

Early Cognitive Changes and Nondementing Behavioral Abnormalities in Parkinson's Disease

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Despite a large number of studies in the literature that examine neuropsychologic deficits in Parkinson's disease (PD), relatively few studies have specifically addressed the issue of early cognitive changes. Most studies examine heterogeneous PD samples, in which disease duration, age, motor symptom severity, and treatment regimens vary. Studying patients in the earlier stages of the disease provides important insights into discrete cognitive changes associated with selective basal ganglia dysfunction (1). Furthermore, the potentially confounding factors that exist in the advanced stages of the disease, such as medication side effects, global cognitive impairment, and severe motor symptoms, are less likely to be prominent.

A definition of "early PD" is controversial because short disease duration and mild disease severity each represent an early stage of the disorder. For the purpose of this chapter, early PD is defined as a recent-onset disease (five years' duration or less) or as symptom severity at Hoehn and Yahr stages I and II. Studies that combine patients with early PD and patients with more advanced PD are not reviewed in this chapter unless patients with earlier PD can be examined as a separate group.

CLINICAL CORRELATES OF COGNITIVE DECLINE

Dementia, as defined by *The Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria, is rare in early PD; mild cognitive changes are more prevalent but remain

the subject of controversy. One problem is that cognition in PD cannot be studied independently from other clinical parameters that influence the type and pattern of cognitive change. These clinical correlates include age and age of onset, motor symptom severity, side of onset, and medication effects.

Age and Age of Onset

Early-onset PD was once believed to produce more severe clinical symptoms (2,3), but other well-controlled studies comparing the effects of early (<50 years) and later (>70 years) age of onset now indicate that the opposite may be true: Compared with younger patients with PD, older patients exhibit a higher incidence of cognitive impairment and overall dementia and a more rapid course of disease progression. First described by Celesia and Wanamaker (4), these findings have subsequently been observed by other investigators (5), including those using standardized neuropsychological tests (6-10).

Some studies have been criticized for examining subjects at only one point in time, thus bypassing the question of whether the older subjects were nondemented in their younger years and deteriorated with advancing age. Longitudinal studies have now documented a similar outcome associated with advanced age. Biggins et al. (11) conducted serial assessments of cognition, mood, and motor symptomatology at 9-month intervals on 87 patients with PD and 50 control subjects. Initially, 6% of the patients with PD were demented (based on DSM-III-R), but 54 months

later, the cumulative incidence of dementia among the patients with PD was 19%, whereas none of the control subjects were demented. Biggins et al. found that patients with PD who became demented were older, had PD longer, and had an older age of onset. In a prospective cohort study of 250 patients with PD, Stern et al. (12) found advanced age to be one of the antecedent risk factors for dementia. Locascio et al. (13) also reported select cognitive deficits that appeared earlier in the disease for patients with late-onset PD. More recently, Marras et al. (5) reviewed a series of studies to identify predictors of prognosis in PD and found, with only one exception, older age at onset to be an adverse prognostic factor associated with rapid decline.

Medication Effects

Consensus regarding the effect of pharmacologic treatment on cognition in PD patients is lacking. Levodopa treatment has been shown to result in improved performance on tasks of delayed verbal memory (14), choice reaction time (15), and attention (16) but may interfere with other tasks associated with frontal lobe functions (17). Still other studies find modest effects on cognitive function and psychiatric status (18) or report an initial improvement on levodopa in overall cognitive functioning that gradually reverts to baseline performance levels (19–21).

A similar lack of consensus exists regarding the effects of anticholinergic treatment on memory function in PD, with some studies showing impaired recent and recognition memory (22–24), whereas others find no evidence of memory deterioration (25).

The lack of consistency between these studies is attributable to a host of factors that prevent interstudy comparisons. These factors include differing drugs, dosages, modes of administration, and length of treatment. Other methodologic confounds include lack of consistency in the type of method used to assess each of the cognitive domains, and differences between subjects' ages, disease durations, and disease severities.

Few studies have examined the effects of pharmacologic treatment in the early stages of PD. Canavan (26) found that anticholinergic

medication did not disrupt either associative learning performance or conceptual set shifting in early PD. Levin et al. (25) compared four groups of patients with early PD ($n = 54$) on two verbal memory measures and one visuospatial recognition task. Subjects were either unmedicated, taking anticholinergics or dopamine alone, or taking a combination of these drugs. No significant differences were observed between the four groups on any of the memory measures.

Cooper et al. (27) tested 82 patients with newly diagnosed PD, who had never received drug therapy, with a full battery of neuropsychological measures. Subjects were then randomly assigned to one of three monotherapy treatment groups—levodopa, bromocriptine, or anticholinergic drugs—and retested approximately 4 months later. The investigators found that although levodopa and anticholinergic medication improved motor control, their effects on cognitive function differed. Anticholinergic medication impaired short-term memory, specifically the registration of new information, whereas dopaminergic medication improved performance scores on a working memory task. Although the study by Cooper et al. underscores the importance of controlling for treatment variables, it is also clear that for some patients with PD, medication may exert a highly selective influence on cognitive performance early in the illness.

Motor Symptoms and Side of Onset

Studies of cognitive function and cardinal motor signs in patients with PD reveal several consistent trends. Prominent tremor is associated with normal or near normal mental status, whereas bradykinesia and rigidity correlate with a wide range of intellectual deficits. Furthermore, it is now recognized that the side of motor onset may influence cognitive outcome (5,28,29). Tomer et al. (30) compared 48 subjects with right-sided motor onset with 40 patients whose motor signs began on the left side of the body. The left-sided onset group performed consistently more poorly than the right-sided onset group on multiple neuropsychological measures, including immediate and delayed verbal memory, word retrieval, semantic verbal fluency, visuospatial analysis,

abstract reasoning, attention span, and mental tracking. These findings imply that cognitive deterioration is linked to an asymmetric disturbance of dopamine pathways, which are established early in the early process.

Language

The degree to which language is affected in PD is difficult to evaluate, because many tasks require competency in nonlinguistic abilities, such as attention, memory, and executive function (31). Nevertheless, there is general consensus that frank aphasias are not part of the parkinsonian symptom complex. There are, however, several studies that find subtle qualitative differences in the higher-order linguistic tasks during the early stages of the illness.

Lees and Smith (32) found that patients with early PD gave a higher number of perseverative intrusions compared to age-matched controls on a word fluency task. The authors interpreted this finding as evidence that patients with PD experience difficulty in shifting between categories under time constraints. Illes (33) analyzed spontaneous language production in five patients with mild PD as defined by Websters' rating scale. Although syntax was intact, they noted the presence of silent hesitations at the beginning of sentences, a finding interpreted as evidence of difficulty in planning upcoming linguistic sequences. In addition, they found an elevated number of open class optional phrases and postulated that this may be an adaptive strategy in generating as much information as possible in a single sentence.

Levin et al. (34) found that patients with early PD did not differ from age-matched and education-matched control subjects on fund of vocabulary, word retrieval, and two measures of verbal fluency. However, these patients performed one of the categoric fluency measures and the recitation of months backwards significantly worse than controls did.

Grossman et al. (35) examined sentence comprehension and praxis in 22 patients with early PD who were receiving either minimal or no antiparkinsonian medication. They found that patients with PD, compared with control subjects, exhibited significantly more difficulty

answering syntactically embedded questions. Patients with PD also exhibited compromised ability to perform learned gestures, according to measures of representational and nonrepresentational praxis. The investigators noted that substitution of a body part for the object was a common error type on representational praxis items. Other studies, such as Lees and Smith (32), did not find evidence of apraxia in the early stages of PD.

Cooper et al. (36) studied 60 nondemented patients, newly diagnosed with PD, who had never received pharmacologic therapy for their disease. These patients were compared with 40 healthy control subjects of comparable age, sex, and premorbid IQ based on the New Adult Reading Test (NART) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) vocabulary. Patients were rigorously screened for other medical and psychiatric conditions, alcoholism, and head injury. The investigators examined word retrieval (Boston Naming Test), expressive language (Reporter's Test), comprehension (Token Test), and semantic fluency (inanimate objects, animals category alternation using colors and birds). The only differences noted between the two groups were in language expression, object word fluency, and the category alternation tasks, in which patients with PD showed mild deficits compared with controls.

These studies support other research on individuals with more advanced stages of the disease, indicating that language ability is largely preserved in PD. No study to date that has employed a comprehensive test battery has found a pervasive language disturbance. When language impairments are found, they are highly circumscribed, subtle, and may involve organizational or fluency skills. Thus, the question arises whether these deficits represent a specific language impairment or are symptoms of a more generalized executive disturbance involving frontal systems.

Visuospatial Skills

Visuospatial abnormalities are among the most common and the most controversial neuropsychological deficits reported in PD. Conceptual and methodologic questions make this area of research a subject of ongoing controversy. A

major problem is that researchers do not agree on the definition of visuospatial deficit. Most studies rely on a particular task to define the construct. As a result, the label "visuospatial deficit" has been applied to patients with PD who have difficulty in any one of a number of spatial tasks including facial recognition, visual analysis and synthesis, visual discrimination, visual recognition, spatial memory, personal space, spatial planning, visuomotor integration, visual attention, and visual orientation (37).

Another problem is how visuospatial abnormalities are assessed. Many visuospatial tasks, particularly those used in earlier studies, are timed and require adept manual dexterity to reach a successful solution. Only recently have investigators employed tasks that are motorfree and untimed, two factors that allow visuospatial deficits to be studied independently from the motor abnormalities associated with the disease.

Very few studies have focused on visuospatial skills in the early stage of PD. Canavan et al. (38) administered three visuospatial tasks to patients with early PD, patients with focal frontal or temporal lobe lesions, and healthy age-matched controls. Their measures included a spatial delayed alternation task, a street plan test of left-right orientation, and a prism adaptation task. They found that three groups of patients, those with PD, frontal lobe lesions, and postoperative right temporal lobectomy, required significantly more trials to reach the criterion on the prism adaptation task than either the healthy controls or patients who had undergone left temporal lobectomy. Interestingly, patients with PD who had predominantly left-sided parkinsonian signs (right basal ganglia pathology) performed worse on this measure than patients with PD who had either bilateral or predominantly right-sided motor symptomatology. No group differences were observed on the other visual-spatial measures.

Montgomery et al. (39) compared 24 mildly impaired (stages I and II) and 24 moderately impaired (stage III) patients with PD with 35 age-matched control subjects on judgment of line orientation and a spatial updating task. The spatial updating task required subjects to maintain their sense of direction after being moved in their

environment while relying on either visual or vestibular sensory information. In the visual condition, subjects were moved in a wheelchair while wearing a headbox that permitted a view of the walls and ceiling but not the floor. In the vestibular condition, subjects were guided through the same route but were blindfolded, leaving only vestibular and somatosensory input. The authors found that difficulty with the visual condition of the spatial updating task correlated with poor performance in judging line orientation, a finding that they interpreted as evidence for mild visual perceptual problems in select patients with early PD.

Cooper et al. (36) found that patients with early PD showed visuomotor constructive deficits when copying a complex geometric figure (Rey Osterrieth Complex Figure) but performed normally on a visuoconstructive task using a three-dimensional model.

Levin et al. (40) administered six visuospatial measures to 184 patients with PD of varying duration and to 90 control subjects matched by age and education. The visuospatial battery consisted of facial recognition (Benton's Facial Recognition Task), line orientation (Judgment of Line Orientation), mental object assembly (a modified version of the Hooper Visual Organization Task), verbal embedded figures (Ghent Embedded Figures), nonverbal embedded figures, and a modified block design test (only 2×2 matrix designs were included). The group with early PD ($n = 84$; disease duration = 1.0-4.0 years) performed as well as control subjects on all of the visuospatial measures except facial recognition. However, Dujardin (41) found deficits in decoding emotional facial expressions in a group of patients with early PD who had not been treated with antiparkinsonian medication.

Although impaired visuospatial skills are commonly found in PD and appear to be independent of motor abnormalities associated with the disease, it is unclear how prominent these changes are in the early stages of the disease. Prism adaptation, recognition of embedded facial figures, copying complex geometric designs, and spatial updating require active planning and strategy as well as a host of other skills, which are not necessarily unique to spatial cognition. It is possible

that the earliest visuospatial changes reflect an executive dysfunction and not a true visuospatial deficit *per se*. This view is compatible with the view that visuospatial deficits in the earliest stages of PD emerge when tasks involve set shifting, another aspect of executive function (42,43).

MEMORY

Memory impairment has been found in the early stages of PD and appears to be independent of dementia. Taylor et al. (44) compared 15 newly diagnosed, untreated patients with PD and 15 healthy control subjects matched by age and verbal IQ. Multiple memory skills were assessed, including short-term and delayed recall of logical discourse and semantically related word lists, recognition span for spatial position, incremental verbal list learning of unrelated words, priming effects, and source memory.

Patients with PD performed comparably with control subjects on immediate and delayed recall of logical discourse and semantically unrelated words, and on delayed recognition of spatial position. However, important differences emerged between the two groups in their spontaneous organization of the stimuli. Patients with PD were consistently worse than control subjects in their recall of semantically related words [California Verbal Learning Test (CVLT)] and used clustering, a strategy presumed to facilitate learning, less often and less efficiently on the five immediate recall conditions. Patients with PD also exhibited deficient source memory, relative to control subjects, and increased sensitivity to interference effects during learning. Taylor et al. interpreted these findings as evidence that recall difficulties among patients with PD result from a basic planning deficit, stemming from frontostriatal dysfunction, that interferes with the acquisition of novel stimuli.

Cooper et al. (45) found that patients with newly diagnosed PD were more impaired than age- and sex-matched controls on backward digit span, immediate and delayed recall of the logical memory passages, and paired associate learning. These investigators also used the Brown-Peterson Distractor Task, a paradigm that assesses patients' ability to recall consonant trigrams after varying

distractor-filled intervals. Patients with PD performed as well as control subjects on the immediate recall condition (no distractor) but performed more poorly on each of the five different distractor-filled intervals. Fischer et al. (46) studied recency and primacy recognition in patients with early PD and healthy control subjects, matched by age, education, and sex, using a modified version of Milner's temporal ordering task. Of the 29 patients in their sample, 23 were in stages I and II. Subjects were presented with 22 black-and-white line drawings and were then asked to indicate the first (primacy) and last (recency) picture from four choices. Patients with PD had more difficulty recalling the recency items than healthy control subjects did. More recent research supports these initial findings. Stoffers (47) found deficits in sequential visuospatial memory, and Pillon et al. (48) reported deficient memory for spatial location in patients with early PD who had not been treated with antiparkinsonian medication.

The issue of memory impairment in PD is complicated, because memory is composed of a diverse group of skills that may be functionally distinct and do not necessarily deteriorate in a uniform fashion. Therefore, what is called "memory impairment" may involve one or more individual deficits, each of which may show a different rate of decline. Yet, despite what appears to be a heterogeneous collection of deficits, much of the research shares a common theme: Early memory dysfunction may stem from a more generalized executive deficit that is not specific to a particular stimulus modality but disrupts the memorization process. Difficulties with anticipation, planning, sequencing, and organization would lead to problems attending to and maintaining information, making it difficult to process and recall stimuli. More recent research points to a problem in working memory, a term first proposed by Fuster (49) to describe the executive process by which the subject holds information on-line for the purpose of maintaining an active representation to guide later action. Fuster proposed that working memory depends on the integrity of the prefrontal cortex. Goldman-Rakic (50), who proposed an experimental model linking working memory to the prefrontal cortex, suggested that this model might

explain some of the cognitive impairments in nonfocal pathologies such as PD.

Executive Functions

There has been a recent surge of interest in executive function deficits associated with PD. Executive functions are an integral part of many cognitive tasks, because they include anticipation, planning, goal selection, monitoring, and using feedback to guide behavior (51). Executive deficits are believed to reflect frontal lobe dysfunction. Early cognitive dysfunction has been linked to executive deficits associated with frontostriatal disturbance. Canavan et al. (52) compared patients with PD and patients who had frontal lobe lesions. Patients with early PD (symptom range, 6–86 months) were compared with healthy control subjects, and with patients who had documented lesions involving either the frontal or temporal lobes, in their ability to reproduce sequences of digits, spatial positions, and hand gestures. The group with PD performed comparably to control subjects on all of the sequencing tasks. Only subjects with frontal lobe lesions and right (but not left) temporal lobectomies showed select performance deficits on motor sequencing and the span tasks.

Canavan (26) also compared the same patient groups on two conditional associative learning tasks, a visual motor task requiring subjects to learn associations between six colors and six movements of a handle, and a visual-visual task requiring subjects to learn associations between color and shapes. The authors also administered the Wisconsin Card Sorting Task (WCST), a set shifting task based on three categoric sorting rules. No differences were noted between patients with PD and age-matched controls on any of the associative learning tasks. Although patients with PD did not differ from control subjects in the number of categories achieved on the WCST, they made more perseverative errors. An important observation noted in this study was that whereas most patients with PD showed no impairments on the learning tasks, an older subset of patients with PD performed consistently poorly on most measures. This finding supports

other studies, such as that by Dubois et al. (10), who found that age has a negative effect on cognition in patients with PD.

Downes et al. (53) reported that patients with both early, nonmedicated and more advanced, medicated PD performed more poorly than healthy control subjects on a discriminative learning task that involved an extradimensional shift. These researchers did not find that patients with PD were more perseverative, nor did they find evidence of a more basic defect in arousal functions. Rather, they argued that patients with early PD have a highly specific attentional dysfunction, characterized by problems ignoring irrelevant stimulus dimensions, that leads to an unpredictable response set and ultimately an increase in errors.

Owen et al. (54) studied 44 patients with idiopathic PD, 15 of whom were nonmedicated (13 in stages I and II; 2 in stage III) and 29 of whom were medicated and had PD that was either mild to moderate ($n = 15$) or severe ($n = 14$). Medicated patients were screened for dementia and depression. The three PD groups were compared with three groups of healthy control subjects, matched by age and premorbid IQ using the NART. Subjects were given a battery of computerized tests sensitive to frontal lobe functions, which included a modified Tower of London test to assess planning performance and an attentional set-shifting task. The set-shifting task required subjects to discern, based on computerized feedback, which of two stimulus dimensions was relevant. On the Tower of London task, the nonmedicated patients with PD were no different from control subjects in terms of their accuracy and initial thinking time. However, all PD groups had difficulty with the attentional set shifting. These subjects not only had impaired set shifting but difficulty formulating and maintaining the correct response set.

Cooper et al. (36) administered several measures of executive function, including the WCST, timed and untimed Picture Arrangement, and a digit-ordering task. On the WCST, the group with PD did not differ from the control group on the number of categories achieved, overall correct responses, "other" or unique errors, percentage of conceptual responses, or ability to maintain set.

However, patients with PD did require significantly more cards to achieve the first category and performed more poorly on Picture Arrangement and digit ordering. The investigators also found that patients with PD and depression made more qualitative errors on Picture Arrangement and scored fewer categories and made more errors on the WCST than nondepressed patients with PD did.

In sum, executive deficits have been repeatedly found in early PD. Because many cognitive tasks rely on one or more executive components, it would follow that patients with PD, even in the earliest stages, may show impairments in a variety of cognitive areas.

Cognitive Processing Time

Although bradykinesia has been extensively studied in PD, whether patients with PD also require longer processing time when solving cognitive tasks remains unknown. Disentangling these two components is difficult, because many cognitive measures use a motor component. Two studies have specifically examined cognitive processing speed in patients with early PD. Zimmermann et al. (55) studied simple and choice reaction time in 10 untreated patients with early PD (duration of illness, 3–24 months), 9 patients with more advanced PD (duration, 2–12 years), and 17 healthy control subjects matched by age, sex, education, and IQ. Three reaction-time tasks were employed, one involving a simple motor response, and two others (choice reaction time) that presented cues requiring different degrees of cognitive processing to complete the task. In all groups, reaction time increased as cognitive load increased. Untreated patients with PD responded similarly to control subjects on the simple and choice reaction-time tasks when cognitive loading was either absent or low.

However, the patients with early PD performed more slowly than control subjects and comparably to medicated patients with PD in the length of decision-making time required for choice reaction-time tasks that incorporated the highest cognitive loading. These findings suggest that decision-making processing is compromised early in PD when cognitive demands are high.

Jordan et al. (56) investigated the extent to which attentional focusing and temporal predictability could explain prolonged response time in patients with PD. These authors compared 32 patients with newly diagnosed PD, 34 patients with PD who were taking medication, and 24 healthy control subjects on two simple reaction-time measures. Both groups with PD showed evidence of increased reaction time on each reaction-time measure but demonstrated normal effects of variable cue stimulus intervals. They hypothesized that the prolonged response time in early PD may be nondopaminergic in origin.

SPECIAL SENSORY CHANGES: OLFACTION AND CONTRAST SENSITIVITY

Loss of olfactory function in PD patients was first noted in 1980 by Korten and Meulstee (57). Although standardized testing was not performed, they reported that 41 of 80 patients with PD under their care were "unable to smell adequately."

Doty et al. (58,59) reported that olfactory dysfunction occurs early in the course of PD and is independent of stage, disease duration, and other cognitive and neurologic manifestations of the illness. They (60) examined 81 patients, of whom 43 were in stage I or II. Although patients with early PD were not studied separately, 75% of the patients showed less sensitivity than control subjects on a threshold detection measure. When patients were given the University of Pennsylvania Smell Identification Test (UPSIT), 90% of the group with PD scored lower than control subjects. No differences were noted between sides of the nose, indicating odor dysfunction was symmetric.

Olfaction deficits in PD may be secondary to use of antiparkinsonian medication. However, Doty et al. (60) compared medicated and unmedicated patients with early PD, all of whom were in stages I and II (except for one subject who was in stage III), and found olfaction deficits in both groups.

Contrast sensitivity deficits are another special sensory change that has been reported in patients with early PD. This deficit is of particular interest to investigators employing behavioral measures

that examine the ability to detect varying degrees of luminance. Bulens et al. (61) studied 39 patients with PD, all but three of whom were in stage I and II, and found that 64% showed contrast sensitivity loss in one or both eyes. Abnormal contrast sensitivity curves were not related to disease severity or visual acuity.

DEPRESSION

The association between depression and PD was recognized in 1817 by Parkinson (62) in his original essay. Although many descriptive reports of depression in PD followed, only relatively recently have changes in mood been systematically assessed using standardized rating scales and structured interviews based on DSM-III criteria. These studies indicate that depression is prevalent in PD, affecting between 30% and 50% of patients and may, even in patients with early PD, exacerbate cognitive deficits (63). Two subtypes have been noted: major depression (moderate to severe symptoms) and dysthymia (mild symptoms). Most patients with PD exhibit a mild to moderate chronic depressed mood. Severe depression in patients with PD is uncommon. A third category that is beginning to receive recognition is subsyndromal depression, a milder form that does not meet strict DSM-IV criteria but is characterized by depression symptoms. Estimates of depressed mood likely are substantially higher when subsyndromal depression is taken into account (64).

The repeated observation that symptoms of depression frequently begin before the onset of PD motor symptoms is especially striking. Mayeux et al. (65) did not specifically examine early PD, but noted that 43% of depressed patients with PD exhibited evidence of depression before their motor symptoms appeared. Santamaria et al. (66) carried out a structured interview based on DSM-III criteria for depression and administered the Beck Depression Inventory (BDI) to 34 patients with early PD (duration between 0.5 and 4 years) and 23 healthy control subjects of comparable age and sex. They reported that patients with PD showed a higher frequency of dysthymia ($n = 10$) and major depression ($n = 1$) compared with control subjects ($n = 4$). For 15 patients (44%), the first episode of

depression began 1.5 to 36 years before the onset of motor symptoms. This subgroup of patients tended to be younger at PD onset and exhibited less severe parkinsonism. No relationship was observed between depression (BDI scores) and disease severity or duration.

Depression in PD may in part be related to asymmetric hemispheric involvement. Starkstein et al. (67) found a relationship between depression and lateralization of PD motor symptoms. When left hemiparkinsonism (LHP) patients were compared with right hemiparkinsonism (RHP) patients, the RHP group showed a higher incidence of depression and scored higher on three depression indices, the Hamilton Rating Scale for Depression, the BDI, and the Present State Examination (PSE).

Depression may be related to the stage of PD. Cummings (68) found that young patients with PD in the early stages of their disease might be more vulnerable to depression than older patients with PD. However, Starkstein et al. (69) found that depression was disproportionately represented in the early and later stages, but for different reasons: Whereas early PD depression may be associated with structural and biochemical changes associated with left basal ganglia pathology, later PD-related depression may arise from progressive deterioration and impairment in activities of daily living (ADLs).

HYPOTHESIS REGARDING NEUROCHEMICAL CORRELATES OF COGNITIVE DECLINE

There is general consensus that parkinsonian symptoms begin after approximately 80% of dopaminergic neurons have been depleted. The mesocortical dopamine system is believed to be less depleted than the nigrostriatal dopamine projections (70). Lewis et al. (71) used event-related functional magnetic resonance imaging (fMRI) to compare cognitively impaired and unimpaired patients with early PD and found a significant signal reduction in the striatal and frontal lobe regions among patients with working memory deficits.

Although degeneration of dopaminergic pathways is believed to be directly related to cognitive

decline, some evidence indicates that the pathophysiology may be more complex. The array of neuropsychologic deficits, even in the earliest stages of the disease, likely cannot be explained by a decline in any one neurotransmitter system. Clinicopathologic correlations are usually obtained from individuals in more advanced stages of the disease. Currently, animal studies provide the best model of early PD, but these data may be limited in their generalizability to human subjects.

In addition to the predominant dopamine deficiency, there are also other alterations in the ascending noradrenergic system, selective and perhaps sporadic serotonergic involvement in the raphe nuclei, and various changes in neuropeptidergic systems. Particular attention has been focused on the locus ceruleus pathology that is seen in PD and that disrupts the cerulocortical noradrenergic systems, resulting in decreased norepinephrine concentrations in the amygdala, hippocampus, and frontal cortex. Although the functions of the cerulocortical pathway are not understood, selective lesions of the locus caeruleus have been reported to produce attentional and memory impairment (72). Furthermore, involvement of serotonergic-raphé neurons in patients with PD has been related to depression and possibly cognitive dysfunction in some patients (73). Cholinergic dysfunction, which may begin quite early in PD patients, also may contribute to cognitive impairment (74).

SUMMARY

Early cognitive changes in patients with PD are often subtle and influenced by factors that interact with the disease process, including age of disease onset, medication, and the specific constellation of motor symptoms.

These factors notwithstanding, ample evidence exists that specific cognitive changes occur early in the course of PD. This evidence does not imply that cognitive deficits are pervasive during the early stages. To the contrary, they are usually subtle and often difficult to detect without formal neuropsychological testing. Executive-function deficits are the most frequently reported cognitive problems and, given that executive skills are an integral part of many tasks, it follows that subtle

difficulties may be seen on a wide range of cognitive measures, particularly in working memory and visuospatial dysfunction, two areas that rely heavily on executive skills. Whereas apraxia and language processing deficits occur infrequently, subtle changes in olfaction and contrast sensitivity have also been repeatedly observed. Finally, depressive symptoms are also common in the early stages of the disease. The significance of the early behavioral changes and their prognostic implications are largely unknown. Prospective studies are needed to understand the longitudinal course of early cognitive changes to determine whether they remain as circumscribed impairments or represent a precursor to a more widespread dementia.

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