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Neuropsychological Aspects of Parkinson's Disease

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The neuropsychological effects of Parkinson's disease have gained wide recognition in recent literature. Effects have been documented in almost all areas of cognitive functioning, including general intellectual functioning, visual-spatial functioning, executive functions, attention and memory functions, language functions, and affective processes. Visual-spatial functions, memory functions, and executive functions have received particular interest. This review of the literature is an attempt to tie together the large number of studies in these cognitive areas and to present a suggestion for a comprehensive neuropsychological battery tailored to the patient with Parkinson's disease. Throughout the review, factors relevant to Parkinson's disease, e.g., dementia, motor symptoms, and hemiparkinsonism, are considered.

KEY WORDS: Parkinson's disease; neuropsychology; cognition.

INTRODUCTION

Recent studies have revealed that patients with Parkinson's disease (PD), once believed to have intact mental status, often show cognitive deficits. The extensive literature that has followed these initial findings typically has focused on three specific issues, i.e., whether the dementia observed in some patients is due to the PD, or to a concomitant senile dementia; the pattern of cognitive

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deficits in PD patients who are not demented; and the effect of different subject variables, in particular hemiparkinsonism, on cognitive functioning in PD.

The first area that will be discussed is that of dementia. The existence of a subcortical dementia in PD patients has been proposed in studies comparing these PD patients to patients with senile dementia of the Alzheimer type (Garron *et al.*, 1972), and is supported by the correlation of cognitive deficits with the motor dysfunction known to be caused by dopaminergic cell loss in the basal ganglia.

The second area that will be discussed is the pattern of cognitive deficits in those PD patients who do not exhibit dementia, and whether these deficits are due to subcortical pathology or to disruption of efferent fibers to the cortex. The most consistent findings of deficits in particular neuropsychological functions are in the areas of visual-spatial functions, particularly spatial orientation (e.g., Bowen *et al.*, 1972), and executive functions, particularly those required in shifting mental set (e.g., Cools *et al.*, 1984). One interesting question arising from these studies is whether PD patients have a specific visual-spatial deficit or whether visual-spatial difficulties are due to a more general deficit in executive functions, e.g., an inability to shift mental set (Brown and Marsden, 1986). Deficits have also been observed in memory functioning, particularly on very effortful memory tasks, such as delayed recall (e.g., Weingartner *et al.*, 1984). While speech and language functions are, for the most part, spared, some difficulty has been noted in generative naming (e.g., Raskin *et al.*, 1989). In addition, there is evidence that some PD patients have a disturbance in affect, which may be manifest in depressive symptoms (e.g., Mindham, 1970).

The final area of focus is the nature of the relationship between unilateral motor symptoms (left- and right-sided) and cognitive impairments. One interesting possibility is that patients with predominantly left-sided motor symptoms exhibit different cognitive impairments than those with predominantly right-sided motor symptoms. Other important subject variables are age at time of testing, age at onset, duration of symptoms, presence or absence of on/off fluctuations, type of medication, and the relative preponderance of tremor vs. bradykinesia as the motor symptom. Each of these variables will be considered within this paper.

Typically, those studies that carefully assess particular cognitive functions focus on one or two functions and do not provide a comprehensive cognitive assessment of the patients studied. To redress this, we have reviewed the extensive literature on cognitive deficits in patients with PD and used this information to formulate a preliminary neuropsychological battery to assess cognitive functioning in these patients. There have been no papers, to our knowledge, that have described the pattern of cognitive deficits seen in patients with PD and that have considered these deficits in terms of these three issues. This review paper is an attempt to provide such an overview of the literature

and to suggest areas where knowledge of PD patients is still incomplete (e.g., the role of the frontal cortex in cognitive deficits in PD, the relationship between dopaminergic deficiency and cognitive deficits, and the existence of subgroups with different patterns of cognitive and emotional symptoms).

DEMENTIA

The concept of subcortical dementia was first introduced to account for the cognitive effects of progressive supranuclear palsy (Albert *et al.*, 1974) and then applied to patients with Huntington's chorea (McHugh and Folstein, 1975) and PD (e.g., Benson, 1984). Subcortical dementia has been defined as a general cognitive decline that includes, in particular, slowness of intellectual functioning, visual-spatial impairment, apathy, and depression (e.g., Benson, 1984; Cummings and Benson, 1984). These deficits are said to occur without the aphasia, apraxia, agnosia, disorientation, and/or indifference typically seen in cortical dementias [e.g., senile dementia of the Alzheimer type (SDAT)].

To document the existence of subcortical dementia in PD, researchers have studied pathology, biochemistry, and behavior, generally comparing PD patients to patients with suspected SDAT and to age-matched normal controls. Difficulties with this approach include the necessity of comparing older SDAT patients with younger subcortical patients who typically seek treatment earlier because of motor difficulties (Whitehouse, 1986), and differences in the overall severity of mental impairments between the subcortical and cortical patients at the time they are likely to be studied (Mayeux *et al.*, 1983).

Neuropsychological Studies

Comparisons to SDAT

Some studies have reported differences in neuropsychological performance between PD patients and SDAT patients, suggesting a subcortical dementia that differs from cortical dementia. Specifically, PD patients have been reported to have reduced fluency, but no difficulty with language comprehension or appropriate use of language. In contrast, SDAT patients have difficulty with the use of language and with language comprehension, but not with verbal output (Cummings *et al.*, 1988; Obler and Albert, 1981). However, no information was given on global cognitive performance, and so the PD patients may not all in fact have had dementia, as it is only a subtype of PD patients that does have dementia. Other studies have reported differen-

ces in performance between patients with PD who have dementia and SDAT patients on tasks of immediate memory, remote memory, visual-spatial skills, apraxia, naming, fluency, depression (Huber *et al.*, 1989), and sequencing (Sullivan *et al.*, 1989). From the findings in other studies of very small differences between demented PD patients and patients diagnosed as having SDAT (e.g., Bayles and Kaszniak, 1987; Danielczyk, 1983), many authors have suggested that PD patients with dementia do not exhibit a unique subcortical dementia but are actually a subtype of PD with concomitant SDAT (Garron *et al.*, 1972; Huber *et al.*, 1986; Lieberman *et al.*, 1979).

The bulk of these studies, then, indicate only that there is a subgroup of PD patients with dementia, which may or may not be due to concomitant SDAT. Evidence for a qualitative difference in subtypes of PD, only one of which has global cognitive deterioration, emanates from findings that PD patients with dementia are older (Birkmayer *et al.*, 1979; Garron *et al.*, 1972; Lichter *et al.*, 1988; Lieberman *et al.*, 1979; Martilla and Rinne, 1976; Stern *et al.*, 1987); have a later onset of symptoms (Birkmayer *et al.*, 1979; Garron *et al.*, 1972; Lieberman *et al.*, 1979); show evidence of both subcortical and frontal cortical atrophy (Lichter *et al.*, 1988); and respond less well to L-dopa (Duvoisin, 1986) and deprenyl (Portin and Rinne, 1983) than PD patients who do not exhibit dementia. Other studies, however, have not found age differences between demented and nondemented PD patients (e.g., Bowen *et al.*, 1973). Pirozzolo *et al.* (1982) report a gradient of cognitive deficits with no evidence for a subtype with dementia (although they report a surprisingly large percentage of patients with cognitive deficits—93% of the PD patients they studied)—and Huber, Shuttleworth, Christy *et al.* (1989) reported no difference between demented and nondemented PD patients on magnetic resonance imaging. While the evidence generally points to a subtype of PD patients who exhibit dementia, this alone, of course, does not prove that this subtype has concomitant SDAT.

Neuropsychological studies generally compare clinical findings from PD patients with those from patients with SDAT and age-matched normal controls. Mayeux *et al.* (1983) matched PD and SDAT patients for degree of impairment in activities of daily living (ADL) and then measured cognitive functioning with the Mini Mental Status (MMS) exam (Folstein *et al.*, 1975). They reported a decline in ADL functioning that coincided with cognitive decline in both groups, and they concluded that PD patients were showing the same clinical (and therefore presumably pathological) changes as the SDAT patients. Huber, Shuttleworth, Paulson *et al.* (1986) designed a battery to specifically differentiate subcortical and cortical dementia, and found the groups performed differently on this battery, with the PD patients superior to SDAT patients on several tests.

Comparisons to Schizophrenia

There have also been reports that schizophrenic patients with tardive dyskinesia have cognitive impairments similar to those seen in patients with PD (e.g., Wade *et al.*, 1987). Since tardive dyskinesia is presumed to reflect dopamine receptor supersensitivity, these findings suggest that the dopaminergic pathway from the basal ganglia may be responsible for the cognitive deficits. However, many schizophrenics have cortical involvement, so their cognitive deficits do not necessarily reflect only disrupted basal ganglia function.

Comparisons to MPTP Patients

To determine whether the basal ganglia pathology is responsible for the cognitive deficits observed in PD, a more promising group to study would be those with PD induced by inadvertent 1-methyl-4-phenyl-1,2,3-tetrahydropyridine (MPTP) toxicity, associated with intravenous drug abuse (Langston, 1985). These relatively young patients have the classic motor features of PD, presumably reflecting the selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra (Stern and Langston, 1985), but they do not show changes in the noradrenergic, serotinergic, or cholinergic systems. Thus, any cognitive changes are most likely due to the loss of cells in the substantia nigra and to a decrease in dopamine. In fact, the only study on cognitive functions in MPTP patients (Stern and Langston, 1985) described deficits similar to those seen in late-onset idiopathic PD. These patients were worse on tests of orientation, verbal abstraction, construction, and long-term recall, and on tests requiring changing mental set (i.e., the Stroop interference color naming test). Of course, diminished dopamine in the substantia nigra of MPTP patients also might affect the inputs to the inferior frontal cortex. More complete studies of these patients should prove fruitful in elaborating our knowledge of the cognitive functions normally sustained by the basal ganglia.

Pathology

Some further evidence supporting the argument that those patients with both PD and dementia (or a global cognitive decline) actually have concomitant SDAT has come from studies documenting SDAT-like pathology occurring more often in PD patients than in age-matched controls. In patients who meet the histological criteria for PD (i.e., Lewy bodies in the substantia nigra or locus coeruleus), many researchers have found pathological changes characteristic of SDAT, especially senile plaques and tangles in the hippocampus (Boller *et al.*, 1980; Hakim and Mathieson, 1977; Leverenz and Sumi, 1986; Mata *et al.*, 1983)

in higher proportions than in age-matched controls. Unfortunately, only one of these studies (Boller *et al.*, 1980) evaluated the mental status of the patients studied. In that study, PD patients, who had previously been assessed as demented, had a higher proportion of these pathological changes. Besides senile plaques and tangles, cell loss has been reported in the nucleus basalis of Meynert (Whitehouse *et al.*, 1983). While cell loss was more frequent in PD patients retrospectively classified as having dementia than in age-matched normal controls, cell loss was also present in PD patients not diagnosed as demented. In contrast, de la Monte *et al.* (1989) demonstrated distinctive pathological differences between patients defined as having PD with dementia and those patients defined as having PD with SDAT. Specifically, patients who had PD with SDAT showed the same subcortical pathology as the other patients, but showed additional global atrophy of the cerebral cortex and white matter. In addition, there was significant gliosis throughout the neocortex of the PD patients with SDAT. Unfortunately, information was not provided regarding criteria used for diagnosing dementia, and, in particular, no information was given regarding the clinical groupings of PD with dementia vs. PD with SDAT. Therefore, this study can only be interpreted as evidence for a subtype of PD that seems to have concomitant SDAT, and no real conclusions can be reached about the other group of patients. In a study involving more gross pathology (Portin *et al.*, 1984), PD patients, followed for 8–10 years, did show both cortical and central atrophy, but only the central atrophic changes correlated with cognitive deterioration. Further, the dementia of the patients with PD involved different clinical symptoms and was less severe than the dementia of matched patients with SDAT. Thus, no study reviewed has clearly established the dementia of PD to be due to SDAT, and few of these studies have focused on the cognitive symptoms of the dementia.

Another method for investigating the pathology responsible for the cognitive symptoms of PD are studies using positron emission tomography (PET) (e.g., Brooks and Frackowiak, 1989). These studies have demonstrated reduced [^{18}F]dopa uptake in the putamen of PD patients (e.g., Leenders *et al.*, 1986) and reduced binding of (+)[^{11}C]nomifensene (e.g., Tedroff *et al.*, 1988), indicating deficiency in both storage and re-uptake of dopamine subcortically. Of even more interest is that PD patients have also shown diminished regional cerebral metabolism of the frontal cortex, suggesting frontal cortical involvement in the cognitive disorders (Brooks and Frackowiak, 1989).

Relationship Between Cognitive and Motor Symptoms

The relationship between cognitive and motor symptoms has been used to investigate whether the dementia exhibited by some PD patients is due to

cortical SDAT-like changes or to the subcortical pathology that causes motor symptoms in PD. Some authors have reported an association between extent of dementia and degree of rigidity and bradykinesia (Martilla and Rinne, 1976; Mortimer *et al.*, 1982), suggesting the possibility of a common etiology between cognitive and motor symptoms. However, in a longitudinal study following PD patients 8–10 years, Portin and Rinne (1986) concluded that the cognitive and motor functions in PD are not correlated. Their conclusion was based on the finding that cognitive performance was affected to a lesser degree and more transiently by L-dopa treatment than was motor performance. This conclusion is supported by studies of patients whose motor symptoms exhibit the on/off phenomenon, as their cognitive fluctuations are much less severe than their motor fluctuations (Delis *et al.*, 1982; Girotti *et al.*, 1986). Recent evidence that dopaminergic medication does not effect degree of dementia and that demented PD patients have reduced cholinergic activity has been used to suggest that there is in fact a subgroup of PD patients who are demented and that these patients, like patients with SDAT, suffer from decreased cholinergic activity (Dubois, 1989).

Conclusions

Unfortunately, pathology and biochemistry studies of PD patients rarely include behavioral observations other than informal bedside evaluations or chart reviews, so it is difficult to make any conclusions on the relationship between the physical and the cognitive aspects of the disease. Those studies that have included careful assessment of cognitive functioning have not followed patients to autopsy when unequivocable diagnoses based on pathological findings could have been made. However, the only conclusions may be (a) some patients who are demented have SDAT-like changes in the brain, and (b) those patients with dementia appear to constitute a subtype, but the etiology of the dementia is unclear.

VISUAL-SPATIAL FUNCTIONS

PD patients have been reported to be impaired on a wide range of visual-spatial tasks. Many of these tasks require manual motor responses, and so observed performance may be influenced by a slowing or impaired planning and coordination of motor movements. However, a large number of authors have also reported that PD patients show deficits on visual-spatial tasks in which no motor response is required.

WAIS-R

PD patients have demonstrated impaired performance on the performance subtests of the Wechsler Adult Intelligence Scale–Revised (WAIS-R) that require manual responses, including the Block Design (Hietanen and Teravainen, 1986; Loranger *et al.*, 1972; Mortimer *et al.*, 1982; Pirozzolo *et al.*, 1982; Reitan and Boll, 1971), Object Assembly (Goldenberg *et al.*, 1986; Loranger *et al.*, 1972; Reitan and Boll, 1971), Picture Arrangement (Asso, 1969; Hietanen and Teravainen, 1986; Reitan and Boll, 1971), and Digit Symbol (Asso, 1969; Mortimer *et al.*, 1982; Pirozzolo *et al.*, 1982) subtests. Botez and Barbeau (1975) found PD patients to be worse than normal controls on the Kohs Block Design Test.

Tasks Requiring Motor Response

PD patients are also impaired on other tests tapping manual functions. Matthews and Haaland (1979) reported deficits in maze learning and on the Grooved Pegboard Test. Boller *et al.* (1984) found PD patients to be worse on the Purdue Pegboard Test than normal controls matched for age, gender, and education. Stern *et al.* (1983) reported that PD patients were significantly worse than controls (matched for IQ) on a task requiring the subject to trace a line with his or her finger. It should be noted that not only was the performance on this test quantitatively impaired but that PD patients made different kinds of errors than did the normal controls (i.e., PD patents were more likely to make errors in which the form of the drawing was incorrect). Goldenberg *et al.* (1986) found PD patients to have difficulty imitating movement sequences on a test of apraxia. This difficulty did not correlate with severity of motor disability but did correlate with performance on other visual-spatial tasks.

As might be expected, PD patients also perform worse than controls on tasks specifically requiring a graphomotor response. PD patients also performed significantly worse than normal controls on the Bender Gestalt Visual-Motor Test, which requires copying simple geometric designs (Talland, 1962). Matthews and Haaland (1979) reported that PD patients performed more poorly on Part A of the Trail-Making Test, a visual sequencing test, than normal controls. PD patients are also impaired on Part B of the Trail-Making Test (Matthews and Haaland, 1979; Mortimer *et al.*, 1982; Reitan and Boll, 1971), which requires sequencing and set-shifting. Similarly, Boller *et al.* (1984) found PD patients to have impairments on the Benton Test of Visual Retention, a visual memory test.

Tasks Without a Motor Requirement

A visual-spatial deficit also has been demonstrated in PD patients on tasks where only minimal motor output is required. Performance of PD patients was significantly worse than age-matched controls on the Raven's Standard Progressive Matrices (Huber *et al.*, 1986), a test of reasoning; the Benton Visual Form Discrimination Test (Boller *et al.*, 1984; Mortimer *et al.*, 1982); and the Visual Discrimination Test of Wepman *et al.*, (1975) (Pirozzolo *et al.*, 1982), a test of basic visual discrimination. Boller *et al.* (1984) reported that the performance of PD patients was significantly impaired on tests of visually matching angles on crosses, which is in agreement with findings of Raskin *et al.* (1990) that PD patients have difficulty on the Benton Line Orientation Test (but see also Goldenberg *et al.*, 1986; Girotti *et al.*, 1986).

Spatial Orientation

Personal and Extrapersonal Orientation

Several studies have concluded that PD patients have a specific deficit in spatial orientation, or in dealing with changing spatial and personal orientations. Bowen *et al.* (1976), Danta and Hilton (1975), Proctor *et al.* (1964), and Teuber and Proctor (1964) reported that PD patients had trouble judging both visual and postural vertical. PD patients also had trouble matching the orientation of two rods to a model (Hovestadt *et al.*, 1987). Ransmayr *et al.* (1987) reported that difficulty with matching the visual vertical and angles was an early symptom of PD. Bowen *et al.* (1976) asked patients to touch parts of their own bodies corresponding to those designated on a diagram. Overall, patients with left-sided and bilateral motor symptoms made more total errors than patients 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 in order to respond correctly). Further, the errors were predominantly on the left side of the body. Bowen *et al.* (1972) found patients to be significantly worse on a route-walking task than normal controls. Importantly, these patients had no difficulty walking north (i.e., straight ahead) but could not follow the map when any change in direction was required. This deficiency did not correlate with severity of tremor, rigidity, or akinesia, but again, patients with left-sided or bilateral symptoms showed greater performance deficits than patients with right-sided symptoms. These findings suggest, first, that PD patients with predominantly left-sided symptoms may differ behaviorally from those with right-sided symptoms, an issue that will be addressed

later in this paper. Second, PD patients may have specific deficits in maintaining spatial orientation, particularly when a change in orientation is required.

Spatial Orientation Memory

In tasks involving spatial orientation memory, Pirozollo *et al.* (1982) found Parkinson's patients to be significantly worse than normal controls. Mortimer *et al.* (1982) also found memory for spatial orientation among PD patients to be worse than among controls. Interestingly, performance on this task was better in patients with severe tremor than in patients with mild tremor.

Mental Rotation

Other investigators have looked at mental rotation as a measure of visual-spatial ability. Boller *et al.* (1984) reported that PD patients performed within normal limits on tests requiring mental rotation ("puppet" test and "rotation" test). However, on the rotation test, they reported that those patients rated as a 1 (unilateral symptoms) on the Hoehn and Yahr scale (Hoehn and Yahr, 1967) performed worse than those with a 2 (bilateral symptoms). Again, it may be those with left-sided unilateral symptoms who have particular difficulty with mental rotation tasks. Goldenberg *et al.* (1986), however, also found no significant differences between PD patients and normal controls on Ratcliff's Mannekin Test of Mental Rotation (1979). Further, there were no significant differences in performance on this test between PD patients with predominantly left-sided symptoms and those with predominantly right-sided symptoms.

Brown and Marsden (1986) designed a task involving mental rotation and right-left discrimination. Subjects were required to judge whether a box (in one of four positions) 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 task, PD patients performed as well as normal controls, and better than controls in some conditions. Similarly, Della Sala *et al.* (1986) devised 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 to be continued. Again, PD patients performed within normal limits.

Conclusions

The results of these studies suggest that patients with Parkinson's disease have a visual-spatial deficit both on tasks with manual response requirements and those without. The deficit seems most clearly observed on tasks involving

spatial and personal orientation, but not mental rotation. It is not clear whether there is a specific deficit in spatial orientation mediated by the basal ganglia, or as Brown and Marsden (1986) and others (e.g., Taylor *et al.*, 1987) have argued, a deficit in changing mental sets, that perhaps reflects diminished inputs from the basal ganglia to the frontal cortex. This question cannot be fully answered from the current literature because many of the studies reviewed use tasks that measure more than one function, and do not carefully describe the particular patient population in terms of variables such as severity of illness and predominant side of motor symptoms.

EXECUTIVE FUNCTIONS

Many researchers have noted the intimate connections of the basal ganglia to the inferior frontal lobes and the decreased dopaminergic input to this region in individuals with PD (e.g., Brown and Marsden, 1986; Taylor *et al.*, 1987). These researchers have suggested that the cognitive deficits present in Parkinson's disease may not reflect disturbed basal ganglia functioning, but rather, disrupted connections to the frontal lobes. Frontal-thalamic disconnections have been suggested to explain the clinical impressions that PD patients typically lack spontaneity and imagination, and exhibit inertia (e.g., Lees and Smith, 1983). On a questionnaire of daily functioning, PD patients were generally rated as more impaired than normal controls on questions relating to inertia, stereotyping, indifference, disinterest, social dependence, and intellectual control (Pillon *et al.*, 1986). Slowness to initiate responses and the tendency to verbalize but not execute correct movements may also provide evidence for frontal lobe involvement in PD patients (Taylor *et al.*, 1987). More empirical evidence has come from studies of functions generally believed mediated by the frontal lobes, particularly those requiring a delayed response or shifting mental sets.

Delayed Response

Early evidence using the delayed response task (Teuber and Proctor, 1964) suggested that lesions of the basal ganglia in monkeys mimic symptoms seen after bifrontal cortical ablations. Electrical stimulation of the caudate also transiently and selectively disrupted delayed response performance in monkeys. Patients with PD have also demonstrated difficulty with delayed response tasks (e.g., Bodis-Wollner *et al.*, 1983), although this may be true only of those PD patients with severe cognitive deficits (Freedman and Oscar-Berman, 1986). On a delayed response task, PD patients who had undergone thalamotomy were found

to be more impaired on a visual matching task than normals (De Lancey Horn, 1971). Taylor *et al.* (1987) found that PD patients were impaired in remembering serial position on a delayed response task. Deficits on delayed response tasks are associated with pathology in the major projections from the dorsomedial nucleus of the thalamus to the dorsolateral and orbital frontal systems.

Maintaining and Shifting Mental Set

Further evidence for the theory that the cognitive deficits seen in patients with PD are due to disruption in frontal pathways comes from studies that require patients to maintain or shift mental sets. PD patients perform more slowly than normal controls on the Stroop task (Hietanen and Teravainen, 1986; Taylor *et al.*, 1987) and Part B of the Trail-Making Test (Hietanen and Teravainen, 1986). Using Nelson's (1976) simplified version of the Wisconsin Card Sorting Test (WCST), Taylor *et al.* (1987), Pillon *et al.*, (1986), and Lees and Smith (1983) found that PD patients acquired significantly fewer categories, but made no more perseverative errors, when compared to normal control subjects. Similarly, Bowen *et al.* (1975) found that both untreated PD patients and those on L-dopa made more total errors on the standard WCST, but reported no differences in terms of perseverative errors. Flowers and Robertson (1985) also reported normal performance on the simplified version of this test.

Flowers and Robertson (1985) designed the "Odd-Man-Out" test as a measure of set maintenance that would be more sensitive than the WCST. This test requires the subject to indicate which set of letters or numbers is different from the other sets based on one of two possible rules. Subjects must use the two rules alternately on successive trials. Patients with PD performed only slightly more poorly than normal controls, clearly indicating an ability to perform the task. However, their pattern of errors was different from that of the controls. The patients made more errors throughout the entire series of 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. It is interesting, however, that there were not more perseverative errors, as might be expected in patients with damage to the frontal lobes, but rather fluctuations in performance and a tendency to revert back to the previous rule.

In other verbal, visual-spatial, and motor tasks requiring set shifting (Cools *et al.*, 1984), PD patients with no computed tomography (CT) scan or electroencephalogram evidence of frontal involvement exhibited reduced fluency and needed more trials to detect a shift.

Verbal Fluency

On tests of fluency, PD patients produced a greater number of words than patients with damage to the frontal lobes (Miller, 1985). PD patients also have been found to perform within the normal range on verbal fluency tests requiring the generation of words that begin with a particular letter (Lees and Smith, 1983; Matison *et al.*, 1982; Weingartner *et al.*, 1984). Performance on a fluency task requiring the generation of words in a specific semantic category, however, has been found to be impaired (Matison *et al.*, 1982; Pillon *et al.*, 1986; Raskin *et al.*, 1989; Stern *et al.*, 1987).

Abstract Reasoning

Performance on the tests described above does not appear attributable to a general deficit in abstract reasoning. PD patients perform normally on the Category Test (Reitan and Boll, 1971), which requires abstract reasoning and concept formation (Matthews and Haaland, 1979). Normal performance is also reported on a sequential test of concept formation, in which the subject must learn a rule to predict the next occurrence of a stimulus (Talland, 1962). Normal performance by PD patients was also reported on the Cognitive Estimates test (Shallice and Evans, 1978) and the Comprehension (Lees and Smith, 1983) and Similarities subtests of the WAIS-R (Lees and Smith, 1983; Pillon *et al.*, 1986).

Motor Sequencing

Bodis-Wollner *et al.* (1983) argue that the abnormal movements (e.g., akinesia) of PD patients are symptomatic of a central defect in motor planning. Thus it is interesting to examine the performance of these patients on tasks that require planned or sequenced movements. In one such study, nondemented PD patients and age-matched controls were required to trace lines that were horizontal, vertical, and in a saw-tooth pattern, some of which had deleted segments (Stern *et al.*, 1983). Again, PD patients showed neither the same improvement with practice as the control subjects nor the same increase in errors with increasing stimulus complexity. The types of errors produced were also different. PD patients exhibited more loss-of-form errors when tracing out the missing segments in a pattern and more hesitation than normal controls. Frith *et al.* (1986) studied pursuit tracking in PD patients. In their first task, a target moved predictably in the horizontal direction but unpredictably in the vertical direction. PD patients, like controls, showed significant improvements between sessions, reflecting a spared ability to make movements automatic. However, PD patients did not show within-session improvements, reflecting an inability

to learn about the target and use that information to produce anticipatory movements. This was interpreted as an inability to initiate a mental set, similar to the deficit seen with the WCST studies. Rafal *et al.* (in press) used a finger-tapping task that required the programming and execution of sequential movements. They found that PD patients were slower in initiating and executing finger movements than control subjects, although PD patients were just as able as controls to use prior information in preparing to make simple responses.

Simultaneous Motor Movements

Similar impairments have been found in tasks requiring two simultaneous motor movements (Benecke *et al.*, 1986; Talland and Schwab, 1964; Taylor *et al.*, 1987). These deficits have also been interpreted as reflections of impairment in frontal lobe function (Taylor *et al.*, 1987). In fact, Taylor *et al.* (1987) suggested a specialized role for the supplementary motor area of the frontal lobes in planning these movements.

Apraxia

A related study by Goldenberg *et al.* (1986) focused on ideomotor apraxia. Patients with PD performed more poorly than normal controls on tests of ideomotor apraxia, but these differences reached significance only for whole limb movement sequences and the total apraxia score, not for finger tapping, pantomime of object use, symbolic gesture, and measures of finger and hand position. In addition, scores on visual-spatial tests correlated strongly with the total apraxia score, while such factors as duration of illness, degree of symptom laterality, severity of tremor, or use of anticholinergic medication were not correlated. The authors suggested that this was a sign of frontal lobe dysfunction, as the patients became more impaired when there were more movements to be remembered. In fact, there was a significant positive correlation for patients, but not for controls, between scores on a memory test and finger-tapping performance.

Complex Movements

Other studies of motor functions have focused on more complex movements and on orientation. Bowen *et al.* (1972, 1976) found that PD patients performed more poorly than controls matched for age, gender, and socioeconomic status on a route-walking task. As mentioned previously, the patients in this study had no trouble following the route when walking north, which was straight ahead. However, they could not follow the map when they

were required to walk in a different direction. This difficulty in changing spatial orientations could be due to a specific spatial orientation deficit or to a more general difficulty with changing mental sets. Bowen *et al.* (1976) asked PD patients to touch parts of their own bodies corresponding to parts designated on a diagram. As mentioned earlier in this review, patients made errors on this task only when the body in the diagram was presented in a frontal view, requiring the patient to make a left–right reversal and a change in orientation. In another study, to determine whether this type of error is due to difficulty in spatial orientation or in changing sets, Brown and Marsden (1986) designed a test that requires changes in spatial orientation. PD patients did not demonstrate deficits on this task. They concluded that their results refute the notion of a visual-spatial deficit in PD patients. Further, they argued that the difficulties generally attributed to such a deficit might actually be due to a more general inability to change mental set.

Conclusions

There is evidence, therefore, for some behavioral deficits in PD patients that suggest frontal lobe impairment. These deficits are specifically difficulty in shifting mental set and in performing planned sequences. However, there have not been clear demonstrations of perseverations or of difficulty with abstract reasoning, which are also common in patients with damage to the frontal lobes. Speculatively, this may suggest a disruption to a particular area of the frontal cortex, leaving other areas intact. Specifically, this constellation of symptoms suggests impairments similar to those seen in patients with lesions of orbitofrontal areas but not the circuits involving dorsolateral prefrontal cortex. This, of course, would have to be investigated anatomically by measuring postmortem levels of dopamine in particular prefrontal areas of patients with associated demonstrated behavioral deficits.

MEMORY AND ATTENTION FUNCTIONS

Patients with PD have been studied with respect to many aspects of memory functioning. Given the current theories of normal memory function and the findings reported in studies of PD, several authors have suggested that the memory deficits in PD occur when tasks require some form of internal control. In particular, using the working memory paradigm of Baddeley (1986), PD patients are proposed to have a deficit in the central executive. The central executive is responsible for allocating mental resources and for integrating information from different sources, including the visual-spatial sketch pad where

visual-spatial information is initially recorded and manipulated, and the articulatory loop where verbal information is maintained while it is processed. The central executive must switch between these various memory stores and integrate information when appropriate.

Automatic Functions

In tasks considered automatic, which do not require integration from various stores, patients with PD typically are intact. Automatic tasks are those that require minimal attention or awareness, and that do not interfere with nonautomatic tasks being performed simultaneously (Hasher and Zacks, 1979). Weingartner *et al.* (1984) compared unmedicated PD patients, with a Wechsler Memory Scale Quotient in the normal range, to matched normal controls. They found that the PD patients were as able as controls to monitor the frequency with which items were presented and to identify the modality (auditory or visual) in which the items were presented. Sagar, Sullivan, *et al.* (1988) reported a deficit in recency discrimination in PD patients on a test in which content recognition was intact.

Recognition Memory

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 as all the information is in one of the slave systems. Lees and Smith (1983) studied unmedicated PD patients using a two-choice recognition test with words and unknown faces (preceded by attention-focusing tasks that involved either reading the words or rating the faces), and found no differences between the PD patients and control subjects. De Lancey Horn (1971) studied post-thalamotomy patients on a visual matching test involving modified Chinese characters. No difference was found between PD patients and controls with respect to either errors or reaction time. Flowers *et al.* (1984) studied PD patients and age-matched controls in a forced-choice paradigm using pictures of common objects, words, numbers, black-and-white histograms, and abstract color pictures. Again, the patients did not differ from controls, and their performance did not correlate with age, duration of illness, or severity of motor impairment. Sagar, Sullivan *et al.* (1988) found no differences between PD patients and controls in a test of word recognition. Tweedy *et al.* (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. Thus, in the intervening

time before the recognition task it is likely that some material had been lost from the short-term memory storage. In addition, the subjects were asked to recognize only those words they had failed to recall. As the Parkinson's patients recalled fewer words, they were required to recognize a larger number of items than the controls.

Delayed Recognition

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 memory stores, while other pieces of information have been encoded into more long-term storage; thus recognition requires 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 delayed tasks, differences have been reported between PD patients and normal controls. De Lancey Horn (1971) found PD patients performed as well as controls on a delayed recognition task involving Chinese characters, but that the nature of their performance was different than that of controls. Control subjects showed faster recognition when a delay preceded the test items than when there was no delay; PD patients did not show this difference. This finding seems consistent with the hypothesis that PD patients exhibit memory deficits only when the task requires integration between memory stores. Tweedy *et al.* (1982) found deficits when there was a delay before recognition. In contrast, Flowers and Robertson (1985) and Flowers *et al.* (1984) found no difference between controls and patients with delays up to 45 minutes, long enough to allow transfer of all information into long-term storage. Sullivan and Sagar (1988), Sagar, Sullivan *et al.* (1988), and Sahakian *et al.* (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.

Learning and Recall

In tests of learning and immediate recall, PD patients have shown clear deficits. Weingartner *et al.* (1984) and Tweedy *et al.* (1982) reported that PD patients are impaired in free recall for words. Tweedy *et al.* (1982) also found these patients benefited less from cues than either controls or patients who had suffered right-hemisphere strokes, suggesting a deficit in storage rather than retrieval. Paired-associate learning has been found to be impaired in PD patients

(El-Awar *et al.*, 1987; Hietanen and Teravainen, 1985; Huber *et al.*, 1986; Pillon *et al.*, 1986; Pirrozolo *et al.*, 1982). Some evidence, however, suggests that only a subgroup of PD patients is impaired in paired-associate learning; this subgroup performs like patients with SDAT (El-Awar *et al.*, 1987). Other authors report that PD performance is superior when compared to performance of SDAT patients (Huber, Shuttleworth, Paulson *et al.*, 1986), but impaired when compared to performance of normal controls. Memory for more complicated verbal material, e.g., on the Logical Memory subtest of the Wechsler Memory Scale, is inferior in PDs compared to normal controls (Hietanen and Teravainen, 1985; Pillon *et al.*, 1986). In addition, recall of visual material is impaired in PD patients as compared to normal controls (Hietanen and Teravainen, 1985; Pillon *et al.*, 1986; Pirozzolo *et al.*, 1982; Weingartner *et al.*, 1984).

Semantic Memory

Tests thought to measure long-term retrieval from semantic memory and thus only one storage system have not demonstrated impairment in PD patients. 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) but within the impaired range on the Information subtest (Pirozzolo *et al.*, 1982). PD patients have been found to perform within the normal range on tests of verbal fluency requiring the generation of words that begin with a particular letter (Lees and Smith, 1983; Matison *et al.*, 1982; Weingartner *et al.*, 1984). Performance on fluency tasks requiring the generation of words by semantic category, however, has been found to be impaired (Matison *et al.*, 1982; Pillon *et al.*, 1986; Stern *et al.*, 1987). Taken together, these findings may reflect a deficit in storage or retrieval specifically by semantic category. Tweedy *et al.* (1982) did report, however, that patients clustered their free recall of categorizable word lists as much as normal controls. On a memory test of public and personal events, only those PD patients with dementia showed impairments, and these impairments followed a temporal gradient in which recall of events from more remote decades were recalled more successfully than events from more recent decades. This pattern is similar to that seen in patients with SDAT, in which the most recent events were most poorly recalled (Sagar, Cohen *et al.*, 1988). On the nonverbal Famous Faces Task, only those patients with clear intellectual impairment (as measured by the MMS exam) performed more poorly than normal control subjects (Freedman *et al.*, 1984; Huber *et al.*, 1986), and no patients showed the temporal gradient observed on this task in patients with SDAT or Huntington's disease. Naming of simple line drawings (Freedman *et al.*, 1984; Hietanen and Teravainen, 1985; Huber, Shuttleworth, Paul-

son *et al.*, 1986) and objects (Pirozzolo *et al.*, 1982) has been found to be normal.

Memory Scanning

The cognitive processes of PD patients have also been studied with the Sternberg memory scanning paradigm. Parkinson's patients have been reported to scan more slowly as set size increases, a finding that becomes more pronounced with age (Wilson *et al.*, 1980). Rafal *et al.* (1984), however, did not find slower per-item performance in nondemented PD patients and reported that L-dopa medications increase the overall speed of performance (i.e., decreased the intercepts of the reaction time functions), but not the speed of processing for each item (i.e., the slope of these functions). These findings have been interpreted as supporting the notion of a slowing of cognitive functioning, independent of the slowing of motor functioning, in a subgroup of older patients, possibly revealing an early sign of dementia (e.g., Bayles and Kaszniak, 1987). Information processing while performing motor tasks has also been reported to be slower in PD patients than in normal controls (Sanes, 1985).

Attention

In contrast, tests of pure attention with little or no memory component have yielded very mixed results. Patients with PD have been found to perform normally on the WAIS-R Digit Span subtest by some authors (Asso, 1969; Huber *et al.*, 1986; Huber, Shuttleworth, Paulson *et al.*, 1986), but other authors have reported impaired performance (Pirozzolo *et al.*, 1982; Reitan and Boll, 1971; Spicer *et al.*, 1987). Normal performance have also been reported on critical flicker fusion (Hietanen and Teravainen, 1985) and running digit span (Talland, 1962) tasks, while impaired performance has been reported on Part A of the Trail-Making Test (Huber, Shuttleworth, Paulson, *et al.*, 1986; Pirozzolo *et al.*, 1982), the Time-Sense Test (Reitan and Boll, 1971), and the K-T Attention Test (Botez and Barbeau, 1975).

Conclusions

Overall, PD patients perform within normal limits on tests involving automatic processes, immediate recognition, access to long-term semantic memory, and short-term memory scanning. However, PD patients have demonstrated impairments on tasks requiring delayed recognition, immediate recall, or delayed recall. These results support 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.

LANGUAGE FUNCTIONS

The most clearly documented effects of PD on language functioning are decreased speed in speech output and loss of voice amplitude. In his description of motor speech behavior in PD patients, Mueller (1971) concluded that there are not sufficient amounts of aerodynamic energy for PD patients to produce normal speech due to motor deficiencies. In addition, deficits in prosody and word finding have been reported. There have been no differences demonstrated between PD patients and normal controls on linguistic measures involving general processing and comprehension (e.g., Scott *et al.*, 1984).

Right Hemiparkinsonism

Patients with greater right- than left-sided motor symptoms (presumably reflecting left-sided neuropathology) have consistently been found to have difficulty on tasks requiring generative naming (Bentin *et al.*, 1981; Blonder *et al.*, 1987; Spicer *et al.*, 1987). Deficits have also been reported in confrontational naming (Bayles and Tomoeda, 1983; Blonder *et al.*, 1987; Spicer *et al.*, 1987), sentence repetition, and sentence completion (Spicer *et al.*, 1987).

Bilateral PD Patients

Matison *et al.* (1982) also reported naming difficulties in chronic, stable PD patients who did not show unilateral symptoms. These patients performed nearly one standard deviation below the mean on the Boston Naming Test (Kaplan *et al.*, 1978). That these PD patients were able to profit from semantic and phonemic cues suggests that the naming difficulty is more likely due to a problem with retrieval rather than to a general loss of linguistic ability. On the other hand, Pillon *et al.* (1986) did not find deficits in object naming. Sentence repetition was also reported to be impaired by Matison *et al.* (1982), but not by Pillon *et al.* (1986), and generative naming was impaired when subjects were asked to name a semantic category (animals) but not when asked to produce words beginning with a particular letter (Matison *et al.*, 1982). These studies suggest that PD patients have difficulty in retrieving semantic information.

Thalamotomy

Patients who have undergone thalamotomy or pallidectomy, particularly on the left side, also have been found to have expressive language deficits. Darley *et al.* (1975) reported that 28 out of 123 PD patients showed such language deficits. These deficits included reduced accuracy and completeness of language production and reduced fluency. Only about half of these patients showed deficits in reading comprehension or auditory comprehension, and only 3 showed naming difficulties.

Conclusions

In summary, patients with PD appear to have significant deficits in the motor aspects of speech. In addition, they have deficits in confrontation and generative naming. Those who have predominant neuropathy to the left side seem to have more serious disturbances in verbal expression than those with predominantly right-sided neuropathy.

AFFECT

There is considerable literature on the association between depression and PD (see review in Gotham *et al.*, 1988). In contrast, there have been relatively few studies on the perception and expression of emotion in PD patients.

Depression

Estimates of depression in PD range from 12% (Rondot *et al.*, 1984) to 90% (Mindham, 1970). In a review of 14 studies, Gotham *et al.* (1988) reported a mean estimate of 46%. The reasons for the large range of prevalence estimates, no doubt, include differences in patient demographics (e.g., hospitalized patients vs. outpatients) and the presence of many physical changes common in PD that appear as somatic complaint items on scales of depression (e.g., disturbances in posture, motor slowing, reduced facial expression).

Theories about the relationship between depression and PD generally fall into one of two types. The first theory claims that depression reflects biochemical and neuroanatomical changes that are intrinsic to PD, the second theory that depression is a reaction to the illness. Evidence for the first theory comes from the finding that PD patients have higher levels of depression than other patients with chronic disabling illness, such as paraplegia (Horn, 1974), hemiplegia (Robins, 1976), medical and surgical conditions (Warburton, 1967),

and arthritis (Gotham *et al.*, 1988). Dakof and Mendelsohn (1986) pointed out differences between these conditions and PD, however. In particular, the relatively acute onset and the lack of cognitive changes in most of these other conditions make comparisons difficult. This hypothesis is called into question by the lack of a correlation in PD patients between the severity of the depression and the duration of the motor impairments (Gotham *et al.*, 1988; Huber *et al.*, 1988; Mayeux, Stern *et al.*, 1984) or the level of functional disability (Horn, 1974; Mayeux, Stern *et al.*, 1984; Warburton, 1967).

In addition, the majority of studies published in this area have failed to find any significant effects of L-dopa therapy on depressive symptoms (Lesser *et al.*, 1979; Marsh and Markham, 1973; Mayeux, Williams *et al.*, 1984). Finally, antidepressants have been found to improve mood in PD patients without any improvement in their motor functions (Bowen *et al.*, 1972; Marsh and Markham, 1973; Mayeux, Williams *et al.*, 1984). While the monoamine oxidase-B inhibitor deprenyl has been found to relieve depression in some PD patients (e.g., Portin and Rinne, 1983), this effect may not be due entirely to an increase in available dopamine, but to the metabolism of deprenyl into amphetamine and metamphetamine (Karoum *et al.*, 1982).

A third theory, however, is consistent with both sets of the preceding evidence. This theory states that there may be a subtype of PD with a decrease in serotonin, as well as dopamine, levels and that it is the serotonin deficiency that leads to depressive illness (Mayeux, Stern *et al.*, 1984; Sano *et al.*, 1989). This has been reinforced by findings of lower concentrations of 5-hydroxindoleacetic acid in the cerebral spinal fluid of PD patients diagnosed as depressed (Sano *et al.*, 1989). Santamaria *et al.* (1986) also suggested that this subgroup of PD patients is younger, less functionally impaired, and more likely to have a family history of PD than other PD patients.

Affective Processing

Early descriptions of affective processing in PD patients suggested that premorbidly these individuals exhibit a limited range of emotional expression and a withholding tendency (for a review, see Todes and Lees, 1985). Another observation that has suggested diminished emotionality in PD patients is that one of the classic PD symptoms is an expressionless face (i.e., masked facies) (e.g., Best and Taylor, 1966).

Vocal Affect

Empirical studies of the expression and perception of facial affect in PD patients, however, have been rare, as have studies of the vocal expression of

emotion. Borod *et al.* (1989) found that PD patients, when asked to intone a neutral sentence with a particular emotion, performed with accuracy and intensity equivalent to normal controls (as judged by trained independent raters), and showed greater accuracy and intensity than either patients with right-hemisphere lesions or schizophrenia. This was true for the production of both positive (e.g., happiness) and negative (e.g., fear) emotions. In another study, however, PD patients were reported to have particular difficulty producing angry or questioning intonations (Scott *et al.*, 1984). Finally, using an objective computerized technique, Alpert *et al.* (1987) reported similar vocal acoustic patterns, reflecting flat affect, in PD, right-hemisphere pathology, and schizophrenic subjects.

One important study for theories of depression in PD reported that PD patients who were depressed did not show the same vocal acoustic pattern as patients with unipolar depression. The authors suggested that the flattening of affect seen in PD patients should not be viewed as merely an overlay of depression (Alpert *et al.*, 1988).

Facial Affect

Since masked facies is a classic symptom of PD, the facial expression of emotion may be a fruitful behavior to investigate. Borod *et al.* (1989) reported that the accuracy of PD patients' expressions was equivalent to that of normal controls but, as might be expected, the intensity of their facial expressions was significantly reduced relative to normal controls. Brozgold (1988) used a quantitative rating system to judge facial expressions and found that PD patients were more expressive in a posed condition than in a spontaneous condition, while the two conditions were equivalent for normal controls. This suggests that the constriction of facial emotion is not due to an inability to create facial expressions but to a reduction in the intensity of emotional expression. This constriction may specifically reflect subcortical damage or it may indicate a general failure to respond spontaneously, reflecting cortical damage as well. In other studies examining spontaneous expression, facial expressions while watching affectively laden slides were impaired in PD patients relative to controls (Buck and Duffy, 1980; Katsikitis and Pilowsky, 1988). The frequency of spontaneous smiling in PD patients inversely correlated with extent of depression (Katsikitis and Pilowsky, 1988). When perception of facial (and prosodic) emotional stimuli was examined, PD patients were not significantly different from normal controls in one study (Borod *et al.*, 1989). In contrast, in another study (Scott *et al.*, 1984), PD patients had difficulty perceiving differences in prosody and in matching facial expressions to the appropriate vocal intonation.

Conclusions

Although the etiology of depression in PD is not understood, PD patients should be routinely assessed for depression because of its high prevalence and because depression always may be a factor in cognitive impairments observed. While PD patients often show decreased facial expressiveness, the evidence for deficits in vocal emotional expression and in perception of facial and vocal emotion remains equivocal. Given the suggestions of frontal-lobe dysfunction in PD, it might be particularly interesting to examine whether PD patients exhibit deficits in the expression of emotion but not in the perception of emotion as would be predicted from theories (e.g., Ross, 1985) suggesting that perception of emotion is localized to right-posterior structures and expression of emotion is localized to right-anterior structures.

HEMIPARKINSONISM

"Hemiparkinsonism" refers to the condition in which the motor symptoms of PD are apparent in the limbs on only, or predominantly, one side of the body. This condition has been studied both from a physiological and neuropsychological perspective.

Physiology

Although it is not universally accepted that unilateral motor symptoms indicate unilateral disease of the basal ganglia, there is some physiological evidence to support this case. Gilbert (1976) reported depigmentation and loss of neurons in the substantia nigra and locus coeruleus, 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 *et al.* (1984) found unilateral atrophy on CT scan contralateral to the clinically affected side in 6 of 8 patients, and when symptoms were bilateral and asymmetrical, atrophy was still predominant contralateral to the more severely affected side of the body. Direnfeld *et al.* (1984) found that while PD patients with predominantly left-sided symptoms had more neuropsychological impairment, they had higher homovanillic acid levels in the cerebrospinal fluid than those with right-sided symptoms, indicating greater dopaminergic activity. The PD patients with left-sided symptoms also had higher levels of acetylcholine esterase (the cholinergic and dopaminer-

gic systems are mutually antagonistic in the striatum). This suggests a functional asymmetry of the dopaminergic system.

Motor Symptoms

Unilateral motor symptoms also have been reported. Perret *et al.* (1969) reported that the contralateral hand improves more after unilateral thalamic surgery and that this effect is stronger in left-sided operations than in right-sided operations. In PD patients who had not undergone surgery, Bowen *et al.* (1972) reported functional differences between those patients with predominantly right-sided symptoms and those with predominantly left-sided symptoms. Those with right-sided symptoms had a bimanual depression of tapping and bilateral visual-motor deficits in visual tracking. Those with left-sided symptoms had only a contralateral depression in tapping and a contralateral visual-motor deficit. They concluded that the asymmetrical cerebral function was produced by an underlying asymmetrical subcortical depletion of dopamine.

Sensory Symptoms

Unilateral lesions have not been reported to produce lateralized sensory deficits. Procter *et al.* (1963) reported no noticeable effects of unilateral chemothalamectomy (alcohol injection aimed at the ventrolateral thalamic nuclei) on the appreciation of passive movement or point localization. Although there were some changes on punctate pressure threshold and two-point discrimination, these changes were not reported to be related to the side of operation, and had disappeared five months after the operation.

Neuropsychological Studies

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. These results are, of course, similar to those reported in studies of patients with unilateral cortical pathology.

Visual-Spatial Functions

Studies of visual-spatial function in hemiparkinsonian 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 *et al.* (1963) and Teuber and Mishkin (1954) found that PD patients with predominantly left-sided symptoms made contralateral overreaction 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 overreactions in any tilt condition. Bowen *et al.* (1976) and Bowen and Yahr (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 *et al.*, 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 *et al.* (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 *et al.*, 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 figural 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 *et al.*, 1987; Villardita *et al.*, 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. Direnfeld *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 *et al.* (1987), however, reported no differences between patients with predominantly right-sided vs. left-sided symptoms on tasks generally considered to be affected by right-hemisphere damage [i.e., on Form Sequence Learning, Facial Recognition, and Judgment of Line Orientation tests (Benton *et al.*, 1983)]. However, patients included in their study were required to have a WAIS-R Verbal IQ not exceeding their WAIS-R Performance IQ by more than 15 points. Thus, this study excluded all patients with substantial visual-perceptual deficits.

Patients who have undergone unilateral subcortical surgery have been found to have cognitive deficits similar to those seen in patients with unilateral symptoms. McFie (1960) described a group of PD patients who had undergone left-sided stereotaxic surgery; the patients exhibited transient drops in WAIS-R Performance IQ immediately postoperatively, but this effect disappeared by four weeks after surgery. Similarly, Meier and Story (1967) reported that patients who underwent left-sided surgery had difficulty afterward on the Porteus Maze task. Perret *et al.* (1969) found that unilateral stereotaxic surgery on the right side was associated with below average scores on the WAIS-R performance subtests and a figural memory test, but that this effect was transient. Riklan and Levita (1964) administered the Rorschach, Wechsler-Bellevue, Bender-Gestalt, and Human Figure Drawing tests to PD patients who had undergone a unilateral chemopallidectomy and/or chemothalamectomy. There were few significant behavioral differences between patients with left-sided surgery and those with right-sided surgery either 16 days or nine months postsurgery, but there was a higher loading for the spatial-perceptual factor for those with right-sided surgery than those with left-sided surgery.

Linguistic Functions

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 *et al.*, 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.*, 1987), naming (Blonder *et al.*, 1987; Spicer *et al.*, 1987), sentence repetition, sentence completion for ideational material (Blonder *et al.*, 1987), and serial digit learning (Spicer *et al.*, 1987).

Darley *et al.* (1986) found PD patients with left thalamotomies were twice as likely as those with right thalamotomies to have language deficits, specifically difficulty in accuracy and completeness of oral language formulation and expression, and reduced fluency. Riklan and Levita (1964) obtained a greater verbal loading for patients with left-sided surgery, and McFie (1960) found those with right-sided surgery had a lowering of the WAIS-R Verbal IQ postoperatively, which disappeared, however, by four weeks after the surgery. Chouza *et al.* (1984) reported greater occurrence of apraxia and lower intelligence levels (on Piaget's tests of physical constants) in patients with right-sided symptoms than in patients with left-sided symptoms.

Conclusions

In general, the literature on hemiparkinsonism 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. Overall, patients with presumed right-sided damage seem to have global deficits while those with left-sided damage have more circumscribed difficulties. Similar findings have been reported following penetrating injuries to the right vs. left precentral gyrus (motor strip) of the cerebral cortex (Semmes, 1968). 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.

GENERAL CONCLUSIONS

While much of the neuropathology and the motor symptoms of PD patients are well known, the cognitive sequelae are less easily understood. The review presented above of the extensive literature concerning the neuropsychology of PD suggests that while certain cognitive changes are frequently observed in patients with PD, other cognitive changes are exhibited only in particular subgroups of PD patients. The relationship between causal factors in the disease, such as neuropathology and subject variables, and the occurrence of these subtypes, warrants further investigation.

The neuropsychological symptoms most commonly reported in large numbers of PD patients are spatial orientation deficits, difficulty in shifting mental set, effortful memory deficits, reduced verbal fluency, difficulty with initiation, and reduced facial expression. 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 the 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. The set-shifting difficulty, difficulty with delayed response, and reduced fluency have all been suggested to be a part of a single syndrome reflecting diminished connections with the frontal cortex. Finally, while reduced facial expression is a commonly recognized symptom of PD, there is some evidence that this is part of a larger difficulty with emotional processing.

Table I. Neuropsychological Test Battery for Parkinson's Disease

I. Dementia
  A. Dementia Rating Scale (Mattis, 1976)
II. General cognitive functioning
  A. Fund of information
    1. WAIS-R Information subtest (Wechsler, 1981)
  B. Abstract reasoning
    1. WAIS-R Similarities subtest (Wechsler, 1981)
III. Basic visual discrimination
  A. Benton Visual Discrimination Test (Benton *et al.*, 1983)
IV. Spatial orientation
  A. Benton Line Orientation (Benton *et al.*, 1983)
  B. Money Map Test (Money, 1976)
  C. Benton Right–Left Orientation (Benton *et al.*, 1983)
V. Set shifting
  A. Stroop Word-Color Interference Test (Stroop, 1935)
  B. Competing Programs (Luria, 1966)
  C. Trail-Making Test (Army Individual Test Battery, 1944)
VI. Memory and attention
  A. Immediate recall
    1. Wechsler Memory Scale-Revised (WMS-R) Digit Span (Wechsler, 1987)
    2. WMS-R Logical Memory
    3. California Verbal Learning Test (Delis *et al.*, 1987)
    4. Benton Visual Retention, 10-second exposure (Benton, 1974)
  B. Delayed recall
    1. WMS-R Logical Memory
    2. California Verbal Learning Test delay trial
  C. Recognition
    1. California Verbal Learning Test recognition trial
    2. Randt picture recognition
VII. Verbal fluency
  A. Controlled Word Association Test (F-A-S) (Benton, 1968)
  B. Animal Naming (Goodglass and Kaplan, 1972)
VIII. Naming
  A. Boston Naming Test (Kaplan *et al.*, 1978)
IX. Depression
  A. Zung Depression Index (Zung, 1965)
X. Motoric functioning
  A. Finger Tapping Test (Halstead, 1947)
XI. Writing
  A. Sentence Writing from the Boston Diagnostic Aphasia Exam (Goodglass and Kaplan, 1983)

In addition to these commonly reported symptoms, other deficits have been observed in particular subgroups of PD patients. There is evidence for a subgroup that is demented, and some evidence suggests that these PD patients have concomitant SDAT. There is also evidence for a subgroup that experiences a depression that is not merely a response to the illness. Finally, there is evidence that those PD patients whose motor symptoms are greater on the right side of the body than on the left, presumably reflecting greater left-sided brain pathology, have a preponderance of language deficits. Those PD patients with

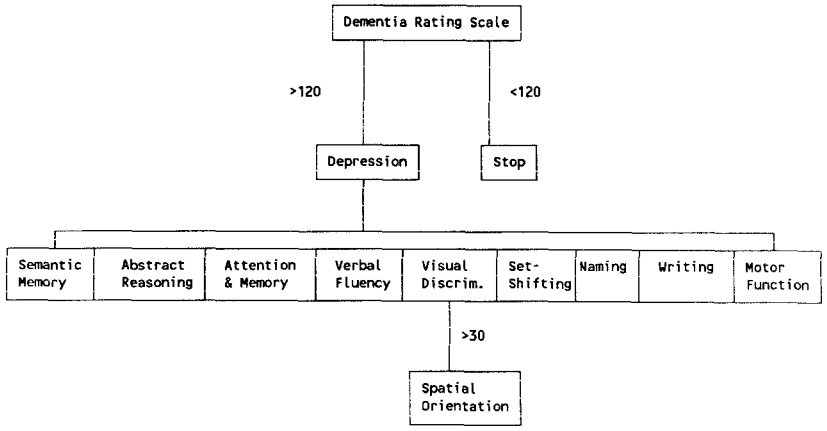

Fig. 1. A suggested system for the use of the battery.

motor symptoms that are greater on the left side of the body than on the right side, in contrast, have more visual-spatial deficits. These results are most evident in those patients who have exclusively unilateral motor symptoms or have had unilateral thalamotomy.

The studies reviewed in this paper clearly indicate the need for thorough neuropsychological evaluation of PD patients to determine the particular constellation of symptoms present in any particular patient. While most studies focus on particular symptoms of interest, the unclear pattern of subgroups warrants a more comprehensive evaluation of all patients. Such an evaluation should emphasize those functions most commonly reported to be compromised in PD patients. A battery of neuropsychological test measures for the evaluation of PD is suggested in Table I. This battery begins with a screening for dementia because of the frequent occurrence of dementia in PD, and in order to eliminate the need for further testing if a patient is initially found to be demented. The battery includes measures of immediate and delayed memory, verbal fluency, set shifting, spatial orientation, and depression since these are areas where deficits have commonly been reported in PD patients. (See literature reviewed above.) In addition, a writing sample will be obtained to assess micrographia, and confrontation naming will be evaluated to aid in differential diagnosis with respect to dementia and hemiparkinsonism. Finally, tests of semantic memory, abstract reasoning, and basic visual discrimination, generally found to be intact in PD patients, are included to determine the specificity of any observed deficits. For each of these cognitive areas (except writing), tasks were selected not to require a motor output. The entire battery should take approximately three hours to administer, and frequent breaks should be allowed when possible.

The battery can also be administered on successive days to reduce fatigue. Figure 1 indicates a suggested system for using the battery.

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