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PRINCIPAL INVESTIGATOR: Kenneth M. Heilman, M.D.

CONTRACTING ORGANIZATION: The University of Florida
Gainesville, Florida 32611-5500

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13. ABSTRACT (Maximum 200 Words) Many of the neuropsychological changes reported with PD are not typically seen early in the disease. Therefore, there is a need to develop new cognitive tests of PD that precede the motor symptoms, are easy to administer and are valid early predictors. Moreover, it is important to understand the effect of the dopaminergic system on the cerebral cortex. One possible action of dopamine on the cerebral cortex is that of influencing activation within semantic networks. Thus, the goal of this project has been to study the semantic organization of verbal information in PD patients and matched controls, and determine the influence of dopamine on these cognitive processes. Data collected in our healthy subjects on the research task confirm our expectations that semantic processing can occur along a continuous gradient. Our preliminary data indicate that, when taking prescribed dopaminergic medication, our PD subjects demonstrate semantic processing that is similar to that of our control subjects. However, after an approximately 12-hour medication abstinence period, our PD subjects rated all semantically-associated stimuli as less similar than did controls. These results tentatively indicate that, as hypothesized, dopamine is involved in the mediation of neural activity (i.e., signal to noise ratio) within the semantic net.				
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Introduction

Patients do not typically develop Parkinson's Disease (PD) until they lose approximately 70% of their dopaminergic neurons. This neural degenerative disorder typically induces motor deficits, but it is possible that subtle cognitive symptoms may precede the onset of the motor symptoms. In addition, screening for cognitive symptoms may be logistically easier than screening for motor deficits. However, it remains unclear as to what the early cognitive symptoms might be. There have been many excellent neuropsychological studies of patients with PD. These studies have revealed that patients with PD do have neuropsychological defects such as visuospatial disorders and evidence of frontal subcortical dysfunction. However, many of the neuropsychological changes reported with PD are not typically seen early in the disease and they are not seen in all subjects. Therefore, there is a need to develop new cognitive tests of PD that precede the motor symptoms, are easy to administer and are valid early predictors. In our research proposal we plan to develop cognitive tests that may be valid and reliable indicators of impending PD. In order to develop cognitive tests that predict the onset of the motor deficits associated with Parkinson's disease it is important to understand the effect of the dopaminergic system on the cerebral cortex. One possible action of dopamine on the cerebral cortex is that it increases the signal to noise ratio. Changing this ratio may influence activation of the semantic networks. One means of examining the activation patterns of semantic networks is to assess lexical priming. If cortical levels of dopamine influences priming, one would expect that patients with PD with a dopamine deficiency to have stronger priming for indirect words than would controls. In addition, the direct relationship may also be weakened in patients with PD. In this study, we will attempt to learn if patients with PD, when compared to control subjects, prime differently. We also plan to learn if PD performance is different when they are on and off L-dopa. We will further assess relationships in the semantic net by having experimental and control subjects judge the relatedness of words. To test self activation of the semantic net, we will assess word generation in these subjects. We will also study PD patients and matched controls ability to inhibit the semantic net through their ability to complete sentences with unrelated words and generate unrelated words. Further, we will induce dopamine blockade using haloperidol in normal subjects, and test these subjects for changes in the function of their semantic network using the same tasks discussed above. As agreed upon with the funding agency, we will not initiate the dopamine blockade component of this study until after we have had a chance to fully evaluate the findings in the PD and similarly-aged control subjects. Finally, as stated in our Revised Statement of Work, we will evaluate and validate a revised version of the computerized semantics judgments task that is to be incorporated into the Automated Neuropsychological Assessment Metric (ANAM), as well as assess the relationship between semantic processing and frontal-executive functions using select subtests from the ANAM.

Body

We spent the first year of this grant in test development. This activity involved reviewing the current literature on verbal and semantic priming, and deriving appropriate tasks to address our hypotheses regarding semantic priming in PD. This review culminated in a selection of word pairs and word primes (Balota & Lorch, 1986, Bennett & McEvoy, in press, McNamara, 1992, McRae & Boisvert, 1998, Nelson et al., 1998, Shelton & Martin, 1992) for our relatedness judgment task and word generation tasks, which have some normative basis. These stimuli also allowed us to assess differences in strength of verbal relatedness, and differences in strength of verbal mediation. The tests that were developed include a word priming task which requires the subject to identify a stimulus as either a real word or a nonsense word. Another test involves having the subject determine the degree of relatedness between two words that have been pre-selected based on normative-based judgments of relatedness. A third task involves having the subject generate a single word to a stimulus cue that has been pre-selected based on a normative-based assessment of semantic activation of that cue. This review also provided us with a list of semantic categories that have normative data for our word generation tasks (Battig & Montague, 1969). The tests derived from this list of categories require the subject to generate exemplars that either match or do not match the target category. As part of this process, we developed computer programs for the administration of some of these tasks that will facilitate data collection and analysis. We also developed referral sources from which to recruit subjects for this study. We initiated data collection at the end of the first year of this grant.

We spent the second year of this study with subject recruitment and data collection. Subject recruitment has involved daily patient screening in the Neurology Clinics of both Shands Hospital at the University of Florida, and the Malcolm Randal VAMC. We also initiated contacts with the Neurology Clinics at the Lake City VAMC and the University of Florida Health Science Center at Jacksonville for subject recruitment through these respective locations. This external recruitment was approved by the University of Florida Health Science Center Institutional Review Board (IRB). Data was collected on 17 volunteers by the end of the second year of this protocol, including seven men and three women with Parkinson's Disease, and three men and four women as control subjects. However, we had some difficulty recruiting appropriate control subjects, and having Parkinsonian patients return "off" their PD medications, thus resulting in incomplete data. Consequently, there was no reportable data at the end of the second year of this project.

The third year of this project was spent with subject recruitment and data collection. Data was collected on nine additional subjects during this last period, including three men with PD, three women with PD, and three female control subjects. Preliminary analyses reveal that control subjects show the typical facilitation in reaction time (e.g., priming) for strongly related associations, yet an increase in reaction time responding to weakly related associations (e.g., negative priming), indicating that concepts that are weakly related appear to require more time in processing the nature of that semantic relationship. The PD subjects showed a similar, albeit diminished, pattern of priming when not taking their prescribed dopaminergic medications. However, these same PD subjects showed priming for the weakly related associations when

taking their prescribed Parkinsonian medications. Thus, exogenous dopamine in PD subjects appears to reverse the negative priming effect associated with weakly associated concepts. A similar pattern of responding was seen in the PD subjects on the relatedness judgment task. The time to process the relationship between two indirectly associated words is much shorter when taking dopaminergic medication than when not taking these medications. Thus, exogenous dopamine in individuals with PD appears to enhance the semantic processing of distantly related concepts. Taken together, these results suggest that dopamine affects semantic processing in a curvilinear manner. Normal dopamine function, as seen in the control subjects, facilitates the semantic processing in strong conceptual relationships and interferes with semantic processing in weak and/or indirect relationships. Severe dopamine depletion, as seen in the PD subjects when not taking their dopaminergic medication results in a similar, but diminished pattern of semantic processing. In contrast, PD subjects show enhanced semantic processing of weak and indirectly related concepts when taking their prescribed medications. We continued to actively recruit subjects and collect data during the remaining time in this project.

The fourth year of this study was spent recruiting and testing subjects, and recording their data. We were granted a two-year extension of this study from the Department of Defense to continue pursuing this line of research. As such, we submitted the report for the fourth year as an Annual Report rather than as the Final Report, and we continued to actively recruit subjects and collect data during the remaining time in this project.

We spent the fifth and sixth years of this study recruiting and testing subjects, and recording their data. To date, data on the Relatedness Judgments Task has been collected from 30 young adults (mean age = 20.9 ± 1.61), 16 older adults (mean age = 68.65 ± 6.9), and 15 adults with Parkinson's Disease (mean age = 67.23 ± 13.51). Data from an additional 30 young adults, 11 older adults, and 5 adults with Parkinson's Disease has also been collected and is being processed. These data are currently being compiled into a database for further analysis. Preliminary results in our healthy subjects indicate that, as expected, semantic processing can occur along a continuous gradient (Crucian et al., 2004; see attached). These data show that, as predicted, strongly associated word-pairs are rated as significantly more similar in meaning than moderately associated word-pairs, weakly associated word-pairs or mediated word-pairs. In fact, the ratings of each word-pair associate group were significantly distinguishable from the other groups (see Table). Thus, consistent with our hypothesis, semantic processing can occur along a continuous gradient in evaluating the conceptual relationship between different words in healthy normal individuals. Preliminary findings also indicate that subjects with Parkinson's Disease who were off their L-dopa medication, when tested on the Judgment Relatedness Test which requires subjects to determine the degree of semantic relatedness between two verbal concepts, showed significant attenuation in their evaluations of distantly-related concepts. That is, compared to the control subjects similar in age and education, PD subjects rated the associated word-pairs as less similar when "off" their dopaminergic medications (45.40 ± 3.40 versus 55.27 ± 3.29) than when "on" these medications (47.59 ± 3.33). No effect for semantic level was found, indicating that dopamine depletion impacted semantic processing globally rather than at

different levels the semantic net. These preliminary findings are consistent with the hypotheses of this study that dopamine is directly involved in the modulation of neural activity within semantic networks. During this fifth year of the study, we have also initiated the work necessary to integrate the Relatedness Judgments Task into the Automated Neuropsychological Assessment Metric battery (ANAM), as requested by the Department of Defense and stated in our approved Revised Statement of Work. As such, we are collecting data on the ANAM version of the Judgment Relatedness Test in order to corroborate this version with the original version of the task. In addition and as stated in our approved Revised Statement of Work, we have begun administering measures of executive function from the ANAM (e.g., Tower of Hanoi Task) as part of our test battery in order to further elucidate the nature of semantic processing and the influence of dopamine on these cognitive functions.

We intend to continue actively recruiting subjects and collecting data during the remaining time in this project. Volunteers are currently being scheduled for research participation. This research recruitment will continue for the duration of funding. As part of this data collection, we intend to re-evaluate the testing procedures of the Relatedness Judgments Task as they are incorporated into the ANAM. We are also in the process of conducting an item analysis of the Relatedness Judgments Task to identify those test items that are most sensitive in the assessment of semantic processing. We are also currently in the process of compiling the rest of the neuropsychological test data from this study (e.g., word generation tasks, sentence completion tasks) for data analysis.

Table: Relatedness Judgments Composite Scores

Test Version	Strongly Associated	Moderately Associated	Weakly Associated	1-Step Med. Associated	2-Step Med. Associated
A	73.42 (15.27)	68.11 (12.07)	50.12 (12.55)	41.03 (13.09)	11.94 (10.15)
B	76.49 (11.66)	72.97 (12.64)	55.38 (14.33)	44.77 (15.75)	25.72 (11.48)

Key Research Accomplishments

We have established a test of semantic processing that involves a continuous scale of measurement rather than a discrete or dichotomous measurement scale. This new test will allow for a more sensitive assessment of semantic processing. Preliminary analyses at this time indicate that this new test is reasonably reliable and stable over time. We have also incorporated this new test of semantic processing into the computerized testing format of the Automated Neuropsychological Assessment Metric (ANAM). In addition to work directly on this DoD-funded project, we have been actively pursuing parallel lines of research on cognitive dysfunction in Parkinson's Disease. This parallel research resulted in a recent publication in which we presented data showing visual-spatial mental rotation deficits in individuals with Parkinson's Disease, particularly men with PD, compared to control subjects similar in age and education (Crucian et al., 2003; see appendices).

Reportable Outcomes

Crucian, G.P., Tulman, J., Sell, S., Grande, L.J., Burks, D.W., Shenal, B.V., Rhodes, R., Mielke, J.B., Riestra, A., Womack, K., Okun, M.S., Reeves, D.L., Crosson, B., & Heilman, K.M. The relatedness judgments task: A test of semantic association. Poster presented at the 32nd annual meeting of the International Neuropsychological Society, Baltimore, MD, February, 2004. (Journal of the International Neuropsychological Society, 10(S1), 108).

Crucian, G.P., Barrett, A.M., Burks, D.W., Riestra, A., Roth, H.L., Schwartz, R.L., Triggs, W.J., Bowers, D., Friedman, W., Greer, M., & Heilman, K.M. (2003). Object spatial orientation in parkinson's disease. Journal of the International Neuropsychological Society, 9, 1078-1087.

Grande, L., Crucian, G., & Heilman, K.M. Semantic priming in patients with parkinson's disease on and off dopamine medication. Poster presented at the 30th annual meeting of the International Neuropsychological Society, Toronto, ON, February, 2002. (Journal of the International Neuropsychological Society, 8(2), 203)

Conclusions

The results to date indicate that 1.) semantic processing can reliably occur along a continuous gradient, and 2.) individuals with PD, when "off" their dopaminergic medications, show significant attenuation in their semantic processing of word-pairs compared to healthy control subjects similar in age and education. These results are consistent with our hypotheses that dopamine is involved in the modulation of activation within the semantic networks. These results suggest that catecholamines (e.g., dopamine) are involved, to some extent, in the evaluation and comparison in meanings of different verbal concepts.

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Submitted Abstract

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Abstract

TITLE:

The Relatedness Judgments Task: A Test of Semantic Association

AUTHORS (ALL): Crucian, Gregory P.^{1,2}; Tulman, Jennifer¹; Sell, Samantha¹; Grande, Laura J.¹; Burks, David W.^{1,2}; Shenal, Brian V.^{1,2}; Rhodes, Robert^{1,2}; Mielke, Jeannine B.^{1,2}; Riestra, Alonso¹; Womack, Kyle¹; Okun, Michael S.¹; Reeves, Dennis L.³; Crosson, Bruce^{1,2}; Heilman, Kenneth M.^{1,2}.

INSTITUTIONS (ALL): 1. Neurology, University of Florida, Gainesville, FL, USA.

2. Neurology Service, Malcom Randall VAMC, Gainesville, FL, USA.

3. United States Navy, San Diego, CA, USA.

ABSTRACT BODY:

Lexical priming and word association tasks provide a measure of semantic organization/processing. In lexical priming, a semantic relationship with the cue facilitates recognition of the target word, suggesting cues increase activation within that semantic network. In word association tasks, subjects say the first word that comes to mind in response to a cue, suggesting a conceptual/associative relationship between words. Whereas both tasks presume existence of a semantic relationship between words, neither takes into account degree of conceptual/associative relationship in semantic processing. Thus, these semantic processing tasks may not reflect the full extent of semantic associations being generated. In this study, we report findings of a semantic processing measure currently under development. In this task, subjects are presented with word pairs and asked to rate degree of "relatedness" using a Likert scale. Strength of relationship between words was manipulated, deriving 3 groups (strong, moderate, weak) based on word association normative data. Two groups of mediated word pairs (the relationship between words is "mediated" by one or two words) were also included to broaden the range of semantic processing being assessed. Results from a group of young (14 men, 16 women; mean age = 20.8 years) and older adults (7 men, 9 women; mean age = 68.5 years) reveal the categories of word pairs are reliably differentiated as expected. That is, strongly-associated word pairs are rated as more related than weakly-associated or mediated word pairs. Findings confirm the premise that semantic processing involves assessment of degree of similarity between two concepts. Results suggest that assessment of degree of conceptual relationship may be an important consideration in evaluating semantic processing. This measure may have utility in assessing neurological conditions such as Alzheimer's and Parkinson's Disease where there might be alterations in semantic representations.

Abstracts Presented at the Thirtieth Annual International Neuropsychological Society Conference

February 13–16, 2002 Toronto, Canada

L. GRANDE, G. CRUCIAN, & K.M. HEILMAN. Semantic Priming in Patients with Parkinson's Disease On and Off Dopamine Medication.

Studies investigating cognition in healthy individuals have indicated a role of dopamine in the modulation of the signal-to-noise-ratio within semantic memory (Newman et al., 1984; Kischka et al., 1996). This study investigated dopamine's effects on semantic networks by testing priming in participants with idiopathic Parkinson's disease (PD) ($n = 10$) and healthy controls (HC) ($n = 8$). Each participant completed a semantic priming-lexical decision experiment involving 3 levels of semantic association: high prototypicality (e.g., gem–ruby), low prototypicality (e.g., gem–quartz), and unrelated (e.g., gem–shoe). Each PD participant completed the experiments both on and off their dopamine medication. For the HC group, comparison of response latencies across conditions revealed priming for targets of high prototypicality and no priming for targets of low prototypicality. In contrast, the PD group on medications demonstrated an overall pattern of semantic priming, but no effect of prototypicality. Additionally, the PD group off medications did not demonstrate an effect of either prototypicality or semantic relatedness. These results appear to support the hypothesis that dopamine may focus semantic activation. Correspondence: *Laura Grande, GRECC (182 JP) VA Boston Healthcare System, 150 South Huntington Ave., Boston, MA 02130. grande@nersp.ncrdc.ufl.edu*

Mental object rotation in Parkinson's disease

GREGORY P. CRUCIAN,¹ ANNA M. BARRETT,⁴ DAVID W. BURKS,^{1,6} ALONSO R. RIESTRA,¹
HEIDI L. ROTH,¹ RONALD L. SCHWARTZ,⁵ WILLIAM J. TRIGGS,¹ DAWN BOWERS,³
WILLIAM FRIEDMAN,² MELVIN GREER,¹ AND KENNETH M. HEILMAN^{1,6}

¹Department of Neurology, University of Florida, Gainesville, Florida

²Department of Neurosurgery, University of Florida, Gainesville, Florida

³Department of Clinical and Health Psychology, University of Florida, Gainesville, Florida

⁴Division of Neurology, College of Medicine, Pennsylvania State University, Hershey, Pennsylvania

⁵Hattiesburg Clinic, Department of Neurology, Hattiesburg, Mississippi

⁶Gainesville VA Medical Center, Gainesville, Florida

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Abstract

Deficits in visual-spatial ability can be associated with Parkinson's disease (PD), and there are several possible reasons for these deficits. Dysfunction in frontal-striatal and/or frontal-parietal systems, associated with dopamine deficiency, might disrupt cognitive processes either supporting (e.g., working memory) or subserving visual-spatial computations. The goal of this study was to assess visual-spatial orientation ability in individuals with PD using the Mental Rotations Test (MRT), along with other measures of cognitive function. Non-demented men with PD were significantly less accurate on this test than matched control men. In contrast, women with PD performed similarly to matched control women, but both groups of women did not perform much better than chance. Further, mental rotation accuracy in men correlated with their executive skills involving mental processing and psychomotor speed. In women with PD, however, mental rotation accuracy correlated negatively with verbal memory, indicating that higher mental rotation performance was associated with lower ability in verbal memory. These results indicate that PD is associated with visual-spatial orientation deficits in men. Women with PD and control women both performed poorly on the MRT, possibly reflecting a floor effect. Although men and women with PD appear to engage different cognitive processes in this task, the reason for the sex difference remains to be elucidated. (*JINS*, 2003, 9, 1078–1087.)

Keywords: Parkinson's disease, Visual-spatial orientation, Mental rotation, Gender differences

INTRODUCTION

Parkinson's disease (PD) has been associated with deficits on visual-spatial tasks (Cummings & Huber, 1992; Growdon & Corkin, 1986; Stern & Mayeux, 1986). However, a recent meta-analysis of this literature (Waterfall & Crowe, 1995) suggested that visual-spatial deficits in PD are not universal because deficits are seen primarily on multifactorial visual-spatial tasks (e.g., Raven's Progressive Matrices) but not more unifactorial measures of visual-spatial ability (e.g., Judgment of Line Orientation, Embedded Figures Test). This conclusion was similar to those of Lazaruk (1994). Thus, the relationship between visual-spatial ability and PD is not clear.

One theory of cognitive dysfunction in PD suggests that these deficits are related to disturbance in the frontal-basal ganglia neural circuits important in executive functions such as attention and concentration, sequencing, working memory, and set-shifting (Brown & Marsden, 1990; Taylor & Saint-Cyr, 1995). This executive dysfunction theory was supported by a study that found a significant relationship between executive dysfunction and visual-spatial deficits in individuals with PD (Bondi et al., 1993). In a group of 19 individuals with mild to moderate PD, these investigators found that statistically controlling for the deficits in executive skills (e.g., Wisconsin Card Sorting Test, California Sorting Test) through an analysis of covariance eliminated the visual-spatial deficits (e.g., WAIS-R Picture Arrangement, Benton Facial Discrimination Test), but statistically controlling for the visual-spatial deficits did not alter the abnormal measures of executive function.

Reprint requests to: Gregory P. Crucian, Box 100236, University of Florida, Gainesville, FL 32610. E-mail: crucigp@neurology.ufl.edu

In contrast, Cronin-Golomb and Braun (1997) provide evidence for a visual-spatial deficit in PD that is independent of executive skills. In a group of 50 non-demented, non-depressed, individuals with mild to moderate PD, these investigators found deficiencies on Subtest A of Raven's Colored Progressive Matrices (RCPM) when compared to matched control subjects. Because Subtest A of the RCPM has a greater visual-spatial component than the remaining portions of the RCPM, and because the PD subjects' RCPM-A performance was related to other measures of visual-spatial ability (e.g., Luria's Mental Rotation Test, Standardized Road-Map Test of Direction Sense), but not measures of executive function (e.g., Stroop test, WAIS-R Picture Arrangement), they concluded that PD was associated with a visual-spatial problem-solving deficit.

Visual-spatial abilities as usually tested involve several distinct cognitive processes (Ekstrom et al., 1976), and the visual-spatial tasks used in the studies reviewed above are generally considered to be complex, involving multiple cognitive processes. Therefore, a significant problem with this literature is the visual-spatial tasks used and their dependence on other cognitive processes (Waterfall & Crowe, 1995). Mental rotation ability is correlated with other visual-spatial skills (Bryden, 1982; McGee, 1979; Stumpf & Eliot, 1999) and may offer a way of more directly examining this issue. However, mental rotation data in PD is also variable. Previous studies have found no significant differences in accuracy of mental rotation between individuals with Parkinson's disease and control subjects (Boller et al., 1984; Brown & Marsden, 1986; Goldenberg et al., 1986; Raskin et al., 1992; Smith et al., 1998; Taylor et al., 1986). One possible limitation of these negative studies, however, was the failure to use sensitive measures that limit verbal mediation and require both two- and three-dimensional rotations. For example, some studies (Boller et al., 1984; Brown & Marsden, 1986; Taylor et al., 1986) used tasks that are limited to two dimensions (e.g., letter rotation, map direction task) and could be verbally mediated. Other studies (Goldenberg et al., 1986; Raskin et al., 1992) used a manikin rotation task that can also be verbally mediated. However, a recent study using a tachistoscopic cube-figure presentation method similar to the mental rotation task of Shepard and Metzler (1971), which requires subjects to make same-different judgments when two objects are presented in different three-dimensional orientations, found that PD subjects were less accurate than control subjects in making "same" judgments (Lee et al., 1998). However, when compared to control subjects, these same PD subjects also had significantly faster response times when making "same" judgments, suggesting that the mental rotation deficit in these PD subjects might have been due to a speed-accuracy trade-off. Supporting this conclusion were the observations that slower response times for "different" judgments of three-dimensional stimuli, and "same" and "different" judgments of two-dimensional stimuli, were associated with normal accuracy. Thus, these findings do not differentiate whether these deficits in PD are due to problems in visual-spatial

ability or deficiencies in psychomotor and mental processing speed which are common in PD. In addition, there was also no other testing to exclude the possible confound of an associated dementia.

Because it remains unclear if mental rotation deficits exist in non-demented individuals with Parkinson's disease, we studied a population of non-demented subjects with PD using the Mental Rotations Test (MRT) which requires the participant to recognize a target stimulus in different two- and three-dimensional spatial orientations (Linn & Petersen, 1985; Shepard, 1978; Shepard & Metzler, 1971). We also examined these PD subjects' performance on other tests of cognitive function, particularly executive skills, to ascertain the relationship between these other cognitive functions and mental rotation ability.

METHODS

Research Participants

Twenty-eight men and 23 women with PD were recruited from the Neurology and the Neurosurgery clinics at the University of Florida Health Science Center as experimental subjects for this study. Most of these volunteers were being evaluated for surgical treatment of their PD, whereas the remaining few were seen in the clinic for their periodic neurological evaluation. Hospital volunteers, as well as family members and friends who accompanied the PD patients to the clinic were recruited as controls (28 men and 28 women). Exclusionary criteria for enrollment in this study (experimental and control subjects) included use of the left hand for writing, a history of learning disabilities, a history of other or concurrent neurological disorders, and a previous history of major psychiatric disorder prior to PD onset.

The presence of dementia was assessed in 105 of 107 subjects with the Mini Mental Status Exam (MMSE; Folstein et al., 1975), with a cut-off criterion of 27/30. A higher than usual cut-off criterion was used in this study to minimize the likelihood of a confounding neurodegenerative disease other than PD being present (Malapani et al., 1994; Reed et al., 1997). Two female control subjects did not receive the MMSE because they were gainfully employed at the time of testing and dementia screening was deemed unnecessary. The motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elston, 1987) was administered to characterize the motor dysfunction of the PD subjects. The Parkinson's subjects were also screened for depression with the Geriatric Depression Scale (GDS; Yesavage et al., 1983). It should be noted that 9 PD subjects did not receive the GDS, and 2 PD subjects did not receive the UPDRS.

Demographic data for the respective groups are presented in Table 1. Please see Table 2 for the PD subjects' medications. There was no statistically significant difference in the numerical composition of the subject groups [$\chi^2 = 0.612$, ($df = 1$, $N = 107$) n.s.]. There were no significant differences between PD patients and control subjects

Table 1. Demographics information for control subjects and PD patients

Demographics	Controls				Parkinson's			
	Males		Females		Males		Females	
	<i>M</i>	(<i>SD</i>)	<i>M</i>	(<i>SD</i>)	<i>M</i>	(<i>SD</i>)	<i>M</i>	(<i>SD</i>)
Age (yrs)	66.44	(9.11)	63.22	(8.82)	62.72	(7.67)	62.23	(9.67)
Education (yrs)	14.32	(3.31)	13.86	(2.35)	14.75	(2.53)	13.39	(2.06)
MMSE	29.04	(0.99)	29.46	(0.81)	29.00	(0.98)	28.78	(0.80)
Duration (yrs)	—		—		11.68	(5.92)	10.15	(6.07)
UPDRS-Motor	—		—		27.57	(11.03)	36.19	(15.12)

in age or education, and no difference between male and female PD subjects in disease duration. However, the female PD patients had significantly more motor symptoms than male Parkinson's patients on the UPDRS Motor Scale (Mann-Whitney $U = 189.50$, $p = .035$). These UPDRS scores place the males with PD generally in the mild to moderate range of motor impairment (approximating a Hoehn & Yahr, 1967, Stage III to Stage IV), and the female PD patients in the moderate range of impairment (approximating a Hoehn & Yahr, 1967, Stage IV). Based on results from the UPDRS Motor Scale, 15 Parkinson's subjects exhibited predominantly right-sided symptoms, 11 exhibited predominantly left-sided symptoms, and 23 subjects exhibited bilateral symptoms. Results from the UPDRS Motor Scale also indicated that 27 Parkinson's subjects exhibited predominantly rigid-akinetic symptoms, 9 exhibited predominantly tremor, and the symptom presentation of 13 Parkinson's subjects could not be differentiated, exhibiting both rigid-akinesia and tremor to a similar degree. Based on responses to the GDS, 21 PD subjects reported no consistent symp-

toms of depression, 16 PD subjects reported symptoms of mild depression, and 5 subjects reported symptoms of moderate to severe depression (see Spreen & Strauss, 1998 for scoring criteria).

Parkinsonian patients also received neuropsychological testing as part of their clinical evaluation. These neuropsychological tests were selected to assess for current level of general intellectual skills, memory for verbal and visual-spatial information, language, visual-spatial ability, and executive functions involving speeded mental processing and set-shifting. Tests included the Information, Similarities, Digit Span, Digit Symbol, and Block Design subtests from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981), Logical Memory I and II and Visual Reproduction I and II from the Wechsler Memory Scale-Revised (Wechsler, 1987), California Verbal Learning Test (CVLT; Delis et al., 1987), Boston Naming Test (BNT; Kaplan et al., 1983), Controlled Oral Word Associations (COWA; Spreen & Benton, 1977), Stroop Color Word Test (Golden, 1978), and the Trail Making Test (Trails; Reitan & Wolfson, 1985). These tests were administered and scored according to standardized instructions using normative data adjusted for age and education where available. Due to time constraints in the clinical evaluation, some of the PD subjects did not receive all of the tests (Table 3). Neuropsychological test results from the cognitive screening are also presented in Table 3. Review of Table 3 indicates that the level of cognitive functioning in this sample of Parkinsonian subjects is generally within normal limits (see Spreen & Strauss, 1998; Wechsler, 1981, 1987 for normative data), with no discrepancies between measures of crystallized knowledge (e.g., WAIS-R Information subtest) and verbal abstract reasoning (e.g., WAIS-R Similarities subtest). Performance on the WAIS-R Block Design, although variable, was within normal limits. These subjects also show no deficits in confrontation naming (e.g., Boston Naming Test), verbal fluency (e.g., COWA), or memory for either verbal or visual-spatial information (e.g., WMS-R, CVLT). Test results are noteworthy for some psychomotor slowing as seen on Trails B of the Trail Making Test. These test findings are generally consistent with the PD subjects' reported level of educational attainment. Taken together, these results do not suggest that these PD subjects have experienced any signif-

Table 2. Summary of medication status of PD subjects

Type of medication	Number of subject
Dopaminergic	51
Carbidopa-Levodopa	49
Selegiline	9
Amantadine	5
Ropinirole	2
Bromocriptine	4
Pergolide	6
Trihexyphenidyl (antispasmodic)	4
Benzotropine (anticholinergic/antihistamine)	1
Pramipexole (dopamine agonist)	1
Tramadol (analgesic)	1
Benzodiazapine	
Lorazepam, Clonazepam, Temazepam	19
Clorazepate	1
Sleep Aids (Phenobarbital, Zolpidem, Tartate)	3
Primidone	2
Antidepressants (doxepin, sertraline, paroxetine)	11

Table 3. Clinical test scores from the Parkinson's disease subjects

Measure	<i>n</i>	<i>M</i>	(<i>SD</i>)
WAIS-R subtests (%ile, age corrected)			
Information	49	64.31	(23.21)
Similarities	47	64.58	(25.37)
Digit Span	48	57.10	(23.10)
Block Design	46	39.96	(20.93)
Digit Symbol	50	37.94	(24.11)
WMS-R subtests (%ile, age corrected)			
Logical Memory I	39	35.72	(28.33)
Logical Memory II	39	35.92	(25.46)
Visual Reproduction I	32	46.81	(28.23)
Visual Reproduction II	32	30.97	(27.84)
CVLT Total Score (%ile)			
Percentile	43	34.10	(20.09)
BNT (Average correct)	51	54.27	(3.66)
COWA (average no. of words)			
FAS	50	35.56	(11.61)
Animals	50	16.26	(4.56)
Trails (time in seconds)			
A	49	54.12	(24.45)
B	49	156.98	(79.38)
Stroop (%iles, age corrected)			
Word	44	26.68	(19.35)
Color	44	23.98	(26.80)
Color-Word	44	30.87	(26.22)
Interference	44	50.36	(23.93)

icant decline in general cognition. Further, it is noteworthy that the Parkinsonian's performances on tests requiring psychomotor output (e.g., Block Design, Digit Symbol, Trails A) were within the average range. Measures of executive function (e.g., Digit Symbol, Stroop, COWA, Trails A) were also within normal limits.

Procedures

Mental rotation ability was assessed with the Mental Rotations Test (e.g., Shepard, 1978; Shepard & Metzler, 1971) which can be administered either individually or in small groups of 2 to 4 volunteers (Vandenberg & Kuse, 1978). This paper-and-pencil test has 20 items with one target stimulus and four choices. Two of the four choices are correct, but are presented in different two- and three-dimensional planes, as if rotated to a different perspective. This test requires the participant to match the two correct choices to the target stimulus from four possible options. Because of the age range of these volunteers and possible difficulties of reduced vision, slight modifications were made to the test to facilitate performance. Test stimuli were enlarged by approximately 20% to enhance viewing (see Figure 1). Each example was presented on a separate page, and experimental test items were presented three per page. The participants responded on a separate answer sheet. Otherwise, test administration followed established procedures, including

standardized instructions and a 10-min time limit (Vandenberg & Kuse, 1978). The dependent variable for this measure was the proportion of correct responses (number of correct items/total number of items attempted). Using a proportion correct score as the dependent variable was intended to correct for differences in psychomotor speed in test completion which may be a confound for individuals with Parkinson's disease.

RESULTS

The total correct scores and proportion correct scores for the men and women of each experimental group are presented in Table 4. Review of Table 4 indicates that the total correct scores of the male and female control subjects are consistent with that of previous research using normal adults of a similar age (Wilson et al., 1975).

The proportion correct data from Table 4 was subjected to a 2 (group) $\times$ 2 (gender) ANCOVA, with age as the covariate. Gender was included as an independent variable because a large male advantage has previously been found on this task (Linn & Petersen, 1985). Age was included as the covariate to account for possible age effects on this task (Wilson et al., 1975). Consistent with this previous research (Wilson et al., 1975), age was a significant factor in this analysis [$F(1,102) = 4.98, p = .028$], and accounted for a small proportion of variance in this analysis, $R^2 = .01$. This analysis also yielded a significant main effect for group [$F(1,102) = 12.13, p \leq .001$], indicating that Parkinson's subjects ($M = 55.94, SD = 12.30$) were less accurate on the MRT than control subjects ($M = 63.71, SD = 15.83$). A significant main effect for gender was also found [$F(1,102) = 18.55, p \leq .001$], indicating that men ($M = 64.81, SD = 16.03$) were more accurate on the MRT than women ($M = 54.73, SD = 11.06$).

The interaction between Group $\times$ Gender was also significant [$F(1,102) = 5.21, p = .025$]. *Post-hoc* analyses with Bonferroni correction ($\alpha = .008$) on the age-corrected scores revealed that male control subjects were significantly more accurate than female control subjects [$t(54) = 4.51, p \leq .001$], whereas there was no difference in accuracy between male and female PD subjects. Male control subjects were also significantly more accurate than male PD subjects [$t(54) = 3.61, p = .001$], although there was no difference in accuracy between female control and PD subjects.

A series of supplementary analyses were conducted to assess the relationship between subject characteristics of the Parkinsonian subjects (e.g., symptom presentation, symptom severity, illness duration, medication status, level of depression) and their spatial orientation performance. To determine if symptom laterality was related to mental rotation performance in these PD subjects, a two-factor ANCOVA was conducted on the proportion correct scores, with laterality (e.g., right, left, bilateral) and gender as a between-subjects variable. Although there was no significant gender difference in MRT accuracy within the PD

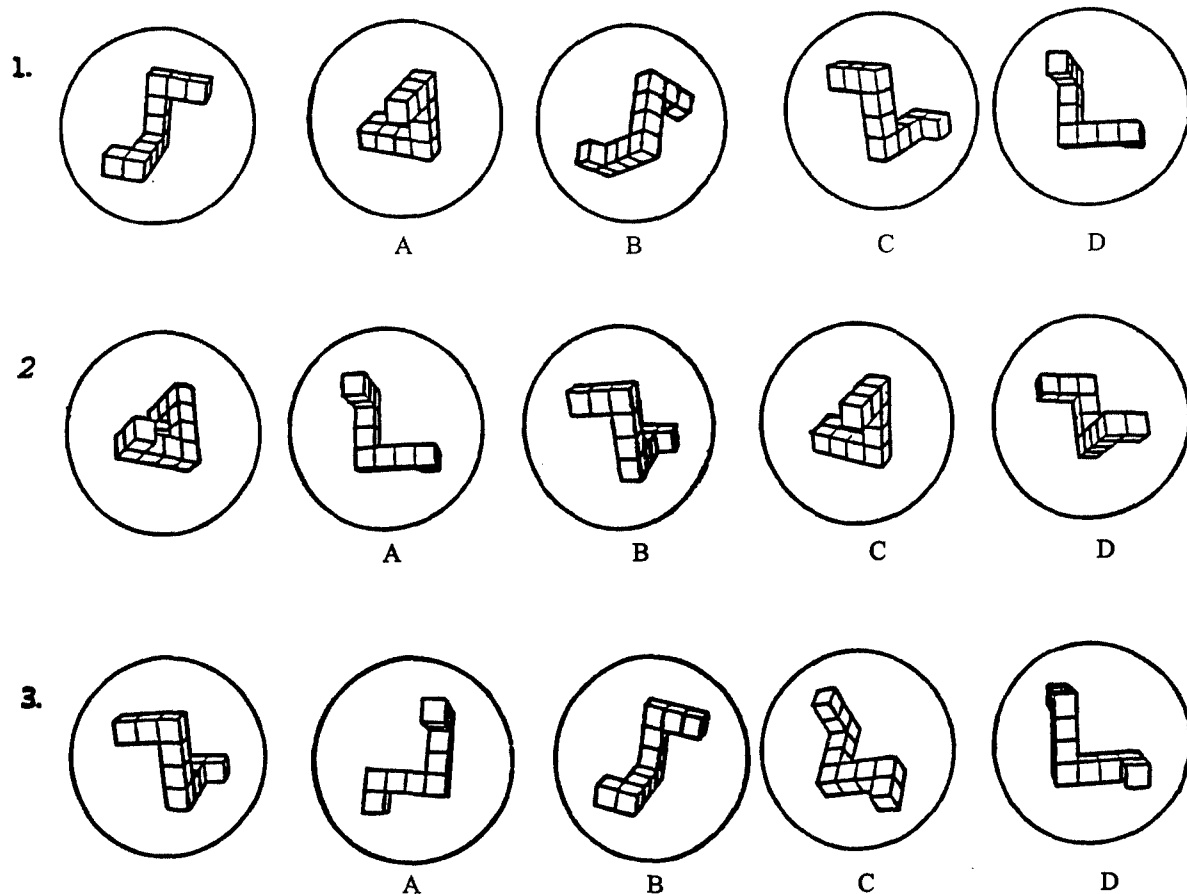


Fig. 1. Mental Rotation Test example.

group, gender was included as a between subjects variable to account for any variability in performance that may interact with symptom laterality. Age was included as a covariate to account for age effects, and maintain consistency with the analysis described above. No significant effect was found for laterality [right $M = 56.10$, $SD = 13.90$; left $M = 58.90$, $SD = 14.29$; bilateral $M = 54.93$, $SD = 10.94$; $F(2,42) = .07$, $p = .93$]. There was also no significant effect for age or gender, nor a significant interaction between Gender $\times$ Laterality.

To determine if the type of Parkinson's symptom (e.g., rigid-akinetic vs. tremulous vs. undifferentiated) exhibited by these subjects was associated with mental rotation ability, another ANCOVA was conducted on the MRT propor-

tion correct scores, with predominant form of symptom and gender as the between subjects variables, and age as the covariate. This analysis revealed no significant difference in mental rotation accuracy associated with the PD symptom type [rigid-akinetic $M = 57.45$, $SD = 14.36$; tremulous $M = 58.48$, $SD = 7.90$; undifferentiated $M = 51.96$, $SD = 10.45$; $F(2,42) = 1.09$, $p = .35$]. Further, there was no main effect for age or gender, or an interaction between Gender $\times$ Predominant Symptom.

To assess the relationship between symptom severity and spatial orientation ability, a correlational analysis was conducted between the UPDRS score and the MRT accuracy score. To account for possible differences associated with sex, separate analyses were done for male and female PD

Table 4. Mental Rotation Test scores

MRT Score	Controls				PD			
	Males		Females		Males		Females	
	<i>M</i>	(<i>SD</i>)	<i>M</i>	(<i>SD</i>)	<i>M</i>	(<i>SD</i>)	<i>M</i>	(<i>SD</i>)
Total correct	22.75	(6.13)	17.21	(4.26)	19.21	(6.21)	15.48	(5.49)
Proportion correct	71.45	(15.76)	55.97	(11.73)	58.16	(13.55)	53.23	(10.24)

subjects. Because the UPDRS score is based on a subjective ordinal scale, the proportion correct score was treated as rank order data for this analysis to allow comparison with the UPDRS score. The correlation between symptom severity and MRT accuracy for both men ($r_s = -.06$) and women ($r_s = .26$) was not significant.

To assess the relationship between the PD subjects' level of depression and spatial orientation performance, an ANCOVA was conducted on the proportion correct scores, with depression group (e.g., depressed, nondepressed) and gender as the between-subjects variables, and age as the covariate. Because of the small number of PD subjects reporting moderate to severe symptoms of depression, the data from these subjects was combined with the data of those reporting mild symptoms of depression to form one group. No significant difference in MRT accuracy were found associated with presence of symptoms of depression [nondepressed $M = 58.25$, $SD = 9.76$; depressed $M = 53.11$, $SD = 12.81$; $F(1,37) = 2.17$, $p = .15$]. There was also no significant effect for age or gender, or the interaction between Gender $\times$ Depression.

To evaluate the association between medication status and mental rotation accuracy, the PD subjects were divided into two groups. Group 1 consisted of those 27 individuals taking additional medications (e.g., analgesics, anxiolytics, sleep aids, antidepressants) that might interfere with cognitive function plus an additional two subjects taking Parkinsonian medications with significant cognitive side effects (e.g., trihexyphenidyl). The remaining 22 subjects taking only Parkinsonian medications with no significant cognitive side effects comprised Group 2. The MRT accuracy scores were then subjected to a 2 (medication status) $\times$ 2 (gender) ANCOVA, with age as the covariate. This analysis revealed no main effect for medication status [Group 1 $M = 55.42$, $SD = 12.90$; Group 2 $M = 56.62$, $SD = 11.74$; $F(1,46) = 0.02$, $p = .89$]. There was also no significant effect for age or gender, or the interaction between Gender $\times$ Medication Status.

Another correlational analysis was conducted between illness duration in years and MRT accuracy. Again, no significant relationship was found between disease duration and mental rotation accuracy for either men ($r = -.08$) or women ($r = -.05$).

A final series of correlational analyses was conducted between the MRT proportion correct score and the neuropsychological test scores. Again, separate analyses were conducted for male and female PD subjects to account for possible differences associated with sex. These results are presented in Table 5. Review of these findings indicates that, for men, mental rotation accuracy was significantly correlated with the Wechsler Adult Intelligence Scale-Revised Block Design subtest, which requires visual-spatial organization and problem-solving, and the Digit Symbol subtest, which requires visual attention, scanning, and matching, as well as psychomotor speed and incidental learning. Mental rotation performance also correlated significantly with the speed of mental processing and response inhibition/

Table 5. Correlation between MRT accuracy score and neuropsychological test scores

Measure	PD subjects	
	Men	Women
WAIS-R subtests		
Information	.21	.31
Similarities	.28	-.08
Digit Span	.36	.13
Block Design	.56 ¹	.10
Digit Symbol	.54 ²	-.30
WMS-R Subtests		
Logical Memory I	.33	-.70 ¹
Logical Memory II	.28	-.65 ³
Visual Reproduction I	.45	.16
Visual Reproduction II	.65 ²	.43
CVLT Total Score	-.08	.18
BNT (average correct)	.03	.35
COWA (average)		
FAS	.01	.12
Animals	.26	.35
Trails		
A	-.37	.04
B	-.19	.21
Stroop		
Word	.47 ⁴	-.32
Color	.53 ⁵	-.14
Color-Word	.58 ⁶	.02
Interference	.01	.42

¹ $p = .004$ (2-tailed); ² $p = .003$ (2-tailed); ³ $p = .008$ (2-tailed); ⁴ $p = .017$ (2-tailed); ⁵ $p = .006$ (2-tailed); ⁶ $p = .002$ (2-tailed).

cognitive set shifting on the Stroop Test, and delayed recall for visual-spatial information on the WMS-R. In contrast, women showed a significant inverse relationship between mental rotation accuracy and both immediate and delayed recall for verbal information on the WMS-R, indicating that higher mental rotation accuracy was associated with lower verbal memory. The correlations between the MRT proportion correct score and these cognitive test scores were further analyzed with Fisher r -to- Z transformation. Using Bonferroni correction ($\alpha = .006$, one-tailed), the difference in correlations between PD men and women were significant for the Wechsler Adult Intelligence Scale-Revised Digit Symbol subtest ($z = 3.00$, $p = .00135$), Stroop Word Reading task ($z = 2.81$, $p = .0026$), the Wechsler Memory Scale-Revised Logical Memory tasks (Logical Memory I, $z = 4.39$, $p = .0001$; Logical Memory II, $z = 3.43$, $p = .0003$). The difference between correlations on the Stroop Color-Naming task was marginally significant ($z = 2.44$, $p = .0073$). The difference between correlations on the WAIS-R Block Design subtest ($z = 1.70$), Stroop Color-Word Reading task ($z = 2.14$), and the Wechsler Memory Scale-Revised Visual Reproduction II ($z = 1.05$) did not achieve significance.

DISCUSSION

The results of this study indicate that Parkinson's disease is associated with deficiencies in mental rotation in men. Specifically, men with PD demonstrated significantly lower scores on the Mental Rotations Test than men of similar age and education, whereas PD and control women performed at a similar low level. This floor effect indicates that the MRT is insensitive to visual-spatial deficits in PD females. Mental rotation performance in PD subjects was not affected by other factors, such as symptom laterality, symptom severity, symptom type, disease duration, medications, or mood. Because mental rotation is believed to be a basic component of visual-spatial ability (Bryden, 1982; Linn & Petersen, 1985; McGee, 1979; Stumpf & Eliot, 1999), these findings are consistent with previous research suggesting that PD is associated with diminished visual-spatial ability (Cummings & Huber, 1992; Growdon & Corkin, 1986; Stern & Mayeux, 1988). The reason men are impaired on the MRT is unknown, but there are several possible reasons.

Gender Differences

The finding of a significant interaction between group and the subject's gender may provide some insight into the mechanisms that underlie mental rotation deficits in PD. Men typically perform better than women on tests of mental rotation (Linn & Petersen, 1985; see also Halpern, 1992; Maccoby & Jacklin, 1974), consistent with our findings. The mechanisms underlying this sex difference are not entirely known, but mental rotation ability is typically mediated primarily by the right hemisphere (Corballis, 1997; see also Benton & Tranel, 1993; Bryden, 1982; Lezak, 1995). There is also evidence that there are sex differences in the lateralization of visual-spatial processing (Harris, 1978; Hiscock et al., 1995; Levy, 1974; Levy & Reid, 1978), and this enhanced male asymmetry might explain the male advantage in visual-spatial tasks (see Levy & Heller, 1992, for review). It has been suggested that there are two different strategies used when performing the MRT task: one might be more verbal categorical (top-bottom, left-right), and the other more non-verbal and continuous (Shepard & Cooper, 1982). This latter strategy, in which the entire stimulus is mentally moved as if in three-dimensional space (Shepard & Cooper, 1982), might be a more efficient process, and based on the superior performance by control men, they are more likely to use this process.

The MRT performance of women with PD was not significantly different from that of control women. Notably, MRT accuracy of both control and PD women was not substantially above chance performance (50%, as defined by the overall probability of responding correctly to the test items; see Table 4), consistent with previous findings (see Wilson et al., 1975). That the men with PD did not perform statistically different from women in either group suggests that the men with PD lost the ability to use this mental rotation process.

The correlational analyses support the postulate that the men with PD might perform mental rotations differently than the women with PD. Men showed a significant relationship between mental rotation ability and executive functions involving mental processing and psychomotor speed (e.g., Stroop Word Reading, WAIS-R Digit Symbol) that was different from women, although this finding was less than consistent (see Stroop Color Naming, Color-Word Naming, Interference, Trail Making Test). Whereas the WAIS-R Digit Symbol subtest does not appear to localize well (see Lezak, 1995, for discussion), a recent functional imaging study revealed bilateral anterior cingulate activation, as well as right parietal and left frontal operculum activation, during performance on the Stroop task (Brown et al., 1999). In contrast, women showed a significant inverse relationship between mental rotation ability and verbal memory. Thus, consistent with the "cognitive trade-off" hypothesis (see Levy & Heller, 1992, for review), women who rely on verbal memory and other verbal mediation processes are more likely to perform more poorly on the MRT. These findings are consistent with the supposition that normally men and women use different hemispherically mediated cognitive processes in performing visual-spatial tasks (Halpern, 1992; Hampson & Kimura, 1992; Levy & Heller, 1992). Additional research on these tasks with normal subjects will help elucidate the nature of these relationships.

Bradyphrenia

Slowed processing is not likely to explain the impaired MRT performance in the men with PD. Although there is some evidence of psychomotor slowing and difficulties with set-shifting in this sample of PD subjects (see Table 3, Trails B data), the majority of neuropsychological tests assessing psychomotor speed in the current study were within normal limits. Further, a proportion correct score was used as the dependent variable rather than the total correct score, thereby correcting for the total number of items each subject completed during the 10-min time limit of the test. This scoring approach was intended to control for the speed in which an individual subject completed the items on the test, and should have minimized the possible influence of psychomotor slowing. Consequently, mental rotation performance would be equated for each subject by taking into account the number of items completed.

Perception, Working Memory, and Imagery

While men with PD showed impaired mental rotation, deficient mental rotation performance can result from dysfunction in one of several possible components. In order for a person to compute a mental rotation, the individual must perceive the target stimulus and hold this perception in working memory as a mental image. The individual must then transform this mental image into a different perspective to learn if it matches each of the choices. With respect to visual perception, some visual disturbances have been re-

ported in PD (Bodis-Wollner, 1990; Bodis-Wollner et al., 1987, 1991, 1993). However, these disturbances are thought to involve peripheral dysfunction in the retina rather than central cortical dysfunction, and these disturbances are responsive to dopaminergic treatment. Further, data from the neuropsychological assessment of our PD subjects do not indicate deficits in visual-spatial perception (Block Design) or working memory (WAIS-R Digit Span and Digit Symbol, WMS-R Logical Memory I and Visual Reproduction I) that could have accounted for the abnormal mental rotation performance of this sample of male PD subjects. Object imagery was not assessed in this sample, and a deficit in object imagery may account, in part, for the findings of this study. A deficit in imagery might be caused by the inability to create and maintain an internal representation of the object, which is consistent with the findings of overreliance on external environmental information in PD (Brown & Marsden, 1990). Other factors involved in mental rotation that could disrupt performance include the degree and/or dimension of the rotation (Corballis, 1997; Shepard, 1978; Shepard & Metzler, 1971), and these remain the topic of future research as well.

Neuropsychological Correlates of Mental Object Rotation

The anatomical localization of brain structures that subserve mental object rotation remains somewhat unclear. Although studies of individuals with lateralized brain damage generally indicate a right hemisphere advantage for mental rotation performance (Ditunno & Mann, 1990; Layman & Greene, 1988; Ratcliff, 1979; but see also Mehta et al., 1987), studies of mental rotation ability in normal subjects using tachistoscopic presentation procedures have been inconsistent in demonstrating a visual field advantage (Cohen & Polich, 1989; Corballis & McLaren, 1984; Corballis & Sergeant, 1989; Fischer & Pelligrino, 1988; Jones & Anuza, 1982; Simion et al., 1980; Ueker & Obrzut, 1993; Van Strien & Bouma, 1990). Results from EEG studies are also inconsistent (Ornstein et al., 1980; Osaka, 1984). Functional imaging studies using magnetic resonance imaging have generally shown bilateral activation in both frontal and parietal regions (Cohen et al., 1996; Tagaris et al., 1997), although one study suggests that a hemispheric asymmetry exists that is dependent on whether the mental rotation is of an egocentric (left hemisphere) or extra-personal object-based (right hemisphere) transformation (Zacks et al., 1999). Studies of cerebral metabolism using positron emission tomography have generally found increased right hemisphere activation during performance of spatial orientation tasks (Deutsch et al., 1988; Gur et al., 1982; Harris et al., 2000). However, one study found no hemispheric asymmetry associated with mental rotation performance (Bulla-Hellwig et al., 1996), and another study found activity in left parietal region and basal ganglia during a mental rotation task involving alphanumeric stimuli (Alivisatos & Petrides, 1996).

Parkinson's disease is primarily a disorder of the basal ganglia, and these results indicate that the ability to perform mental rotations is a complex cognitive function that is dependent on intact function in the basal ganglia and their connections to the frontal lobes and parietal regions. Consequently, our results in the men are consistent with current theories of visual-spatial deficits in PD, which may be due to dysfunction in frontal-striatal circuits (Brown & Marsden, 1990; Taylor & Saint-Cyr, 1995), frontal-parietal systems (Cronin-Golomb & Braun, 1997), or parietal-striatal networks (Clower et al., 2002). Given these interconnections (see also Alexander et al., 1986, 1990; Middleton & Strick, 2000; Owen, 1997; Saint-Cyr, 2003, for reviews), dysfunction in one region can have a cascading effect that disrupts function in linked regions. However, it remains unclear if this deficit is primarily related to basal ganglia or cortical dysfunction. Most likely, however, this cognitive deficit is due to dysfunction within a distributed neural system that subserves visual-spatial perception, mental imagery, and mental manipulation of those images. Further research, however, is needed to elucidate the contribution of the different neuropsychological processes involved in spatial cognition, and to delineate the sex differences in the function of these respective processes.

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