Spatial, but Not Object, Delayed Response Is Impaired in Early Parkinson's Disease

Bradley R. Postle
Massachusetts Institute of Technology

John Jonides and Edward E. Smith
University of Michigan

Suzanne Corkin
Massachusetts Institute of Technology

John H. Growdon
Massachusetts General Hospital

The authors hypothesized that the pathophysiology of early Parkinson's disease (PD) may selectively target structures that support visual working memory for spatial relations but leave structures that support working memory for featural characteristics of objects relatively intact. Fifteen PD and 15 normal control participants took a visual delayed-response test with a spatial condition and a (nonspatial) object condition, equating the perceptual difficulty of the tests for each participant. The stimuli were irregular polygons presented at different locations on a computer screen. Results revealed a selective impairment of spatial delayed response in PD, indicating a disruption of spatial working memory unconfounded by sensory processing difficulties. The selectivity of this deficit may reflect the circumscribed nature of pathophysiological change affecting the caudate nucleus in early PD.

Working memory has been defined as "a brain system that provides temporary storage and manipulation of the information necessary for such complex cognitive tasks as language comprehension, learning, and reasoning" (Baddeley, 1992, p. 556). Recent research has supported a model of working memory as a modular system, consisting, at a minimum, of executive processes that operate on the contents of at least two working memory storage systems, the visuospatial sketchpad and the phonological loop (D'Esposito et al., 1995; Jonides, 1995; Paulesu, Frith, & Frackowiak, 1993; Smith et al., 1995). Advances in our understanding of the

organization of the mammalian visual system into two parallel pathways (Ungerleider & Mishkin, 1982) have led to proposals that visual working memory may be organized into at least two discrete neural circuits supporting independent, material-specific modules of visual working memory. Goldman-Rakic and colleagues (Goldman-Rakic, 1987; Wilson, O'Scalaidhe, & Goldman-Rakic, 1993) have proposed in the monkey that dorsolateral prefrontal cortex supports visual spatial working memory function and that ventrolateral prefrontal cortex supports visual working memory for features of objects. Spatial–object dissociations in visual working memory have also been reported in behavioral (Smith et al., 1995; Tresch, Sinnamon, & Seamon, 1993) and neuroimaging (Courtney, Ungerleider, Keil, & Haxby, 1996; Smith et al., 1995) studies of humans. Petrides, however, has proposed that a region of dorsolateral prefrontal cortex is recruited for the performance of visual working memory tasks, regardless of the nature of the stimulus materials (Owen, Evans, & Petrides, 1996; Petrides, 1994). Elucidating the cognitive and neural architectures that underlie working memory has become an important goal of contemporary memory research.

Parkinson's disease (PD) is a neurological disorder characterized by a loss of dopaminergic cells in the substantia nigra pars compacta and in other pigmented nuclei of the brainstem. These lesions lead to a depletion of dopamine in the striatum, which is heavily interconnected with frontal cortex. Although the disease was first described in 1817, it was until recently viewed as a pure motor disorder: The cardinal signs of PD, often referred to as extrapyramidal signs (EPS), are resting tremor, muscular rigidity, and bradykinesia (slowness of movement; Adams & Victor, 1993). Recent research, however, has indicated that a critical characteristic of PD is a progressive decline in cognition, including memory, and capacities associated with the frontal

lobes, such as problem solving and abstract reasoning (Cronin-Golomb, Corkin, & Growdon, 1994; Growdon & Corkin, 1986; Growdon, Corkin, & Rosen, 1990; Levin & Katzen, 1995; Sagar, Sullivan, Gabrieli, Corkin, & Growdon, 1988; Taylor, Saint-Cyr, & Lang, 1986). Working memory relies in part on the frontal lobes (Cohen et al., 1994; Fuster & Alexander, 1971; Petrides, Alivisatos, Evans, & Meyer, 1993; Stern et al., 1995; Wilson et al., 1993) and is associated with the neurotransmitter dopamine (Brozoski, Brown, Rosvold, & Goldman, 1979; Murphy, Arnsten, Goldman-Rakic, & Roth, 1996; Williams & Goldman-Rakic, 1995). PD, therefore, is an appropriate model for examining the effects of frontal-lobe dysfunction and impaired dopaminergic neurotransmission on working memory in humans.

Previous research has revealed a deficit in spatial working memory in PD: Taylor et al. (1986) have reported impaired performance in PD on a spatial delayed-recognition test; Freedman and Oscar-Berman (1986) on a test of delayed response; Morris et al. (1988) on a spatial reasoning test (Tower of London); Bradley, Welch, and Dick (1989) on a test of spatial mental imagery for a road map; and Owen, Beksinska, et al. (1993) and Owen, James, et al. (1992) on spatial subject-ordered choosing, block tapping, and the Tower of London. Three of these reports have also provided evidence for intact performance in PD on memory tasks for which the critical to-be-remembered variable was nonspatial: Taylor et al. on delayed-response tests using novel nonsense designs or words; Bradley et al. on a verbal memory task; and Owen et al. (1992) on a delayed pattern recognition test. These results, however, were not interpreted as evidence for "what/where" dissociations. Taylor et al. hypothesized that their spatial delayed-response test taxed participants' abilities to make recency judgments, a capacity the authors attributed to the frontal lobes (which they assumed were compromised in PD), whereas they hypothesized that their object and word delayed-response tests placed stronger demands on novelty judgments, a capacity that they attributed to the temporal lobes (assumed to be intact in PD). Bradley et al. concluded that PD results in reduced storage capacity in the visual–spatial sketchpad, but their choice of tasks did not permit assessment of object working memory. The spatial and nonspatial memory tasks used by Owen et al. (1992) differed procedurally as well as materially and, thus, could not provide conclusive evidence for a selective deficit in spatial working memory in PD. In our laboratory, we have observed a selective impairment in spatial conditional associative learning in PD (Postle, Corkin, & Growdon, 1993). This task required participants to learn the randomly determined pairings of six paired associates. The trial-and-error learning process required by this task placed considerable demands on working memory. Our results indicated that PD participants performed poorly in a condition requiring memory for locations in space, and performed at the level of age- and education-matched normal control participants on a condition requiring memory for objects. Additional analyses also indicated that PD patients made a disproportionately large number of working memory errors in the spatial condition (Postle, Locascio, Corkin, & Growdon, in press). Thus, there is preliminary evidence for a selective spatial working memory deficit in PD.

The deficit in spatial working memory in PD could result if PD pathophysiology selectively targets structures that support working memory for spatial relations between objects but leaves structures that support working memory for features of visual stimuli relatively intact. Neuroanatomical findings in nonhuman primates indicate that the basal ganglia and frontal cortex are strongly interconnected by a series of discrete, parallel "loops" of neural circuitry (Alexander & Crutcher, 1990; Hoover & Strick, 1993; Middleton & Strick, 1994). For example, dorsolateral frontal cortical regions project preferentially to dorsal and central regions of the head and body of the caudate nucleus, whereas more caudally and ventrally situated frontal cortical regions project preferentially to ventral and central regions of the head and body of the caudate nucleus (Pandya & Yeterian, 1991). Posterior cortical regions corresponding to the dorsal and ventral visual streams also project to discrete regions of the caudate nucleus, with posterior parietal-lobe efferents terminating dorsolaterally and temporal-lobe efferents terminating ventromedially (Selemon & Goldman-Rakic, 1985). Evidence from neuropathological studies of PD patients suggests that PD pathology may result in a gradient of depletion of dopamine in the head of the caudate nucleus, so that dorsolateral caudate nucleus is impacted more severely (Kaufman & Madras, 1991; Kish, Shannak, & Hornykiewicz, 1988). Thus, reduction of dopamine in the dorsolateral head of the caudate nucleus consequent to degeneration of nigrostriatal projections could affect spatial working memory by disrupting function in the regions of the caudate nucleus that receive projections from posterior parietal cortex and dorsolateral prefrontal cortex, and that, in turn, project back to dorsolateral prefrontal cortex through the thalamus. In contrast, a relative sparing of dopaminergic afferents to the ventromedial head of the caudate nucleus in the early stages of PD may leave the loop of neural circuitry linking the temporal cortex, the ventromedial head of the caudate nucleus, and the ventrolateral prefrontal cortex relatively intact. Thus, early PD pathophysiology would not disrupt object working memory.

We designed the present experiment to test the hypothesis that early PD pathophysiology creates a selective deficit in spatial visual working memory. We gave PD patients and a group of normal control participants a visual delayed-response test with a spatial condition and a (nonspatial) object condition. Participants viewed two abstract target stimuli that appeared briefly on a computer screen, and then, after a 3-s delay, judged whether a third stimulus matched either of the previous two in either spatial location or featural identify. The two conditions differed only in the instructions and, thus, provided a direct test of our hypothesis. We predicted that PD patients would be selectively impaired on the spatial condition of the task.

In addition to our principal hypothesis, we designed our study to investigate three questions that have important implications for cognitive function in PD: the interaction of EPS and cognitive dysfunction (as indexed by working memory in our study), the interaction of side-of-onset of disease with working memory performance, and the interac-

Table 1
Subject Characteristics

Group	No. of participants		Age		Education		Blessed dementia scale score: Memory and orientation section[a]		Hoehn & Yahr Stage (max. = 5)
	M	F	M	SD	M	SD	M	SD	
Parkinson's disease[b]	12	3	62.7	10.0	16.1	2.7	0.53	0.8	0–2[c]
Normal control	9	6	66.1	5.9	16.7	2.9	0.46	0.66	—

Note. Max. = maximum.
[a]Statistics from Blessed, Tomlinson, & Roth (1968). [b]Of the 15 PD patients, 12 were tested on anti-parkinsonian medications, and 3 were unmedicated at the time of testing. [c]Hoehn & Yahr Stages 0 ($n = 1$), 1 ($n = 7$), 1.5 ($n = 1$), and 2 ($n = 6$).

tion of age with working memory performance. First, because the degree of motoric dysfunction in PD is believed to be related to the loss of dopaminergic pigmented cells in the substantia nigra pars compacta (Adams & Victor, 1993), and because we have hypothesized that a deficit in spatial working memory in PD may result from dopamine depletion, we also tested PD participants on several measures of basic and complex motor functions. Previous work in our laboratory indicated that no relation exists between degree of motor dysfunction and motor learning in PD (Corkin, Snow, Mapstone, & Growdon, 1991). The delayed-response task used in the present study, however, undoubtedly recruits neuronal networks different from those recruited by motor learning tasks. Second, a positron emission tomography (PET) study of normal participants performing the delayed-response task that was used in the present study (Smith et al., 1995) found lateralized activation of cortical areas, with right-hemisphere areas being preferentially activated during performance of the spatial condition, and left-hemisphere areas being preferentially activated during performance of the object condition. Because onset of PD motor signs is typically restricted to one side of the body (and, thus, PD pathology is presumed to begin earlier in one cerebral hemisphere), we included the independent variable side-of-onset of motor signs in our analyses as a test of the lateralization hypothesis. Finally, beginning in young adulthood, dopamine levels decline steadily as a function of age (De Keyser, Eibinger, & Vauquelin, 1990; Morgan & Finch, 1988; Morgan, May, & Finch, 1987; Rinne, Lonnberg, & Marjamaki, 1990). Canavan et al. (1989) have speculated that an interaction between parkinsonian nigrostriatal degeneration and age-related dopamine loss may result in more severe cognitive deficits in older than in younger PD patients (regardless of age of disease onset). Thus, we planned to test for an interaction of age with performance on the delayed-response task in the PD group.

Method

Participants

Participants in this study included 15 patients with PD and 15 normal control participants (Table 1). A power analysis performed with preliminary data (that showed a between-group difference in spatial delayed-response performance of 7.3%) indicated that these sample sizes were sufficient to permit detection of the hypothesized effect (power = .8; $p = .05$, two-tailed test). The two groups did

not differ significantly in mean age or in mean years of education. The PD participants were selected from the Massachusetts General Hospital Movement Disorders Unit, where the diagnosis of idiopathic PD was established by clinical examination according to standard neurological criteria (Calne, Snow, & Lee, 1992). All of the PD patients were in the early stages of disease (Hoehn & Yahr Stages 0–2).[1] Of the 15 PD patients, 11 had left-sided onset of motor signs, and 4 had right-sided onset. In addition to the hospital examination, each PD and normal control participant was examined at the MIT Clinical Research Center by a neurologist at the time of testing. These examinations assessed participants' current neurological status and established that none had dementia or depression.

EPS were measured in the PD patients with tests of both basic motor functions (assessed with simple tasks that do not require visual guidance) and complex motor functions (assessed with tests requiring high-order planning and precise coordination between sensory input and motor output). Tests of complex motor function are sensitive to bradykinesia. To explore whether delayed-response performance was associated with a deficit in basic or high-order motor capacities, we tested the PD patients on three tests of basic motor function: fine finger movement (Corkin, Growdon, & Sullivan, 1981), finger tapping (in which participants depressed a button as many times as possible for 30 s with the index finger of the left hand, the right hand, and both hands simultaneously), and grip strength (Stevens & Mack, 1959). These measures contributed to a composite basic motor score and were selected on the basis of an oblique factor analysis of data from another study (Corkin et al., 1991). The basic motor score for each participant was computed as the sum of these variables, each measured with the participant's preferred hand and each weighted by the reciprocal of its standard deviation. The formula for computing the basic motor score was as follows:

$$[((1/8.17)*\text{Fine Finger Movement Unimanual}) + ((1/8.48)*\text{Fine Finger Movement Bimanual}) + ((1/10.75)*\text{Finger Tapping Unimanual}) + ((1/11.02)*\text{Finger Tapping Bimanual}) + ((1/22.55)*\text{Grip Strength})].$$

Similarly, we explored the influence of complex motor capacities on delayed-response performance using two variables: the bradyki-

---

[1] The Hoehn and Yahr (1967) rating scale is an indicator of severity of parkinsonian EPS that is determined through neurological examination. A Hoehn and Yahr score of 0 indicates that a patient shows no evidence of EPS when taking dopamine replacement medication. A score of 1 indicates that EPS are unilateral, with minimal or no functional impairment. A score of 1.5 indicates that EPS are unilateral, with axial involvement. A score of 2 indicates that EPS are bilateral but do not impair balance.

nesia score from the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987, Table 3) and performance on the Purdue Pegboard test (Tiffin & Asher, 1948). The UPDRS bradykinesia rating is a composite of four measures: finger taps, hand movements, rapid alternating movement of hands, and body bradykinesia and hypokinesia. This ordinal measure can vary from a rating of *no bradykinesia* (0) to *severe bradykinesia* (4).

Procedure

The visual delayed-response test was modified from Smith et al. (1995) for testing participants with neurological disease. The previous study had used PET to uncover an anatomically defined double dissociation of function between two distributed cortical networks, one associated with performance of a spatial delayed-response task, the other associated with performance of an object delayed-response task (Smith et al., 1995). In the present experiment, each trial began with the presentation of two target stimuli, followed by a delay period, which was followed by the presentation of a probe stimulus (Figure 1). The stimuli were irregular polygons adapted from Attneave and Arnoult (1956) and Vanderplas and Garvin (1959). There were two conditions, spatial and object; the procedure for the two conditions differed only in the instructions. In the spatial condition, participants were instructed to judge whether the probe was in the same location on the screen or in a different location from either of the two targets. Targets appeared in randomly determined positions that lay on the circumference of an imaginary circle with a radius of 3.2° of visual angle. The three types of spatial trials included 50% match trials, in which the probe matched the spatial location of one of the targets; 25% near trials, in which the probe appeared in a spatial location that was near that of one of the targets (15°–25° distant); and 25% far trials, in which the probe appeared in a spatial location that was far from the nearest

Figure 1. Schematic diagram of a single trial in the Perceptual Test and a single trial in the Memory Test.

target (40°–50° distant). In the object condition, participants judged whether the probe matched (or mismatched) either of the targets. The three types of object trials included 50% match trials, in which the probe looked identical to one of the targets; 25% similar trials, in which the probe closely resembled one of the targets; and 25% dissimilar trials, in which the probe clearly looked different from both of the targets. The experiment used 60 archetypal shapes, with a similar, a dissimilar, and an irrelevant shape derived from each archetype. The irrelevant shape, unlike the similar and dissimilar shapes, bore no resemblance to the archetypal shape. On each trial, one archetypal shape and its associated irrelevant shape were the targets. Similarity ratings of probe stimuli had been obtained in an earlier study (Smith et al., 1995) from 15 university undergraduates, who rated the similarity of pairs of shapes on a 7-point scale. In the spatial trials, the object characteristics of the probe were always different from the targets and were systematically varied so that one half of the trials could be classified as object-similar and the other half as object-dissimilar. Conversely, in the object trials, the spatial location of the probe was always different from the locations of the two targets and was systematically varied so that one half of the spatial trials could be classified as spatial-near and the other half as spatial-far. Participants responded on each trial by pushing one of two response keys with the right and the left hands, respectively, the right-hand key indicating a "yes" response and the left-hand key a "no" response. Trials were initiated by the experimenter. On all of the tests, the dependent measure was accuracy. Participants were instructed to strive for accurate performance rather than for rapid responses. No limit was placed on response time (RT) because we did not want to penalize PD patients for their dyskinesias. RTs were recorded and analyzed, however.

Within each condition, there were two types of tests: a Perceptual test and a Memory Test. During the Perceptual Test, we held the delay constant at 250 ms and systematically varied the exposure duration of the targets on each 20-trial block until the participant achieved a criterion level of performance of 80–90% correct on two consecutive blocks. When a participant achieved this level, we began the Memory Test by keeping the exposure duration of the targets at the level determined during the Perceptual Test and increasing the delay to 3 s. In this way, we equated the perceptual demands of the Memory Test for each participant and ensured that the Memory Test assessed memory and not other confounding variables. The Memory Test consisted of four 40-trial blocks in each condition. Testing was conducted in two sessions, one for each condition—spatial and object memory—which were separated by several hours. The order of the two conditions was counterbalanced within each group.
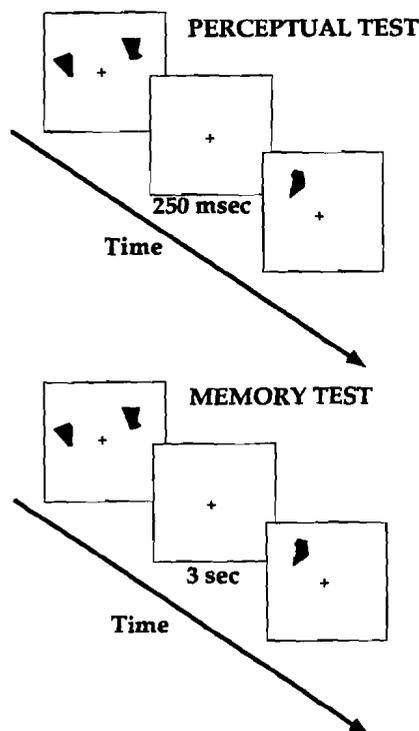
Results

Perceptual Test

Participants in each group required longer target exposures to achieve a criterion level of performance in the Object test than in the Spatial test (normal controls: $p = .01$; PD: $p < .01$; paired Wilcoxon signed-rank tests), and PD patients on average required longer target exposure durations than did the normal control participants in both conditions (Table 2). The between-group difference achieved statistical significance only in the object condition, $t(28) = 2.25, p < .05$.

Memory Test

A comparison of the mean percentage correct for normal control and PD participants in the Spatial Memory and Object Memory tests showed that the two groups differed in performance in the Spatial but not in the Object test (Figure 2). This observation was confirmed by a 2 × 2 within- and between-subjects univariate analysis of variance (ANOVA) analyzing the dependent measure of number of errors (variables: group [normal controls, PD], condition [i.e., spatial or object]) that revealed main effects of group, $F(1, 28) = 6.91, p < .05$, and condition, $F(1, 28) = 5.6, p < .05$, and an interaction of group and condition $F(1, 28) = 5.2, p < .05$. Post hoc t tests indicated that the normal control participants made significantly fewer errors than did the PD patients in the spatial condition, $t(28) = .01$, but that the two groups did not differ significantly in the object condition. Also, paired t tests indicated that the normal control participants made significantly fewer errors on the Spatial Memory test than on the Object Memory test, $t(14) = -3.38, p < .005$, but that PD patients did not.

Varying the parameter of spatial difficulty in the Spatial Memory test had a significant effect on the performance of both groups on nonmatch trials—normal controls: $t(14) = 9, p < .0001$; PD: $t(14) = 12.6, p < .0001$. Varying the parameter of object difficulty in the Spatial Memory test, however, had no significant effect on the performance of either group on nonmatch trials (Figure 3). Similarly, varying the parameter of object difficulty in the Object Memory test had a significant effect on the performance of both groups on nonmatch trials—normal controls: $t(14) = -10.4, p < .0001$; PD: $t(14) = -8.5, p < .0001$—whereas varying the parameter of spatial difficulty in the Object Memory test had no significant effect on the performance of either group on nonmatch trials (Figure 3).

Each group had faster mean RTs for the Spatial Memory test than for the Object Memory test (Table 3), but the two groups did not differ statistically in terms of RT: A 2 × 2 ANOVA analyzing the dependent measure of RT, with the measures of group and condition, revealed a main effect of condition, $F(1, 28) = 28, p < .0001$, no main effect of group and no interaction.

Interactions of EPS, Side-of-Onset, and Age With PD Memory Test Performance

Memory Test performance of PD patients was not affected by overall level of disease severity: t tests comparing Hoehn and Yahr Stage 1 participants ($n = 7$) and Hoehn and Yahr

Table 2
Perceptual Test: Target Exposure Durations

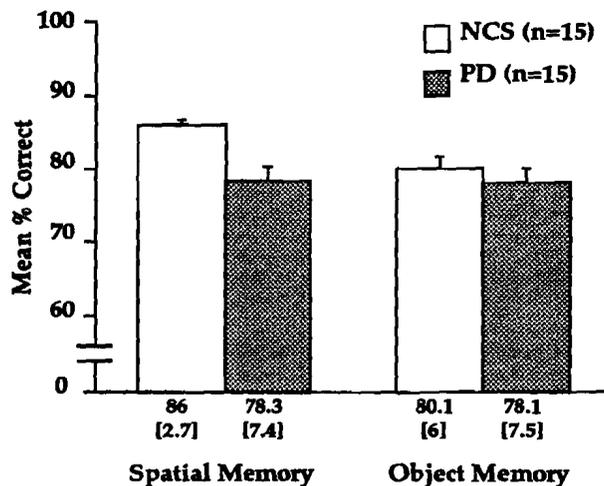| Group | Target exposure duration (ms) | | | |
| | Spatial condition | | Object condition | |
	M	SD	M	SD
Parkinson's disease	1,000	819	1,837	931
Normal control	620	615	1,236	449

Figure 2. Memory Test results: Numbers indicate mean percentage correct. Bracketed numbers indicate standard deviation. NCS = normal control participants; PD = Parkinson's disease.

Stage 2 participants ($n = 6$) on Spatial Memory test errors and Object Memory test errors revealed no significant differences between these two groups. Similarly, Memory Test performance did not correlate with degree of basic motor deficit: A repeated measures ANOVA, with the measures of condition and basic motor score, revealed no main effects and no interaction.

Memory Test performance, however, did vary in relation to measures of complex motor function. A between- and within-factors ANOVA investigating the effects of different levels of bradykinesia, 0 ($n = 4$), 1 ($n = 6$), and 2 ($n = 5$), on performance on the two conditions of the Memory Test revealed a marginally significant effect of bradykinesia, $F(2, 12) = 3.4, p = .068$, no effect of condition, and no interaction. A post hoc contrast comparing the pooled mean of bradykinesia Levels 0 and 1 to bradykinesia Level 2 revealed a significant effect of bradykinesia level, $F(1, 14) = 6.5, p < .05$, indicating that PD patients with a higher bradykinesia score performed worse on both conditions of the Memory Test (Table 4). A repeated measures ANOVA investigating the relation between Purdue Pegboard score and performance on the two conditions of the Memory Test revealed a main effect of Purdue Pegboard score, no main effect of condition, and no interaction. Post hoc regression analyses revealed a significant correlation between Purdue Pegboard score (high score indicates better performance) and Object Memory test percentage correct ($r = .576, p < .05$) and a trend toward the same relation between Purdue Pegboard score and Spatial Memory test percentage correct ($r = .43, p = .11$).

An analysis of the effect of side-of-onset of clinical motor signs in the PD group, although lacking in power because of a small number of participants in the right-side group, indicated that side-of-onset had no effect on performance: A 2 × 2 within- and between-subjects ANOVA analyzing the dependent measure of number of errors (side-of-onset of motor signs [left = 11, right = 4]; condition) revealed no
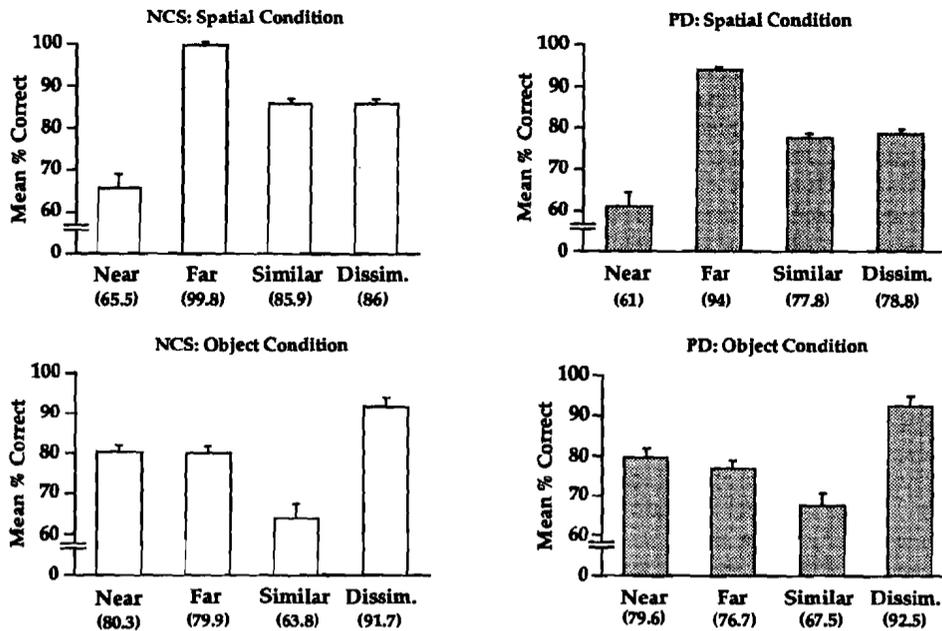
Figure 3. Effects of varying probe difficulty on nonmatch trials in the Memory Test. Numbers in parentheses indicate mean percentage correct. NCS = normal control participants; PD = Parkinson's disease; Dissim = dissimilar.

main effects and no interaction. Finally, correlations between age and Memory Test performance were not significant for either group in either condition.

Discussion

We tested the hypothesis that the neuropathological changes during the early stages of PD selectively disrupt visual working memory for spatial material. The results for a delayed-response task revealed a selective impairment of spatial delayed response in 15 PD patients relative to 15 normal control participants. This result was obtained after we had equated the perceptual demands of the test for each participant. Further analyses of the PD data indicated that this result was not influenced by basic motor function, severity of EPS, or age. Poorer performance on tests of complex motor function was associated to the same extent with lower scores on both conditions of the Memory Test, and thus, the selective deficit in spatial delayed response cannot be attributed to bradykinesia nor to the influence of a subset of PD participants more severely affected by the disease.

Our results are consistent with a model of visual working memory consisting of, at a minimum, two independent, material-specific modules, one responsible for storing and manipulating memory for locations in space and the other responsible for storing and manipulating memory for the features of objects. This interpretation would be consistent with previous reports of spatial–object dissociations in visual working memory in monkeys (Wilson et al., 1993) and in humans (Courtney et al., 1996; Postle et al., 1993; Smith et al., 1995; Tresch et al., 1993). The strongest evidence for independent systems in neuropsychological investigations comes from demonstrations of double dissociations of function (Teuber, 1955). Our experiment has shown a single dissociation, but we feel confident about our interpretation of the data because PD participants showed a performance deficit on the less difficult condition (the normal control participants achieved significantly more correct responses on the Spatial Memory test than on the Object Memory test). Thus, it cannot be argued that our results reflect an erosion of PD performance on the more difficult condition, the standard problem with interpretation of single dissociations. Additional evidence for a spatial–

Table 3
Memory Test: Reaction Time Performance

| | Reaction time (ms) | | | |
| | Spatial condition | | Object condition | |
Group	M	SD	M	SD
Parkinson's disease	1,523	532	1,757	364
Normal control	1,421	308	1,688	360

Table 4
PD Memory Test Performance (Mean % Correct) by Bradykinesia Rating

| | Bradykinesia rating | | |
Condition	0 (n = 4)	1 (n = 6)	2 (n = 5)
Spatial	80.3	81.8	72.6
Object	80.5	80.8	73.1

Note. PD = Parkinson's disease.

object distinction in visual working memory comes from the manipulation of probe difficulty. Varying spatial difficulty had considerable effect on performance of the Spatial Memory test but no effect on performance of the Object Memory test, and the converse was true for the manipulation of the parameter of object difficulty. This double dissociation replicates the finding of Smith et al. (1995) in healthy college-aged participants and provides additional evidence for two functionally independent visual working memory modules.

Our results are also consistent with previous demonstrations of impaired spatial working memory in PD (Bradley et al., 1989; Freedman & Oscar-Berman, 1986; Morris et al., 1988; Owen et al., 1992, 1993; Taylor et al., 1986) and demonstrates that early PD pathophysiology, whereas disrupting spatial visual working memory, does not interfere with object visual working memory. Our hypothesis that the spatial working memory deficit in early PD is due to a pattern of degeneration in the nigrostriatal pathway does not make assumptions about the functional organization of visual working memory in prefrontal cortex. If prefontal cortex in humans is organized into discrete dorsal and ventral networks (Wilson et al., 1993), the dopamine depletion in the dorsolateral head of the caudate nucleus would be expected to result in a functional deafferentation of an area preferentially recruited by spatial working memory tasks (dorsolateral prefrontal cortex). In contrast, if dorsolateral prefrontal cortex computes many types of working memory (Petrides, 1994), the selective disruption of spatial information projecting from the posterior parietal cortex to the dorsolateral head of the caudate nucleus (which is disproportionately affected by early PD) could lead to selectively impaired working memory processing for the spatial aspects of stimuli.

Caudate nucleus lesions have long been known to impair performance on memory tasks (Battig, Rosvold, & Mishkin, 1960; Rosvold & Delgado, 1956). Divac, Rosvold, and Szwarcbart (1967) demonstrated in the monkey that lesions placed in discrete regions of the caudate nucleus, selected by the region from which they received cortical efferents (anterodorsal head of the caudate nucleus from dorsolateral prefrontal cortex, ventrolateral head of the caudate nucleus from orbitofrontal cortex, and tail of the caudate nucleus from inferotemporal cortex), resulted in deficits that were qualitatively similar to deficits caused by lesions placed directly in the anatomically associated cortical regions. Previous studies of PD have also hypothesized that basal ganglia–prefrontal cortical interactions underlie cognitive deficits in PD (Cronin-Golomb et al., 1994; Gabrieli, Singh, Stebbins, & Goetz, 1996; Gotham, Brown, & Marsden, 1988; Owen & Robbins, in press; Taylor et al., 1986). These hypothesized interactions have been studied directly by Owen et al. (1992), who demonstrated that some of the mnemonic and attentional impairments in PD resemble those seen in patients with frontal-lobe lesions, and by Bondi et al. (1993), who found that deficits in PD on tests of verbal and visual memory and of visuoperceptual skills ceased to reach significance when performance on tests of frontal-lobe function was used as a covariate. It is likely that the selective

spatial visual working memory deficit in PD is not due to dopamine decreases directly in the prefrontal cortex, because degeneration of neurons in the ventral tegmental area (the major dopamine projection to frontal cortex) lags behind degeneration of the substantia nigra pars compacta in early stages of disease (Agid, Javoy-Agid, Ruberg, 1987).

Research in monkeys (Brozoski et al., 1979; Murphy et al., 1996; Williams & Goldman-Rakic, 1995) and in PD has established an important role for dopamine in working memory. These studies indicate that either an overabundance or an underabundance of dopamine in the principal sulcus of the monkey can result in disrupted spatial working memory performance. Two studies in humans indicate that administering L-dopa to PD patients (and thereby raising dopamine levels in the brain) has a deleterious effect on working memory performance. Thus, Gotham et al. (1988) reported that L-dopa withdrawal is associated with improved conditional associative learning and participant-ordered choosing performance (both tasks having a strong working memory component), and Owen et al. (1992) found that, on a participant-ordered choosing task, early PD patients who were nonmedicated were superior to early PD patients receiving L-dopa. In contrast, the present study lends some support to the view that decreases in dopamine levels lower working memory scores. We observed an across-conditions decline in working memory (different from the selective spatial memory deficit) that was associated with the severity of complex motor dysfunction. Although an increase in EPS may be inversely correlated with lower dopamine levels in the striatum (Cooper et al., 1991; Kieburtz et al., 1994; Richards et al., 1993), it is unclear whether a single disease process affects working memory and EPS or whether two distinct disease processes are at work. The emergence of working memory dysfunction and of EPS in PD may be due to degeneration of any one or a combination of the neurotransmitter systems targeted by PD pathophysiology—dopaminergic neurons of the substantia nigra pars compacta and of the ventral tegmental area, noradrenergic neurons of the locus coeruleus, serotonergic neurons of the raphe nuclei, or cholinergic neurons of the ventral forebrain (Growdon et al., 1990). The fact that dopaminergic drugs did not restore normal spatial working memory function emphasizes the complexity of underlying neurotransmitter deficits.

An alternative explanation for the selective deficit in spatial working memory in PD that we found in the present study is that most of the PD patients presented in clinic with an onset of EPS on the left side of the body, indicating disproportional right putaminal abnormality. The results of a PET study using our task (Smith et al., 1995) found lateralized activation of the cortical areas associated with the performance of the two conditions, with the spatial condition producing right-hemisphere activation. Thus, if unilateral striatal pathology in PD leads to a disruption of function in ipsilateral cortex, lateralization models of visual working memory would predict selective deficits in PD patients with right-hemisphere dysfunction. In our sample, however, the hemisphere linked to the onset of PD signs was not a predictor of the kind of working memory impairment.

It remains to be determined whether the selective deficit

in spatial working memory in PD shares a common etiology with other cognitive deficits associated with this disease (Brown & Marsden, 1988; Growdon et al., 1990; Levin & Katzen, 1995). Future research must now focus on the neurochemical and neurophysiological aspects of PD pathophysiology that result in the selective impairment of spatial working memory in PD.

References

Adams, R. D., & Victor, M. (1993). *Principles of neurology.* New York: McGraw-Hill.

Agid, Y., Javoy-Agid, F., & Ruberg, M. (1987). Biochemistry of neurotransmitters in Parkinson's disease. In C. D. Marsden & S. Fahn (Eds.), *Movement disorders* (Vol. 2, pp. 166–230) London: Butterworth.

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: Neural substrates for parallel processing. *Trends in Neurosciences, 13,* 266–271.

Attneave, R., & Arnoult, M. D. (1956). The quantitative study of shape and pattern perception. *Psychological Bulletin, 53,* 452–471.

Baddeley, A. (1992). Working memory. *Science, 255,* 556–559.

Battig, K., Rosvold, H. E., & Mishkin, M. (1960). Comparison of the effects of frontal and caudate lesions on delayed response and alternation in monkeys. *Journal of Comparative and Physiological Psychology, 53,* 400–404.

Blessed, G., Tomlinson, B. E., & Roth, M. (1968). The association between quantitative measures of dementia and of senile change in the grey matter of elderly subjects. *British Journal of Psychiatry, 114,* 797–811.

Bondi, M. W., Kaszniak, A. W., Bayles, K. A., & Vance, K. T. (1993). Contributions of frontal system dysfunction to memory and perceptual abilities in Parkinson's disease. *Neuropsychology, 7,* 89–102.

Bradley, V. A., Welch, J. L., & Dick, D. J. (1989). Visuospatial working memory in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 52,* 1228–1235.

Brown, R. G., & Marsden, L. D. (1988). 'Subcortical dementia': The neuropsychological evidence. *Neuroscience, 25,* 363–387.

Brozoski, T. J., Brown, R. M., Rosvold, H. E., & Goldman, P. S. (1979). Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science, 205,* 929–932.

Calne, D. B., Snow, B. J., & Lee, C. (1992). Criteria for diagnosing Parkinson's disease. *Annals of Neurology, 32,* S125–S127.

Canavan, A. G. M., Passingham, R. E., Marsden, C. D., Quinn, N., Wyke, M., & Polkey, C. E. (1989). The performance on learning tasks of patients in the early stages of Parkinson's disease. *Neuropsychologia, 27,* 141–156.

Cohen, J. D., Forman, S. D., Braver, T. S., Casey, B. J., Servan-Schreiber, D., & Noll, D. C. (1994). Activation of the prefrontal cortex in a nonspatial working memory task with functional MRI. *Human Brain Mapping, 1,* 293–304.

Cooper, J. A., Sagar, H. J., Jordan, N., Harvey, N. S., & Sullivan, E. J. (1991). Cognitive impairment in early untreated Parkinson's disease and its relation to motor disability. *Brain, 114,* 2095–2122.

Corkin, S., Growdon, J. H., & Sullivan, E. V. (1981). Dissociation of sensorimotor function in Alzheimer's disease. *American Aging Association Abstracts, 11,* 20.

Corkin, S., Snow, M., Mapstone, M., & Growdon, J. H. (1991). *Impaired skill learning in Parkinson's disease is not related to*

motor or spatial deficits. Poster session presented at the Third IBRO World Congress of Neuroscience, Montreal, Quebec, Canada.

Cronin-Golomb, A., Corkin, S., & Growdon, J. H. (1994). Impaired problem solving in Parkinson's disease: Impact of a set-shifting deficit. *Neuropsychologia, 32,* 579–593.

Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1996). Object and spatial visual working memory activate separate neural systems in human cortex. *Cerebral Cortex, 6,* 39–49.

De Keyser, J., Eibinger, G., & Vauquelin, G. (1990). Age-related changes in the human nigrostriatal dopaminergic system. *Annals of Neurology, 27,* 157–161.

D'Esposito, M., Detre, J. A., Alsop, D. C., Shin, R. K., Atlas, S., & Grossman, M. (1995). The neural basis of the central executive system of working memory. *Nature, 378,* 279–281.

Divac, I., Rosvold, H. E., & Szwarcbart, M. K. (1967). Behavioral effects of selective ablation of the caudate nucleus. *Journal of Comparative and Physiological Psychology, 63,* 184–190.

Fahn, S., Elton, R. L., & Members of the UPDRS Development Committee. (1987). Unified Parkinson's disease rating scale. In S. Fahn, C. D. Marsden, M. Goldstein, et al. (Eds.), *Recent developments in Parkinson's disease II* (pp. 153–163). New York: MacMillan.

Freedman, M., & Oscar-Berman, M. (1986). Selective delayed response deficits in Parkinson's and Alzheimer's disease. *Archives of Neurology, 43,* 886–890.

Fuster, J. M., & Alexander, G. E. (1971). Neuron activity related to short-term memory. *Science, 173,* 652–654.

Gabrieli, J. D. E., Singh, J., Stebbins, G. T., & Goetz, C. G. (1996). Reduced working memory span in Parkinson's disease: Evidence for the role of a frontostriatal system in working and strategic memory. *Neuropsychology, 10,* 322–332.

Goldman-Rakic, P. (1987). Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In V. B. Mountcastle (Ed.), *Handbook of physiology* (Vol. 5, pp. 373–417). Bethesda, MD: American Physiological Society.

Gotham, A. M., Brown, R. G., & Marsden, C. D. (1988). "Frontal" cognitive function in patients with Parkinson's disease "on" and "off" levodopa. *Brain, 111,* 299–321.

Growdon, J. H., & Corkin, S. (1986). Cognitive impairments in Parkinson's disease. In M. D. Yahr & K. J. Bergmann (Eds.), *Advances in neurology: Parkinson's disease* (Vol. 45, pp. 383–392). New York: Raven Press.

Growdon, J. H., Corkin, S., & Rosen, T. J. (1990). Distinctive aspects of cognitive dysfunction in Parkinson's disease. In M. B. Steifler, A. D. Korczyn, E. Melamed, & M. B. H. Youdim (Eds.), *Advances in neurology: Parkinson's disease* (Vol. 53, pp. 365–376). New York: Raven Press.

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression, and mortality. *Neurology, 17,* 427–442.

Hoover, J. E., & Strick, P. L. (1993). Multiple output channels in the basal ganglia. *Science, 259,* 819–821.

Jonides, J. (1995). Working memory and thinking. In D. Osherson & E. E. Smith (Eds.), *Invitation to cognitive science: Vol. 3. Thinking* (pp. 215–265). Cambridge, MA: MIT Press.

Kaufman, M. J., & Madras, B. K. (1991). Severe depletion of cocaine recognition sites associated with the dopamine transporter in Parkinson's-diseased striatum. *Synapse, 9,* 43–49.

Kieburtz, K., McDermott, M., Como, P., Growdon, J., Brady, J., Carter, J., Huber, S., Kanigan, B., Landow, E., Rudolph, A., Saint-Cyr, J., Stern, Y., Tennis, M., Thelen, J., Shoulson, I., & the Parkinson's Study Group. (1994). The effect of deprenyl and tocopherol on cognitive performance in early untreated Parkinson's disease. *Neurology, 44,* 1756–1759.

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. *New England Journal of Medicine, 318*, 876–880.

Levin, B. E., & Katzen, H. L. (1995). Early cognitive changes and nondementing behavioral abnormalities in Parkinson's disease. In W. J. Weiner & A. E. Lang (Eds.), *Advances in neurology: Behavioral neurology of movement disorders* (Vol. 65, pp. 85–95). New York: Raven Press.

Middleton, F. A., & Strick, P. L. (1994). Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science, 266*, 458–461.

Morgan, D. G., & Finch, C. E. (1988). Dopaminergic changes in basal ganglia. *Annals of the New York Academy of Sciences, 515*, 145–160.

Morgan, D. G., May, P. C., & Finch, C. E. (1987). Dopamine and serotonin systems in human and rodent brain: Effects of age and neurodegenerative disease. *Journal of the American Geriatric Society, 35*, 334–345.

Morris, R. G., Downes, J. J., Sahakian, B. J., Evenden, J. L., Heald, A., & Robbins, T. W. (1988). Planning and spatial working memory in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 51*, 757–766.

Murphy, B. L., Arnsten, A. F. T., Goldman-Rakic, P. S., & Roth, R. H. (1996). Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys. *Proceedings of the National Academy of Sciences, USA, 93*, 1325–1329.

Owen, A. M., Beksinska, M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., Sahakian, B. J., & Robbins, T. W. (1993). Visuospatial memory deficits at different stages of Parkinson's disease. *Neuropsychologia, 31*, 627–644.

Owen, A. M., Evans, A. C., & Petrides, M. (1996). Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: A positron emission tomography study. *Cerebral Cortex, 6*, 31–38.

Owen, A. M., James, M., Leigh, P. N., Summers, B. A., Quinn, N. P., Marsden, C. D., Quinn, N. P., & Robbins, T. W. (1992). Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain, 15*, 1727–1751.

Owen, A. M., & Robbins, T. W. (in press) Attention and working memory in movement disorders. In M. Jahanashi & R. Brown (Eds.), *Neuropsychology of movement disorders*. Amsterdam: North-Holland.

Pandya, D., & Yeterian, E. (1991). Prefrontal connections in relation to cortical architectonic organization in rhesus monkeys. *Journal of Comparative Neurology, 312*, 43–67.

Paulesu, E., Frith, C. D., & Frackowiak, R. S. J. (1993). The neural correlates of the verbal component of working memory. *Nature, 362*, 342–345.

Petrides, M. (1994). Frontal lobes and working memory: Evidence from investigations of the effects of cortical excisions in nonhuman primates. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (Vol. 9, pp. 59–82). Amsterdam: Elsevier.

Petrides, M., Alivisatos, B., Evans, A. C., & Meyer, E. (1993). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Sciences, USA, 90*, 873–877.

Postle, B. R., Corkin, S., & Growdon, J. H. (1993). Dissociation between two kinds of visual working memory in Parkinson's disease. *Society for Neuroscience Abstracts, 19*, 1002.

Postle, B. R., Locascio, J. J., Corkin, S., & Growdon, J. H. (in press). The time course of spatial and object learning in Parkinson's disease. *Neuropsychologia*.

Richards, M., Stern, Y., Marder, K., Cote, L., & Mayeux, R. (1993). Relationships between extrapyramidal signs and cognitive function in a community-dwelling cohort of patients with Parkinson's disease and normal elderly individuals. *Annals of Neurology, 33*, 267–274.

Rinne, J. O., Lonnberg, P., & Marjamaki, P. (1990). Age-dependent decline in human brain dopamine D1 and D2 receptors. *Brain Research, 508*, 349–352.

Rosvold, H. E., & Delgado, J. M. R. (1956). The effect on delayed-attention test performance of stimulating or destroying electrically structures within the frontal lobes of the monkey's brain. *Journal of Comparative and Physiological Psychology, 49*, 365–372.

Sagar, H. J., Sullivan, E. V., Gabrieli, J. D. E., Corkin, S., & Growdon, J. H. (1988). Temporal ordering and short-term memory deficits in Parkinson's disease. *Brain, 111*, 525–539.

Selemon, L. D., & Goldman-Rakic, P. S. (1985). Longitudinal topography and interdigitation of corticostriatal projections in the Rhesus monkey. *The Journal of Neuroscience, 5*, 776–794.

Smith, E. E., Jonides, J., Koeppe, R. A., Awh, E., Schumacher, E., & Minoshima, S. (1995). Spatial versus object working memory: PET investigations. *Journal of Cognitive Neuroscience, 7*, 337–356.

Stern, C. E., Corkin, S., Carr, C. A., Sugiura, R. M., Guimaraes, A. R., Baker, J. R., Rosen, B. R., & Gonzales, R. G. (1995). The neural substrate for working memory extends beyond prefrontal cortex. *Society for Neuroscience Abstracts, 21*, 275.

Stevens, J. C., & Mack, J. O. (1959). Scales of apparent force. *Journal of Experimental Psychology, 58*, 405–413.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1986). Frontal lobe dysfunction in Parkinson's disease. *Brain, 109*, 845–883.

Teuber, H.-L. (1955). Physiological psychology. *Annual Review of Psychology, 6*, 267–296.

Tiffin, T., & Asher, E. J. (1948). The Purdue Pegboard: Norms and studies of reliability and validity. *Journal of Applied Psychology, 32*, 234–237.

Tresch, M. C., Sinnamon, H. M., & Seamon, J. G. (1993). Double dissociation of spatial and object visual memory: Evidence from selective interference in intact human subjects. *Neuropsychologia, 31*, 211–219.

Ungerleider, L., & Mishkin, M. (1982). Two cortical visual systems. In D. J. Ingle, M. A. Goodale, & R. J. W. Mansfield (Eds.), *Analysis of visual behavior* (pp. 549–586). Cambridge, MA: MIT Press.

Vanderplas, J. M., & Garvin, E. A. (1959). The association value of random shapes. *Journal of Experimental Psychology, 57*, 147–154.

Williams, G. V., & Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature, 376*, 572–575.

Wilson, F. A. W., O'Scalaidhe, S. P., & Goldman-Rakic, P. S. (1993). Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science, 260*, 1955–1958.