the groups, none of the patients exhibited more than a minimal level of self-reported depression, and on average, the GDS scores of the patients were not in the depressed range. Further, analyses to be discussed in the results did not indicate that differences in depression levels accounted for any of the observed deficits. Thus, despite the differences between the groups on the GDS, this does not appear to have contributed to the pattern of results reported below.

were different. Median reaction times were computed and transformed into z-scores for the non-match trials. Pairs with the longest reaction times were classified as "similar" and used in the working memory task as "similar" target-probe pairs. Pairs with reaction times clustered around a median reaction time z-score of zero were considered "dissimilar" and used as "dissimilar" target-probe pairs. Pairs with the shortest reaction times were considered "irrelevant."[5] Adjustments were made to balance the number of times each shape appeared in each category.

The similarity of target-probe pairs also varied in terms of location. Possible locations were 24 equidistant points around the circumference of an imaginary circle centered on the fixation cross with a radius of 11.3° visual angle. Spatially similar targets were 15 or 30 degrees from their corresponding probe, spatially dissimilar targets were 45 or 60 degrees from the probe, and irrelevant targets were 75 to 285 degrees from the probe. See Figure 1 for an example of the stimulus display.

Procedure

Participants gave written informed consent, and the study was approved by the University of California, San Diego Institutional Review Board. Spatial and object conditions were presented that differed only in which stimulus aspect the participants were instructed to attend to: stimuli locations or stimuli shapes. The spatial and object conditions were presented on two different days and the order of presentation of conditions was counterbalanced across groups. For the two conditions, each trial began with the presentation of a centered white fixation cross for 500 ms, followed by two target stimuli for 2 seconds. The screen was blank during the subsequent variable delay (1, 5, or 10 seconds), which was followed by presentation of the probe stimulus (see Figure 1). Participants were instructed to press the "match" key with their left hand if the probe stimulus matched one of the target stimuli in location or shape (depending on the experimental condition), or the "different" key with their right hand if it did not. The probe remained on the screen until the participant responded. The participants were instructed to strive for accuracy and no limit was placed on reaction time. Although accuracy was the primary metric of analysis, reaction times were also recorded and analyzed.

Within each trial of the spatial working memory condition, the probe stimulus was more similar in location to the "relevant" target stimulus than to the "irrelevant" target stimulus. Likewise, within each trial of the object working memory condition, the probe was more similar in shape to the "relevant" target than to the "irrelevant" target. Twenty-five percent of relevant target stimuli were classified as "similar" to their corresponding probe stimulus, 25 percent as "dissimilar," and 50 percent were an identical match. These classifications applied to both spatial and object similarity within both conditions. Spatial similarity of the relevant target-probe pair was fully counterbalanced within levels of object similarity so that spatial similarity did not predict object similarity, and object similarity was counterbalanced within levels of spatial similarity so that object similarity did not predict spatial similarity. Furthermore, spatial and object similarity were counterbalanced within delay period. In total, there were 240 randomly presented trials in each condition with breaks provided after every 40 trials.

So that the relationship between working memory impairment and motor symptoms could be investigated, all patients underwent the UPDRS motor examination and the Finger Tapping Test (Reitan, 1969). The UPDRS was administered by one of the authors (D. Song), who is a movement disorders specialist.

[5]Although clearly all stimuli are relevant to the task, the term "irrelevant" is used to describe those stimuli that are most distant in terms of location and shape from the probe stimulus.

Results

The primary trials of interest were the "similar" and "dissimilar" non-match trials. Because the correct response is always "no" on these trials, a response bias could affect the proportion correct. If response bias differed across various test conditions, it could affect the pattern of results and mask true task-related differences in working memory. Therefore, response bias was examined across conditions and experimental manipulations before carrying out the primary working memory analyses.

Response bias

Response bias was examined using the response-bias index from the two-high threshold model of recognition discriminability (Snodgrass & Corwin, 1988). This index is defined as the probability of responding "yes" (i.e., the target matches the probe) when in the uncertain state. A 2 (group) X 2 (condition) X 3 (delay) mixed-model analysis of variance (ANOVA) was performed to examine the effects of group and condition (spatial vs. object) manipulations on response bias. Similarity level was not included in this analysis because the same proportion correct value for match trials is used in the response bias calculations for similar and dissimilar non-match trials. The group X condition X delay interaction was significant, $F(2, 68) = 3.19$, $p = .047$, $\eta_p^2 = .09$,[6] and was explored with separate 2 (group) X 3 (delay) ANOVAs for each condition. In the spatial condition, the group X delay interaction was not significant, $F(2, 68) = 1.29$, $p = .28$, $\eta_p^2 = .04$, but there was a main effect of delay, $F(2, 68) = 13.21$, $p < .01$, $\eta_p^2 = .28$, indicating that response bias for both groups changed from "yes" to "no" between the 1- and 5-second delays. In the object condition, the group X delay interaction was not significant, $F(2, 68) = 2.17$, $p = .12$, $\eta_p^2 = .06$, but there was a main effect of delay, $F(2, 68) = 39.89$, $p < .01$, $\eta_p^2 = .54$, indicating that response bias changed from "yes" to "no" with increasing delays. The groups did not differ in their overall response bias in the spatial, $F(1, 34) = .47$, $p = .50$, $\eta_p^2 = .01$, or object, $F(1, 34) = .06$, $p = .80$, $\eta_p^2 < .01$, conditions.

Based on these results, correction for response bias was used in the primary working memory analyses for several reasons. First, the group X condition X delay interaction was significant indicating that the response biases of the groups differed across the two conditions and delay periods. Second, response bias at the individual subject level could impact the results if not accounted for in the primary working memory analyses. Third, initial examination of the accuracy data for similar and dissimilar trials (see Table 3) indicated that delay had little or no impact on either groups' working memory performance, but the response bias analyses suggested that this surprising effect was an artifact of response-bias changes over the delay. For these reasons, the recognition discriminability index from the two-high threshold model of recognition memory was used as the measure of working memory accuracy, which is calculated as the hit rate minus the false alarm rate. This recognition discriminability index was chosen because it has been shown to be independent of response bias (Snodgrass & Corwin, 1988).

Working memory performance

Proportion correct and recognition discriminability index are presented as a function of group, type of working memory task (spatial vs. object conditions) and task manipulations (delay and similarity) in Table 3. Recognition discriminability values approach 1.0 as accuracy increases and approach 0 as accuracy approaches chance levels (i.e., 50% correct). The recognition discriminability scores were analyzed using a 2 (group) X 2 (condition) X 2 (similarity) X 3 (delay) mixed-model ANOVA.[7] The results of this ANOVA revealed that the group X

[6]Partial eta-squared was selected to quantify the proportion of variability attributable to each effect because unlike classical eta-squared, it can be used to compare effect sizes across studies with different factors in the model.

condition X similarity X delay interaction was not significant, $F(2, 68) = 0.59$, $p = .56$, $\eta_p^2 = .02$. Significant three-way interactions were the group X condition X similarity interaction, $F(1, 34) = 6.28$, $p = .02$, $\eta_p^2 = 16$, the group X condition X delay interaction, $F(2, 68) = 5.07$, $p < .01$, $\eta_p^2 = .13$, and the condition X similarity X delay interaction, $F(2, 34) = 14.88$, $p < .01$, $\eta_p^2 = .30$. Neither the group X similarity X delay interaction, $F(2, 68) = 0.56$, $p = .58$, $\eta_p^2 = .02$, nor the group X condition interaction, $F(1, 34) = 0.16$, $p = .69$, $\eta_p^2 = .04$, were significant. There was a main effect of group, $F(1,34) = 5.60$, $p = .02$, $\eta_p^2 = .14$, indicating that, on average, the PD patients had lower recognition discriminability scores than controls. Similar trials were more difficult than dissimilar trials, $F(1, 34) = 137.43$, $p < .01$, $\eta_p^2 = .80$, trials with longer delays were generally more difficult than those with shorter delays, $F(2, 68) = 21.72$, $p < .01$, $\eta_p^2 = .39$, and the spatial condition was more difficult than the object condition, $F(1, 34) = 13.44$, $p < .01$, $\eta_p^2 = .28$.

To further examine the group X condition X similarity interaction separate 2 (group) X 2 (similarity) ANOVAs were performed within each condition after collapsing across delay (see Figure 2). For the spatial condition, the group X similarity interaction was significant, $F(1, 34) = 5.49$, $p = .03$, $\eta_p^2 = .14$. Independent samples t-tests indicated that the PD patients were significantly impaired relative to controls on the similar trials, $t(34) = 2.36$, $p = .02$, $\eta_p^2 = .14$, but not on the dissimilar trials, $t(34) = 1.10$, $p = .28$, $\eta_p^2 = .03$. For the object condition, the group X similarity interaction was not significant, $F(1, 34) = 0.02$, $p = .89$, $\eta_p^2 < .01$, but there was a main effect of group, $F(1, 34) = 4.40$, $p = .04$, $\eta_p^2 = .12$. In sum, the PD patients exhibited a working memory deficit with spatially-similar stimuli but not with spatially-dissimilar stimuli, while they were equally impaired in working memory for similar and dissimilar object-based stimuli.

To further examine the group X condition X delay interaction separate 2 (group) X 3 (delay) ANOVAs were performed for each condition after collapsing across similarity (see Figure 3). For the spatial condition, the group X delay interaction was not significant, $F(2, 68) = 0.65$, $p = .52$, $\eta_p^2 = .02$, but there was a trend for a main effect of group, $F(1, 34) = 3.48$, $p = .07$, $\eta_p^2 = .09$, with PD patients' overall discriminability scores tending to be lower than those of the controls, and there was a main effect of delay, $F(2, 34) = 10.97$, $p < .01$, $\eta_p^2 = .24$, which is examined in the next paragraph separately for similar and dissimilar stimuli. For the object condition, the group X delay interaction was significant, $F(2, 68) = 5.11$, $p < .01$, $\eta_p^2 = .13$. Post-hoc independent samples t-tests indicated that the groups did not differ significantly in their recognition discriminability at the 1 s delay, $t(34) = 1.24$, $p = .22$, $\eta_p^2 = .04$, or at the 5 s delay, $t(34) = 1.05$, $p = .30$, $\eta_p^2 = .03$. However, PD patients were less accurate than controls at the 10 s delay, $t(34) = 3.00$, $p < .01$, $\eta_p^2 = .21$. The PD patients' significant loss of information over the 10 s delay in the object condition suggests that they have a specific deficit in maintaining object-based information in working memory. Their normal performance at the 1 s and 5 s delays indicates that object-based processes required to perceive, attend to, and encode information is not impaired. In contrast, the delay did not impact the overall poor discriminability of the PD patients in the spatial working memory condition, which suggests that their ability to maintain spatial information in working memory remains intact.

To further examine the condition X similarity X delay interaction, separate 2 (similarity) by 3 (delay) ANOVAs were performed within each condition, collapsed across group. In the spatial task, the similarity by delay interaction was significant, $F = 13.88$, $p < .01$, $\eta_p^2 = .28$. Recognition discriminability for dissimilar items declined between 1 s and 5 s, $t(35) = 3.00$, $p < .01$, $\eta_p^2 = .21$, and there was a trend for decline between 5 s and 10 s, $t(35) = 2.0$, $p = .06$,

[7]The same ANOVA was performed with accuracy as the dependent variable. The same effects were significant, except for the group by task by delay interaction, $F(2, 68) = 0.30$, $p = .74$. As noted earlier, this had to do with the fact that the accuracy results did not take into account the response bias differences across the delay and between the two groups.

η_p^2 = .10. Recognition discriminability for similar items improved between the 1 s and 5 s delays, t = −3.27, p < .01, η_p^2 = .23, but declined between the 5 s and 10 s delays, t(35) = 4.25, p < .01, η_p^2 = .34. The similarity by delay interaction was also significant in the object task, F = 13.28, p < .01, η_p^2 = .28. Recognition discriminability for dissimilar items declined between both the 1 s and 5 s delays, t(35) = 6.63, p < .01, η_p^2 = .56, and the 5 s and 10 s delays, t(35) = 3.67, p < .01, η_p^2 =.28. Recognition discriminability for similar items declined between the 1 s and 5 s delays, t(35) = 2.48, p = .02, η_p^2 =.15, but did not significantly change between the 5 s and 10 s delays, t(35) = .29, p = .78, η_p^2 < .01.

Mood and Motor Correlates of Object and Spatial Working Memory

The relationships among mood, motor performance and the spatial and object working memory deficits in PD patients were also examined. For these analyses, we created indices that best reflected the spatial and object working memory deficits shown by the patients. The spatial working memory index was operationally defined as the recognition discriminability score on spatially similar trials of the spatial working memory task collapsed across all delay periods. The object working memory index was operationally defined as the recognition discriminability score at the 10 s delay of the object working memory task collapsed across similar and dissimilar trials. The scores of PD patients on the GDS were not significantly correlated with the spatial working memory index, r = −.30, p = .23, or the object working memory index, r = .06, p = .81, suggesting that mood state was not significantly contributing to the working memory deficits observed in the PD patients. Total scores on the UPDRS motor examination section were not significantly correlated with spatial working memory, r = −.40, p = .097 (although there was a trend) or object working memory, r = −.25, p = .32. An objective measure of bradykinesia based on the average of patients' right and left Finger Tapping Test (Reitan, 1969) scores was significantly correlated with spatial working memory, r = .58, p = .02, but not object working memory, r =.23, p = .37. Factor scores were calculated based on a UPDRS factor analysis performed by Stebbins and Goetz (1998) to operationalize rest tremor (Factor 2) and bradykinesia (sum of Factors 1, 4, and 5).[8] Tremor factor scores did not significantly correlate with spatial working memory, r = .23, p = .35, or object working memory, r = .13, p = .61, and bradykinesia factor scores did not significantly correlate with spatial working memory, r = −.41, p = .09 (although there was a trend) or object working memory, r = −.29, p = .24.

Reaction time

A 2 (group) X 2 (condition) mixed-model ANOVA with median reaction time on correct response trials (collapsed across similarity and delay) revealed only a main effect of condition, F(1, 34) = 20.58, p < .01, η_p^2 = .38 (see Table 4). Although all participants responded slower in the object condition than in the spatial condition, reaction times of the PD and NC participants did not differ, F(1, 34) = .69, p = .41, η_p^2 = .02.

Discussion

The results of the present study indicate that distinct processing impairments underlie the deficits in visual-object and visual-spatial working memory exhibited by patients with mild to moderate PD. The visual-object working memory deficit of PD patients seems to primarily reflect an inability to maintain information because their performance was normal after 1 s and 5 s delays but impaired after a 10 s delay. Maintenance of spatial information in working memory does not appear to be impaired because the magnitude of the patients' deficit did not worsen as a function of the length of the delay period, which is consistent with previous findings

[8]Continuous measures of bradykinesia and tremor were used rather than comparing the akinetic-rigid and tremor-dominant subtypes so that all subjects, including those with mixed symptom presentations, could be included in the analyses.

(Fournet et al., 2000; Ketcham et al., 2003; LeHeron et al., 2005). Rather, the patients showed an equal impairment across the delay intervals and only when a high degree of specificity was required to judge whether locations were the same or different (i.e., when the non-match spatial locations were similar).

Although several previous studies found visual-object working memory to be intact in mild to moderate PD patients who were impaired in spatial working memory (e.g., Owen et al., 1993,1997;Postle, Jonides, et al., 1997;Taylor et al., 1986), this dissociation is usually only seen with relatively short delay intervals. Consistent with these findings, spatial working memory was equally impaired across the delay intervals, whereas it was only at the 10 s delay interval that object working memory was impaired. Similarly, Costa and colleagues (2003) found that object working memory was more impaired than spatial working memory in patients with PD when they imposed an 11 s delay. These results support the notion that the spatial and object working memory deficits in PD are mediated by distinct processes.

The findings from this study suggest that the PD patients' impairment in the spatial condition is not due to an impaired maintenance process; however, it is not completely clear as to why the patients were impaired in this condition. Their deficit was only seen on trials when precise location parameters were required, and it emerged from the earliest (1 s) delay and was consistent across the delays, suggesting that the impaired process in question involved an earlier stage of processing. One possible interpretation is that the patients were not able to specifically encode the target locations, which impacted the grain of resolution of spatial representations transferred into working memory stores. This possibility is suggested by the finding that PD patients were impaired for similar but not dissimilar trials on the spatial task. It may be that such an encoding deficit is related to a pure spatial encoding process that is specifically associated with working memory, but is not part of the maintenance stage. Furthermore, such an encoding deficit may not be related to lower-level perceptual encoding processes. We previously found that PD patients were equally impaired on a spatial and object perceptual matching task (Possin & Filoteo, 2007), suggesting that the spatial difficulties shown by the PD patients in the present study are more likely due to a higher-level encoding process that occurs after perceptual encoding is complete, an encoding process that may be specific to the transfer of information into spatial working memory stores.

Another possibility is that the PD patients' deficit in the spatial working memory condition is due to problems with spatial attention. Numerous studies have identified altered spatial attention in PD (Filoteo et al., 1997; Filoteo et al., 2002; Pollux & Robertson, 2001; Wylie & Stout, 2002; Wright, Burns, Geffen, & Geffen, 1990; Yamaguchi & Kobayashi, 1998; but see Hsieh, Lee, Hwang, & Tsai, 1997), whereas other studies suggest that these patients are unimpaired on some purely object-based attentional tasks (Lee, Wild, Hollnagel, & Grafman, 1999; Possin, Cagigas, Strayer, & Filoteo, 2006). These past studies suggest that PD patients' deficit in the spatial condition may be related to attentional deficits. There is also evidence that inhibitory spatial attention and spatial encoding are related or may represent overlapping processes. Specifically, Castel, Pratt, & Craik (2003) demonstrated that performing a secondary spatial working memory task eliminated the effects of spatial-based inhibitory attention in normal subjects, and based on their findings, suggested that the inhibited locations were encoded into spatial working memory stores. These findings suggest a possible link between spatial working memory and inhibitory attention. Future research should compare PD patients on tests of spatial-based and object-based inhibitory attention to examine whether an attentional impairment may help explain the spatial working memory deficit that has frequently been reported in PD.

The spatial working memory condition was more difficult than the object working memory condition for both groups, and so one might wonder if the spatial task required more effortful

processes and that this might account for the present results. Although we can not completely rule this out from the results of this study, Postle, Jonides, et al (1997) showed that PD patients were selectively impaired on a similar spatial working memory task, but not on an object working memory task, with a 3 s delay after equating the perceptual difficulty for each participant and using spatial and object working memory tasks that were equally difficult for controls. Furthermore, the different pattern of deficits we observed in the present study on the spatial and object working memory tasks can not necessarily be accounted for by one type of process (spatial vs. object processing) being more effortful than the other. That is, it is not completely clear why a less effortful task (such as the object task) would result in a deficit in working memory maintenance, and why a more effortful task (such as the spatial task) would result in a possible encoding or attentional deficit.

For both patients and controls, recognition discriminability on the spatial working memory task improved between the 1 s and 5 s delays when the to-be-remembered targets were spatially similar to their probes, but not when they were dissimilar. This was somewhat surprising because one might expect performance to remain stable or decline between these delays. One possible explanation for this finding is that encoding processes, which continue after stimuli offset (Vogel & Luck, 2002) were not maximally complete by 1 s, and so the trials that placed greater demands on working memory encoding processes (by requiring more precise representations in working memory stores) were more difficult at 1 s than at 5 s. This interpretation is consistent with findings that encoding processes are slower to complete when the memory load is greater (Akyürek, Elkan, Hommel, Bernhard, & Pierre, 2007; Crewther, Lawson, & Crewther, 2007). It is not clear why the same finding was not seen for object-based stimuli, but it is possible that object-based information may have been maximally consolidated more quickly than the spatial-based information. Importantly, these interesting effects of similarity at each delay period by condition were the same for both patients and controls, suggesting that whatever the underlying cause of the increased performance at the 5 s delay in the spatial condition, it cannot necessarily account for the pattern of differences between patients and controls.

The PD patients' deficit on the spatial working memory condition showed an association with bradykinesia, which is thought to be mediated by dopamine loss in the caudate nucleus (as well as the putamen) (Brucke et al., 1997; Grafton, 2004; Otsuka et al., 1996). Dopamine loss in the striatum may affect spatial encoding and/or attentional processes either directly or through the disruption of cortical-striatal circuits. Spatial encoding and attention may be more disrupted than object encoding in PD because of disproportionate dopamine depletion in the anterodorsal extent of the head of the caudate nucleus (Kish et al., 1988). A number of studies have shown that this region of the caudate plays an important role in spatial working memory (Cohen, 1972; Divac et al., 1967; Levy et al., 1997; Postle & D'Esposito, 1999) and receives projections from dorsolateral prefrontal and posterior parietal cortical regions involved in spatial working memory and spatial attention (Awh & Jonides, 2001; Baizer et al., 1993; Levy & Goldman-Rakic, 1999; Selemon & Godman-Rakic, 1985; Ungerleider & Mishkin, 1982; Yeterian & Pandya, 1991, 1993).

The neuropathological underpinnings of the maintenance deficit in object working memory observed in the present study are less clear. It is possible that neural circuits that include the tail of the caudate nucleus could be involved in the object maintenance deficit that we observed. These circuits include inferior temporal and ventral prefrontal cortices (Baizer et al., 1993; Saint-Cyr, Ungerleider, & Desimone, 1990; Yeterian & Pandya, 1991, 1995) that play critical roles in processing visual-object information (Iverson, 1979; Sala, Rama, & Courtney, 2003; Ungerleider & Mishkin, 1982) and maintaining information in working memory (D'Esposito, Postle, & Rypma, 2000; Petrides, 1989, 1994). This possibility remains tentative, however, because the inferior temporal cortex appears to be important for perceptual, but not mnemonic,

aspects of object working memory (Belger et al., 1998), and levels of dopamine in the ventral prefrontal cortex are relatively preserved in early PD (Cools, Barker, Sahakian, & Robbins, 2001; Swainson et al., 2000). Furthermore, the extent to which PD pathology directly affects the tail of the caudate is unknown because most neuropathological studies have examined the head and body of the caudate nucleus (Joyce, 1993; Kaufman & Madras, 1991; Kish et al., 1988; Piggott et al., 1999). Clearly, additional research is needed to clarify the neuropathological basis of the object working memory maintenance deficit of patients with PD.

In interpreting the results of the present study, it is important to consider that all patients were on dopamine replacement therapy at the time of testing. Studies that have examined the effects of dopaminergic medications on spatial working memory in PD have found either no effect of medication (Fournet et al., 2000; Lange, Paul, Naumann, & Gsell, 1995) or improved performance (Costa et al., 2003; Lange et al., 1992), and improved performance on object-based working memory tasks with dopaminergic medications has also been reported (Costa et al., 2003; Mollion, Ventre-Dominey, Dominey, & Broussolle, 2003). These results suggest that the working memory deficits observed in the present study are due to the effects of PD pathology rather than dopamine treatment, although it cannot be ruled out that the medications may have had differential effects on the various aspects of working memory under study. Future research is needed to better understand these medication effects on working memory in PD.

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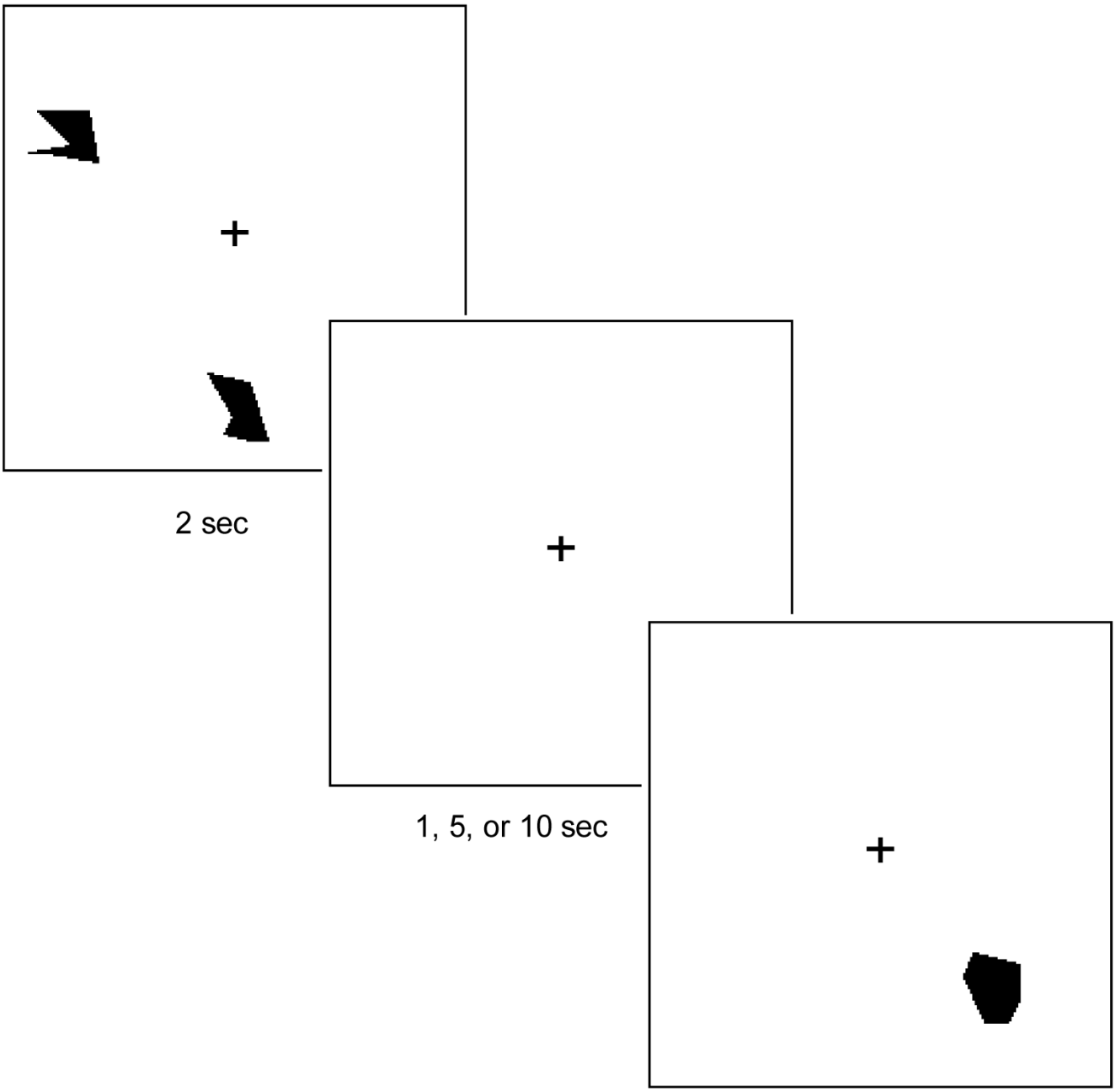

Figure 1.
Schematic diagram of a single trial. Colors have been inverted for this figure.

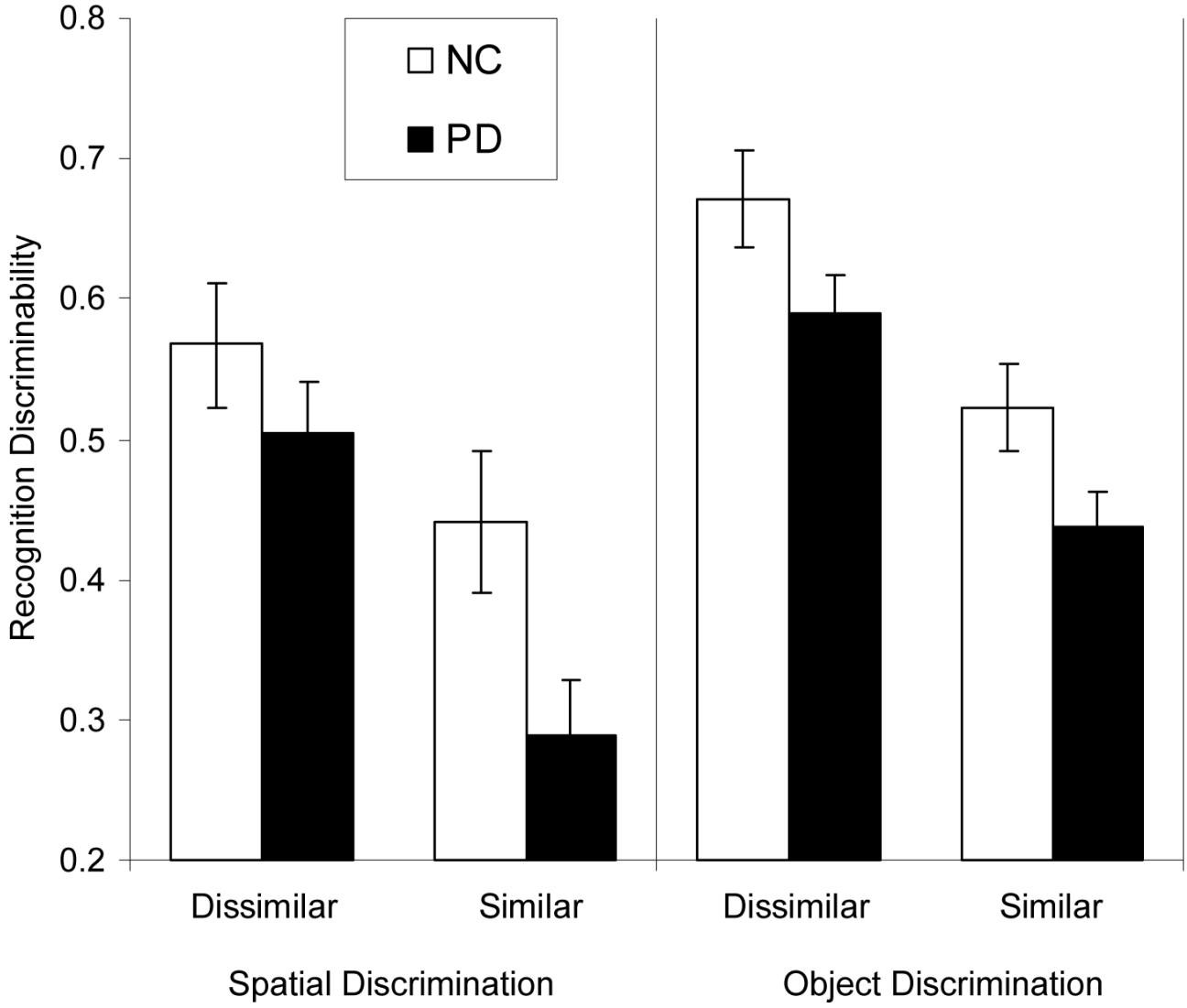

Figure 2.
Mean spatial and object recognition discriminability as a function of group and similarity. Bars represent standard errors.

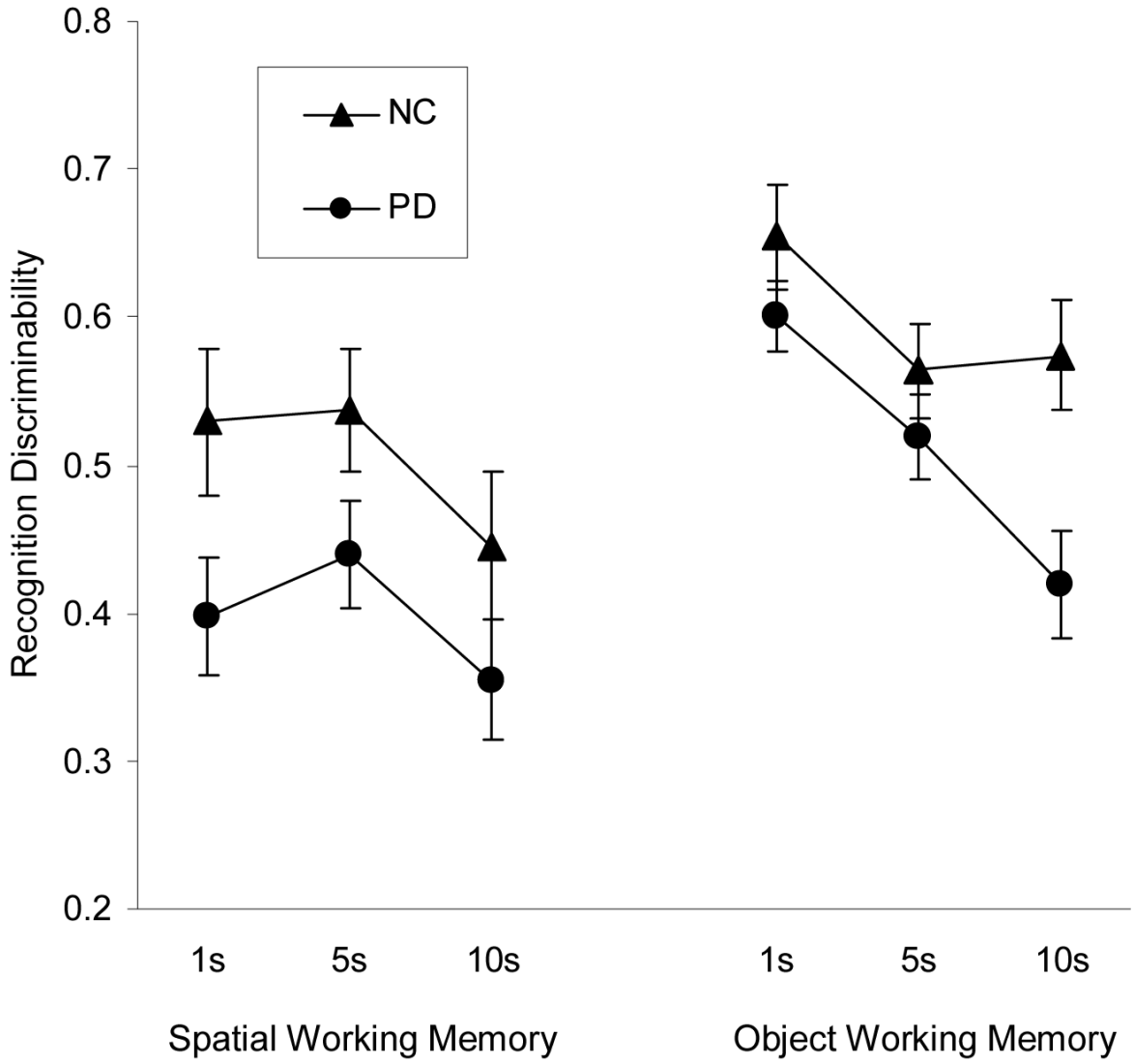

Figure 3.
Mean spatial and object recognition discriminability as a function of group and delay. Bars represent standard errors.

Table 1

Disease Characteristics and Medications of the Patients

No.	Age	Disease duration[a]	H & Y Stage	Antiparkinsonian medication, daily dose (mg) [b]
1	68	20	2.0	LeCa 300/75, En 800, Pr 1
2	67	4	2.5	LeCa 600/150, Pr 5, Am 100
3	63	4	2.5	Se 10, Ro 5
4	63	4	1.0	LeCa 400/100
5	57	4	1.0	LeCa 200/50, Pr 2, Se 5
6	72	10	2.0	LeCa 1200/300, Pr 2
7	48	8	1.0	LeCa 400/100, Ca 100, En 600, Pr 23
8	53	1	2.0	Pr 3
9	68	4	1.5	LeCa 200/50
10	66	10	2.0	LeCa 1000/250, Pr 14
11	75	4	2.0	LeCa 100/25
12	56	7	2.5	LeCa 400/100, Pr 2
13	64	14	2.5	LeCa 100/25, LdCaEn 350, Se 10
14	75	3	2.5	LeCa 400/100, En 200
15	79	4	2.0	LeCa 800/200, Se 5
16	64	3	2.0	Se 1
17	79	5	2.0	LdCaEn 300, Se 10, Ro 15
18	88	3	2.5	LeCa 300/75, Ro 3

[a] Age and disease duration in years.

[b] LeCa, levodopa-carbidopa; En, entacapone; Pr, pramipexole; Am, amantadine; Ro, ropinirole; Se, selegiline; Ca, carbidopa; LdCaEn, levodopa-carbidopa-entacapone.

Table 2

Demographic Characteristics of Patients and Normal Controls

	Age[a]	Education[a]	Proportion male	DRS	GDS	Rosenbaum
PD	67.4 (10.1)	16.7 (2.3)	.6	139.4 (3.4)	5.2 (3.7)	20/28.8 (8.2)
NC	67.3 (7.8)	16.4 (2.2)	.6	141.1 (2.4)	1.9 (2.4)	20/27.5 (6.6)

[a]Age and disease duration in years.

Values represent mean (s.d.).

Table 3

Proportion Correct and Recognition Discriminability by Condition, Delay, Group, and Similarity

	Spatial working memory			Object working memory		
	1s	**5s**	**10s**	**1s**	**5s**	**10s**
	Proportion correct					
PD						
Similar	.51 (.16)	.67 (.14)	.54 (.16)	.60 (.11)	.72 (.14)	.77 (.11)
Dissimilar	.81 (.10)	.80 (.09)	.81 (.09)	.84 (.10)	.88 (.09)	.86 (.12)
Match	.75 (.08)	.72 (.09)	.69 (.10)	.89 (.07)	.75 (.11)	.62 (.11)
NC						
Similar	.67 (.16)	.76 (.13)	.62 (.19)	.69 (.14)	.73 (.16)	.80 (.16)
Dissimilar	.84 (.09)	.83 (.10)	.83 (.10)	.90 (.09)	.89 (.12)	.89 (.10)
Match	.79 (.12)	.76 (.10)	.71 (.11)	.88 (.15)	.77 (.16)	.75 (.18)
	Recognition discriminability					
PD						
Similar	.26 (.21)	.38 (.18)	.23 (.22)	.49 (.11)	.44 (.15)	.38 (.16)
Dissimilar	.53 (.16)	.50 (.16)	.48 (.16)	.71 (.12)	.60 (.12)	.46 (.17)
NC						
Similar	.45 (.24)	.50 (.20)	.37 (.26)	.55 (.16)	.49 (.13)	.53 (.17)
Dissimilar	.61 (.20)	.57 (.18)	.52 (.19)	.75 (.16)	.64 (.16)	.62 (.16)

Values represent mean (s.d.).

Table 4

Median Reaction Time by Condition and Group (msec)

	PD	NC
Spatial Working Memory	1,582 (523)	1,489 (876)
Object Working Memory	1,916 (568)	1,640 (709)

Values represent median (s.d.).