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Visual-spatial and set-shifting functions in patients with Parkinson's disease

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Visual-Spatial and Set-Shifting Functions in Patients with Parkinson's Disease

by

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Abstract

VISUAL-SPATIAL AND SET-SHIFTING FUNCTIONS

IN PATIENTS WITH PARKINSON'S DISEASE

by

Sarah A. Raskin

Co-Advisers: Joan C. Borod, Ph.D. and James R. Tweedy, Ph.D.

Patients with Parkinson's disease (PD) (N=20) were compared to age and education-matched normal control subjects (N=20) on 18 paper-and-pencil neuropsychological measures. These tests were chosen to measure two specific functions. The first set of tests was chosen to measure spatial orientation, and these tests were divided into those that measure personal orientation, extrapersonal orientation, mental rotation, and right/left orientation. The second set of tests was chosen to measure the ability to shift mental set. Hotelling's multivariate T^2 tests revealed a significant difference between the PD patients and the normal control subjects on the tests chosen to measure set-shifting ability but no difference between the groups on those tests chosen to measure spatial orientation. These results are related to other studies that have demonstrated deficits in PD patients similar to those observed in patients with damage to the frontal lobes, supporting the hypothesis that a disruption of dopaminergic fibers to the prefrontal cortex may partly account for the cognitive deficits observed in patients with PD.

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INTRODUCTION

Parkinson's disease (PD), once believed to affect only the motor system, leaving mental functions intact, is now known to involve a spectrum of cognitive deficits. The extensive literature documenting these deficits has generally followed two lines of investigation.

The first involves patients who exhibit a global dementia. Investigators have attempted to determine whether this dementia results from the subcortical pathology responsible for the motor system dysfunction, and therefore constitutes a subcortical dementia, or whether there is some secondary cortical pathology such as a concomitant senile dementia of the Alzheimer's type.

The second line of investigation has been to study the specific deficits seen in patients who do not exhibit a global dementia and to try to determine if these deficits are due to subcortical pathology or to disruption of efferent fibers to the cortex. The neuropsychological deficits most commonly reported in PD patients who do not exhibit dementia are spatial orientation deficits, difficulty in shifting mental set, effortful memory deficits, reduced verbal fluency, and difficulty with initiation. Spatial orientation deficits are observed on tests of personal orientation, such as route-walking. Effortful memory tasks (e.g., those requiring the imposition of a delay between the presentation of a stimulus and the recall task) are difficult for patients with PD;

however, on immediate memory tasks, PD patients perform within the normal range. The deficit on effortful memory tasks is observed for both verbal and visual memory. PD patients also exhibit a slowness in responding on tests of memory scanning, verbal fluency, and set-shifting.

Spatial Orientation Versus Set-Shifting in PD

The set-shifting difficulty, difficulty with delayed response, and reduced fluency have all been suggested to be part of a single syndrome reflecting diminished connections with frontal cortex. Further, recent reports have questioned the existence of the spatial orientation deficits (e.g., Brown & Marsden, 1986). These reports suggest instead that the deficits observed also reflect an inability to shift mental set, secondary to disruption of basal ganglia connections with the frontal lobes. The current study employs a behavioral approach, using neuropsychological measures to separately examine spatial orientation functions and functions presumed to require a shift in mental set.

Examination of the current literature in cognitive functions of patients with PD does not permit a clear answer to this issue for three reasons: 1) spatial orientation has not been carefully studied separately from other visual spatial functions, 2) many studies that have reported deficits in shifting mental set have used tasks with a spatial orientation component, and 3) individual subject variables known to effect cognitive function have not been carefully

controlled or measured.

Spatial Orientation

Spatial orientation is manifested in many behaviors. The spatial orientation tasks that have been used to study patients with PD can be divided into four types. The first is personal orientation, in which it is necessary to make judgments about the self in space. The second is extrapersonal orientation, or judgments of the orientation of objects in space that do not involve the subject. The last two are right-left orientation, or judgments of whether objects are on the right or left side, and mental rotation, or judgments of how an object would be if rotated along a plane.

These spatial orientation functions have been studied separately in other patient populations. Semmes, Weinstein, Ghent, and Teuber (1963) described personal orientation as related to body schema or a "topographical model of the body which is developed and organized through multi-sensorial past experience and serves to modify present sensory images." This has been tested using the Weinstein Body Scheme Test (Weinstein, Semmes, Ghent, & Teuber, 1956) and the Money Map Test (Money, 1976).The Weinstein Body Scheme Test requires the subject to point to parts on his/her own body that are indicated on the body of a figure. The Money Map Test requires the subject to follow a path which has been drawn on a map and indicate at each turn of this path whether the turn

is a right turn or a left turn. Patients with left anterior lesions have exhibited the largest deficits on these tests (Butters, Soeldner, & Fedio, 1972). However, localization of one's own body parts appears also to be impaired in patients with left parietal lesions (Semenza, 1988).

Extrapersonal orientation, on the other hand, does not involve the body schema and has been tested using a route-walking task. One such route-walking task consists of a grid of spots laid out on the floor. The subject is given a "map" which is a drawing of the same grid of spots with a path indicated on it. The subject must then walk along the grid following the path indicated. In this case, patients with right posterior lesions were the most significantly impaired (Semmes, Weinstein, Ghent, & Teuber, 1955; Semmes et al., 1963). Patients with damage to the right hemisphere are more impaired than those with left-sided damage or normal controls on a test of judging the position of crosses (DeRenzi & Faglioni, 1967) and a stick reversal test (Butters, Soeldner, & Fedio, 1972). Patients with right posterior cerebral artery occlusion (and corresponding damage to the right parahippocampul gyrus) have difficulty following routes in external space, though they are able to read maps and perform visual discrimination tasks (Semenza, 1988)

Right-left disorientation has been described in patients with parietal lobe damage, particularly damage to the left parietal lobe, possibly reflecting the involvement of verbal

labels (Butters & Barton, 1970). There is evidence that damage to both the frontal and parietal lobes is associated with right-left disorientation (Borod, Carper, Goodglass, & Naeser, 1984), though patients with frontal lobe damage alone are equivalent to normal control subjects (Borod, Carper, Goodglass, & Naeser, 1984; Butters & Barton, 1970).

Mental rotation is often reported to be difficult for patients with both right- and left-sided cortical injuries (e.g., Butters, Barton, & Brody, 1970; Royer & Holland, 1975). Attempts to specify the neural substrate involved in mental rotation have also been made with measures of cerebral blood flow in normal subjects (Deutsch, Bourbon, Papanicolaou, & Eisenberg, 1988) and with a commissurotomized subject (Corballis & Sergent, 1989a). However, no unequivocal localizing evidence has been attained. Corballis and Sergent (1989b) concluded that both hemispheres most likely participate in normal subjects. Therefore, the only spatial orientation functions which have been demonstrated to be disrupted following frontal lobe damage alone are those of personal orientation. Thus, if the visual spatial deficits observed in PD are due solely to frontal lobe dysfunction, the only type of tests on which they might be expected to perform poorly are those that measure personal orientation.

Spatial Orientation in PD

In tests of personal orientation, patients with PD have trouble judging both the visual vertical and the postural

vertical, i.e., when the body is in a vertical position using conditions of body tilt (Proctor, Riklan, Cooper, & Teuber, 1964; Teuber & Proctor, 1964; Bowen, Burns, Brady, & Yahr, 1976). In this task the patients are placed in an apparatus that tilts their body to a specified angle and then are asked to indicate when a) a luminous line is vertical, and b) their bodies have reached the vertical from this tilted position. Bowen et al. (1976) asked patients to touch parts of their own bodies corresponding to those designated on a diagram using the Weinstein Body Scheme Test. Overall, patients with left-sided and bilateral motor symptoms made more total errors than those with right-sided symptoms. However, these errors only occurred when the body in the diagram was in a frontal view (requiring the patient to perform a left-right reversal). Bowen, Hoehn, and Yahr (1972) found patients to be significantly worse on a route-walking task than controls. Importantly, these patients had no difficulty walking north (straight ahead) but could not follow the map when any change in direction was indicated. Those patients with left-sided or bilateral symptoms again showed the greatest deficits in performance. These findings suggest first, that PD patients with predominantly left-sided symptoms may differ behaviorally from those with right-sided symptoms. Some evidence has indicated, in fact, that those PD patients with predominantly left-sided symptoms exhibit more visual-spatial deficits and those patients with right-sided symptoms exhibit more language

deficits (e.g., Spicer, Roberts, & LeWitt, 1987). Second, PD patients may have specific deficits in maintaining personal orientation only when a change in orientation is required. This, therefore, could reflect either a spatial orientation deficit or a deficit in shifting mental set.

However, patients with PD also have trouble performing tests of extrapersonal orientation. Patients with PD have difficulty judging the visual vertical even when they are in an upright posture (Danta & Hilton, 1975). Boller, Passafiume, Keefe, Rogers, Morrow, and Kim (1984) reported that PD patients performed significantly worse than normal controls on a test of visual angle matching and on matching crosses. Stern, Mayeux, Rosen, and Ilson (1983) and Stern, Mayeux, and Rosen (1984) also found PD patients to be significantly worse than controls on a task requiring the subject to trace a line with his/her finger. It should be noted that not only was the performance on this test quantitatively impaired but that patients made different kinds of errors than did the normal controls (i.e., PDs were more likely to make errors in which the form of the drawing was incorrect). This is in agreement with findings of Wasserstein, Borod, Bodis-Wollner, Raskin, Coscia, and Yahr (1987) that PD patients have difficulty with the Benton Judgment of Line Orientation test. Wasserstein et al. (1987) suggest that PD patients have a particular difficulty with tasks that require the judgement of orientation of lines in

space. In fact, PD patients in the early stages of the disease, who have not been treated with any medication, had difficulty matching the orientation of a rod, given a model (Hovestadt, deJong, & Meerwaldt, 1987). Hovestadt et al. (1987) argue that impaired spatial perception is an early symptom of the disease which is no longer clinically evident once the decline in motor functions becomes more severe. PD patients have also been found to be impaired on a task which requires visual imagery (Ransmayr, Schmidhuber-Eiler, Engler-Plorer, Poewe, & Liedlmair, 1987), though only those patients over 60 years of age exhibited this deficit. Other authors, however, have reported normal performance on the Benton Line Orientation test (Girotti, Carella, Grassi, Soliveri, Marano, & Caraceni, 1986; Goldenberg, Wimmer, Auff, & Schnaberth 1986) and on a spatial forecast task, in which patients were required to judge at which point a line segment would cross a second line if it were extended (Dellasala, DiLorenzo, Giordana, & Spinnler, 1986). Thus, the data on exptrapersonal orientation in PD are equivocal even when identical or similar tasks are used, possibly reflecting differences in PD patients of different ages or different stages of the disease.

Though right-left orientation has not been specifically studied, the study in which PD patients had difficulty identifying body parts on a model suggests a possible deficit in this area.

In contrast, on tests of mental rotation, PD patients

are generally reported to be intact (Boller et al., 1984; Ransmayr, Schmidhuber-Eiler, Engler-Plorer, Poewe, & Leidlmair, 1987). Goldenberg et al. (1986) found no significant differences between PD patients and controls on Ratcliff's Mannikin Test (Ratcliff, 1979), a test of mental rotation and right/left discrimination.

Brown and Marsden (1986) argue that a deficit in spatial orientation in PD has not been clearly demonstrated. In their study, they used a visual spatial test which involves mental rotation and right-left discrimination. Patients had to judge whether a box was to the right or left of an arrow in conditions where the arrow pointed upward, downward, to the right, or to the left. On this test, PD patients performed as well as normal controls. The authors claim that all previous studies reporting deficits in visual spatial function can be explained as a reflection of an inability to change mental set, resulting from diminished frontal cortical control of behavior.

Set-Shifting

Mental set can be defined as a state of brain activity that predisposes a subject to respond in one way when several alternatives are present (Flowers & Robertson, 1985). Changes in mental set may reflect changes in such a response tendency based on an ongoing behavioral program, internal motivation, or prior instruction to change set at a particular point in time, rather than the result of an immediate prompt from a

change in the stimulus situation.

Set-Shifting in PD

A review of the performance of PD patients on tests that require a shift in mental set reveals some evidence for a specific deficit in this area. PD patients perform more slowly than normal controls on the Stroop task (Hietanen & Teravainen, 1985; Taylor, Saint-Cyr, & Lang, 1986) and the Trailmaking Test (Hietanen & Teravainen, 1985; Pirozzolo, Hansch, Mortimer, Webster, & Kuskowski, 1982), but this may reflect a general slowing in performance time rather than a specific inability to change mental set. On the Wisconsin Card Sorting Test (WCST), PD patients made more total errors and completed fewer categories than normal control subjects, but there were no differences between the groups in number of perseverative errors (Bowen, Kamienny, Burns, & Yahr, 1975; Dubois, Pillon, Legault, Agid, & Lhermitte, 1988; Lees & Smith, 1983; Flowers & Robertson, 1985; Taylor, Saint-Cyr, & Lang, 1986). Gotham, Brown, and Marsden (1988), however, found PD patients both completed fewer categories and made more perseverative errors than normal controls. Using the modified and simplified version of the WCST, PD patients perform in the normal range (Flowers & Robertson, 1985). This version of the test is more structured by informing the subject when a change in set is made. This suggests that these patients may indeed have a difficulty with shifting of mental set that is based on internal cues or initiation.

Flowers and Robertson (1985) designed the "Odd-Man-Out" test as a more sensitive test of set-shifting than the WCST. This test requires the subject to indicate which of a set of letters or numbers is different from the others based on one of two possible rules. The subject must use the two rules alternately on successive trials. Patients with PD performed only slightly more poorly than normal controls, indicating a clear ability to perform the task. However, their pattern of errors was different from that of the controls. The patients made more errors throughout the trials, while controls made significantly more errors at the beginning; PD patients made errors on later trials for items that they had originally categorized correctly. Again, there were not more immediate perseverative errors, but there were fluctuations in performance and a tendency to revert back to a previously indicated rule.

In addition, Cools, Van Den Bercken, Horstink, Van Spaendonck, and Berger (1984) reported that PD patients have difficulty shifting set in both the verbal and motor domains, and Stern, Mayeux, Hermann, and Rosen (1988) found that PD patients did not maintain set as normal control subjects did in a prism adaptation task once the external aid (the prisms) was removed.

Other studies of set-shifting in the motor domain have found that PD patients have difficulty executing two concurrent motor tasks (Talland & Schwab, 1964). Cools et

al. (1984) also suggest that PD patients have difficulty shifting motor behavior when the movement is initiated and guided by self-generated information (which corresponds to "open loop" or "feed-forward" processing). Sagar, Sullivan, Gabrieli, Corkin, and Growdon (1988) and Mortimer, Warrior, Kuskowski, Jun, and Webster (1989) also attribute PD patients' memory deficits to a difficulty in the discrimination of stimuli from different memory stores and thus an inability to shift set.

Basal Ganglia-Frontal Cortex Loops

There is other evidence from both anatomical and behavioral sources for frontal lobe dysfunction in disorders resulting from basal ganglia lesions. There are intimate connections from the basal ganglia to the frontal lobes, and in PD, there is decreased dopaminergic input to this cortical region. Frontal-thalamic disconnections have been suggested to explain anecdotal reports of lack of spontaneity, poverty of imagination, and inertia exhibited by patients with PD (e.g., Lees & Smith, 1983). Empirical measures of imitation behavior, prehension behavior, inertia, and indifference (as defined by a qualitative rating scale of commonly observed behaviors in patients with frontal lobe lesions) also have shown impairment in PD patients when they are compared to normal control subjects (Dubois et al., 1988).

Anatomical evidence regarding the relationship between the basal ganglia and the frontal cortex supports the notion

of frontal lobe dysfunction following cell loss in the basal ganglia. There is now considerable evidence for basal ganglia outputs directed at the frontal lobes (Goldman-Rakic, 1987) and prominent inputs to the basal ganglia from the frontal lobes (Evarts, Kimura, Wurtz, & Hikosaka, 1984). DeLong, Georgopoulos, and Crutcher (1983) suggested, based on anatomical evidence, that the basal ganglia and frontal cortex were connected by two loops via the thalamus, a 'motor' loop and a 'complex' loop. The 'motor' loop integrates agranular sensorimotor and premotor cortex with the putamen, caudal portions of the basal ganglia, and the diencephalic relay via nucleus ventralis lateralis back to supplementary motor areas in frontal cortex. This pathway is primarily involved in the control of movement. The 'complex' loop, on the other hand, involves all areas of association cortex and the caudate nuclei. This loop transmits information to the rostral basal ganglian efferent system with diencephalic relays via the nucleus ventralis anterior and medialis dorsalis to the frontal eye fields and the granular frontal cortical association areas. It is this loop that is postulated to be involved in complex mental functions. In fact, lesions to nuclei involved in the caudatoprefrontal loop have a significant effect on cognitive functions in monkeys, whereas lesions in the thalamic nuclei involved in the motor loop do not (Gotham, Brown, & Marsden, 1988).

Other studies (e.g., Alexander, DeLong, & Strick, 1986)

have suggested five or more segregated circuits involving discrete frontal cortical areas and striatofugal pathways that return via ventrolateral, ventral anterior, and medial dorsal thalamic nuclei to the supplemental motor area, the frontal eye fields, dorsolateral, lateral and orbitofrontal cortex, and anterior cingulate cortex. Among these are two circuits involving specific areas of the prefrontal cortex. The first is the dorsolateral prefrontal circuit which involves the dorsolateral prefrontal cortex (pars parvocellularis), posterior parietal cortex, and arcuate premotor area. These regions project 1) to the dorsolateral portion of the head of the caudate as well as a rostrocaudal section, which then project back to the caudal prefrontal region via the globus pallidus and thalamic nuclei, and 2) via the substantia nigra and thalamic nuclei back to the dorsolateral prefrontal cortex. The second circuit is the lateral orbitofrontal circuit which projects from the orbitofrontal cortex (pars magnocellularis) to the ventromedial sector of the caudate which then projects via both the globus pallidus and substantia nigra to the lateral orbitofrontal cortex.

Frontal Lobe Involvement in PD

Studies of PD have, in fact, revealed anatomical evidence for frontal cortical involvement. Some radiographic studies have revealed frontal cortical atrophy in PD (Lichter, Corbett, Fitzgibbon, Davidson, Hope, Goddard, Sharples, & Pollock, 1988). In addition, PD patients do not show the

hyperfrontal pattern of cerebral blood flow (increased flow to frontal regions when compared to other cortical brain regions) shown in normal control subjects (Bes, Guell, Fabre, Dupui, Victor, & Geraud, 1983).

Neurochemical studies of PD have also suggested changes in frontal cortex. Postmortem evidence indicates dopamine depletion in both the nigrostriatal and mesocorticolimbic dopaminergic systems in PD with some depletion throughout the prefrontal loops. The dopamine (DA) cell bodies responsible for the cortical innervation are in the ventral mesencephalic tegmentum and the substantia nigra. In fact, DA is depleted in the frontal cortex to approximately 40% of the level seen in normal brain samples. Of course, the functional significance of dopamine depletion is not clear (Gotham et al., 1988), but there is evidence that selective depletion of dopamine in prefrontal areas results in behavioral deficits seen after prefrontal lesions, such as impaired performance on the delayed alternation task (Brozoski, Brown, Rosvold, & Goldman, 1979). Selective prefrontal cortical dopaminergic lesions produce increased dopamine receptors in the striatum and nucleus accumbens (Glowinski, Tassin, & Thierry, 1984). Since the mesocortico-prefrontal DA neurons exert inhibitory influence on cells in the antero-medial cortex, there may also be evidence of cholinergic involvement in PD. Choline acetyltransferase activity and increased binding of muscarinic receptors have been demonstrated in both the frontal lobes and

substantia innominata of PD patients, and these have been correlated with degree of dementia (Dubois, Ruberg, Javoy-Agid, Ploska, & Agid, 1983).

Frontal Lobe Functions

Cognitive functions proposed to be disturbed by lesions to the frontal lobes are widely varied, and include such functions as disinhibition, inability to verbally monitor performance (Luria, Pribram, & Homskaya, 1964), cognitive estimation (e.g., Smith & Milner, 1984), abstract reasoning, and possibly deficits in personal orientation (Semmes, Weinstein, Ghent, & Teuber, 1963). Prefrontal cortical lesions have been associated with deficits in new learning, flexible thinking and sequencing, drive and motivation, planning and goal setting, and self awareness in relation to the environment (Stuss, 1986). In addition, shifting set, the ability to focus on one aspect of information, using knowledge learned, and using simultaneous or multiple sources of information are impaired, as well as temporal ordering and delayed recall (Stuss, 1986). It is not yet understood whether these deficits result from discrete lesions of the frontal lobes in the absence of more generalized cerebral damage (Canavan, Janota, & Schurr, 1985), or whether different regions of the frontal cortex are necessary for different functions. In particular, many researchers have investigated the different behavioral effects of damage to the orbitofrontal and the dorsolateral prefrontal regions.

The functions of the orbitofrontal regions of the cortex in humans have been studied in schizophrenic patients who have undergone orbitofrontal leukotomy. These patients have difficulty with set-shifting and the ability to maintain a sequence of correct responses (Stuss, Benson, Kaplan, Weir, Naeser, Lieberman, & Ferrill, 1983), though performance on such tasks as the WCST are not consistently impaired (Stuss et al., 1983; Milner, 1964), and abstract reasoning and abstraction remain intact (Stuss et al., 1983). Patients with damage to this region are sensitive to proactive interference in consonant trigrams and relatively spared in the ability to retrieve previously learned information (Stuss, Kaplan, Benson, Weir, Chiulli, & Sarazin, 1982). In addition, patients with orbitofrontal lesions do not show the perseverations common in patients with dorsolateral lesions (Stuss et al., 1983). Of course, it is difficult to assume that all deficits observed in schizophrenic patients who have had orbitofrontal leucotomy can be directly ascribed to orbitofrontal functions, especially given evidence of more generalized structural changes in the brains of these leucotomised patients (Pakkenberg, 1989).

Patients with dorsolateral lesions show difficulty with divergent thinking, verbal fluency, recency discrimination, delayed response and self-ordered pointing (Milner & Petrides, 1984). These patients show perseverations on the WCST and do not learn from their errors on a stylus maze task. They are

impulsive and have difficulty with conditional associative learning, in which there are several possible responses and the subject must choose correct based on stimulus.

Frontal Lobe Functions in PD

Common measures of frontal lobe pathology, particularly of the prefrontal region, have also been used to assess patients with PD. Deficits on delayed response are linked to the major projections to the dorsolateral frontal and orbitofrontal systems from the dorsomedial nucleus of the thalamus (Freedman & Oscar-Berman, 1986). Studies using the delayed response task (Teuber & Proctor, 1964) have suggested that lesions of the basal ganglia in monkeys reproduced symptoms seen after bifrontal cortical ablations. Patients with PD have also demonstrated difficulty with delayed response tasks (Bodis-Wollner, Harnois, Bobak, & Mylin, 1983; DeLancey Horn, 1971; Sahakian, Morris, Evenden, Heald, Levy, Philpot, & Robbins, 1988; Taylor, Saint-Cyr, & Lang, 1987), though this may simply reflect overall cognitive deficits (Freedman & Oscar-Berman, 1986).

Tests of verbal fluency, sensitive to frontal lobe pathology (Benton, 1968; Milner, 1964), have also been cited as evidence for frontal involvement in PD patients. PD patients have been found to perform within the normal range on tests of verbal fluency requiring generation of words that begin with a particular letter (Lees & Smith, 1984; Matison et. al, 1982; Weingartner et. al, 1984). Performance on a

fluency task requiring generation of words in a particular semantic category, however, was found to be impaired (Gotham, Brown, & Marsden, 1988; Matison et al., 1982; Pillon et al., 1986; Stern, Sano, & Mayeux, 1987). On a task that requires successive shifting between two semantic categories (Newcombe, 1969), PD patients were also found to be impaired (Gotham et al., 1988), though this may be due solely to the difficulty producing words in specific semantic categories rather than shifting between them. When specifically compared, PD patients produced a greater number of words than patients with damage to the frontal lobes (Miller, 1985).

In addition, other common measures of injury to the frontal lobes have not revealed deficits in PD patients. Subject-ordered pointing, while impaired in patients with frontal lobe pathology (Petrides & Milner, 1982), was intact in patients with PD (Gotham et al., 1988). Conditional associative learning tasks are similarly sensitive to prefrontal pathology (Canavan & Passingham, 1985; Petrides, 1985) but do not demonstrate an impairment in PD patients (Gotham et al., 1988; Sahakian, Morris, Evenden, Heald, Levy, Philpot, & Robbins, 1988). Interestingly, both subject-ordered pointing and conditional associative learning tasks were performed more poorly by patients on medication than normal controls but this was not true of those who were not on medication. This suggests first that the neuropsychological deficits of PD, while similar in some

respects, are not identical to those seen in frontal lobe pathology, and second that dopaminergic medication may be detrimental to some functions. Utilization behavior, common in patients with frontal lobe pathology (e.g., Lhermitte, Pillon, & Sersaru, 1986) also has not been observed in studies of patients with PD (Dubois et al., 1988).

Subject Variables

The dissociation between spatial orientation deficits and deficits in shifting mental set is made more difficult because many studies have reported contradictory findings and attributed this to differences in subject characteristics. The characteristics that have been suggested to effect the performance of PD patients are age (e.g., Girotti, Soliveri, & Carella, 1988), age at onset (e.g., Lieberman, Dziatolowski, & Kupersmith, 1979), laterality of motor symptoms (e.g., Starkstein, Leiguarda, Gershanik, & Berthier, 1987), type of motor symptom (e.g., Mortimer, Pirozzolo, Hansch, & Webster, 1982), duration of symptoms (e.g., Mayeux, Stern, & Rosenstein, 1988), severity of symptoms (e.g., Huber, Paulson, & Shuttleworth, 1988), medication, and duration of medication (e.g., Portin & Rinne, 1980). In addition, two distinct types of PD have been suggested, one with pathology confined to the substantia nigra, that does not develop dementia and one with cortical pathology as well as subcortical pathology, that produces dementia (Lieberman et al., 1979, Boller et al., 1980).

Regarding age, there is substantial evidence that a PD subtype exists which exhibits a global deterioration of mental functions. The patients in this subtype are older (Girotti, Soliveri, & Carella, 1988; Huber, Shuttleworth, & Paulson, 1986; Martilla & Rinne, 1976; Stern, Sano, & Mayeux, 1987), develop symptoms at a later age (Lieberman, Dziatolowski, & Kupersmith, 1979), and respond less well to medication (Birkmayer, Riederer, & Youdim, 1979) than other PD patients. Age alone, in the absence of PD, does not explain the cognitive deficits in this particular subtype of PD patients as they are significantly worse than age-matched controls on measures of overall cognitive functioning (Garron, Klawans, & Narin, 1972; Lieberman, Dziatolowski, & Kupersmith, 1979). Importantly, there is some neuropsychological (Garron, Klawans, & Narin, 1972) and pathological (Boller, Mizutami, Roessmann, & Gambetti, 1980; Whitehouse, Hedreen, White, & Price, 1983) evidence that this "globally impaired" subgroup of PD patients has concomitant senile dementia of the Alzheimer's type (Benson, 1984; Pirozzolo, Hansch, Mortimer, Webster, & Kuskowski, 1982). Though more recent evidence has suggested instead that the process of PD itself brings on Alzheimer-like changes including the histological signs of AD (plaques, tangles) and a decrease in acetylcholine transferase activity in the frontal cortex and the substantia innominata (Dubois, Ruberg, Javoy-Agid, Ploska, & Agid, 1983). Whether this is a subtype of PD or an endpoint of the progressive

process in not clear.

Laterality of motor symptoms has been studied both from a physiological and a neuropsychological perspective. Though it is not universally accepted that unilateral motor symptoms indicate unilateral disease of the basal ganglia, there is some evidence to support this case. Gilbert (1976) reported depigmentation and loss of neurons in the substantia nigra and locus coereleus, as well as neurofibrillary tangles and granulovascular degeneration, on the side of the brain contralateral to the side of the body exhibiting the most pronounced symptoms. They suggested that a unilateral deficiency of basal ganglia dopamine might produce unilateral pyramidal tract disease. Chouza, Romera, Laguardia, Pou, Lorenzo, Flores, Wozniak, Feres, Caomino, and Shroeder (1984) found unilateral atrophy on CT scan contralateral to the clinically affected side in six of eight patients, and when symptoms were bilateral and asymmetrical, atrophy was still predominant contralateral to the more severely affected side of the body. Direnfeld, Albert, Volicer, Langlais, Marquis, and Kaplan (1984) found that while PD patients with predominantly left-sided symptoms had more neuropsychological impairment, they had higher homovanillic acid (HVA) levels in the cerebral-spinal fluid. The PD patients with left-sided symptoms also had higher levels of acetylcholine esterase (AChE). This is relevant because the dopaminergic and cholinergic systems function in a negative feedback system in

the striatum so that increased AChE would be expected concurrently with increased HVA. This suggests a functional asymmetry of the dopaminergic system.

Neuropsychological studies with patients who have exclusively or predominantly unilateral symptoms or with patients who have had unilateral surgery generally have reported that patients with predominantly left-sided symptoms (presumed right-hemisphere involvement) have more difficulty with visual-spatial material, and that patients with predominantly right-sided symptoms (presumed left-hemisphere involvement) have more difficulty with linguistic material or verbally-mediated processes (e.g., Starkstein et al., 1987). These results are, of course, similar to those reported in studies of patients with unilateral cortical pathology.

Studies of visual-spatial function in hemi-parkinsonian patients have reported impairment in those PD patients with left-sided symptoms but not those with right-sided symptoms. In an examination of spatial orientation, Proctor, Riklan, Cooper, and Teuber (1964) and Teuber and Mishkin (1954) found that PD patients with predominantly left-sided symptoms made contralateral over-reaction to body tilt on the Aubert task, which requires judging the orientation of a luminous line in the dark under various conditions of body tilt. Those with right-sided symptoms, on the other hand, did not make consistent over-reactions in any tilt condition. Bowen, Burns, Brady, and Yahr (1976) and Bowen (1976) reported that

only PD patients with left greater than right or bilateral symptoms made significantly more errors than controls on an inventory of personal orientation items that required the matching of parts of the body to those numbered on a figure. Similarly, those patients with left-sided or bilateral symptoms were worse than those with right-sided symptoms on a task of route-walking (Bowen, Hoehn, & Yahr, 1976). Deficits were most pronounced when subjects were required to walk in any direction but straight ahead, i.e., in directions requiring mental rotation of the map's representation of the route to be taken. These patients did not show any deficits in identifying body parts to verbal command or tactile stimulation.

Patients with left-sided symptoms appear to have a specific deficit with visual-spatial material. Bentin, Silverberg, and Gordon (1981) found that patients with predominantly left-sided symptoms had deficits on the WAIS-R Block Design and Object Assembly subtests and on the Benton Facial Recognition Test (Benton, Hamsher, Varney, & Spreen, 1983). Blonder et al. (1987) found that patients with left greater than right-sided symptoms had the most difficulty on spatial (WAIS-R Block Design) and figure memory (Wechsler Memory Scale Visual Reproductions) tasks. Visual neglect has been reported in patients with left-sided or bilateral symptoms, but not in patients with right-sided symptoms (Starkstein, Leiguarda, Gershanik, & Berthier, 1987;

Villardita, Smirna, & Zappala, 1983). Chouza et al. (1984) demonstrated that even patients with predominantly left-sided symptoms in early stages of the disease had deficits in visual-spatial memory. Durenfeld et al. (1984) reported that PD patients with predominantly left-sided symptoms performed more poorly than controls on both memory and visual-spatial tasks.

Spicer, Roberts, and LeWitt (1988), however, reported no differences between patients with predominantly right-sided versus left-sided symptoms on tasks generally considered to be affected by right hemisphere damage (i.e., Form Sequence Learning, Facial Recognition, and Judgement of Line Orientation tests [Benton et al., 1974]). However, patients included in their study were required to have a WAIS-R Verbal I.Q. not exceeding their WAIS-R Performance I.Q. by more than 15 points. Thus, this study excluded all patients with substantial visual-perceptual deficits.

Patients with predominantly right-sided symptoms are reported to have difficulty on verbal tasks, such as the verbal subtests of the WAIS-R (Starkstein et al., 1987), paired associate learning (Perret, Kohenof, & Siegfried, 1969), Logical Memory subtest of the Wechsler Memory Scale (Blonder et al., 1987), digit span, verbal fluency (Bentin et al., 1981; Blonder et al., 1987; Spicer et al., 1988), naming (Blonder et al., 1987; Spicer et al., 1988), sentence repetition, sentence completion for ideational material

(Blonder et al., 1987), and serial digit learning (Spicer et al., 1988).

In general, the literature on hemi-parkinsonism suggests that unilateral symptoms are associated with behavioral changes generally similar to those observed in cases of unilateral cortical damage: patients with left-sided lesions have difficulty with linguistic tasks, and patients with right-sided lesions have difficulty with visual-spatial tasks. In addition, patients with presumed right-sided damage seem to have "global" deficits (in visual-spatial and general intellectual functions) while those with left-sided damage have more "circumscribed" deficits (in linguistic functions). Similar findings have been reported following penetrating injuries to the right versus left precentral gyrus (motor strip) of the cerebral cortex (Semmes, 1969). It must be noted, of course, that the finding of unilateral motor symptoms in PD does not necessarily reflect unilateral lesions of the contralateral basal ganglia. It may instead reflect unilateral damage to pathways connecting the basal ganglia and cerebral cortex.

Regarding duration of symptoms, a subtype of PD patients has been described to have a more rapid progression of cognitive deterioration and greater cognitive loss (Birkmayer, Riederer, & Youdim, 1979; Pederzoli, Girotti, Scigliano, Aiello, Carella, & Caraceni, 1983; Mayeux, Stern, & Rosenstein, 1988). This increased speed of progression has

been demonstrated in a longitudinal study (Portin & Rinne, 1986)

The motor symptoms of PD are generally described as a typical triad of bradykinesia, tremor, and rigidity. However, some patients may have predominant symptoms of only one of these three, presumably reflecting differences in the cells involved in the disease process. Furthermore, different patterns of cognitive deficits have been described in patients in which different motor symptoms predominate. Patients with more severe bradykinesia have been shown to have more significant deficits in visual-spatial reasoning, psychomotor speed (Mortimer, Pirozzolo, Hansch, & Webster, 1982), and general intellectual functions (Huber, Paulson, & Shuttleworth, 1988), though this is not necessarily attributable to a slowing of information processing speed, termed "bradyphrenia" (Rafal, Posner, Walker, & Friedrich, 1984). Patients with more severe tremor actually performed better than patients with less severe tremor on a test of spatial memory (Mortimer, Pirozzolo, Hansch, & Webster, 1982) and of general intellectual status (Huber, Paulson, & Shuttleworth, 1988). In addition, increased tremor has been associated with increased muscarinic binding sites in the frontal cortex (Dubois, Ruberg, Javoy-Agid, Ploska, & Agid, 1983). In addition, the severity of the motor symptoms has been correlated with intellectual impairment, suggesting a common subcortical etiology (Huber, Paulson, & Shuttleworth,

1988).

The effects of medication on patients with PD have also been investigated. The first medication used to treat PD was, of course, dopaminergic medication such as L-Dopa. Studies of cognitive effects of dopaminergic treatment have revealed transient positive effects of the treatment with some possible long-term detrimental effects. After short-term treatment, PD patients show improvement in memory functions (Halgin, Riklan, & Misiak, 1977; Mohr, Fabrini, Ruggieri, Fedio, & Chase, 1987; Portin & Rinne, 1980). However, PD patients receiving levodopa over several years are impaired, compared to untreated patients, on tests of recent memory function (Halgin, Riklan, & Misiak, 1977; Portin & Rinne, 1980; Riklan, Whelihan, & Cullinan, 1976), visual-spatial functions and language functions (Portin & Rinne, 1980). While many of these studies matched treated and untreated patients with equivalent durations of disease, those requiring treatment most likely had more severe symptoms. Comparing individual PD patients when on and off levodopa treatment, PD patients were impaired on a test of verbal fluency only when off levodopa, but were impaired on associative conditional learning and subject-ordered pointing only when on levodopa (Gotham, Brown, & Marsden, 1988). There is also some evidence of a state-dependent effect of dopamine levels, wherein absolute dopamine levels had no effect on memory performance but a change in dopamine level between time of original

learning and time of attempted retrieval resulted in impaired memory performance (Huber, Schulman, Paulson, & Shuttleworth, 1987).

More recently, PD patients have also been treated with anti-cholinergic medications. This is particularly important when studying cognitive functions since the cholinergic system has been demonstrated to be involved in memory, presumably because of the rich cholinergic innervation of the hippocampus and the frontal cortex. This is more significant in PD patients who have reduced acetyltransferase activity in the frontal cortex and an associated increase of muscarinic cholinergic receptors compared to normal control subjects (Smet, Ruberg, Serdaru, Dubois, Lhermitte, & Agid, 1982). In addition, PD patients have extensive reductions of choline acetyl-transferase, and this reduction correlated with the degree of mental impairment (Perry, Curtis, Dick, Candy, Atack, Bloxham, Blessed, Fairbairn, Tomlinson, & Perry, 1985). PD patients who are demented have been shown to develop gross confusional states when given anti-cholinergic medication (Smet et al., 1982). PD patients who do not exhibit dementia and are treated with anti-cholinergic medications have reduced free recall of information and a reduced ability for associative learning (Koller, 1984).

Hypotheses

A thorough examination will include paper-and-pencil neuropsychological tests of spatial orientation function

without the requirement of shifting mental set and tests of shifting mental set without a spatial orientation requirement. If patients with PD have a deficit in spatial orientation they should perform poorly on the first type, but like normal controls on the second. If the deficit is in set-shifting, PD should perform normally on those tests of spatial orientation function that do not require set-shifting.

Based on the preceding review of the literature, the following hypotheses are posited:

1. Given the recent findings of set-shifting deficits in PD patients (e.g., Cools et al., 1984), and the use in previous studies of spatial orientation tasks that require set-shifting or other executive functions for successful completion (e.g., Bowen, Burns, Brady, & Yahr, 1976), the primary hypothesis of the current study is that the PD patients will perform significantly more poorly than the normal control subjects on the tests designed to measure set-shifting functioning and will not differ from normal control subjects in their performance on the spatial orientation tasks.

2. The age of the PD patients, and the age of onset of parkinsonian symptoms will correlate negatively with the performance of the PD patients on set-shifting tasks.

3. The severity of the motor symptoms exhibited by the PD patients will correlate negatively with their performance on the spatial orientation tasks.

4. Those PD patients receiving anti-cholinergic medication will perform significantly more poorly on the set-shifting tasks than the PD patients not receiving anti-cholinergic medication.

5. Those PD patients with predominantly left-sided motor symptoms will perform significantly more poorly on the spatial orientation tasks than those PD patients with predominantly right-sided motor symptoms.

6. Those PD patients with bradykinesia presenting as the major motor symptom will perform significantly more poorly on the visual-spatial tasks than the other PD patients.

METHOD

Subjects

Thirty-five PD patients at Mount Sinai Medical Center were screened for participation in this study. Three were excluded because they had sustained secondary neurological disorder, e.g., cerebro-vascular accident. Two were excluded due to previous psychiatric illness, e.g., depression. Seven were excluded due to dementia on the basis of the Dementia Rating Scale (Mattis, 1976). No patients were included who scored at 127 or below, corresponding to the 8th percentile or below (Montgomery, 1982). Three discontinued participation before completion of the tasks in the test battery. Of the remaining 20 patients, 14 were tested as inpatients of the Clinical Research Center at Mount Sinai Medical Center. These patients were admitted to the Clinical Research Center for an initial trial of deprenyl (an MAO-B inhibitor) because they had experienced on/off fluctuations of parkinsonian symptoms in spite of dopaminergic medication. Four of the remaining patients were members of a PD support group at Mount Sinai who volunteered to participate. The remaining two patients were outpatients who were being seen for evaluation of their symptoms. All of these patients were being treated with dopaminergic medications at the time neuropsychological testing was conducted. Unfortunately information on drug dosages at time of testing is not available, and might not be as meaningful in these patients, many of whom were having

medication dosage titrated around the time of testing. No patients had received neurosurgery, had any other neurological disorder, or a history of substance abuse, including alcohol. Two were left-handed, and the rest were right-handed. Ten were women and 10 were men. The mean age was 64.6 years, s.d. 10.3, and the mean level of education was 15.2 years, s.d. 3.7. The mean age at onset of motor symptoms was 57.6 years, s.d. 9.9, and the mean duration of treatment with dopaminergic medication was 7.0 years, s.d. 3.2. Seven had symptoms appear first on the right side of the body and 12 had symptoms appear first on the left. Five currently had symptoms which were greater on the right side of the body than on the left, and 11 had symptoms greater on the left side of the body than on the right. Five had bradykinesia as the predominant motor symptom and nine had tremor as the predominant motor symptom.

Twenty normal volunteers served as control subjects. Four were spouses of the PD patients. Five had volunteered in previous studies and the remaining 11 were recruited through word of mouth. Nineteen were right-handed and one was left-handed. Twelve were women and eight were men. The mean age was 62.6, s.d. 10.9, and the mean level of education was 15.2 years, s.d. 3.4. None had any previous history of neurologic disorder, psychiatric illness or substance abuse. All normal controls received $10.00 for participation in this study.

The number of subjects was determined before initiation

of the study by using a power analysis (Ramsey & Ramsey, 1985). This power analysis used the noncentrality variable (lambda) and degrees of freedom from Brown and Marsden (1986) which was the study used to develop the primary hypothesis of the current study. The critical F value was determined from alpha set at .001. Given these parameters, 40 was the number of subjects required to obtain a power value greater than .80.

Materials

Eighteen paper-and-pencil neuropsychological tests were administered to all subjects. In general, tests were chosen that had been used in previous studies to measure the functions described. While these tests are not always clean measures of the respective functions, it was decided that the same tests should be used as had been used previously so that direct comparisons to previous studies could be made. These tests were selected to test two major functions. The first is spatial orientation processing. In addition, tests of spatial orientation processing were selected to separately measure personal orientation, extrapersonal orientation, mental rotation, and right-left orientation.

The tests of personal orientation chosen for the current study were the Money Map test (Money, 1976), the Weinstein Body Scheme Test (Weinstein, Semmes, Ghent, & Teuber, 1956) and the Body Center Test (Diller, 1974). The Money Map Test and the Weinstein Body Scheme Test were chosen because they

had been used as measures of personal orientation in early studies of PD (e.g., Bowen, Burns, Brady, & Yahr, 1976). In order to specifically investigate a possible deficit in personal orientation, tasks which had previously been used to measure this function were chosen. However, examination of these two tasks indicates that both tasks require the performance of right/left orientation and some degree of set-shifting. Therefore, the Body Center Test was included because it was judged to be a measure of personal orientation without the requirement of mental rotation, right/left orientation, or set-shifting for any of the items.

The tests of extrapersonal orientation chosen were the Benton Line Orientation Test (Benton, 1974), the Parietal Lobe Battery Geographic Orientation Test (Goodglass & Kaplan, 1972), and the Benton Geographic Orientation Test (Benton, 1974). The Benton Line Orientation Test was chosen because it has previously been used to demonstrate a deficit in extrapersonal orientation in PD patients (e.g., Wasserstein et al., 1987). The tests of geographic orientation tasks were chosen because they were judged not to require personal orientation for successful completion. While both these tasks of geographic orientation do require retrieval of information from memory, this has not been a deficit reported in PD patients and was not judged to be problematic in this study.

The tests of mental rotation chosen are the Item 99 from the Luria-Nebraska battery (Golden, Purisch, & Hammeke, 1980)

and the Ratcliff Mannekin Test (Ratcliff, 1979). The Ratcliff Mannekin Test was chosen because it had been used previously to measure mental rotation in PD patients (Goldenberg et al., 1986), though it also involves right/left orientation and some set-shifting. The Item 99 was chosen because it was judged to require only mental rotation for successful completion, though verbal mediation could certainly be employed.

The tests of right/left orientation chosen were the Benton Right/Left Orientation Test, the Parietal Lobe Battery Right/Left Orientation subtest, and the Brown and Marsden task. The first two tests were chosen because of their previous use as measures of right/left orientation in many subject populations (e.g., Borod, Carper, Goodglass, & Naeser, 1984), though the Benton test does require some set-shifting and the Parietal Lobe Battery Test may require some personal orientation. The Brown and Marsden task was used because this study was designed as a response to the study of Brown and Marsden (1986) and since data on that particular task were judged to be useful in making direct comparisons.

Second, tests which require the shifting of mental set are included. The alternating verbal fluency task, Competing Programs (Luria, 1966), Motor Programs I (Golden et al., 1980), Motor Programs II (Golden et al., 1980), and Sequential Categorization (Hibbard, unpublished) tests were all chosen because they were judged to require the immediate shifting between two mental sets without requiring any spatial

orientation functions. In addition, to more precisely specify the set-shifting functions of PD patients, the Digit Span test (Wechsler, 1981) was included to measure shifting between two sets that is not immediate; the Uses of Objects test (Getzel & Jackson, 1962) was included to measure a higher order type of set-shifting in abstract thought; and the Go/No-Go task (Luria, 1966) was included to measure shifting between responding and response inhibition.

Additional tests were administered to estimate premorbid functioning and basic visual discrimination. The test of premorbid functioning was the WAIS-R Information subtest, and the tests of basic visual discrimination were the Benton Visual Discrimination Test and the Visual Matrices. For a complete list of tests with a brief description of each test, see Appendix.

Procedures

Inpatients were tested at their bedside. Three outpatients were tested in an office at Mount Sinai, and three were tested in their homes. Nine normal controls were tested in an office at Mount Sinai, and 11 were tested in their homes. Total testing required approximately one and one-half hours per subject. All subjects were asked to read and sign a consent form which had been approved by the Institutional Review Board of the Mount Sinai Medical Center. The order in which tests were presented was completely randomized across subjects.

RESULTS

Of primary interest in this study was whether the PD patients would exhibit deficits when compared to the normal control subjects on the eight tests which measured set-shifting but would not exhibit deficits on the eleven tests which measured spatial orientation. In order to determine whether the PD patients were exhibiting deficits on the set-shifting tasks rather than the spatial orientation tasks, it was necessary to compare the PD patients to the normal control subjects first on the set-shifting tasks as a whole and then on the spatial orientation tasks as a whole.

Demographic Variables

To ensure that the PD group and the normal control group did not differ on demographic variables that are known to influence performance on neuropsychological tests, Student's t-tests (using Crunch Statistical Package, 1987) were run between the groups for age, gender, handedness (as determined by self-report), years of education, and occupational level (as determined by the Hollingshead Four Factor Index of Social Status [Hollingshead, 1977]). No significant differences were found for any of these variables. Table 1 includes the mean and standard deviation values for the two groups on each of these demographic variables, as well as the p values for the t-tests between the groups on each of these demographic variables.

In addition, tests were included to insure the groups did not differ on basic visual perception (Visual Matrices, Benton Visual Form Discrimination) and general intellectual ability (Wechsler Adult Intelligence Scale-Revised Information Subtest). Again, when t-tests were conducted, the groups did not differ on any of these variables, and so the groups were considered to be reasonably well-matched in terms of basic visual discrimination and general intellectual ability. Table 2 includes the means and standard deviations for the two groups on each of these cognitive variables, as well as the p values for the t-tests.

To compare the groups on the spatial orientation tests and on the set-shifting tests, the multivariate Hotelling's T^2 test for two independent samples using the Statistical Package for the Social Sciences/PC+ (Noursis/SPSS Inc., 1988), were run. See Table 3 for a list of all experimental tests, the abbreviation for each test that will be used subsequently, and the corresponding function which each test is presumed to measure. Table 4 provides the means, standard deviations, minimum score, and maximum score for each test, separately for each subject group.

Multivariate Comparisons

When the Hotelling's T^2 test was conducted on the set-shifting tasks, a significant difference was found between the groups, $F(9,30)=4.62$, $p=.001$. No significant difference

was found for the spatial orientation tasks, $F(10,20)=1.66$, $p=.160$. Thus, the PD patients did in fact exhibit deficits, when compared to normal controls, on tasks designed to measure set-shifting ability. However, the PD patients did not exhibit deficits on tasks designed to measure spatial orientation functions.

Testing the assumptions of the Hotelling's T^2, Box's M indicated that the variances of the two groups on the set-shifting tests are similar $F(45,4743)=1.40$, $p=.039$. However Box's M for the spatial orientation tests indicated that the variances of the two groups may not be equal and therefore the homogeneity-of-variance assumption may not be met ($F[55, 2495]=1.53$, $p=.007$). Bartlett's test of sphericity for the set-shifting tests was .586, indicating that the hypothesis that the population correlation matrix is an identity matrix cannot be rejected. For the spatial orientation tests, Bartlett's test of sphericity was .007, also indicating that the hypothesis that the population correlation matrix is an identity matrix cannot be rejected. Wilks lambda was calculated to determine the proportion of variance not explained by the multivariate test. For the set-shifting tests, the proportion of variance not explained was 42 percent. For the spatial orientation tests, the proportion of variance not explained was 55 percent.

Univariate Tests of Set-Shifting

Given the significant results of the multivariate T-test

for the set-shifting items, univariate Student's t-tests were performed to determine which of the particular tests was contributing to the significant difference between the groups. The results of these t-tests are provided in Table 5. As shown in table 5, all of the set-shifting tasks revealed significant differences between the groups except for the Go-No Go task and the difference between Digit Span forwards and backwards. Those tests that revealed significant differences were alternating verbal fluency, uses of objects, competing programs, sequential categorization, and motor programs.

Breakdowns of Spatial Orientation Tasks

The result that there was no difference between the PD and control groups on the spatial orientation tasks does not completely answer the questions of this study. It is possible that the PD patients had a deficit in personal orientation, as would be predicted specifically from the review of the literature, but not in the other areas of spatial orientation functioning. Such a selective deficit would not necessarily be apparent in the Hotelling's T^2 which grouped all spatial orientation functions together. To determine if this was in fact the case, a Hotelling's T^2 was run for those tests which measure personal orientation (N=3) and for all the other spatial orientation tasks (N=8). Again, however, there was no significant group difference for the tests of personal orientation ($F[3,33]=1.29$, $p=.293$) or for the other tests of spatial orientation tasks ($F[7,20]=1.46$, $p=.237$).

Univariate Tests of Spatial Orientation

Further, given the fact that the tests used were standardized tests and were not designed specifically to test the hypotheses of this study, the possibility exists that some of the tests may be adding error variance resulting in the nonsignificant Hotellings T^2. Therefore, while these analyses are not justified given the nonsignificance of the multivariate test, univariate Student's t-tests were performed on each of the individual spatial orientation tests to analyze whether a meaningful pattern emerged. Listed in Table 6 are the results of these t-tests for each of the individual tests of spatial orientation, as well as the mean and standard deviations for each of the groups on these tests. As indicated in Table 6, the only significant differences revealed were for the two mental rotation tests. Since both tests that yielded significant results were tests designed to measure the same function, it is interesting to consider whether mental rotation may be a deficit in this group of PD patients. This finding is puzzling, however, because mental rotation is one spatial orientation function for which previous studies have not found deficits for PD patients (Boller et al., 1984; Goldenberg et al., 1986; Ransmayr et al., 1987)

Subject Variables

There has been considerable evidence in previous studies (as reviewed in the Introduction) that subject variables, such

as age, age at onset of motor symptoms, side of the body on which motor symptoms predominate, type of symptoms, duration of symptoms, and current medication, may affect the cognitive status of PD patients. The effect of these subject variables on the spatial orientation and set-shifting tasks was then analyzed with Spearman's rank order correlation or analysis of variance, as appropriate (using Crunch, 1987). To ensure against Type I errors, given the large number of analyses (N=98), all analyses were run with alpha set at the .01 level. The results of these analyses are presented in Table 7. Table 7 provides first the results for those variables for which correlations were performed and then provides the results of the analyses of variance.

Since age and age at onset were predicted to affect all aspects of cognitive functioning, analyses were conducted for all 19 dependent variables. While no patients with dementia were included in this study, there is evidence to suggest that PD patients who are older and particularly those whose onset is at a later age have more cognitive deficits. In our sample, however, neither age nor age at onset of symptoms correlated significantly with any of the 19 dependent variables (see Table 7). This suggests that age is not a factor in PD patients who have already been selected as not having evidence of dementia.

Regarding duration of symptoms, there is some evidence that a group of PD patients with a fast progression of motor

symptom severity develops spatial disorientation as an early marker of cognitive deficits. Therefore, correlations were conducted to determine if there was a relationship between duration of symptoms and performance on tasks of spatial orientation. However, none of the spatial orientation tasks were significantly correlated with duration of symptoms (see Table 7).

Medication status was predicted to demonstrate differences specifically on the tests of set-shifting because these tests depend on the integrity of the frontal lobes and therefore the cholinergic system. Thus, patients receiving anti-cholinergic medications should perform more poorly on these tests. Since there were two possible types of medication status (dopaminergic medication alone, and both dopaminergic and anti-cholinergic medication), an analysis of variance was performed (see Table 7). The two groups did not differ significantly on any of the tests of set-shifting.

Laterality of motor symptoms was predicted to influence performance on the spatial orientation tasks. Specifically, those patients with predominantly left-sided motor symptoms were expected to perform significantly more poorly on the spatial orientation tasks than those patients with predominantly right-sided motor symptoms. PD subjects were grouped first according to the side of the body on which motor symptoms were first apparent. The two subgroups (those whose initial side of motor symptoms was the right, and those whose

initial side was the left) did not differ significantly on any of the spatial orientation variables (see Table 7). Then PD subjects were grouped according to the side of the body on which the motor symptoms were predominant at the time of testing. The three subgroups (those whose current predominant side of motor symptoms was the right, those with both sides equal, and those whose current predominant side of motor symptoms was the left) also did not differ significantly on any of the spatial orientation tasks (see Table 7).

The predominant motor symptom exhibited was predicted to reveal different groups in terms of set-shifting tasks. Those patients with bradykinesia were expected to perform more poorly than the other groups on these tasks. PD patients were divided into three groups according to the predominant motor symptom, i.e., bradykinesia, tremor, or rigidity. The three groups did not differ significantly on any of the eight tests of set-shifting.

If the cognitive deficits observed in PD patients result directly from basal ganglia dysfunction, cognitive deterioration should be related to the degree of motor deficit severity. Some reports have demonstrated that PD patients with dementia have more severe motor symptoms than those without dementia (Girotti, Soliveri, Carella, Piccolo, Caffarra, Musicco, & Caraceni, 1988). Of interest in this study is whether performance on those tasks presumed not to depend on frontal lobe functioning is related to severity of

motor symptoms. Severity of motor symptoms was coded using the Hoehn and Yahr scale (1967), which has five levels. All of the patients in this study were rated at levels I, II, or III. The three subgroups did not differ significantly on any of the tests of spatial orientation (see Table 7). Therefore, it is unlikely that severity of motor symptoms and severity of spatial orientation functions are related.

DISCUSSION

The results of this study establish first that some of the cognitive deficits observed in PD patients are of the type seen in patients with frontal lobe dysfunction, and second that PD patients do not exhibit clear evidence of deficits in spatial orientation when compared to normal control subjects.

Set-Shifting in PD

This study confirms previous studies which have demonstrated a set-shifting deficit in PD, e.g., those using the Stroop task (Hietanen & Teravainen, 1985; Taylor et al., 1986), Part B of the Trail Making Test (Hietanen & Teravainen, 1985), and the Wisconsin Card Sorting Test (Gotham, Brown, & Marsden, 1988; Lees & Smith, 1983). Similar findings have been reported with experimental tasks that required PD patients to sort blocks by shifting between different visual characteristics and to sort items on cards by shifting between different semantic categories (Cools et al., 1984). Another experimental task demonstrated that PD patients have difficulty shifting and maintaining mental set when presented with two alternative response sets (Flowers & Robertson, 1985). While performing motor sequences, PD patients had no difficulty with executing the movement per se but had trouble making correct responses when the movement sequence changed, presumably when a shift in mental set was required (Cools et al., 1984).

Given the significant difference between the PD patients and the normal control subjects on the set-shifting tasks as a whole, further analyses were performed to determine which of the specific set-shifting tasks revealed significant differences between these groups to more discretely specify the nature of the set-shifting deficit. In fact, not all of the measures of set-shifting revealed significant differences between PD patients and the normal control subjects. Those tasks that did reveal a significant difference in performance between the PD patients and the normal control subjects were verbal fluency with alternating categories, abstract uses of objects, Competing Programs, motor sequences, and sequential alternation. These results indicate that PD patients not only have difficulty with tasks that require an immediate alternation between two mental sets, but also with shifting between concrete and abstract thought.

Those tasks which did not demonstrate differences were the Go-No Go task and the difference between Digit Span forwards and Digit Span backwards. Go-No Go may be a different type of task from the other set-shifting tasks used in this study. Adequate performance involves response inhibition, and thus it is possible that while PD patients have difficulty shifting from one store of information to another, they may have no difficulty retrieving information consistently from the same store and merely inhibiting the response on a particular trial. In addition, there is some

evidence that the Go-No Go task depends on the integrity of a specific region of the brain that is not the orbitofrontal cortex per se. Iverson and Mishkin (1970) demonstrated that this task was disrupted with removal of the inferior convexity but not from lesions of the orbitofrontal cortex that left the inferior convexity intact, even when the lesions were of larger size. The orbitofrontal cortex was, however, necessary for successful completion of object reversal and spatial alternation in the same animals. This suggests that the Go-No Go task is a different type of task than other set-shifting tasks and that performance on this kind of task may be unaffected by PD.

The other task on which PD patients performed as well as the normal control subjects was the Digit Span task. In an attempt to obtain a pure measure of the set-shifting required to reverse the digits, the measure used was the difference between performance on Digit Span forwards and Digit Span backwards. In this way, it was presumed that other functions required to perform this task, such as vigilance, immediate memory, and general motivation would be eliminated from the comparison, though there are most likely still differences between the tasks besides set-shifting (e.g., auditory attention). Previous studies using the Digit Span task with PD patients have yielded mixed results. Patients with PD have been reported to perform normally on this test by some authors (Asso, 1969; Huber et al., 1986a; Huber et

al., 1986b), but other authors have reported impaired performance (Pirozzolo et al., 1982; Reitan & Boll, 1971; Spicer, Roberts, & LeWitt, 1988). However, only one study specifically compared forwards and backwards performance. PD patients demonstrated normal performance on both parts of the Digit Span task while patients with frontal lobe lesions demonstrated normal performance on Digit Span forwards but these patients were impaired on Digit Span backwards compared to normal control subjects (Canavan, Passingham, Marsden, Quinn, Wyke, & Polkey, 1989).

It should be mentioned that the tests used in this study were chosen because of their known clinical utility and to allow direct comparisons between the current study and previous studies. However, because there is no way to match these particular spatial orientation tests with the set-shifting tests, no overall analysis could be performed that would simultaneously compare the two groups of subjects on the two types of tasks. Therefore, the argument could be made that no differential deficit in set-shifting has been demonstrated, but rather that the set-shifting tasks chosen are merely more sensitive to some general pathology (see Chapman & Chapman, 1989 for a discussion of this issue). In fact, the experiment provides evidence against this argument in that the set-shifting tasks in this study explain more of the variance between the groups (proportion explained=.58) than the spatial orientation tasks (proportion explained=.45).

To explore this issue, several further analyses were performed. First, Spearman's rank-order correlations were constructed for each group of tests (i.e., personal orientation, extrapersonal orientation, mental rotation, right/left orientation, set-shifting) to determine whether the tests in each group "hang together" and, therefore, appear to be measuring a particular function. However, as shown in Tables 10-14, there are relatively low correlations between the tests within any one grouping. This is not altogether surprising, as these tests would not intuitively be expected to be clean measures of the particular functions. Second, to examine the possibility that the spatial orientation tests are simply easier to perform than the set-shifting tests, each test item was examined for skewness by calculating w_1 from cubed Z scores for each test (Ramsey & Ramsey, 1985). Comparing these statistics to critical values at the .05 level, for the PD group, six of the 11 spatial orientation tests had a significant skew and four of the eight set-shifting tasks did. For the normal control subjects five of the 11 set-shifting tasks had a significant skew, and four of the eight set-shifting tasks did. Thus, while quite a few tasks showed significant departures from normality, there was not a greater percentage of spatial orientation tasks than set-shifting tasks that did for either group of subjects. Furthermore, it seems unlikely that the spatial orientation tasks were merely too easy to detect deficits as these same

tasks have demonstrated spatial orientation deficits in patient populations with other neurological disorders (e.g. Butters, Soeldner, & Fedio, 1972; Semmes, Weinstein, Ghent, & Teuber, 1955). Thus, the tests chosen do not appear to be only measuring some general pathology, however, they also do not appear to be clean measures of the functions they are presumed to measure. Further studies using experimental measures designed to measure each of these functions more precisely would help further demonstrate the nature of the deficits observed in PD patients for these cognitive functions.

Visual-Spatial Functions in PD

The findings from the current study are in agreement with previous studies that have failed to demonstrate a deficit in spatial orientation in PD. This includes studies of extrapersonal orientation, i.e., recognizing embedded or superimposed figures (Taylor, Saint-Cyr, & Lang, 1986), judging distances (Stelmach, Phillips, & Chau, 1989), judging the visual vertical (Danta & Hilton, 1975), forecasting the direction of lines (Dellasala, Di Lorenzo, Giordano, & Spinnler, 1986), and judging angles (Goldenberg et al., 19986; Girotti, Carella, Pia Grassi, Soliveri, Marano, & Caraceni, 1986), right-left orientation (Brown & Marsden, 1986), mental rotation (Boller et al., 1984; Goldenberg et al., 1986;

Ransmayr et al., 1987; Taylor, Saint-Cyr, & Lang, 1986), and personal orientation, such as the Money Map Test (Taylor, Saint-Cyr, & Lang, 1986). These studies have all yielded similar results, indicating PD patients are within normal limits on these tasks.

While Boller, Passafiume, Keefe, Rogers, Morrow, and Kim (1984) concluded that there is a visual-spatial impairment in PD patients, in fact, they did not demonstrate significant differences between the PD patients and the control subjects on any of visual-spatial tasks that did not require a motor response. Nonmotor tasks that failed to distinguish the groups included extrapersonal tasks (matching crosses and angles), mental rotation tasks, and visual discrimination tasks.

However, the current results do not agree with previous studies that have demonstrated spatial orientation deficits in patients with PD (e.g., Bowen, Burns, Brady, & Yahr, 1976). There are at least three possible explanations for this discrepancy. The first is that prior findings of a spatial orientation deficit results from tasks that, in fact, required shifting of mental set or other cognitive functions (e.g., memory). There are several previous studies of spatial orientation which have discussed the possibility of a set-shifting component in the spatial orientation tasks. Bowen, Burns, Brady, and Yahr (1976) noted that PD patients only had difficulty on the Weinstein Body Scheme Task when the body in

the diagram was in a frontal view and required the patient to perform a left-right reversal. These authors suggested that the deficit observed may not be in personal orientation per se, but rather in the set-shifting required to perform that left-right reversal. Similarly, Bowen, Hoehn, and Yahr (1976) noted that on a route-walking task patients had no difficulty walking north, but instead had difficulty whenever a transformation from the direction shown directly on the map (i.e., north) was required. Ransmayr et al. (1987) demonstrated differences between PD patients and normal control subjects on a visual spatial task, the Rybakoff task. However, this task also involves problem-solving, attention and memory functions. The findings (a) that PD patients were not different from normal controls on simpler visual spatial tasks (line cancellation and a three-dimensional cube matching task), and (b) that performance on the Rybakoff task correlated with both verbal I.Q. and scores on the Wechsler Memory Scale suggest that the deficit demonstrated in PD patients on this task cannot be attributed solely to a spatial orientation deficit.

The second is that the tasks used in the current study differed in the specific spatial orientation requirements from those used in studies that have previously demonstrated deficits in spatial orientation. The tasks used in this study were chosen specifically because they have little or no motor component. In this way, they differ from many of the spatial

orientation tasks used in previous studies (e.g., Loranger, Goodell, McDowell, Lee, & Sweet, 1972). It has been suggested that patients with PD have a deficit in planning and executing motor movements (Bowen, Hoehn, & Yahr, 1972; Frith, Bloxham, & Carpenter, 1986; Stern et al., 1983; Stern et al., 1984). These authors have concluded that PD patients may have an impairment in the motor control of sequential voluntary movements and in the maintenance of set while performing repetitive motor sequences. Patients could not generate a proper motor plan to guide the movements or could not carry out that plan. Thus, PD patients had difficulty in coordinating the motor and perceptual activities necessary to successfully carry out these tasks. It has also been suggested that the critical component is external guidance from the environment and that without it PD patients are unable to plan and carry out such sequential motor movements. While difficulty with carrying out a motor plan may be a reflection of an underlying cognitive set-shifting deficit, it may also result from specific difficulty with motor planning (e.g., corollary discharge) in PD. The studies by Boller et al. (1984) and Stelmach, Phillips, and Chau (1989) which carefully included perceptually comparable visual-spatial tasks that do and do not require a motor component suggest that there is a specific difficulty with motor movements. A comparable study using set-shifting tasks that do and do not require a motor movement would be necessary to

demonstrate this unequivocally.

The tests used in this study were standardized tests. Most measured more than one function (e.g., the Ratcliff Mannikin test involves both mental rotation and right/left orientation). Therefore, it is possible that significant differences between the groups on a particular spatial orientation function would have been obscured. Each individual test item on each test was therefore examined and sorted into one or more of the four spatial orientation categories (personal orientation, extrapersonal orientation, right/left orientation, and mental rotation). For example, some items of the Ratcliff Mannikin test were placed in the mental rotation category and some in the right/left orientation category. If a single item measured two different functions, it was included in both categories. A description of these placements is provided in Table 7. Items judged to measure set-shifting (e.g., items on the Money Map Test on which it is necessary to travel south) were removed from the analyses. Four different Hotelling's T^2 tests were then performed to determine if the groups differed on any of these categories in isolation. The results of these analyses (shown in Table 8) indicate that the groups did not differ significantly on any item category.

Finally, the third possible explanation is that groups of PD patients who differ on particular demographic variables may exhibit corresponding differences in the pattern of cognitive deficits observed and that the patients in this study differed from those examined in previous studies. The possibility exists that the patients examined in this study differed from those in other studies. For instance, Pirozzolo et al. (1982) demonstrated visual-spatial deficits, but the patients in their sample also demonstrated a general cognitive decline, unlike the patients in the current study which specifically excluded patients exhibiting general cognitive decline. The PD patients in the current study did not exhibit a relationship between age, age at onset of motor symptoms, duration of motor symptoms, type of medication, initial laterality of motor symptom, current laterality of motor symptoms, primary type of motor symptom, or severity of motor symptoms and the cognitive functions measured, whereas these variables have been shown to correlate with cognitive functioning in previous studies. This discrepancy will be examined for each variable in turn.

Subject Variables

In previous studies, a PD subgroup has been identified which is older and exhibits global cognitive deficits (e.g., Girotti, Soliveri, & Carella, 1988). Since the PD patients used in this study were specifically selected not to have global cognitive deficits, such a subgroup would not have been

part of the current study. The results of this study suggest that age is not in itself related to degree of impairment on set-shifting or visual-spatial tasks.

Severity of motor symptoms (as measured by the Hoehn and Yahr scale, 1967) did not correlate with spatial orientation functions. This may be because these patients were all intact on spatial orientation tasks and thus did not demonstrate enough variability to measure differences between groups.

Type of medication also was not related to degree of impairment on the set-shifting tasks. Again, this may be because the patients used in the current study were fairly homogenous in the medication they were using. All of the PD patients were using dopaminergic medication, and 11 were taking anti-cholinergic medication as well. Presumably, those who were given the additional anti-cholinergic medication differed from those who were not in terms of neurochemical response to medication. The results of the current study demonstrate only that patients who receive anti-cholinergic medication in addition to dopaminergic medication do not differ significantly from PD patients who receive only dopaminergic medication in terms of performance on set-shifting tasks. There was no opportunity to measure the performance of particular patients on and off either of these types of medication as was done by Gotham, Brown, and Marsden (1988), because all patients were stable on their medication at the time of the testing and preparing to receive a trial

of Deprenyl. It would be necessary to compare an individual patient's performance on and off anti-cholinergic medication to determine the exact effects of such medication on set-shifting performance.

It is perhaps most interesting to note that no differences were found in performance on visual-spatial tasks between PD patients with predominantly left-sided symptoms and those with predominantly right-sided symptoms. While none of the patients in this study were strictly hemi-parkinsonian, many did report predominant motor symptoms on one side or the other. Similar patients in previous studies have demonstrated differences in visual-spatial functions depending on the side of the body on which symptoms predominate (e.g., Blonder, et al., 1987). However, all of the patients in the current study did have bilateral symptoms presumably reflecting bilateral subcortical damage (even though symptoms on one side might predominate). Therefore, they may not exhibit the lateralized deficits previously reported. It is also possible that laterality differences are only apparent when cognitive deficits become pronounced, and since in the current study all subjects were intact on the visual-spatial tasks no laterality differences would occur.

The finding that these patients did not differ according to primary motor symptom (bradykinesia, tremor, rigidity) conflicts which previous studies that have found such differences. In particular, there are several studies that

suggest that patients with prominent tremor are relatively intact for cognitive performance (e.g., Mortimer, Pirozzolo, & Hansch, 1982), while patients with prominent bradykinesia and rigidity are impaired, particularly on visual-spatial tasks (e.g., Garron, Klawans, & Narin, 1972). It is possible that a more refined system of measuring motor symptomatology than that used in this study (i.e., The Hoehn and Yahr Scale) might have provided a basis for this distinction. Pillon, Dubois, Cuusimono, Bonnet, Lhermitte, and Agid (1989) have suggested that akinesia, rigidity and tremor are mediated by a common system as they all respond well to dopaminergic medication, whereas dysarthria and gait disorder do not. However, it is dysarthria and rigidity which they found to predict performance on tasks measuring frontal lobe functioning and to correlate with residual symptoms after the optimum treatment level is reached. In the current study, neither degree of dysarthria nor degree of gait disorder were quantitatively measured, though many patients did mention during testing that it was the gait imbalance that was perceived to be their major motor disability. Had this disability been entered into the analyses, it may have been found to correlate with the set-shifting tasks. Moreover, none of the motor symptoms were measured in a quantitative fashion that would permit correlational analysis.

Unfortunately, given the size of the sample of patients included in this study and the number of analyses necessary

to distinguish each of the relevant subject variables, the question of the effect of these variables on neuropsychological functioning in PD could not be comprehensively addressed. For the purposes of this study, alpha levels were set very stringently to reduce Type I errors with the understanding that the power was then reduced and may explain, in part, the lack of significant findings.

Finally, many of the PD patients included in this study had been admitted expressly to evaluate their on/off symptoms. In general, previous studies of patients who experience on/off symptoms have not noted significant cognitive changes associated with the motor fluctuations (Brown, Marsden, Quinn, & Wyke, 1984; Delis, Direnfeld, Alexander, & Kaplan, 1982; Girotti, Carella, Pia Grassi, Soliveri, Marano, & Caraceni, 1986). Instead, the only consistent finding has been an increase in symptoms of depression while in the "off" phase (Brown, Marsden, Quinn, & Wyke, 1984; Girotti et al., 1986). Since no patients in this study were tested in the "off" phase, this should have no effect on the results of this study. However, there is some evidence of changes in functions mediated by the frontal lobes during motor fluctuations in PD (Delis et al., 1982). Specifically, patients in the off state appear to have a disinhibition of frontal systems reflected in increased verbal fluency and increased verbal perseverations. If, in fact, on/off effects reflect dopamine fluctuations affecting the frontal lobes

through the mesocortical system, it is plausible that the frontal functions tested in this study would be affected by them. Again, however, these patients were all tested in their "on" phase, most likely reflecting an optimum state of functioning. Of course, this does not rule out the possibility that patients who experience on/off symptoms are a particular subgroup of PD patients whose mesocortical dopaminergic system is affected differently by the disease than other patients. It would be necessary to make direct comparisons of these patients and PD patients who do not show these on/off fluctuations on set-shifting tasks to be sure that this was not the case.

Frontal Lobe Functions in PD

The results of this study do suggest that patients with Parkinson's disease demonstrate deficits in the ability to shift mental set. Shifting mental set is a function commonly associated with pathology in the frontal lobes. Therefore, to integrate that findings of the current study within a general framework of cogntive functioning in PD, other deficits commonly seen after damage to the frontal lobes should be examined. In fact, previous studies have demonstrated deficits in PD patients in neuropsychological functions that are generally assumed to be mediated by the frontal lobes. Previous studies have investigated a variety of neuropsychological functions, including memory functioning and verbal fluency.

Memory Function in PD

Recent reports of memory functioning in PD have concluded that the memory deficits observed in PD are due to a difficulty shifting mental set. Several authors have suggested that the memory deficits in PD occur when tasks require some form of internal control. For example, Sagar et al. (1988) suggest PD patients have a deficit in the "Central Executive," responsible for allocating mental resources and for integrating information from different sources.

In tasks considered to be automatic, such as frequency of occurrence discrimination, which do not require integration from various stores, patients with PD typically are intact (Weingartner, Burns, Diebel, & LeWitt, 1984).

Patients with PD also have been tested with recognition paradigms using words, common objects, abstract drawings, and unknown faces. Immediate recognition tasks using all visual or all verbal stimuli do not require a shift between different memory stores. PD patients have generally been reported to be intact (Flowers, Pearce, & Pearce, 1984; Horne, 1971; Lees & Smith, 1983; Sagar et al., 1988). Tweedy, Langer, and McDowell (1982) found that PD patients had poorer recognition of words than controls. However, for the recognition task, subjects were shown only those words they had failed to recall spontaneously or with cues. During the recall activity preceding the recognition task, it is likely that some

material had been lost from the short-term memory storage. As the Parkinson's patients recalled fewer words, they were required to recognize a larger number of items.

While the precise components of memory are not yet clearly understood, the working memory hypothesis, as interpreted in PD by Mortimer (1989), would predict that tests thought to measure retrieval from long-term semantic memory, and thus only one storage system, would not demonstrate impairment in PD patients, and this has been the case. On verbal tests, patients with PD have been reported to score within the normal range on the WAIS-R Vocabulary subtest (Matison et al., 1982; Pirozzolo et al., 1982). Naming of simple line drawings (Freedman, Rivoira, Butters, Sax, & Feldman, 1984; Heitanen & Teravainen, 1985; Huber et al., 1986b) and objects (Pirozzolo et al., 1982) has been found to be normal. On a memory test of public events, only those PD patients with dementia showed impairments, and these impairments followed a temporal gradient similar to that seen in patients with senile dementia of the Alzheimer type (SDAT), in which the most recent events were most poorly recalled (Sagar, Cohen, Sullivan, Corkin, & Growdon, 1988). On the nonverbal Famous Faces Task, only those patients with clear intellectual impairment (as measured by the Mini Mental Status Exam) performed more poorly than normal control subjects (Freedman, Rivoira, Butters, Sax, & Feldman, 1984; Huber, Shuttleworth, & Paulson, 1986), and no patients showed the

temporal gradient observed on this task among patients with SDAT or Huntington's disease.

In tests of learning and immediate recall, PD patients have shown clear deficits (El-Awar, Becker, Hammond, Nebes, & Boller, 1987; Hietanen & Teravainen, 1985; Huber, Shuttleworth, & Paulson, 1986; Pillon, Dubois, Lhermitte, & Agid, 1986; Pirrozolo et al., 1982; Tweedy et al., 1982; Weingartner et al., 1984)

These results offer some support for the suggestion that the memory deficit in PD is apparent only when the task requires the integration of information from different memory storage systems and not the storage or retrieval of information, per se. This is consistent with findings in patients with frontal lobe lesions (Baddeley et al., 1986) and with theoretical conceptions of frontal lobe functioning (e.g., Goldberg & Bilder, 1987). However, the studies reviewed need not be interpreted as indicating a deficit in shifting sets, which conclusively demonstrates a deficit in the "Central Executive". Further studies would need to be performed to directly test this hypothesis, such as performance on concurrent tasks known to make competing demands on the Central Executive (e.g., concurrent digit span [Baddeley et al., 1986]).

Tasks that implement a delay before the recognition test may require a shift between different stores. If the delay is of a short duration, some of the information may still be

in one of the short-term storage systems, while other pieces are in long-term storage. Thus, recognition would require the integration of both stores. Once the delay period is long enough, however, all of the information is in long-term storage and no integration is necessary. On short delay tasks, differences have been reported between PD patients and normal controls (Horne, 1971; Tweedy et al., 1982). In contrast, Flowers and Robertson (1985) and Flowers, Pearce, and Pearce (1984) found no difference between controls and patients with delays up to 45 minutes, presumably long enough to allow transfer of all information into long-term storage. Sullivan and Sagar (1988), Sagar et al. (1988), and Helkala, Laulumaa, Soininen, and Riekkinen (1988) found that PD patients, while impaired in immediate recognition, actually improved with a delay (while patients with SDAT and the patient H.M. showed worse performance with increasing delay), lending more support to the notion of improved performance in PD patients once all the information has been transferred to one storage system.

Verbal Fluency in PD

Patients with PD have been shown to have decreased verbal fluency (e.g., Gotham, Brown, & Marsden, 1988; Lees & Smith, 1983; Matison et al., 1982; Stern, Sano, & Mayeux, 1987), a symptom common after injury to the prefrontal cortex. However, the results have not been completely consistent. The studies cited above required PD patients to retrieve words by

semantic category (e.g., animals). Other studies which have required PD patients to retrieve words by initial letter have reported no difference in the performance of PD patients and normal control subjects (e.g., Lees & Smith, 1984).

Raskin, Sliwinski, and Borod (1989) compared the performance of patients with PD and normal control subjects on both of these types of tasks and analyzed the number of semantic and phonemic clusters produced by both groups on both tasks. They reported that, while PD patients did perform more poorly than normal control subjects on the task which required retrieval by semantic category, they produced an equal percentage of semantic clusters. The groups did not differ in performance on the task which required the retrieval of words by initial letter. The results of this study are comparable to those reported in patients with left anterior lesions, who also produced normal semantic clusters even though the total number of words produced was reduced (Laine & Niemi, 1988).

Caudal-Cortical Connections

Thus, there is evidence for a variety of frontal lobe symptoms in PD. However, there have also been many studies that have not demonstrated deficits in PD patients on other tests of frontal lobe functioning (e.g., Gotham, Brown, & Marsden, 1988). However, current conceptions of the prefrontal cortex describe discrete areas of the prefrontal cortex. There are presumed to be separate cognitive functions

that depend on the integrety of each of these individual areas of the prefrontal cortex. Thus, perhaps the deficits observed in patients with PD are due to selective destruction of certain area(s) of the prefrontal cortex.

There is evidence that PD attacks cells in the substantia nigra selectively, and that the degree of dementia in PD correlates with neuronal loss in the medial part of the substantia nigra only and not with cell loss in the lateral part. Substantia nigra neurons are organized topographically, and neurons in the medial part project to the caudate, which is connected to prefrontal cortex through the "complex loop" (Rinne, Rummukainen, Paljarvi, & Rinne, 1989). This topographic organization then continues between the caudal projections and the prefrontal cortex (Divac, Rosvold, & Szwarcbart, 1967). Given this topographic organization, it is possible that PD attacks a particular caudo-cortical system and so the behavioral deficits of PD patients will mimic those of frontal lobe patients. However, the behavioral performance of PD patients does not precisely reproduce the deficits seen in either dorsolateral or orbitofrontal lesions.

Studies demonstrating the topographic organization of these connections have identified three regions of the caudate with connections to three different regions of the cortex. The tail of the caudate has projections from the inferotemporal cortex. Lesions to either structure result in deficits in visual discrimination.

Dorsolateral Prefrontal Cortex

The second region, the anterodorsal portion of the head of the caudate receives connections from the dorsolateral prefrontal cortex. Lesions to either of these regions result in deficits in delayed response, particularly spatial delayed response tasks (Funahashi, Bruce, & Goldman-Rakic, 1989; Pribram, 1987; Schulman, 1964; Teuber, 1976). Deficits in delayed response have also been demonstrated in patients with damage to the dorsolateral prefrontal cortex (Milner & Petrides, 1984).

Like patients with lesions of the dorsolateral prefrontal cortex, PD patients have demonstrated deficits on delayed response tasks. However, in one of these studies, the PD subjects were post-thalamotomy (Horne, 1971), and in another, only those patients who exhibited dementia showed deficits on the delayed response task (Freedman & Oscar-Berman, 1986). PD patients also demonstrate reduced verbal fluency, like patients with lesions to the dorsolateral prefrontal cortex (Milner & Petrides, 1984), though the nature of this deficit is still unclear (e.g., Raskin et al., 1989).

However, PD patients do not exhibit the deficits in subject-ordered pointing or conditional associative learning observed in patients with damage to dorsolateral prefrontal cortex (Gotham, Brown, & Marsden, 1988).

Orbitofrontal Cortex

Finally, the third region, the ventrolateral head of the

caudate receives input from the orbitofrontal region of the cortex. Lesions to either of these brain regions produce deficits in object reversal and in response inhibition on go-no go tasks (Battig, Rosvold, & Mishkin, 1962; Pribram, 1987).

PD patients exhibit difficulty shifting set and sequencing and do not exhibit evidence of perseveration. Perseveration, however, has been defined in different ways (e.g., Luria, 1965). Nelson (1976) defines a perseverative error on the WCST as in incorrect response which follows the same category concept as the immediately preceding response, and this definition will be used in the current paper. However, Milner (1963) defines a perseveration as an error that follows the category concept which had previously been correct. Using the former definition, PD patients have not demonstrated evidence of perseverative errors, however, they have shown the type of errors described by Milner.
In this way, they appear similar to patients with lesions of orbitofrontal cortex.

Dompamine Reduction in PD

While it is parsimonious at this time to explain nearly all of the cognitive deficits in PD as dysfunction of frontal cortex, it is clear that PD patients are not identical to patients with frontal lobe damage. Perhaps intracellular disruption in dopaminergic connections between the caudate and the frontal cortex, and corresponding disruption in the functions of specific brain regions produce behavioral

symptoms that are not necessarily identical to symptoms observed after more complete, larger structural lesions of the same area. In part, this may be because the deficits observed after lesions of the prefrontal cortex are due to the large widespread connections involving this cortical area (e.g., Goldberg & Bilder, 1987) that may be relatively spared after basal ganglia dysfunction. Stern (1983) suggested that the cortex and the basal ganglia work in series with each region contributing a separate necessary component to the successful completion of tasks such as set-shifting and so perhaps with PD it is only the basal ganglia component that is eliminated.

There is some evidence that this set-shifting deficit specifically depends on such a connection, the mesocorticodopaminergic system. For instance, patients with idiopathic spasmodic torticollis who are treated with Haloperidol exhibit post-treatment deficits on set-shifting and verbal fluency tasks (Berger, Van Hoof, Van Spaendonck, Horstink, Van Den Bercken, Jaspers, & Cools, 1989). These same patients are unimpaired on visuoperceptual tasks and, of particular interest for the current study, are unimpaired on Digit Span. In addition, Gotham, Brown, and Marsden (1988) reported that PD patients were impaired on a set-shifting verbal fluency task when off of dopaminergic medication but not when on levodopa treatment, suggesting a direct effect of dopamine levels. Similar findings were reported for the

effect of dopamine stimulation on delayed memory performance (Mohr, Fabbrini, Ruggieri, Fedio, & Chase, 1987). However, not all reports agree with this conclusion. Pillon, Dubois, Cusimano, Bonnet, Lhermitte, & Agid (1989) reported that performance on frontal lobe tests (i.e., the WCST, verbal fluency, and a graphic series) did not correlate with those symptoms that respond to dopaminergic medication, and these authors concluded that the cognitive impairment in PD results instead from cholinergic system dysfunction. Though in another study, the severity of the motor symptoms correlated with intellectual impairment (Huber, Paulson, & Shuttleworth, 1988), different patterns of cognitive deficits have been described in patients in which different motor symptoms predominate (e.g., Mortimer, Pirozzolo, Hansch, & Webster, 1982), possibly reflecting the interaction of different systems.

Further study is needed which directly compares patients with PD to those with lesions of the frontal lobes. PD patients have been found to be superior in learning a series of motor sequences (Canavan et al., 1989), and verbal fluency (Laine & Niemi, 1988) performance when directly compared to patients with frontal lobe lesions.

Practical Implications

In terms of daily functioning, the results of this study have several implications. First, patients with PD may have difficulty in tasks that require direct set-shifting, such as

switching from one activity to another, or switching from one train of thought or one conversation to another. Second, as demonstrated on the Uses of Objects Test, PD patients may have difficulty in wide areas of functioning such as decision making, initiating new activities, being flexible in planning and responding to changes in plans. Further study could take the form of patient and care-giver questionnaires to document any such difficulties, perhaps modeled after the Executive Function Behavioral Rating Scale (Sohlberg & Geyer, 1989). If such difficulties are demonstrated, methods for educating patients and care-givers could be devised to help them structure these processes (e.g., creating contingency plans ahead of time, structuring time and activities so that patients know what to expect ahead of time). In this way, patients may be made more autonomous, and care-givers and others will know better what to expect so they do not become impatient or attribute negative characteristics such as unwillingness to compromise or willful inflexibility to the patient. Then, once a conception of the functional effects of these deficits is reached perhaps specific cognitive remediation strategies could be devised. These strategies could start with training on the level of simple, specific set-shifting tasks, such as the ones used in the current study. Of course, predetermined goals would have to be set with each patient for the generalization of these skills (e.g., to be able to make appropriate contingency plans for

a specific event). If an increase in performance on the initial tasks is observed, the tasks used in training could gradually increase in complexity in the direction of the predetermined goals. In conjunction, pre- and post-testing of both specific task-related performance and the corresponding functional deficits would be necessary.

Conclusions

The results of this study indicate that PD patients do have difficulty on tasks that require a shift in mental set. This study failed to demonstrate any deficits in spatial orientation functions on tasks that had no set-shifting or motor requirement. The performance of these patients on the set-shifting and spatial orientation tasks was not influenced by individual variables of the disease (i.e., age, age at onset of symptoms, etc.), which suggests that such variables do not have a significant effect on these neuropsychological functions, at least in middle-stage, well-medicated, non-demented patients.

Table 1

Demographic Variables for PD Patients and Normal Control Subjects

		PD		NC			
Variable	Scoring	Mean	S.D.	Mean	S.D.	T	p
Age	years	64.60	10.29	62.60	10.98	0.59	0.56
Gender	1=female 2=male	1.50	0.51	1.40	0.50	0.62	0.50
Handedness	1=right 2=left	1.10	0.31	1.05	0.22	0.59	0.56
Education	years	15.25	3.73	15.25	3.40	0.00	1.00
Occupation	9 levels*	6.90	1.80	7.45	1.60	1.01	0.32

* Nine levels of the Hollingshead Four Factor Index of Social Status (1977), where Score "1"= Farm Laborers, Service Workers;
Score "5"=Clerical and Sales Workers, Small Farm and Business Owners;
Score "9"=Higher Executives, Proprietors of Large Businesses, and Major Professionals

Table 2

Performance of PD Patients and Normal Control Subjects on Control Tasks

		PD		NC			
Test	Score Range	Mean	S.D.	Mean	S.D.	T	p
Visual Form Discrimination	0-32	30.05	2.33	30.95	2.37	1.46	0.23
Visual Matrices	0-24	24.00	0.00	24.00	0.00	n/a	n/a
WAIS-R Information Age-Corrected Scale Score	1-19	12.30	2.29	13.45	2.50	1.51	0.13

Table 3

Test Variables Listed By Function

Test Name	Variable Abbreviation	Function Measured
Benton right/left orientation	BenRL	Right/Left Orientation
Brown and Marsden Task	B&MRLO	Right/Left Orientation
Parietal Lobe Battery Right/Left Orientation	PLBRLO	Right/Left Orientation
Luria-Nebraska Item 99	L-NMR	Mental Rotation
Ratcliff Mannikin Test	RatMR	Mental Rotation
Benton Line Orientation	BenLO	Extrapersonal Orientation
Parietal Lobe Battery Geographic Orientation	PLBGO	Extrapersonal Orientation
Benton Geographic Orientation	BenGO	Extrapersonal Orientation
Body Center Test	BodyCtr	Personal Orientation
Money Map Test	MonMap	Personal Orientation
Weinstein Body Scheme	WBS	Personal Orientation
Controlled Word Association Test (alternation modification)	CWAT	Set-Shifting
Digit Span (difference between backwards and forwards)	DigSp	Set-Shifting
Uses of Objects Test (difference between number of concrete and abstract responses)	UseObj	Set-Shifting
Competing Programs	CompProg	Set-Shifting
Go-No Go	GONOGO	Set-Shifting
Sequencing	Seq	Set-Shifting
Motor Programs 1	MotProg1	Set-Shifting
Motor Programs 2	MotProg2	Set-Shifting

Table 4
Performance of PD patients and NC subjects on each task

	PD				NC			
Variable	Mean	Std.Dev.	Min.	Max.	Mean	Std.Dev.	Min.	Max.
Right/left:								
BenRLO	19.60	1.79	12	20	20.00	0.00	20	20
B&MMR	7.70	0.73	5	8	7.95	0.22	7	8
PLBRL	29.50	8.36	0	38	31.25	5.32	20	38
Mental Rotation:								
L-NMR	6.80	2.63	2	10	9.05	1.36	6	10
RatMR	6.55	1.28	5	8	7.50	0.89	5	8
Extrapersonal Orientation:								
BenLO	21.73	5.23	12	30	22.95	4.58	17	30
PLBGO	11.95	1.57	9	14	12.85	0.99	11	14
BenGO*	6.00	3.39	1	11	4.87	3.83	0	11
Personal Orientation:								
BodyCtr*	0.70	1.17	0	3	0.25	0.55	0	2
MonMap	26.90	5.39	15	32	27.10	4.42	19	32
WBS*	1.00	2.11	0	7	0.32	1.00	0	4
Set-Shifting:								
CWAT	0.80	2.44	-3	4	2.90	3.35	-6	8
DigSp	1.35	2.39	-3	6	1.75	2.12	-3	6
Obj	2.90	9.55	-14	28	11.80	10.76	-11	26
CompProg*	0.80	0.83	0	2	0.10	0.31	0	1
GoNogo*	0.95	1.28	0	4	0.45	0.60	0	1
Seq*	2.35	3.07	0	10	0.65	1.39	0	5
MotProg1	7.40	2.76	2	13	13.05	4.47	7	23
MotProg2	8.70	3.20	4	14	11.50	2.88	7	17

* Score is number of errors

Table 5

Univariate analyses of individual set-shifting tasks

Test	T	DF	P
FASDIFF	-2.26	34.71	0.0299*
DSDIFF	0.56	37.48	0.5792
OBJDIFF	-2.77	37.48	0.0087**
COMPROG	3.52	24.09	0.0018**
GONOGO	1.58	27.12	0.1250
SEQ	2.26	26.47	0.0323*
MOTOR1	-4.81	31.67	0.0000**
MOTOR2	-2.91	37.58	0.0060**

*p<.05
**p<.01

Table 6

Univariate analyses of spatial orientation tests

Test	PD Mean	NC Mean	T	DF	P	Function
BENRL	19.60	20.00	-1.00	38.00	0.3236	Right/Left
BROWN	7.70	7.95	-1.46	22.51	0.1583	Right/Left
PARRL	29.50	31.25	-0.79	32.21	0.4355	Right/Left
MENTOT	26.90	27.10	-2.73	33.91	0.0099*	Ment. Rot.
ITEM99	6.80	9.05	-3.40	28.45	0.0020*	Ment. Rot.
LOTOT	21.73	22.95	-0.72	27.94	0.4788	Extra. Or.
PARGEO	11.95	12.85	-2.17	31.99	0.0377	Extra. Or.
BENGEO	6.00	4.867	0.88	28.23	0.3859	Extra. Or.
BODCTR	0.70	0.25	1.55	26.96	0.1324	Pers. Or.
MONEYTOT	26.90	27.10	-0.13	36.61	0.8986	Pers. Or.
WBSTOT	1.00	0.32	1.25	23.99	0.2246	Pers. Or.

*p<.01

Table 7

Results of analyses on PD patients' subject variables

Correlations

1. Age

	L-NMR	B&MRL	PLBRLO	PLBGO	BenGO	BenRL	BodyCtr	Wbs
r	-0.37	-0.35	-0.13	-0.28	-0.13	99.00	0.41	0.14
p	0.24	0.27	0.69	0.38	0.69	1.00	0.18	0.66

	MonMap	RatMR	BenLO	CWAT	UseObj	DigSp	MotProg1	MotProg2
r	-0.48	-0.43	-0.51	-0.06	-0.53	-0.01	0.17	0.13
p	0.11	0.16	0.09	0.85	0.08	0.97	0.60	0.68

	CompProg	GoNogo	Seq
r	0.44	0.21	0.08
p	0.15	0.50	0.81

2. Age at Onset of Symptoms

	L-NMR	B&MRLO	PLBRLO	PLBGO	BenGO	BenRLO	BodyCtr	Wbstot
r	-0.31	-0.09	-0.22	-0.23	0.07	99.00	0.45	0.19
p	0.33	0.79	0.48	0.47	0.83	1.00	0.14	0.56

	MonMap	RatMR	BenLO	CWAT	UseObj	DigSp	MotProg1	MotProg2
r	-0.64	-0.56	-0.55	-0.17	-0.36	-0.11	0.17	-0.15
p	0.02	0.06	0.06	0.60	0.24	0.74	0.59	0.63

	CompProg	GoNogo	Seq
r	0.64	0.26	0.20
p	0.02	0.42	0.53

3. Duration of Symptoms

	L-NMR	B&MRLO	PLBRLO	PLBGO	BenGO	BenRLO	BodyCtr	Wbstot
r	0.14	-0.09	0.03	-0.41	0.59	99.00	-0.02	0.41
p	0.62	0.69	0.90	0.14	0.02	1.00	0.94	0.14

	MonMap	RatMR	BenLO
r	-0.26	-0.15	-0.52
p	0.37	0.60	0.06

Analyses of Variance

1. Medication (1=Dopaminergic alone [N=6], 2=Both Anti-cholinergic and Dopaminergic [N=11])

	CWAT	UseObj	DigSp	MotProg1	MotProg2	CompProg	GoNoGo	Seq
$\bar{X}$ 1	0.17	5.00	0.83	6.33	7.33	0.83	0.67	4.17
	(2.99)	(11.71)	(2.23)	(2.06)	(2.50)	(0.98)	(0.81)	(3.55)
$\bar{X}$ 2	0.90	0.09	2.00	7.36	8.90	0.63	1.18	1.90
	(2.07)	(8.19)	(2.28)	(2.97)	(3.48)	(0.67)	(1.53)	(2.84)
F	0.37	1.03	1.03	0.56	0.95	0.24	0.57	2.06
p	0.55	0.32	0.32	0.46	0.34	0.63	0.46	0.17

2. Laterality of Motor Symptoms (1=right [N=5], 2=both equal [N=4], 3=left [N=11])

	L-NMR	B&MRLO	PLBRLO	PLBGO	BenGO	BenRLO	BodyCtr	Wbstot
$\bar{X}$ 1	6.40	8.00	34.60	11.40	7.25	18.40	1.40	1.25
	(2.89)	(0.00)	(2.07)	(1.82)	(3.50)	(3.58)	(1.34)	(2.50)
$\bar{X}$ 2	7.00	7.50	30.25	11.75	5.25	20.00	0.00	2.75
	(3.37)	(0.58)	(6.24)	(1.89)	(4.19)	(0.00)	(0.00)	(3.40)
X 3	6.90	7.63	26.90	12.27	5.78	20.00	0.64	0.20
	(2.51)	(0.92)	(9.94)	(1.42)	(3.27)	(0.00)	(1.21)	(0.63)
F	0.07	0.58	1.56	0.54	0.36	1.59	1.74	2.48
p	0.93	0.57	0.23	0.59	0.70	0.23	0.20	0.11

	MonMap	RatMR	BenLO
$\bar{X}$ 1	25.00	6.60	24.00
	(4.47)	(1.52)	(4.36)
$\bar{X}$ 2	28.75	6.50	20.67
	(3.40)	(1.29)	(3.21)
$\bar{X}$ 3	27.09	6.55	21.33
	(6.36)	(1.29)	(6.16)
F	0.53	0.69	0.33
p	0.60	0.53	0.72

3. Original laterality of Motor Symptoms (1=right [N=7], 2=left [N=12])

	L-NMR	B&MRLO	PLBRLO	PLBGO	BenGO	BenRLO	BodyCtr	Wbs
$\bar{X}$ 1	6.14	7.85	33.00	11.89	7.33	18.86	1.00	1.50
	(2.64)	(0.37)	(8.39)	(1.59)	(3.50)	(3.02)	(1.29)	(2.34)
$\bar{X}$ 2	7.00	7.58	26.83	12.25	5.70	20.00	0.58	0.18
	(2.41)	(0.90)	(9.48)	(1.35)	(3.09)	(0.00)	(1.16)	(0.60)
F	0.45	0.58	2.59	1.68	0.95	1.79	0.52	3.25
p	0.51	0.46	0.12	0.21	0.35	0.20	0.48	0.09

	MonMap	RatMR	BenLO
$\bar{X}$ 1	26.28	6.86	23.50
	(4.27)	(1.34)	(3.70)
$\bar{X}$ 2	26.83	6.42	21.50
	(6.13)	(1.31)	(5.84)
F	0.04	0.49	0.39
p	0.84	0.49	0.54

4. Primary Motor Symptom (1=Tremor [N=9], 2=Rigidity [N=6], 3=Bradykinesia [N=5])

	CWAT	UseObj	DigSp	MotProg1	MotProg2	CompProg	GoNogo	Seq
$\bar{X}$ 1	-0.33	6.44	1.77	8.33	9.55	1.11	1.11	2.33
	(2.92)	(10.24)	(1.79)	(2.64)	(2.96)	(0.78)	(1.27)	(3.28)
$\bar{X}$ 2	2.33	4.67	0.83	7.00	9.17	0.50	0.67	3.17
	(1.63)	(7.03)	(2.56)	(2.68)	(3.87)	(0.84)	(1.63)	(3.37)
$\bar{X}$ 3	1.00	-5.60	2.80	6.20	6.60	0.60	1.00	1.40
	(1.22)	(6.19)	(2.05)	(3.03)	(2.19)	(0.89)	(1.00)	(2.60)
F	2.52	3.38	1.19	1.06	1.55	1.18	0.20	0.43
p	0.11	0.06	0.32	0.37	0.24	0.33	0.82	0.66

5. Severity of Motor Symptoms (1=Stage 1 [N=3], 2=Stage 2 [N=6], 3=Stage 3 [N=11])

	L-NMR	B&MMR	PLBRLO	PLBGO	BenGO	BenRLO	BodyCtr	Wbs
$\bar{X}$ 1	9.66	8.00	29.00	13.00	4.50	20.00	0.00	0.00
	(0.58)	(0.00)	(6.08)	(1.00)	(0.71)	(0.00)	(0.00)	(0.00)
$\bar{X}$ 2	4.66	7.33	24.83	12.17	5.00	20.00	1.00	2.75
	(2.50)	(1.21)	(13.01)	(1.17)	(3.16)	(0.00)	(1.26)	(3.40)
$\bar{X}$ 3	7.18	7.82	32.18	11.54	6.64	19.27	0.73	0.64
	(2.14)	(0.40)	(4.44)	(1.81)	(3.75)	(2.41)	(1.27)	(1.57)
F	5.86	1.17	1.60	1.10	0.53	0.38	0.71	2.11
p	0.01	0.33	0.23	0.35	0.60	0.69	0.51	0.15

	MonMap	RatMR	BenLO
$\bar{X}$ 1	31.33	7.00	25.00
	(0.58)	(1.00)	(4.58)
$\bar{X}$ 2	23.17	6.17	18.00
	(6.85)	(1.17)	(4.97)
$\bar{X}$ 3	27.73	6.64	23.37
	(4.08)	(1.43)	(5.01)
F	3.18	0.45	1.87
p	0.07	0.65	0.19

Table 8

Regrouping of Test Items According To Function

Test	Criteria For Items	Function
RatMR	All upright items	Right/Left Or.
MonMap	Items in which the subject travels north, east, or west	Right/Left Or.
PLBRLO	All items	Right/Left Or.
BenRLO	All items	Right/Left Or.
B&MRLO	All items which do not require mental rotation	Right/Left Or.
WBS	All items with dorsal figure	Right/Left Or.
RatMR	Items in which the figure is upside-down	Mental Rotation
L-NMR	All items	Mental Rotation
B&MRLO	All items which require mental rotation	Mental Rotation
MonMap	Items in which the subject travels south	Mental Rotation
WBS	All items with dorsal figure	Personal Or.
MonMap	All items in which the subject does not travel south	Personal Or.
BodyCtr	All items	Personal Or.
PLBGO	All items	Extrapersonal Or.
BenGO	All items	Extrapersonal Or.
BenLO	All items	Extrapersonal Or.

Table 9

Results of Analyses Using Test Breakdowns from Table 8

Function	F	(DF)	p
Right/Left Or.	0.623	(12,23)	.343
Mental Rotation	0.386	(5,31)	.060
Personal Or.	0.216	(5,30)	.292
Extrapersonal Or.	0.178	(3,24)	.260

Table 10

Spearman's rho correlations for personal orientation for each subject group

I. PD

	MonMap	WBS	BodCtr
MonMap	1.00 (0.00)	-0.05 (0.87)	0.02 (0.94)
WBS		1.00 (0.00)	0.21 (0.47)
BodCtr			1.00 (0.00)

II. NC

	MonMap	WBS	BodCtr
MonMap	1.00 (0.00)	-0.03 (0.91)	0.17 (0.58)
WBS		1.00 (0.00)	-0.32 (0.28)
BodCtr			1.00 (0.00)

III. Both groups combined

	MonMap	WBS	BodCtr
MonMap	1.00 (0.00)	-0.04 (0.86)	0.13 (0.53)
WBS		1.00 (0.00)	-0.25 (0.23)
BodCtr			1.00 (0.00)

Table 11

Spearman's rho correlations for extrapersonal orientation

I. PD

	PLBGO	BenGO	BenLOT
PLBGO	1.00 (0.00)	0.51 (0.06)	0.33 (0.25)
BenGO		1.00 (0.00)	0.68 (0.01)
BenLOT			1.00 (0.00)

II. NC

	PLBGO	BenGO	BenLOT
PLBGO	1.00 (0.00)	0.85 (0.01)	0.14 (0.65)
BenGO		1.00 (0.00)	-0.19 (0.53)
BenLOT			1.00 (0.00)

III. Both groups combined

	PLBGO	BenGO	BenLOT
PLBGO	1.00 (0.00)	0.66 (0.01)	0.21 (0.32)
BenGO		1.00 (0.00)	0.26 (0.20)
BenLOT			1.00 (0.00)

Table 12

Spearman's rho coefficients for mental rotation

I. PD

	L-NMR	RatMan
L-NMR	1.00 (0.00)	-0.12 (0.67)
RatMan		1.00 (0.00)

II. NC

	L-NMR	RatMan
L-NMR	1.00 (0.00)	0.11 (0.71)
RatMan		1.00 (0.00)

III. Both groups combined

	L-NMR	RatMan
L-NMR	1.00 (0.00)	0.03 (0.87)
RatMan		1.00 (0.00)

Table 13

Spearman's rho correlations for right/left orientation

I. PD

	PLBRLO	BenRLO	B&MRLO
PLBRLO	1.00 (0.00)	------	0.16 (0.57)
BenRLO		------	------
B&MRLO			1.00 (0.00)

II. NC

	PLBRLO	BenRLO	B&MRLO
PLBRLO	1.00 (0.00)	-----	0.03 (0.91)
BenRLO		------	-----
B&MRLO			1.00 (0.00)

III. Both groups combined

	PLBRLO	BenRLO	B&MRLO
PLBRLO	1.00 (0.00)	------	0.09 (0.65)
BenRLO		------	------
B&MRLO			1.00 (0.00)

------ indicates that there was no variance on this test

Table 14

Spearman's rho coefficients for the set-shifting tasks

I. PD

	Go-NoGo	ComProg	Seq	Mot1	Mot2	DSDiff	UseObj	CWAT
Go-NoGo	1.00 (0.00)	0.67 (0.01)	-0.31 (0.27)	-0.09 (0.77)	-0.58 (0.03)	-0.08 (0.78)	-0.35 (0.22)	0.18 (0.54)
ComProg		1.00 (0.00)	-0.14 (0.64)	0.17 (0.56)	-0.32 (0.26)	0.28 (0.33)	-0.02 (0.94)	0.28 (0.33)
Seq			1.00 (0.00)	-0.11 (0.21)	-0.11 (0.71)	0.10 (0.72)	0.66 (0.01)	-0.34 (0.23)
Mot1				1.00 (0.00)	0.67 (0.01)	0.14 (0.64)	0.12 (0.68)	0.33 (0.24)
Mot2					1.00 (0.00)	0.17 (0.55)	0.25 (0.39)	0.34 (0.23)
DSDiff						1.00 (0.00)	0.37 (0.19)	-0.18 (0.54)
UseObj							1.00 (0.00)	-0.22 (0.45)
CWAT								1.00 (0.00)

II. NC

	Go-NoGo	ComProg	Seq	Mot1	Mot2	DSDiff	UseObj	CWAT
Go-NoGo	1.00	0.67	-0.31	-0.09	-0.58	-0.08	-0.35	0.18
	(0.00)	(0.01)	(0.27)	(0.77)	(0.03)	(0.78)	(0.22)	(0.54)
ComProg		1.00	-0.14	0.17	-0.32	0.28	-0.02	0.28
		(0.00)	(0.64)	(0.56)	(0.26)	(0.33)	(0.94)	(0.33)
Seq			1.00	-0.11	-0.11	0.10	0.66	-0.34
			(0.00)	(0.21)	(0.71)	(0.72)	(0.01)	(0.23)
Mot1				1.00	0.67	0.14	0.12	0.33
				(0.00)	(0.01)	(0.64)	(0.68)	(0.24)
Mot2					1.00	0.17	0.25	0.34
					(0.00)	(0.55)	(0.39)	(0.23)
DSDiff						1.00	0.37	-0.18
						(0.00)	(0.19)	(0.54)
UseObj							1.00	-0.22
							(0.00)	(0.45)
CWAT								1.00
								(0.00)

Spearman's rho coefficients for the set-shifting tasks

III. Both groups combined

	Go-NoGo	ComProg	Seq	Mot1	Mot2	DSDiff	UseObj	CWAT
Go-NoGo	1.00 (0.00)	0.67 (0.01)	-0.31 (0.27)	-0.09 (0.77)	-0.58 (0.03)	-0.08 (0.78)	-0.35 (0.22)	0.18 (0.54)
ComProg		1.00 (0.00)	-0.14 (0.64)	0.17 (0.56)	-0.32 (0.26)	0.28 (0.33)	-0.02 (0.94)	0.28 (0.33)
Seq			1.00 (0.00)	-0.11 (0.21)	-0.11 (0.71)	0.10 (0.72)	0.66 (0.01)	-0.34 (0.23)
Mot1				1.00 (0.00)	0.67 (0.01)	0.14 (0.64)	0.12 (0.68)	0.33 (0.24)
Mot2					1.00 (0.00)	0.17 (0.55)	0.25 (0.39)	0.34 (0.23)
DSDiff						1.00 (0.00)	0.37 (0.19)	-0.18 (0.54)
UseObj							1.00 (0.00)	-0.22 (0.45)
CWAT								1.00 (0.00)

Appendix I

I. Spatial Orientation

A. Pure Visual Discrimination

1. Benton Visual Discrimination Test (Benton 1974): a simple visual matching test of geometric shapes

2. Visual search (Goldstein & Shelly, 1973): the subject is required to find a visual pattern of squares from several choices

B. Mental Rotation

1. Item 99 from Luria-Nebraska battery (Golden, Purisch, & Hammeke, 1980): the subject is required to rotate each of 10 test squares to match to four possible choices

2. Mannekin Test (Ratcliff, 1979): the subject is required to determine whether a black ball is in the right or left hand of a drawing of a man who may be presented upside-down or right-side up, and either facing or with his back to the subject

C. Right/Left Orientation

1. Hands from Parietal Lobe battery (Goodglass & Kaplan, 1972): requires the judgement of whether hands in various positions are right hands or left hands

2. Right/Left Orientation Test (Benton, Hamsher, Varney, & Spreen, 1983): the subject points to right and left parts on his/her own body and that of the examiner

D. Personal Orientation

1. Money map test (Money, 1976): the subject must follow a path on a map and decide whether each turn is a right or left turn

2. Weinstein body scheme test (Weinstein, Semmes, Ghent, & Teuber, 1956): requires the subject to match parts of a figure to the same part on his/her body

3. Body Center Test (Diller, 1974): requires the subject to indicate the center of his/her own back

E. Extrapersonal Orientation

1. geographic orientation (Benton, 1974):
subject must find cities and states on a map

2. geographic orientation (Goodglass & Kaplan, 1972):
subject must find cities and states on a map

3. Benton Judgment of Line Orientation (Benton, 1974):
requires the subject to match lines which are at various angles to a sample

II. Set-Shifting Functions

A. Verbal fluency with alternating categories:
subject must generate category members alternating between words that begin with "A" and words that begin with "S"
Subjects also required to give words that begin with only one letter ("F") as a comparison

B. Uses of objects test (Getzels & Jackson, 1962):
subject must provide uses of common objects with prompts for unusual items (e.g., brick as bookend, doorstop)

C. Digits Backwards subtest of WAIS-R (Wechsler, 1981):
subject must repeat a string of digits in reversed order
subject also required to give digits forwards as a comparison

D. Competing Programs (Luria, 1966):
subject required to hold up 1 finger when examiner holds up 2 fingers and vice versa

E. Go-No Go (Luria, 1966):
subject must squeeze examiner's hand when examiner says "red" and do nothing when the examiner says "green"

F. sequential categorization (Hibbard, unpublished):
subject say "check" if an item is a
member of a category and "x" if it is not a member

G. Motor Programs I (Golden, Purisch, & Hammeke, 1980):
subject must alternately clench their fist and extend their fingers as many times as possible in 10 seconds

H. Motor Programs II (Golden et al., 1980):
subject must turn hand palm upward and then palm downward as many times as possible in 10 seconds

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