6

Neuropsychological Aspects of Parkinson's Disease and Parkinsonian Syndromes

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INTRODUCTION

Consistent with the clinical focus of this volume, this chapter first acquaints the reader with basic distinctions between the clinical "brain-behavior" disciplines, namely neuropsychology, behavioral neurology, and neuropsychiatry. After describing the most common approaches to neuropsychological evaluation and the goals of neuropsychological evaluation in Parkinson's disease (PD), the chapter highlights the cognitive alterations most frequently accompanying PD and those that occur in and differentiate dementias seen in PD from other neurodegenerative conditions. A discussion of the impact of emotional comorbidity on cognition makes clear the importance of treating anxiety, depression, and psychiatric symptoms in optimizing the afflicted person's functioning and quality of life. Both medical and surgical treatments, the latter enjoying a renaissance after a protracted, relative absence from the treatment armamentarium after the introduction of levodopa, have the potential to impact cognition. Only a sparse literature devotes itself to treatment-related neurobehavioral complications and less frequent improvements. The chapter concludes with a brief comparison of the most common cognitive alterations

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accompanying parkinsonian and related syndromes, such as multiple system atrophy, progressive supranuclear palsy (Steele-Richardson-Olzewski syndrome), and essential tremor. Although the neuropsychological features in parkinsonian syndromes probably lack the specificity and sensitivity to be of differential diagnostic utility, the neurobehavioral differences observed among groups of patients with various disorders can guide diagnostic hypotheses and inform about the plural neurobehavioral roles of the basal ganglia.

Neuropsychology, Behavioral Neurology, and Neuropsychiatry

Sir William Osler first used the term neuropsychology in 1913; however, neuropsychology, at least as a clinical endeavor, did not emerge as a subdiscipline of psychology until the 1940s, largely in response to demands for the assessment and rehabilitation of brain-injured soldiers in World War II (1). Neuropsychology shares with behavioral neurology and neuropsychiatry the goal of relating behavior to underlying brain structure and function, but it differs from its two sister disciplines in several dimensions (2). Neuropsychology's principal clinical method, namely its standardized, quantitative, norm-referenced approach to the evaluation of cognition and behavior, is perhaps the characteristic that most clearly distinguishes it from behavioral neurology and neuropsychiatry.

Common Approaches to Neuropsychological Evaluation

Neuropsychological assessment approaches fall broadly into three categories: (1) the *fixed battery* (or cognitive-metric) approach; (2) the *process* (or hypothesis-testing) approach; and (3) the *flexible battery* approach. These approaches can readily be conceptualized as differing along two dimensions: test selection and administration/interpretation. Test selection may be fixed or flexible; administration and interpretation are characterized, respectively, as standardized and actuarial at one extreme, and as nonstandardized and qualitative at the other extreme. Each approach has strengths and weaknesses (see Table 1).

The *fixed battery* approach falls at the extremes of fixed test selection, standardized administration, and actuarial interpretation. It is best exemplified by the Halstead-Reitan Battery (HRB) (3). The *process*, or hypothesis-testing, approach emphasizes qualitative aspects of neuropsychological functions that are founded in developmental and cognitive psychology. Champions of the process approach, most notably Edith Kaplan, promote "testing the limits" with patients and assessing the component processes of cognition rather than relying exclusively upon

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TABLE 1 Advantages and Disadvantages of Three Major Approaches to Neuropsychological Assessment

	Fixed	Flexible	Process
Comprehensiveness	−	+/−	+
Ease of administration	+	−	−
Compatibility with research database	+	−	−
Ease of training technical personnel	+	−	−
Cost	−	+	+/−
Time required	−	+	+/−
Information about cognitive mechanisms underlying impairment	−	+	+
Normative data	+/−	+/−	+/−
Ease of incorporating new technical developments	−	+	+
Information redundancy	+	−	−
Comparability of scores across tests	+/−	+/−	−

+, advantage/strength; −, disadvantage/weakness; +/−, test battery dependent.

summary scores. In other words, the process approach sees as critical "how" a task is solved and how the solution unfolds over time, rather than the achievement score quantifying the quality of the end-product.

Although the fixed battery and process approaches dominated neuropsychology initially, the *flexible battery* has recently emerged as the most commonly used approach to neuropsychological evaluation (4). Flexible batteries benefit from the strengths of the fixed battery and process approaches by striving to quantify the qualitative aspects of cognition and task performance (5). In this way, the flexible battery approach capitalizes on advances in cognitive neuroscience while remaining firmly grounded in psychometric theory. In addition, the flexible battery approach incorporates a standard battery of tests from which the clinician can tailor his or her evaluation to address particular clients needs and explore given domains of function in greater detail as desired. Many clinicians, in the tradition of Benton, will utilize a small fixed battery and then elaborate this battery depending upon the referral question, the patient's ability to cooperate with certain tasks, patient and family concerns, and presenting diagnoses.

The particular components and length of a neuropsychological evaluation will vary across clinical settings, but typically include the following:

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- A clinical interview and review of records to ascertain relevant biopsychosocial background information
- Informal observations regarding patient behavior, cognition, and affect
- The administration of psychometric tests to measure intelligence, attention and executive functions, language, learning and memory, visuospatial perception, praxis, motor and sensory-perception, mood state, quality of life, and personality/coping variables (see Table 2 for a sample of tests and the domains of functioning they evaluate)
- An integration of findings and recommendations into oral and/or written feedback that is provided to the patient, family, and healthcare providers

THE ROLE OF NEUROPSYCHOLOGY IN THE MANAGEMENT OF PARKINSON'S DISEASE

Neuropsychology provides an important contribution to the management of patients with PD. A neuropsychological evaluation delineates the nature and extent of cognitive changes, if any, and a profile of relative neuropsychological strengths and weaknesses. Such knowledge is helpful in:

- The determination of the most probable etiology of mild and new-onset cognitive changes
- Development and formulation of strategies or treatments to ameliorate the impact of cognitive deficits on functioning
- Guidance of the patient and family in making and requesting adaptive changes in the patient's home, leisure, and work environments that enhance functioning and minimize handicap
- Decision making about the appropriateness of medical and neurosurgical interventions for a patient;

ASSESSMENT OF COMPETENCE TO CONSENT TO TREATMENT

Financial, Legal, and Placement Planning

Given the noteworthy prevalence of cognitive and behavioral changes in PD, every patient would, in ideal circumstances, receive a baseline evaluation when first diagnosed with PD. Such a baseline neuropsychological evaluation would facilitate the accurate detection and diagnosis of subsequent neurobehavioral changes and permit the evaluation of treatment effects. This, however, occurs rarely and probably reflects cost-effectiveness issues in a managed care environment, and the reluctance of many patients, and some physicians, to contemplate in the early disease stages the threat of

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TABLE 2 Commonly Used Neuropsychological Tests by Cognitive Domain Assessed

Cognitive domain	Test
Premorbid Estimates	Barona Demographic Equations; North American Adult Reading Test (NAART); Wechsler Test of Adult Reading (WTAR); Wide Range Achievement Test (WRAT)
Neuropsychological screening	Mattis Dementia Rating Scale (DRS); Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
Intelligence	Kaufman Brief Intelligence Test (KBIT); Raven's Progressive Matrices; Wechsler Abbreviated Scale of Intelligence (WASI); Wechsler Adult Intelligence Scale (WAIS)
Attention and working memory	Auditory Consonant Trigrams (ACT); Brief Test of Attention (BTA); Continuous Performance Tests (CPT); Digit and Visual Spans; Paced Auditory Serial Addition Test (PASAT); Stroop Test
Executive function	Cognitive Estimation Test (CET); Delis-Kaplan Executive Function Scale (DKEFS); Halstead Category Test; Trailmaking Test (TMT)[a]; Wisconsin Card Sorting Test (WCST)
Memory	Benton Visual Retention Test (BVRT-R); California Verbal Learning Test (CVLT); Rey Auditory Verbal Learning Test (RAVLT); Rey Complex Figure Test (RCFT)[a]; Wechsler Memory Scale (WMS)[a]
Language	Boston Naming Test (BNT); Controlled Oral Word Association Test (COWAT); Sentence Repetition; Token Test; Complex Ideational Material
Visuoperception	Benton Facial Recognition Test; Benton Judgment of Line Orientation (JLO); Hooper Visual Organization Test (VOT)
Motor and sensory perception	Finger Tapping[a]; Grooved Pegboard[a]; Hand Dynamometer[a]; Sensory-Perceptual Examination
Mood state and personality	Beck Anxiety Inventory (BAI); Beck Depression Inventory (BDI); Hamilton Depression Scale (HDS); Minnesota Multiphasic Personality Inventory (MMPI); Profile of Mood States (POMS); State-Trait Anxiety Inventory (STAI)
Quality of life, coping, and stressors	Parkinson's Disease Questionnaire (PDQ); Coping Responses Inventory (CRI); Ways of Coping Questionnaire; Life Stressors and Social Resources Inventory (LISRES)

[a] Test may not be appropriate for patients with marked motor impairment.
Source: Adapted from Ref. 96.

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later, possibly significant, cognitive compromise. In the absence of an early baseline evaluation, a neuropsychological evaluation in the context of cognitive morbidity relies on less accurate, probabilistic estimation of premorbid functioning to detect and estimate the extent of impairments.

Accordingly, if a full evaluation is not indicated or cannot be achieved soon after diagnosis, a cognitive screening should be contemplated as an alternative. Such screening can be readily achieved in the neurologist's office using the Mattis Dementia Rating Scale (DRS) (6) or comparable instruments. Likewise, the administration of brief self-report measures of mood state and quality of life [e.g., the Beck Depression (7) and Anxiety Inventories (8) and Parkinson's Disease Questionnaire 8-item short form (9)], are invaluable in screening for mood disturbance and the extent to which treatments impact quality of life. Affective disturbances are crucial to screen for on a regular basis considering the high prevalence of anxiety and depression in patients with PD (10) and the high likelihood of these entities going undiagnosed in routine neurologic practice (11). The optimization of quality of life, from the patient's perspective, facilitates a patient–physician collaboration and treatment adherence.

A more comprehensive neuropsychological evaluation that supplements screening should be strongly considered under the following circumstances:

- If the patient, caregiver, and/or clinician suspect changes in the patient's ability to carry out fundamental and/or instrumental activities of living that are unlikely to be related to motor dysfunction.
- If there is concern regarding a possible evolving dementia related to depression, PD, Alzheimer's disease (AD), or any other medical and/or psychiatric condition.
- If the neurologist suspects that brief cognitive screening tests [e.g., the Mini Mental State Exam (12)] are not sufficiently sensitive to detect possible changes in cognitive functions; indeed, screening measures designed to detect cognitive decline in AD are typically poorly sensitive to mild subcortical dementias as often seen in PD (13).
- If the patient is being considered for surgical treatment of PD. In fact, recently published guidelines emphasize the need for neuropsychological evaluation in this regard (14). Such evaluation facilitates patient selection and provides a baseline against which to evaluate potential post-surgical neurobehavioral changes and their implications.
- If a patient experiences difficulties at work likely unrelated to motor symptoms and signs.

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- When issues and questions arise regarding a person's competence to manage financial affairs, prepare an advanced directive or living will, or consent to treatment (15).
- When questions arise about the most appropriate environment for the continued care of the patient.
- When patient and/or family report that the patient experiences emotional changes and/or is withdrawing from social roles, to determine whether this is associated with cognitive changes.
- Once a patient has experienced delirium or hallucinosis, given that such phenomena may be harbingers of dementia (16).

Prior to making a referral for neuropsychological evaluation, it is important to determine whether neuropsychological evaluation is appropriate to address the specific question the clinician or patient might have. Of equal importance is that the referring clinician carefully articulates the referral question, which allows the neuropsychologist to tailor evaluative procedures accordingly, and that the neuropsychologist clearly communicates findings and their possible implications to the referring clinician, patient, and family, while specifically addressing the referral question.

NEUROPSYCHOLOGICAL FINDINGS IN PARKINSON'S DISEASE

James Parkinson (17) contended that patients with shaking palsy did not exhibit significant intellectual changes; however, by the late 1800s, investigators had begun to recognize the presence of cognitive deficits in patients with PD (18). Mild neuropsychological changes are now widely accepted to occur in early PD; such changes are evident in about 20% of persons with PD (19) and most often include deficient information-processing speed, visuospatial abilities, verbal fluency, recall, and frontal/executive functions (20,21). The neuropsychological dysfunction associated with early PD is hypothesized to reflect nigrostriatal dopamine (DA) depletion and the resultant disruption of frontal-subcortical pathways. More pronounced cognitive dysfunction is evident only later in the disease and is probably attributable to neurochemical changes extending beyond the dopaminergic systems (22–24), in addition to structural neuropathology. The dementia (prevalence of about 30%), or perhaps more accurately dementias, observed in PD probably reflect diverse neuropathological entities. At autopsy, dementia in clinically diagnosed PD most often reveals AD or Lewy body dementia (LBD) pathology or some combination of pathologies associated with these two conditions. Consequently, although dementia in PD generally conforms neurobehaviorally to a "subcortical

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dementia'' profile early in its course, the dementia in PD is neuropsychologically heterogeneous across individuals and, almost invariably, later in its course has both cortical and subcortical features. Nonetheless, many cognitive features of early dementia in PD represent an exacerbation of the cognitive changes observable in PD without dementia.

Neuropsychological Dysfunction in Parkinson's Disease Without Dementia

In reviewing the PD literature, Lieberman (25) reported that approximately 19% (range 17–53%) of treated and untreated PD patients without dementia demonstrate cognitive dysfunction. Unfortunately, few of the studies reviewed reported formal criteria for determining what did or did not constitute dementia, thus making it difficult to determine whether patients were in the early stages of dementia. When present in early PD, cognitive dysfunction is typically mild and most commonly involves bradyphrenia (a slowness of thought) and subtle deficits in executive functions, recall, and/or visuoperceptual/spatial functions (26).

Attention and Executive Functions

Attention and executive deficits in PD are most often ascribed to frontal lobe dysfunction secondary to striato-frontal deafferentation and, in particular, pathophysiological alterations in the basal ganglionic-dorsolateral frontal loops (with medial nigral dopamine depletion impacting the caudate and its frontal projections) (27). Performance on simple tasks of attention, for example, forward digit span, is most often preserved in patients with PD (28). On the other hand, deficits on tasks requiring complex attention, planning, reasoning, abstraction, conceptualization, and cognitive flexibility are more readily identified in PD. Deficits are most apparent on tasks that require spontaneous, self-directed information-processing strategy formulation and deployment (29). Executive dysfunction may account for some of the deficits observed on recall, verbal fluency, and visuoperceptual tasks (30), but it is unlikely that executive deficits alone can explain the range of cognitive changes observable in PD (31,32).

Language

Hypophonia and dysarthria sometimes characterize speech in patients with PD. As compared to patients with AD, aphasia and paraphasic errors are rarely observed in PD, though production and comprehension of complex syntax may be reduced on occasion (33–35). Comprehension of written material and writing (limited by motor impairments) are also relatively preserved in PD. More common are deficits on verbal fluency tasks

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requiring, within time constraints, the oral generation of words belonging to semantic categories or beginning with certain letters of the alphabet (36,37). Verbal fluency decrements are not universally observed in PD but, when present, probably reflect deficient use of word-retrieval strategies such as clustering and/or switching (37), meaning grouping of words by component sound or category, and moving efficiently between sounds and categories.

Learning and Memory

Deficits in memory are not a characteristic of PD. Patients with PD display difficulty retrieving newly learned information from memory stores, as indicated by mild impairments in free recall, but relatively intact recognition and cued recall (38). Patients with PD may also show an increased reliance on serial encoding (recalling words in the order they are presented) and reduced semantic encoding (recalling words according to their semantic category) (39). Although retrieval and semantic encoding deficits are evident in group studies of PD, there is diversity in memory profiles of individual patients with PD (40). Remote memory is generally preserved in early PD (41). Findings regarding performance on measures of nondeclarative memory, which refers to ''knowing how'' and is a form of remembering that can be expressed only through the performance of task operations, appear to be task-dependent (42). Thus, impairments in the learning of new motor, perceptual, and cognitive skills may or may not be evident (43–46), while priming is typically intact (44,47).

Visuospatial Perception

Visuoperceptual impairments are thought to occur in early PD, even when motoric task demands are minimized (48,49); however, some argue that visuoperceptual impairments are secondary to deficits in set-shifting, spatial memory, bradyphrenia, and dexterity (30,50). Visuospatial impairments do not appear to improve with dopamine replacement and do not reliably vary with motor ''on'' and ''off'' periods. Thus, if dopamine impacts visuoperceptual abnormalities in PD, it is probably in conjunction with other neurochemical or pathophysiological processes (51).

Neuropsychological Dysfunction in Parkinson's Disease with Dementia

The annual incidence of clinically diagnosed dementia in PD (PDD) is about 3% for individuals younger than 60 years and 15% or less for those 80 years and older (52,53). Estimates of PDD prevalence vary between 9% and 93%, depending on which diagnostic criteria, ascertainment methods, and sampling methods are implemented (20), but most commonly range from

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30 to 50%. Dementia is very rarely present early in the disease course; moreover, dementia that precedes or accompanies the evolution of motor symptoms should raise concern that the dementia might be related to factors other than PD, for example AD, LBD, or depression. Indeed, recent consensus criteria and recommendations (54) propose that the clinical diagnostic term "PD with dementia" be reserved for individuals who have a clinical diagnosis of PD and have had only motor symptoms for at least 12 months (admittedly an arbitrary period) before developing fluctuating cognition and other neuropsychiatric symptoms such as hallucinations. When the neuropsychiatric presentation precedes any extrapyramidal signs, the differential diagnoses include LBD, AD, and vascular dementia. Whether PDD and LBD turn out to be neuropathologically distinct entities remains to be resolved, as does the issue of whether PDD and LBD are neuropsychologically distinct.

Dementia in PD, like other dementias, involves multiple cognitive impairments and a related decline in day-to-day functioning. Cummings's (55) categorization of dementia as "cortical" and "subcortical" on the basis of neurobehavioral features has been criticized on neuroanatomical grounds, but nevertheless remains a useful clinical heuristic. While recent work suggests that the cognitive profile of dementia in PD is likely heterogeneous (perhaps reflecting variability in neuropathological findings) at the group level, the neuropsychological deficits evident in PDD resemble those of the "subcortical" dementias. Perhaps the most striking features of the "subcortical" dementias, including PDD, are bradyphrenia, memory-retrieval deficits, executive dysfunction, diminished spontaneity, and depression. Features of the "cortical" dementias such as AD (e.g., aphasia, agnosia, and apraxia) are typically absent in PDD, often even later in the course of dementia.

Attention and Executive Functions

Performance on more complex attentional tasks—i.e., those that require the self-allocation of attentional resources, divided attention, and selective attention—is impaired in PDD (56,57). As the disease progresses, patients with PDD may show difficulty even on those attentional tasks in which external cues are provided (58).

Executive functions are tied to frontal-striatal-thalamic circuit integrity, especially to the dorsolateral circuit (59). Frontal lobe dysfunction in PDD most likely stems from nigrostriatal dopaminergic deficits (60) resulting in a striato-cortical deafferentation effect, although cholinergic dysfunction secondary to neuronal loss in the septal and basal nuclei likely also plays a role in executive dysfunction (61). Executive deficits are particularly evident on tasks that require patients to develop, deploy, and

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maintain efficient information-processing strategies. It has been hypothesized that the basal ganglia and frontal-subcortical circuits function as a subcognitive, internal navigational system that limit PDD patients' available options for efficient problem solving (60,62).

Poor performance on tasks that require coordination of complex mental and motor functions (e.g., operation of an automobile) may be conditioned by visuospatial deficits leading to the defective planning and execution of strategies to accomplish a task (e.g., turning a corner while walking or driving) (63).

Language

Verbal fluency findings in PDD are inconsistent. In general, patients with PDD are impaired comparably to patients with AD on lexical and semantic verbal fluency tasks (64), and in some cases verbal fluency deficits may be even more severe in PDD (24). Impairment in visual confrontation naming, most often measured by the Boston Naming Test, is less pronounced in PDD than in AD, if present at all (65).

Memory

Memory deficits are evident in PDD, although the profile of memory impairment in PDD is both qualitatively and quantitatively different than is observed in patients with AD. As in patients with PD, the memory deficit in early PDD is typically characterized by deficits in retrieval, rather than consolidation. That is, patients with early PDD are sufficiently able to retain information over time, but show deficits in retrieving the information from memory in free recall trials, i.e., without the aid of recognition or cueing. As the dementia becomes more severe, patients with PDD display broader memory deficits, including deficient encoding and consolidation that is comparable to patients with AD (16). While remote memory is typically intact early in PDD, deficits in this area become increasingly evident as the dementia progresses (49,66). However, the remote memory impairment is milder in PDD than in AD. Also, in contrast to AD, in which more remote memories are relatively preserved, PDD affects recall of the various decades of a patient's life similarly (67). In contrast to nondemented patients with PD, patients with PDD typically perform poorly on most nondeclarative memory tasks (44).

Visuoperceptual Functions

Impaired visuospatial and visuoconstructive functions have been found consistently in PDD relative to nondemented patients and healthy controls, even when tasks minimize or eliminate motor demands (68–70). Findings from studies comparing the visuoperceptual abilities of PD and AD groups

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are not conclusive. However, it appears that patients with LBD show more prominent visuoconstructional and visuospatial deficits than do patients with AD (71,72).

Affect and Emotion

In contrast to AD, depression is much more frequent in PDD. In fact, the presence of depression is often considered an important distinguishing feature between subcortical and cortical dementia syndromes.

Depression has been found to exacerbate cognitive dysfunction in PD, an issue discussed in greater detail below. Patients with PDD and LBD, in particular, experience hallucinations more commonly than do patients with AD (73).

Risk Factors for Dementia in Parkinson's Disease

Various demographic and disease variables predict dementia in PD (see Table 3). More recent work suggests that neuropsychological evaluation may also facilitate early identification of PDD. Jacobs et al. (74) and Mahieux et al. (75) noted that poorer performance by patients with PD on verbal fluency, attentional, and visuospatial tasks was associated with subsequent development of dementia. Woods and Tröster (76) found that nondemented PD patients who met criteria for dementia at one-year follow-up evaluation demonstrated poorer baseline performance on measures of word list learning and recognition, complex auditory attention, and executive function relative to PD patients who did not develop a dementia.

IMPACT OF DEPRESSION AND ANXIETY ON COGNITION IN PARKINSON'S DISEASE

Affective disturbances such as anxiety and depression are common in patients with PD. What follows is a review of findings concerning the impact of affective symptoms on neuropsychological functions in PD.

TABLE 3 Risk Factors for Dementia in Parkinson's Disease

Demographic variables	Disease variables	Neurobehavioral variables
Greater age	Later onset	Depression
Lower education	Disease duration	Diminished cognitive test performance:
Lower socioeconomic status	Disease severity	Executive/attention
Family history of Parkinson's dementia	Susceptibility to levodopa-induced psychosis or confusion	Verbal fluency
		Visuoperceptual
		List learning

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Depression

Symptoms of depression are commonly observed in patients with PD. Prevalence rates for depression in PD range from 7 to 90% (although 40% is the most frequently cited estimate). Approximately one half of PD patients become depressed at some point during the disease course (77), with about half of these patients developing minor depression, while the other half develops major depression. Depression is a known risk factor for PD and PD-related dementia (52,78) and has been shown to adversely impact functional ability (79,80) and accelerate the progression of cognitive decline in PD (81,82).

Depression in PD is unique in that, unlike in other neurodegenerative conditions such as AD, it significantly affects cognition (83). Executive functions and memory are foremost among the neuropsychological abilities impaired by depression (84–86). The negative impact of depression on cognition is more readily evident in the latter stages of PD, and depression must be of at least moderate severity before it markedly impacts cognition (87,88).

In light of depression's detrimental effect on cognition, an important clinical question with treatment implications is whether cognitive and/or functional decline in PD is a dementia due to neurodegeneration or due to depression. Little literature addresses the incidence and prevalence of dementia due to depression in PD and whether dementia in patients with comorbid depression improves with treatment and resolution of depressive symptomatology (89). Etiological inferences about an individual PD patient's dementia, when the dementia is accompanied by marked depression, should probably be deferred until such time as the depression has been adequately treated and neuropsychological revaluation has been performed. Recent attention has also been drawn to the need to distinguish depression from apathy in PD (90). Apathy may occur in as many as 45% of patients with PD and, like depression, may be associated with executive deficits (91).

Anxiety

Anxiety disorders are seen in approximately 40% of patients with PD (92). Despite their frequent occurrence and contribution to morbidity and caregiver burden (10), anxiety symptoms in PD have received relatively little attention, perhaps because they overlap with symptoms of depression and medication effects and are thus difficult to measure (93). The relationship between anxiety and cognition in PD has received virtually no attention. Ryder et al. (94) found that self-reported symptoms of anxiety, but not

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depression, were related to cognitive functioning in a small sample of male patients with PD. Self-reported trait anxiety was negatively related to performance on a neuropsychological screening battery, accounting for approximately 70% of the variance. The authors posit that anxiety may partly explain the association between depression and cognition in PD, although replication of their findings and additional large-scale studies are needed.

EFFECT OF PHARMACOLOGICAL AND SURGICAL TREATMENTS ON COGNITIVE FUNCTIONS IN PARKINSON'S DISEASE

Modern treatment algorithms for patients with PD consist of both pharmacological and surgical intervention strategies (95). Neuropsychological evaluation can facilitate objective measurement of cognitive, neurobehavioral, emotional, and quality-of-life outcomes associated with treatment as well as aid in determinations regarding treatment (96).

Pharmacological Treatments

Anticholinergics and Cholinesterase Inhibitors

Anticholinergic medications used to treat motor symptoms in PD potentially produce adverse effects on memory, executive functions, as well as global cognitive abilities. In placebo-controlled studies, Bedard and colleagues found anticholinergics to induce executive deficits in PD but not in control participants (97,98). Although anticholinergic-induced memory decrements are observable even in patients without preexisting cognitive impairments (99), Saint-Cyr (100) found that confusional states are more likely to be induced by anticholinergics in patients with preexisting cognitive impairment. Thus, anticholinergics should be avoided in elderly patients who are susceptible to developing confusional states (101).

Cholinesterase inhibitors were initially used sparingly and rarely in PDD and LBD. There is increasing recognition that cholinesterase inhibitors such as rivastigmine may improve not only cognition, but also neuropsychiatric symptoms in both conditions, and that these agents are well tolerated by patients with PD (102,103).

Levodopa and Dopamine Agonists

Findings concerning the impact of levodopa on cognitive functions are inconsistent, with studies showing improvement, decrements, and an

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absence of significant cognitive changes associated with levodopa therapy or its withdrawal (104). Despite these inconsistent findings, evidence is accumulating that levodopa has short-term effects on certain aspects of memory and executive functions, perhaps as mediated by disease stage. For example, Kulisevsky and colleagues (105) reported short-term improvements in learning and memory, visuoperception, and certain executive functions associated with dopamine-replacement therapies but stated that these cognitive improvements were not maintained over time. Relatedly, Owen et al. (106) found that only certain aspects of executive functioning (i.e., planning accuracy) were improved with levodopa therapy early in the disease, whereas other aspects (response latency) remained relatively unaffected. That levodopa affects only certain components of cognitive functions is consistent with the findings of Fournet and colleagues (107), who reported poorer performance only on working memory tasks in patients with PD after withdrawal from levodopa, and of Lange et al. (108), who also found that levodopa withdrawal impacted performance on only a minority of executive function measures. Levodopa's rather selective effects on working memory and certain executive functions may be related to its mediation of dorsolateral frontal cortex blood flow in response to executive task activation (109).

Selegiline

Selegiline, a selective monoamine oxidase-B inhibitor, has been hypothesized to exert a neuroprotective effect in PD by way of reducing physiological stress associated with MAO-B oxidation of dopamine. Along with improvement in motor functions, several small, uncontrolled studies have found selegiline to be associated with improved global cognitive functioning, P300 latencies, and/or memory in patients with PD (110–113). In contrast, selegiline was reported not to significantly impact cognition in a large sample of untreated patients with early PD (114).

Surgical Interventions

Ablative Surgeries

Ablative surgical interventions for treatment of PD involve stereotactic procedures in which lesions are placed in the globus pallidus, thalamus, or subthalamic nucleus to reduce motor symptoms. Cognitive and emotional outcomes after ablative procedures for PD in the 1950s and 1960s are sparsely documented. Wilkinson and Tröster (115) pointed out that outcomes in early and more recent studies are difficult to compare for a

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variety of reasons. In general, however, modern studies reveal that ablative procedures such as pallidotomy, thalamotomy, and subthalamotomy (especially unilateral) are relatively safe from a cognitive perspective.

With regard to unilateral pallidotomy, declines in verbal fluency performance have been reported in approximately 75% of outcome studies that included a measure of verbal fluency (48,116–118). Postoperative decrements on measures of attention, memory, and executive functions (typically mild and transient) have been reported occasionally, and significant cognitive complications even more rarely (for review, see Refs. 119, 120). Preexisting cognitive impairment, advanced age, and dominant hemisphere surgery have been proposed as increasing the risk for postoperative cognitive decline.

Few formal neuropsychological studies of bilateral pallidotomy have been undertaken, despite the observation that the most frequent adverse events among such patients are declines in speech and cognition (120). Remarkably, despite their small number, these studies yield inconsistent findings. While some suggest that cognitive declines after bilateral pallidotomy may be limited in scope and severity (121,122) or, indeed, that some gains in memory might be observed (123), others report marked morbidity (124,125).

Although early studies examining outcomes after thalamotomy reported decrements in language and memory with regularity (see Ref. 96 for review), modern thalamotomy is associated with minimal risk of cognitive morbidity (126,127). Initial reports of the apparent cognitive safety of subthalamotomy (128,129) remain to be confirmed by larger, controlled studies.

Deep Brain Stimulation

Nonablative surgical procedures for the treatment of PD involve either unilateral or bilateral implantation of high-frequency stimulation electrodes into deep brain nuclei. Studies detailing neuropsychological outcomes after unilateral pallidal (GPi) deep brain stimulation (DBS) have supported the neurobehavioral safety of this technique (see Refs. 96, 130 for reviews), although a few studies have demonstrated minor postoperative declines in verbal fluency (131–133). The majority of studies indicate that even bilateral GPi stimulation is cognitively well tolerated (134–136), although in isolated cases cognitive declines can occur (125,137).

There remain few studies evaluating cognitive outcomes after thalamic DBS, but preliminary findings suggest that this procedure is associated with minimal cognitive morbidity soon after (138,139) and up to one year after surgery (140). Indeed, subtle and limited cognitive improvements might be witnessed after thalamic DBS.

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The majority of DBS procedures now target the subthalamic nucleus (STN). Modest decrements in verbal fluency are the most commonly reported adverse cognitive sequelae associated with STN DBS. Findings regarding possible postoperative declines and/or improvements in global cognitive abilities, memory, attention, and executive functions are inconsistent (see Refs. 96, 141 for reviews). When considered in the context of the considerable benefits of surgery on motor functions, mood state, and quality of life (142), the cost of possible minor and/or transient cognitive declines in a minority of well-selected patients seems to be overshadowed by the benefits. Preliminary evidence indicates that elderly patients (>69 years), as well as those patients displaying presurgical cognitive deficits, might be at greater risk for neurobehavioral morbidity after STN DBS.

Transplantation

Fetal mesencephalic tissue transplantation studies have indicated variability in neurocognitive outcomes among individual patients, but given small sample sizes, the source of variability is difficult to identify (see Ref. 96 for review).

NEUROPSYCHOLOGICAL ASPECTS OF PARKINSON-PLUS SYNDROMES AND ESSENTIAL TREMOR

"Parkinson-plus syndromes" traditionally include progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal ganglionic degeneration (CBGD). Although sparse, preliminary neuropsychological studies indicate that the cognitive impairment profiles likely differ across the parkinson-plus syndromes (see Ref. 143 for review). A summary of key differences is presented in Table 4.

Progressive Supranuclear Palsy

Prevalence rates of dementia in PSP range between 50 and 80%, although some authors contend that these numbers reflect overdiagnosis due to bradyphrenia, emotional problems, and visual dysfunction that accompany PSP. Cognitive deficits are seen in approximately 50% of patients with PSP (143), with the neuropsychological profile in PSP being typical of diseases with subcortical involvement, including slowed information processing, executive dysfunction, and information-retrieval deficits (144). As compared to patients with PD, cognitive slowing and executive dysfunction in PSP emerge earlier in the disease course, are more severe, and progress more rapidly (145–148), and this differential executive dysfunction may reflect radiographically demonstrated differences in frontal atrophy between the

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TABLE 4 Comparison of Neurobehavioral Features of Parkinson's Disease with Dementia (PDD), Lewy Body Dementia (LBD), Corticobasal Ganglionic Degeneration (CBGD), Progressive Supranuclear Palsy (PSP), and Multiple System Atrophy (MSA)

	PDD	LBD	CBGD	PSP	MSA
Attention	-	—	-	-	—
Executive (e.g., problem solving, conceptualization, planning, flexibility)	—	—	-	—	0/-
Language					
Letter fluency	—	—	-	-/—	-
Category Fluency	—	—	-	-	-
Visual confrontation naming	0/-	-/—	0/-	0	0
Memory for new information					
Recall	—	-/—	0/-	0/-	0/-
Recognition	0/-	-	0	0	0
Memory for old information	-	?	?	0	0
Praxis	0/-	0/-	—	0/-	0
Alien-hand sign	0	0	-/—	0	0
Visuoperceptual/ constructional functions	-	—	-	-	-
Depression	—	—	-	0/-	0/-
Apathy	-	-	-	—	—
Fluctuating cognition	0/-	—	0	0	0

0, impairment absent; -, mild to moderate impairment; —, moderate to severe impairment.

two conditions (149). Executive dysfunction in PSP may also differ qualitatively from that in PD (150). Memory and attention are relatively intact in PSP, although retrieval deficits and accelerated rates of forgetting may be present (151,152). The early presence of cognitive impairment distinguishes PSP from MSA (153).

Multiple System Atrophies

The MSA nomenclature includes several different diseases, including olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND), and Shy-Drager syndrome (SDS). Cognitive deficits are relatively mild in most forms of MSA, and dementia is not a common feature of these conditions (154), except perhaps in OPCA, in which 40–60% of patients may develop dementia, with dementia prevalence greater in familial forms of the

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disease (155). Mild executive and memory deficits have been reported in MSA (SND and SDS) (156) but are considered to be of similar severity to those observed in nondemented patients with PD (147,157). Patients with MSA may show more pronounced attentional impairments and longer reaction times than patients with PD (157,158).

Corticobasal Ganglionic Degeneration

The prevalence of cognitive impairment and/or dementia in CBGD is not established. Neuropsychological functions appear to be relatively preserved in the early stages of CBGD (at least within an average of 5 years of diagnosis (159), with dementia emerging as a more common feature later in the disease course (160). While the neuropsychological profile of CBGD reveals both cortical and subcortical features (161), it is possible to differentiate CBGD from AD and PSP at the group level (147,162). The neuropsychological profile associated with CBGD is marked by significant executive dysfunction, which is comparable in severity to PSP, but relatively milder than is observed in patients with AD. Also evident in CBGD is asymmetric apraxia (not evident in PSP or AD), alien-hand sign (not reported in PSP or AD), impairment in motor programming and speed (similar to PSP but unlike AD), attentional dysfunction, and deficits in verbal fluency (comparable to AD). Memory impairment in CBGD is characterized by deficient retrieval—a finding comparable to PSP, but qualitatively and quantitatively different from AD, which is more likely to be marked by deficient consolidation and retention of information over time. Recall on remote memory tests is impaired, but unlike in AD, recognition is intact (163).

Essential Tremor

Recent findings raise the possibility that patients with essential tremor (ET) may display deficits in complex attention, verbal fluency, and executive functions, perhaps related to disruption of cerebello-thalamo-cortical circuits (164–167). Although the neuropsychological dysfunctions of ET and PD overlap, those in PD are more widespread.

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