

## Clinical Diagnostic Criteria for Dementia Associated with Parkinson's Disease

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**Abstract:** Dementia has been increasingly more recognized to be a common feature in patients with Parkinson's disease (PD), especially in old age. Specific criteria for the clinical diagnosis of dementia associated with PD (PD-D), however, have been lacking. A Task Force, organized by the Movement Disorder Study, was charged with the development of clinical diagnostic criteria for PD-D. The Task Force members were assigned to sub-committees and performed a systematic review of the literature, based on pre-defined selection criteria, in order to identify the epidemiological, clinical, auxiliary, and pathological features of PD-D. Clinical diagnostic criteria were then developed based on these findings and group consensus. The incidence of dementia in PD is increased up to six times,

point-prevalence is close to 30%, older age and akinetic-rigid form are associated with higher risk. PD-D is characterized by impairment in attention, memory, executive and visuo-spatial functions, behavioral symptoms such as affective changes, hallucinations, and apathy are frequent. There are no specific ancillary investigations for the diagnosis; the main pathological correlate is Lewy body-type degeneration in cerebral cortex and limbic structures. Based on the characteristic features associated with this condition, clinical diagnostic criteria for probable and possible PD-D are proposed. © 2007 Movement Disorder Society

**Key words:** Parkinson's disease; dementia; Parkinson's disease dementia; diagnosis; diagnostic criteria.

Historically, Parkinson's disease (PD) has been considered largely as a motor disorder. It has been increasingly recognized, however, that PD is frequently associated with cognitive deficits, and that dementia eventually develops in a substantial number of patients. Currently there are no specific and operationalized criteria to diagnose dementia associated with PD (PD-D). The existing criteria in DSM IV subsume PD-D under "dementia due to other medical conditions", and the section specifically devoted to PD-D is rather descriptive. As potential therapeutic approaches for PD-D become available and clinical trials are underway, it is important to establish specific and operationalized diagnostic criteria for PD-D in order to include homogenous groups of patients in these trials. This would also help to prospectively determine the natural history and other characteristics of this condition in a more systematic way and would allow more accurate clinico-pathological correlation studies.

The Movement Disorder Society (MDS) recruited a Task Force to define the clinical diagnostic criteria for PD-D. This article summarizes the process and conclusions of this effort.

## METHODS

### The Task Force Composition and Procedure

The MDS Task Force comprised 23 members with different areas of expertise in the field. They were invited to join the Task Force because of their interest and track records in diverse aspects of the disease including epidemiology, clinical aspects, ancillary methods, and pathology, and representing various disciplines to include neurology, geriatric psychiatry, neuropsychology, and pathology as well as different geographical regions with differing medical traditions. The group was divided into five sub-committees, each in charge of systematically reviewing the literature related to epidemiology, cogni-

tive and neuropsychiatric features, motor and other clinical features, ancillary examinations, and clinico-pathological correlations, based on pre-defined criteria for selection of publications to be included (Appendix). To exclude cases with Dementia with Lewy Bodies (DLB), those papers which used the 1-year rule with regard to the onset of dementia were grouped together and constituted the primary source, whereas those which did not use the 1-year rule or did not indicate if this rule was applied were considered as secondary. Findings and typical features emerging from these reviews, described in detail later, were tabulated (Table 1) and used to describe consensus-based definitions of probable and possible PD-D (Table 2).

### Relation of PD-D to DLB

DLB and PD-D share many pathological and clinical features, and probably represent two clinical entities on a spectrum of Lewy body disease.<sup>1</sup> While the time-course of the symptoms and presenting features primarily differentiate these disorders, there are also pathological differences such as different patterns of Lewy body distribution. Indeed, there is no rational clinical or pathological basis to dictate a definite time interval between development of motor symptoms versus onset of dementia in differentiating PD-D from DLB. Nevertheless, based on an empirical approach and to avoid diagnostic confusion in clinical practice, we recommend that a diagnosis of PD-D should be made when dementia develops within the context of established PD, whereas a diagnosis of DLB is appropriate when the diagnosis of dementia precedes or coincides within 1 year of the development of motor symptoms. This recommendation is operationally consistent with that described in the Third Report of the DLB Consortium<sup>2</sup>: "DLB should be diagnosed when dementia occurs before or concurrently

with parkinsonism, and PD-D should be used to describe dementia that occurs in the context of well-established PD. The appropriate term will depend upon the clinical situation and generic terms such as Lewy Body disease are often helpful. In research studies in which distinction is made between DLB and PD-D, the 1-year rule between the onset of dementia and parkinsonism for DLB should be used.”

### EPIDEMIOLOGY

The epidemiology of PD-D has usually been studied among hospital-based populations. Few door-to-door studies have reported the prevalence or, in particular, incidence, of PD-D in the general population, and the methodology for identifying PD-D patients has varied. Most studies are cross-sectional, providing an estimate of the proportion of PD patients who are demented (point prevalence). For several reasons, including the higher mortality rate in PD-D versus non-demented PD subjects,<sup>3</sup> more accurate information can be drawn from the few longitudinal studies. These provide information on the incidence of PD-D, while studies including a control group can also deduce the relative risk of developing dementia in PD versus non-PD subjects. In addition, period prevalence, i.e. the proportion of demented patients in a PD cohort during a specified time, by combining prevalence, incidence and mortality rates, provides important information concerning the total proportion of PD patients who will eventually develop dementia.

#### Point Prevalence

Wide variations of the proportion of PD patients with dementia have been reported, which is most likely due to variations in methods including the population studied, age structure, diagnostic criteria for PD, assessment of cognition, and definition of dementia.

In a review of 27 studies representing 4,336 patients with PD, Cummings<sup>4</sup> found a mean prevalence of 40%. Although the studies were critically considered, most studies were based on patients referred to neurology clinics and may not be representative of unselected PD populations. In addition, at that time, studies did not include the identification and exclusion of patients with DLB.

In the first systematic review of the prevalence of dementia in PD employing strict methodological inclusion and exclusion criteria, 13 studies with a total of 1,832 patients were included. Of these 575 were diagnosed with dementia, yielding a prevalence of 31.5% (95% confidence interval 29.3–33.5). This review also included 24 studies focusing on dementia populations,

and found that 3 to 4% of dementia cases in the general population were due to PD-D. The estimated prevalence of PD-D in the general population aged 65 and over was found to be 0.2 to 0.5%.<sup>5</sup> In more recent studies, prevalence rates of dementia in PD patients of 48%,<sup>6</sup> 23%,<sup>7</sup> and 22%<sup>8</sup> were reported. The Rotterdam study, based on a door-to-door survey, found a lower prevalence rate, though this pattern is typical of such methodology which usually includes a larger proportion of mildly affected cases, when compared with clinic-based studies.<sup>8</sup>

A few studies have focused on the prevalence of dementia in newly diagnosed PD patients. In the Sydney study, prevalence of dementia was 16%.<sup>9</sup> Recent population-based studies have reported rates of 8%<sup>10</sup> and 17%<sup>11</sup> of “marked cognitive impairment” defined as a Mini-Mental State Examination score below 24.

#### Incidence

In community based studies, incidence rates of 95.3,<sup>12</sup> 107.1,<sup>13</sup> and 112.5,<sup>14</sup> in 1,000 patient-years were reported, indicating that ~10% of a PD population will develop dementia per year. The reported relative risk for developing dementia in PD compared to non-PD subjects ranges from 1.7,<sup>14</sup> to 4.7,<sup>8</sup> 5.1,<sup>6</sup> and 5.9.<sup>12</sup> There are several reasons for this variation, such as case selection procedures and the use of different estimates of risk. In one of the very few incidence studies of dementia in general including subjects with PD (diagnosis based on self-report), the odds ratio for dementia in PD was 3.5.<sup>15</sup>

#### Period (Cumulative) Prevalence

Since the mortality is higher among demented than non-demented subjects, point-prevalence is an underestimate, and period prevalence provides more reliable figures. Compared to an incidence cohort, a prevalence cohort is usually older and has a higher proportion with dementia.

Only one study to date has prospectively followed newly diagnosed PD patients to assess the frequency of dementia. After 3 and 5 years, 26 and 28% were demented.<sup>9</sup> After 15 years, 48% of the evaluated patients had dementia, a further 36% evidence of mild cognitive impairment, and only 15% remained without evidence of cognitive impairment.<sup>16</sup> In an earlier study with follow-up over 8 to 10 years, 70% of the patients showed a “significant deterioration of cognitive functions” and “approximately half of these were evaluated as clinically demented.”<sup>17</sup> In the only study providing period-prevalence rates based on a strictly epidemiological cohort, 8-year cumulative prevalence of dementia was reported to be 78%.<sup>18</sup>

The mean duration from onset of PD to development of dementia was reported to be ~10 years,<sup>18,19</sup> there are, however, wide variations. Some patients develop cognitive impairment and subsequent dementia within few years after onset of PD, whereas others may develop dementia 20 or more years after disease onset.<sup>20</sup> The type and extent of pathology may vary in patients with early versus late onset dementia.<sup>21</sup> Age is a crucial factor, and dementia is infrequent in patients with young onset and who are chronologically still young at the time of assessment, despite very long disease duration.<sup>22</sup>

### Risk Factors

Many demographic and clinical features have been assessed as potential risk factors, with inconsistent findings. The most consistent risk factors in longitudinal studies were higher age, more severe parkinsonism, in particular rigidity, postural instability and gait disturbance, and mild cognitive impairment at baseline. Age and severity of motor symptoms seem to have a combined rather than additive effect on the risk of dementia.<sup>23</sup> Inconsistent findings have been reported for old age at onset, male gender, education, depression, visual hallucinations, and other clinical features. A recent study found that age at onset does not influence the risk for dementia after adjusting for age.<sup>20</sup> A significant relationship between drug use and risk for dementia has not been convincingly demonstrated. The effect of genetic disposition as a risk factor is discussed in "Genetic Aspects of PD-D."

### Conclusions From Epidemiological Studies

The point prevalence of dementia in PD is close to 30% and the incidence rate is increased 4 to 6 times as compared to controls. The cumulative prevalence has been reported to range between 48 and 78% after 15 and 8 years of follow-up, respectively. The main risk variables are higher age, more severe parkinsonism, in particular rigidity, postural instability and gait disturbance, and mild cognitive impairment at baseline.

## THE COGNITIVE AND NEUROPSYCHIATRIC PROFILE OF PATIENTS WITH PD-D

### Onset and Time Course

Mild cognitive impairment was found already at the time of diagnosis in some patients in an incident cohort of PD.<sup>10</sup> There is some evidence that dementia is merely a progression of this early cognitive impairment,<sup>24</sup> while other evidence suggests a different profile in PD-D and non-demented PD patients.<sup>25</sup> Epidemiological studies suggest that dementia usually develops years after the

onset of motor symptoms. This could be a methodological bias however, since patients with early dementia may be excluded due to subjects not fulfilling PD criteria.

The onset is insidious. In one prospective study, the mean annual decline on the MMSE during 4 years was 1 point in non-demented and 2.3 points in the PD-D group, the latter figure being similar to the decline observed in patients with AD.<sup>26</sup> A similar rate of decline was reported in another longitudinal study, mean decline in MMSE over 2 years was 4.5, and comparable to that seen in patients with DLB, with a mean decline of 3.9 points.<sup>27</sup>

### Cognitive Features

The majority of studies on cognitive function in patients with PD have reported on non-demented patients or on non-selected groups including those with dementia. A wide variety of cognitive impairments have been reported, even early in the course of the disease, including memory, visuospatial function, and executive function.<sup>28-33</sup> Although the latter deficits are often described as dominating the cognitive profile, there is some evidence of heterogeneity, with some patients expressing an amnesic profile, while others present with a predominantly dysexecutive or mixed profile.<sup>32</sup> There is some indication from prospective studies that executive deficits may be the more important predictors of subsequent decline.<sup>34,35</sup> However, the relationship between initial deficits and subsequent profile of dementia has not been clearly established. Therefore, this review was restricted to studies that report explicitly on cognitive function in groups of PD patients with dementia. Most studies included patients with mild or moderate dementia, with little published evidence on the cognitive manifestations of more severe PD-D. Unless clearly stated, the evidence reviewed relates only to the profile of cognitive impairment in mild-moderate PD-D. Comparative studies considered in this review successfully matched dementia groups on the basis of an extended mental status examination (e.g. Dementia Rating Scale [DRS]), or clinical rating of dementia severity.

Most of this review focuses on cognition defined in terms of primary domains. However, some caution must be exercised, as terms such as "attention" and "executive function" has been used interchangeably in different studies. Many neuropsychological tests tap a number of different domains, and patients may perform poorly on a given test for different reasons. Unfortunately, most published studies have not employed tests that permit the underlying cognitive processes to be defined in detail.



### Attention.

Assessment of attention has typically employed composite tasks that confound attention and vigilance with motor speed and working memory, such as the DRS Attention subscale. Deficits on this scale are reliably shown in PD-D, although these tend not to be distinguishable in severity from those in patients with DLB or AD.<sup>36–39</sup> Differential impairments have been found in some studies using other measures. In one, a test involving letter cancellation revealed that PD-D and DLB groups were not only slower than a group with AD, but also showed more errors.<sup>40</sup> Another study employing a composite index of attention also showed a greater deficit in PD-D than AD.<sup>41</sup> Finally, in one of the most detailed investigations, attention was measured in terms of variability in performance over time in a series of reaction time tasks.<sup>42</sup> This showed increased variability in both PD-D and DLB groups relative to controls and patients with AD. Clinically, 29% of the PD-D patients showed evidence of attentional fluctuation compared to 42% of those with DLB. On the basis of these studies, it can be concluded that attention is impaired in PD-D and may fluctuate, more so than in AD.

### Memory.

Memory complaint was reported to be the presenting problem in 67% of patients with PD-D, compared to 94% with DLB and 100% with AD.<sup>40</sup> On the Memory subscale of the DRS significant deficits in mild PD-D have been reported, equivalent to DLB, but less severe than matched groups of patients with AD.<sup>36–39</sup> However, in more severe dementia the severity appears to match that seen in AD.<sup>36</sup>

Studies using more detailed and comprehensive assessments of memory function have produced variable results. Short-term memory has received little attention, although digit span performance, more an attentional test, does not appear to distinguish PD-D and AD.<sup>43</sup> Verbal tests of list learning, paired-associate learning, and story recall all show deficits in PD-D on initial learning and immediate recall that do not differ from those seen in AD<sup>40,43–46</sup> except for selected measures in one study.<sup>38,47</sup> Although delayed free recall has been reported to be more impaired in AD than PD-D,<sup>40,44</sup> other similarly powered studies have failed to confirm this result.<sup>43,45,46</sup>

A common claim is that the memory deficit in PD is one of retrieval, rather than encoding and storage. Evidence for this comes primarily from studies in non-demented patients with PD who tend to show intact recognition memory and enhanced performance when given retrieval cues. However, patients with PD-D also

appear to be impaired on cued recall.<sup>44,48</sup> There is also growing evidence for recognition memory deficits in PD-D for both verbal<sup>40,46,48</sup> and non-verbal<sup>40</sup> material (see<sup>49</sup> for a review). In some studies the recognition deficit in PD-D is less severe than that in AD,<sup>40,44,46</sup> although comparable deficits have been reported on tests of visual recognition memory.<sup>40</sup> However, all of these studies involved patients with predominantly mild-moderate PD-D. Implicit memory has been studied in one study considered for this review, which found no deficit in either PD-D or AD.<sup>45</sup> On the basis of these studies it can be concluded that both verbal and visual memory are impaired in PD-D, that the degree of this impairment is probably less than that seen in AD, and that recognition may be less affected than recall in mild to moderate PD-D.

### Executive Function.

Verbal fluency has been extensively studied in PD-D. It accounts for the major part of the Initiation and Perseveration Scale of the DRS, where impaired performance is typical in patients with PD-D.<sup>36–39</sup> Relative to AD, patients with PD-D may be more impaired on this scale,<sup>36</sup> although other studies have found no significant difference.<sup>37,38,44</sup> In more severe dementia, patients with PD-D, AD, and DLB appear equally impaired.<sup>44</sup> Several other studies have used specific tests of verbal fluency, both phonemic and semantic, with similar results. The severity of the fluency deficit does not appear to differ in AD and PD-D.<sup>37,43,44</sup>

Concept formation has been tested using the “Conceptualization subscale” of the DRS, “Similarities subtest” of the Wechsler Adult Intelligence Scale (WAIS), Raven’s Progressive Matrices (RPM) and Wisconsin Card Sorting Test (WCST). Performance on such measures is impaired in PD-D relative to controls and/or non-demented patients with PD.<sup>36–40,43,50</sup> Compared to patients with AD, similar performance is observed on the DRS subscale in most,<sup>36,39,40,42</sup> but not in all studies.<sup>38</sup> On the WCST patients with PD-D were more impaired in terms of total errors, but not on any other index of performance including number of categories sorted,<sup>50</sup> while greater impairment of PD-D patients on the RPM has been noted.<sup>43</sup> There is no evidence that patients with PD-D are generally more perseverative than patients with AD, at least as measured by WCST.<sup>50</sup> The results of these studies reveal that executive functions are impaired in patients with PD-D, probably more so than in patients with AD. There is also some suggestion that the memory deficits in PD-D may be more closely associated with executive dysfunction than those in AD.<sup>44</sup>

### Construction and Praxis.

Typically, drawing tests are used to assess constructional ability and praxis, either copying designs or drawing common objects. The Clock-Drawing Test (CDT) is markedly impaired in PD-D as evidenced by the baseline data in the large cohort recruited for a clinical trial.<sup>51</sup> A deficit on the same task was identified in a smaller study that failed to distinguish the performance of patients with PD-D, DLB, and AD,<sup>52</sup> although there was evidence that the former two groups showed more “planning” errors in their performance. Other studies using design copying tests all showed impairment in PD-D. These studies have shown either no difference in performance between groups with PD-D and AD,<sup>36–38,40,41,43</sup> or more severe deficits in PD-D,<sup>39,53</sup> particularly with more severe dementia.<sup>36</sup> Comparisons of PD-D and DLB have revealed either no difference<sup>42</sup> or greater deficit in DLB.<sup>40</sup>

Construction/drawing tasks involve significant motor control and a range of cognitive functions. The contribution of motor dysfunction to such deficits has rarely been examined in PD-D. This may account for at least part of the reported performance deficit. In terms of cognitive function, the tasks tap both visuo-perceptual and visuo-spatial processes, and executive processes in terms of planning or response alternation. Little is known about the primary source of the deficits in PD-D in performing such tasks, although one study employing a qualitative assessment of the CDT suggested that PD-D and DLB patients showed more evidence of a planning deficit than a group with AD.<sup>52</sup> Based on these studies, it can be concluded that visuo-spatial construction is impaired in PD-D, probably to a greater extent than that seen in AD.

### Visuo-spatial Function.

The assessment of visuo-spatial function without the demands of fine motor control has received little attention in PD-D. One study used the Raven’s Progressive Matrices test, which involves complex visuo-perceptual/spatial function,<sup>43</sup> and reported the PD-D group to be more impaired than a group with AD. However, the test also requires significant conceptual processing so that at least part of the deficit may have been due to executive problems. In another study, visual perception (as measured by tests of visual discrimination, space-motion, and object-form perception without needing manual responses) was globally more impaired in PD-D than in non-demented controls, but was not different from DLB. Compared to AD, PD-D patients tended to perform worse in all perceptual scores.<sup>54</sup> It is concluded that PD-D is associated with substantial visuo-perceptual impairments similar to DLB, but different from AD.

### Language.

Language function has received little attention in PD-D, perhaps because clinically evident aphasia is rare. In one study, performance on verbal comprehension, naming, and repetition did not show any significant difference between AD and PD-D patients,<sup>40</sup> although a more severe picture naming deficit in AD has been reported.<sup>44</sup> In another study, patients with AD were also found to have significantly more impoverished information content of spontaneous speech, more impaired word list generation, and more severe anomia as compared to those with PD-D, and a stepwise discriminant analysis revealed that 96% of patients were correctly classified on the basis of information content of spontaneous speech (worse in AD) and speech melody (worse in PD-D).<sup>55</sup> Verbal fluency is sometimes included in the language domain, and in this review it is considered as a test of executive function. Based on the little available data, it is suggested that patients with PD-D have less impairment in core language functions as compared to AD.

### The Pattern of Cognitive Impairment Across Domains.

Rather than considering individual domains, additional evidence can be obtained by considering relative performance across domains. In a study by Janvin et al.,<sup>56</sup> the DRS was used to define a “cortical profile” (performance on the Memory subscale relatively worse than that on the Initiation and Perseveration subscale) and a “subcortical profile” with the opposite pattern of relative performance. Both profiles were present in patients with mild-moderate PD-D, as well as in DLB and AD. This may reflect the similar clinical heterogeneity reported in non-demented PD patients.<sup>57</sup> The “cortical” profile predominated in the AD group by a ratio of 2:1 while the opposite was seen in the groups with PD-D and DLB. Only PD-D and DLB patients showed a pattern of severe global impairment in memory and executive function. Another study used pairs of performance indices from a standardized neuropsychological battery.<sup>41</sup> In this case, a “subcortical” score was derived from tests of visuo-spatial function, construction, and attention, and a “cortical” score from language and delayed memory. In the PD-D group, the mean subcortical score was greater than the cortical score, with the opposite pattern for the AD group. Although relatively accurate at distinguishing the groups, the indices also showed significant overlap between the groups and cannot be considered of primary diagnostic significance.

### Conclusions on the Profile of Cognitive Impairment

Impaired cognitive domains in PD-D include attention, memory, visuo-spatial, constructional, and executive functions. There are some phenomenological differences between PD-D and AD, particularly in executive functions, so that a “subcortical” or “dysexecutive” pattern predominates in PD-D, although there are overlaps. These differences are most apparent in the early and middle stages of dementia and difficult to identify in the later stages. Many studies involving a wide range of tests have failed to distinguish between patients with PD-D and AD with certainty. The differentiation between PD-D and DLB in terms of cognitive profile is even less evident. Many of the tests used may be insufficiently sensitive to disentangle alternative mechanisms underpinning impaired performance, such as role of impaired attention in poor memory function as opposed to primary deficits in memory.

Neuropsychological assessment serves an important role in providing objective evidence of cognitive impairment to support the clinical diagnosis of dementia in PD. However, its role in differential diagnosis is not conclusive, at least with the standard tests typically employed in published studies. While indicative profiles can be described on the basis of sets of tests, the evidence is not yet sufficiently robust to use these as the sole basis of diagnosis.

### Behavioral and Neuropsychiatric Symptoms

While formal diagnostic criteria can be applied to elicit symptoms such as depression or anxiety, the majority of clinical features are identified by informant ratings, the most popular one in the assessment of PD-D being the Neuropsychiatric Inventory (NPI).<sup>58</sup> While there is evidence that symptoms often occur in clusters,<sup>59</sup> the organization of this review is based on individual symptoms. The review focused on those symptoms that occur in a significant proportion of PD-D patients, namely, hallucinations, delusions, mood disturbance, and apathy.

### Hallucinations and Delusions.

Hallucinations have been reported as common in both population-based studies of PD (25%)<sup>60,61</sup> and in clinic samples (40%)<sup>62</sup> assessed by NPI, with a substantially higher prevalence in PD-D (45–65%).<sup>62–65</sup> When found in non-demented patients, hallucinations are a major predictor of subsequent dementia,<sup>18</sup> and nursing home placement.<sup>66</sup> In DLB, hallucinations are even more common than in PD-D, with figures in the range of 60 to 80%.<sup>63,67,68</sup> The high prevalence of hallucinations in

PD-D and DLB contrasts with relatively low rates reported in mild-moderate AD (4–8% on NPI).<sup>67,69,70</sup> The significance of hallucinations as marker of Lewy-body pathology has been confirmed by both retrospective and prospective post-mortem studies.<sup>68,71,72</sup>

The phenomenology of hallucinations in PD-D and DLB is very similar. Visual hallucinations occur twice as frequently as auditory ones, the majority being complex, formed hallucinations.<sup>62,63,73</sup> Most common are anonymous people, but they may also be family members, body parts, animals, or machines. They tend to be in color, static and centrally located, and occur with similar frequency and severity in PD-D and DLB.<sup>62,73</sup>

Delusions are less common than hallucinations in PD-D, although the two symptoms often coexist. While occurring in ~17% of patients with PD overall,<sup>60,61</sup> their prevalence in PD-D is 25 to 30%,<sup>63–65</sup> somewhat lower than rates seen in AD,<sup>64,67,70,74</sup> and particularly in DLB where rates of 57 to 78% have been reported.<sup>63,67,74</sup> Another study suggested that when delusions occur they do so with similar frequency over time and severity in DLB and PD-D,<sup>73</sup> and with similar phenomenology. Paranoid delusions and “phantom boarder” are among the most common content in both disorders.<sup>63</sup> Mis-identification syndromes appear to be particularly prevalent in DLB occurring in up to 40% of patients, compared to 10% in AD.<sup>68</sup> Whether mis-identification delusions are also characteristic of PD-D is currently unclear. The prevalence of Capgras delusions is reported to be 10% in DLB, when compared with no cases in patients with PD-D.<sup>63</sup>

### Mood Disturbance.

In a community-based sample applying formal diagnostic criteria, the rate of major depression in PD-D has been reported as 13%, compared to 9% for non-demented patients, and 19% for patients with DLB.<sup>63</sup> Both severity of depressed mood and prevalence of major depression may be higher in PD-D than in AD.<sup>43</sup> However, dysphoric mood as assessed by the NPI occurs with the same frequency in PD-D and AD (40–58%),<sup>64</sup> possibly higher than seen in patients with DLB.<sup>65,74</sup>

Anxious mood occurs at a similar frequency (30–49%) to depressed mood; the two disturbances are frequently co-morbid,<sup>75</sup> or occur in the same symptom cluster.<sup>59,65</sup> The prevalence of anxious mood in PD-D, DLB, and AD appears similar to that of depressed mood.<sup>64,68,70,74,76</sup> Irritable mood and problems with anger and aggression, common in AD, are not prominent clinical features of PD-D, while the frequency in DLB is similar to that seen in AD.<sup>76</sup> Irritability has a prevalence of less than 10% in non-demented patients with PD,<sup>61</sup>

with only a slightly higher rate in PD-D (14%).<sup>64</sup> and tends to be infrequent even in patients who show significant problems in other domains.<sup>59</sup>

Elevated mood is rare in PD-D, being reported as either absent,<sup>43</sup> or occurring in only 2% of the population.<sup>64</sup> A similar picture is reported in DLB,<sup>74</sup> with a somewhat higher rate in AD, although it remains relatively rare.<sup>70,74</sup>

### **Apathy.**

Apathy is often regarded as a hallmark feature of frontotemporal dementia<sup>67</sup> and progressive supranuclear palsy,<sup>61</sup> where frequencies of 80% or more have been reported. Similar rates are also reported in DLB,<sup>67</sup> with increasing severity with worsening dementia.<sup>77</sup> However, apathy is also a significant problem in AD, with frequencies of 50% or more,<sup>64,70,74</sup> increasing with cognitive deterioration.<sup>70</sup> In PD-D, lower figures had been reported with a frequency of 23 to 24%,<sup>64</sup> although a recent study analyzing a large sample of mild-moderate PD-D patients reported a higher figure (54%),<sup>65</sup> compared to 17% in non-demented patients.<sup>61</sup>

### **Conclusions on Behavioral and Neuropsychiatric Features**

Neuropsychiatric symptoms are common in all types of dementia and are of little specific differential diagnostic value. Hallucinations stand out as one of the few features that usefully distinguish between DLB/PD-D and AD. In general, patients with PD-D appear to have less frequent or less severe psychiatric symptoms than patients with DLB. Such differences, however, may simply reflect disparity in the overall dementia severity. Similar issues apply when trying to distinguish demented and non-demented patients with PD, as all of the symptoms may occur in non-demented patients. Thus, although psychiatric symptoms may be risk factors for developing dementia, and may support the diagnosis of dementia, they do not appear to be useful in differentiating PD-D from DLB and AD in individual cases.

### **MOTOR, AUTONOMIC AND OTHER FEATURES**

#### **Motor Phenotype**

The majority of studies identified examined motor features/phenotype as risk factors for incident dementia in a longitudinal design rather than comparing demented versus non-demented PD patients cross-sectionally. In general increasing age and severity of extrapyramidal signs (EPS) are important determinants of dementia, and their effects are not independent, but synergistic: in one

study patients with older age/high severity had a relative risk of incident dementia of 9.7 when compared with the younger age/low severity group.<sup>3</sup> Tremor dominance at presentation has been associated with relative preservation of mental status in some, but not all studies.<sup>78,79</sup> Other neurological features at baseline associated with increased risk of dementia include symmetric EPS, suboptimal response to levodopa (L-dopa) and dystonic dyskinesias.

A number of studies considered putative dopaminergic-responsive and non-responsive features and their relationship with PD-D. Non-L-dopa responsive features are classically considered to be axial disturbance, including gait, posture and balance, as well as facial masking and speech disturbance. These features are predictive of incident dementia,<sup>18,80,81</sup> while the "postural instability gait disorder" (PIGD) phenotype is also over-represented in prevalent PD-D.<sup>82</sup> In a recent study, patients with tremor-dominant subtype at baseline did not become demented until they had a transition to PIGD subtype, and dementia did not occur among patients with persistent tremor-dominant subtype.<sup>83</sup>

### **Rate of Progression**

Development of dementia may be associated with a more aggressive motor disease course.<sup>78,84</sup> Dementia at baseline was associated with more rapid motor decline in two studies,<sup>85,86</sup> but this remained significant in only one after adjusting for other baseline factors,<sup>86</sup> where PD-D patients had 7.9 points higher annual decline in UPDRS motor scores compared to those without dementia at baseline.<sup>86</sup> In the only longitudinal study, a more rapid decline in UPDRS III scores was reported in PD-D than in PD patients over 2 years (9.7 vs. 5.1 points, respectively).<sup>27</sup> Although not statistically significant, the absolute deterioration at 2 years was greater in the PIGD than the tremor-dominant PD subgroup. Rate of motor decline in the PD-D patients was independent of baseline disease duration.

### **Falls**

In an early questionnaire-based study dementia (not operationally defined) was not related to falling.<sup>87</sup> A prospective study, however, found dementia to be a risk factor for falls in patients with PD.<sup>88</sup> Another questionnaire study in 1,092 patients with a parkinsonian disorder, examining occurrence of any fall during the previous 2 years, found that dementia (definition unspecified) was present in 5.1% of non-fallers versus 18.8% of fallers, giving an odds ratio of 3.24.<sup>89</sup> In a cross-sectional clinical study, gait and balance disorders were more common in PD-D (93%), than non-demented PD cases (43%).<sup>90</sup> In



a retrospective clinicopathological study (73.3% of patients with documented falls), “cognitive dysfunction” as a late clinical feature was significantly more common in fallers (71.7%) versus non-fallers (49.5%).<sup>91</sup>

### Eye Movements

Although quantitative electro-oculography (EOG) can reveal abnormalities of ocular movements in non-demented PD patients,<sup>92</sup> with the exception of convergence deficits and age-related limitation of upgaze, the bedside examination of eye movements in PD is normal. Using EOG to compare saccadic eye movements in patients with PD, PD-D, DLB, and AD as compared to controls, PD patients had only minimal impairment on reflexive tasks.<sup>93</sup> PD-D and DLB patients were similarly impaired on both reflexive and complex saccades, but AD patients only on complex saccades. Nevertheless, there is no evidence that bedside clinical examination of eye movements can distinguish between these disorders.

### Sleep Disorders

Circumstantial evidence suggests that REM sleep behavior disorder (RBD) may be a risk factor for dementia, as PD patients with RBD show impairments of some logical abilities as compared to subjects without RBD,<sup>94</sup> and the presence of RBD is associated with an increased risk of hallucinations and delusions.<sup>95</sup> RBD is also associated with DLB, and is considered to be a feature “suggestive” of the diagnosis.<sup>2</sup> In a consecutive series of 93 cases with RBD, 10 of 25 patients with PD had dementia.<sup>96</sup> There are, however, no longitudinal studies to confirm RBD as a risk factor for PD-D. On the other hand, excessive daytime sleepiness (EDS) has been reported to be a risk factor for PD-D.<sup>97</sup> Using the Epworth Sleepiness Scale, 57% of PD-D, 50% of DLB, and 41% of PD subjects were classified as having EDS, when compared with 18% of AD and 10% of controls (Boddy, personal communication). In the same study, EDS was more frequent at baseline in PD-D patients with PIGD phenotype than PD-D patients without. Furthermore, sleep quality was poorer in PD-D, PD, and DLB patients, when compared with AD and normal controls.

### Autonomic Features

A higher frequency of symptomatic orthostasis was reported in association with cognitive impairment in PD in one study that used cluster analysis.<sup>84</sup> A high frequency of carotid sinus syndrome and orthostatic hypotension has been reported in DLB as compared to patients with AD.<sup>98</sup> There was a reduction in heart rate variability in all frequency bands in PD patients both with and without dementia in one study, and notably

there were no significant differences between DLB and PD-D subjects.<sup>99</sup>

### L-dopa Responsiveness

Axial symptoms are commonly viewed as less L-dopa responsive and are assumed to be caused by “non dopaminergic” lesions.<sup>100</sup> The L-dopa responsiveness could therefore be expected to be less pronounced in PD-D where these symptoms predominate. However, available cross-sectional and longitudinal studies have failed to directly assess L-dopa response in demented versus non-demented patients.<sup>3,14,18,80–82,101–103</sup> Those studies reporting doses of L-dopa have produced inconsistent findings indicating either no difference<sup>102</sup> between groups or higher doses in patients with cognitive impairment.<sup>104</sup> Decreased responsiveness of PIGD symptoms to adequate doses of L-dopa has not been established in a formal study, particularly after controlling for confounders like subcortical small vessel disease.<sup>105</sup> A recent study using 200 mg single-dose L-dopa challenges failed to detect significant differences in mean improvement on UPDRS motor score; although more non-demented patients experienced greater than 20% improvement compared to those with PD-D (90% vs. 65%).<sup>106</sup> There was also no significant differences in numbers of patients judged clinically as showing a moderate to marked response to chronic L-dopa. A similar study included patients with DLB, PD, and PD-D and failed to detect differences in L-dopa responsiveness between PD and PD-D.<sup>107</sup> A longitudinal study found greater cognitive decline over a 3-year period in those patients with less than 50% improvement of UPDRS scores after a L-dopa test performed at baseline.<sup>108</sup> A post-mortem study suggested that loss of L-dopa response is correlated with dementia via greater loss of striatal D3 receptors.<sup>109</sup> Overall, there is insufficient evidence to allow for firm conclusions on differences in the degree of L-dopa responsiveness between PD with and without dementia.

### L-dopa-Induced Motor Complications

While fewer dyskinesias were reported in the demented PD patients in a cross-sectional study,<sup>78</sup> a longitudinal study found greater mental deterioration in those patients exhibiting dystonic L-dopa-induced dyskinesias at baseline.<sup>108</sup> These data are insufficient to infer differences in the occurrence of L-dopa induced motor complications in PD-D versus PD.

### Neuroleptic Sensitivity

While placebo-controlled studies have excluded patients with PD-D, open label studies with clozapine in PD psychosis have included PD-D subjects and found

that the drug was similarly well tolerated in demented and non-demented patients, sedation and hypotension being the main side-effects.<sup>110</sup> One study reported greater risk for low-dose quetiapine (mean dose 50 mg/day) to induce motor worsening in PD-D compared to PD without dementia.<sup>111</sup> Severe neuroleptic sensitivity has been reported in up to 40% of PD-D patients exposed to neuroleptic drugs.<sup>112</sup>

### Conclusions on Motor, Autonomic, and Other Features

A PIGD phenotype is more frequent in PD-D, and also constitutes a risk factor for incident dementia. Patients with PD-D have a more rapid motor decline, and falls are more frequent. RBD and EDS occur both in demented and non-demented PD patients, but may be more frequent in association with dementia, the presence of RBD may be useful in differentiating PD-D from AD. The relative frequency of autonomic symptoms between demented and non-demented patients is not known. L-dopa responsiveness and L-dopa related dyskinesias may differ between demented and non-demented patients, but cannot be relied upon for predictive or diagnostic purposes.

## ANCILLARY INVESTIGATIONS

### Structural Neuro-Imaging

Neuroimaging studies examining structural changes in PD-D patients have focused on MRI-based evaluations of whole brain<sup>113–115</sup>; regions of interest were selected in the gray matter<sup>113,116–119</sup> and white matter.<sup>120</sup> The reviewed studies indicate that whole brain and regional structural changes are present in PD as compared to AD and normal controls. Studies suggest greater whole brain atrophy rates in PD-D and a pattern of regional temporal lobe atrophy greatest in AD, followed by PD, then normal controls. Significant differences between non-demented PD patients and PD-D were reported bilaterally in the occipital lobes. There appears, however, to be an overlap of the pattern of regional atrophy in PD-D, PD, and DLB, compared to AD and normals. As a result, no consistent pattern of structural changes clearly separates PD-D from non-demented PD or from other comparison groups. Sample sizes have not been large enough in the cited studies to allow for statistical modeling to control for the increased motor impairment and longer disease duration often seen in PD-D compared to non-demented PD subjects.

### Brain Perfusion and Cerebral Blood Flow Assessed by SPECT and PET

As compared to healthy controls, PD-D patients exhibit brain hypoperfusion or decreased CBF in several areas of association cortex, in particular in the temporal, lateral parietal, precuneus, posterior cingulate, and occipital regions,<sup>121–130</sup> whereas in non-demented patients there are either no changes<sup>128,129</sup> or decreased CBF is limited to the frontal lobes.<sup>121,123</sup> However, extensive cortical hypoperfusion in non-demented PD patients was reported in two studies, including the parietal and temporal cortices,<sup>125,127</sup> suggesting that, although temporal-parietal-occipital hypoperfusion is usually associated with PD-D, it should be used cautiously to distinguish PD-D from non-demented patients.

No difference in the topographical pattern of changes was observed in PD-D as compared to patients with DLB.<sup>122,123</sup> Over a period of 1-year, reduction in brain perfusion in PD-D and DLB were comparable. An increase in striatal perfusion was interpreted as a compensatory mechanism in response to decreasing dopaminergic striatal input.<sup>131</sup> The topographical pattern of hypoperfusion in PD-D was similar to that of AD, except that it was more pronounced in AD.<sup>129</sup>

### Glucose Metabolism

A greater decrease of glucose metabolism was found in the inferior parietal<sup>132,133</sup> and occipital<sup>133</sup> cortices in PD-D as compared to PD. A globally similar pattern of decreased cerebral glucose metabolism, affecting the frontal, parietal and parietal association cortices, and posterior cingulate area, was observed in PD-D compared to AD,<sup>132,134</sup> in PD-D, a greater decrease of glucose metabolism was observed in the occipital visual cortex.<sup>134</sup>

### Studies of Neurotransmitter Abnormalities

Studies of brain cholinergic transmission, using PET-scan and MP4A binding<sup>135</sup> or measuring acetylcholinesterase activity,<sup>136</sup> demonstrated a more profound cortical cholinergic deficit in PD-D as compared to PD, although in one study, the difference was not significant.<sup>136</sup> Conflicting results were obtained regarding the relationship between dopaminergic loss and PD-D. Whereas Ito et al.<sup>137</sup> demonstrated that 18F-dopa uptake in PD-D was significantly more decreased in the ventral striatum, right caudate nucleus and in the anterior cingulate area as compared to PD, no differences in terms of dopaminergic loss and rate of decline between PD and PD-D were found in other studies.<sup>138–139</sup>

Loss of nigro-striatal dopaminergic terminals can be visualized using markers of dopamine transporter, such

as FP-CIT SPECT. Significant reductions were found in FP-CIT binding in the caudate, anterior and posterior putamens in subjects with DLB compared to those with AD and controls. Transporter loss in DLB was of similar magnitude to that seen in PD, the greatest loss in all three areas was seen in patients with PD-D.<sup>140</sup> Thus, this method can be used to differentiate patients with DLB or PD-D from AD patients with extrapyramidal symptoms, e.g. because of post-synaptic dysfunction such as neuroleptic use, but cannot differentiate from other conditions associated with degeneration of nigro-striatal pathways.

#### **In vivo Biochemical Studies Using Proton MR Spectroscopy**

Lactate/*N*-acetyl aspartate ratio was found to be increased in the occipital lobes in PD, and in particular in PD-D patients as compared to healthy controls, suggesting that the impairment of oxidative energy metabolism is greater in PD-D.<sup>141</sup> Similarly, Summerfield et al.<sup>142</sup> found a decreased ratio of *N*-acetylaspartate in the occipital lobes in PD-D as compared to PD.

#### **Cardiac Metaiodobenzylguanidine Scintigraphy**

Metaiodobenzylguanidine (MIBG) is a specific marker for noradrenergic transporters. Cardiac MIBG uptake is significantly reduced in PD<sup>143–147</sup> as well as in DLB,<sup>148</sup> because of neurodegeneration of post-ganglionic sympathetic nerve fibers.<sup>149</sup> Cardiac MIBG is useful for the differentiation of PD from MSA<sup>143,147,150–152</sup> and from PSP,<sup>143</sup> as cardiac MIBG uptake usually remains normal in these non-Lewy body parkinsonian disorders. Thus, although specific studies in PD-D are lacking, cardiac MIBG may differentiate LB-related dementias from non-LB related types, but cannot differentiate PD-D and DLB.

#### **EEG**

PD-D patients were reported to have distinctly slower baseline EEG activity than patients without dementia.<sup>153</sup> Significant decrease in relative alpha power was also reported in PD-D compared to PD.<sup>154</sup> A positive correlation between EEG frequency and MMS scores was reported.<sup>155</sup>

#### **Event-Related Potentials**

Prolongation of P300 latency in PD-D was reported in several studies, with no difference between PD-D and DLB.<sup>156–158</sup> Controversial results have been reported in P300 latency in non-demented PD patients, prolonged latencies being found in some,<sup>159,160,161,162</sup> but not in other studies,<sup>156,157,163,164</sup> Thus, P300 latency is usually prolonged in PD-D, but this may be the case also in

non-demented patients, so that P300 latencies cannot differentiate PD-D from PD. Prepulse inhibition of the N1/P2 component of auditory evoked potentials was significantly reduced in DLB compared to controls and AD; the impairment was of intermediate intensity in PD-D.<sup>165</sup>

#### **Conclusions on Ancillary Investigations**

Although there are differences between PD-D and non-demented PD patients in structural and functional imaging as well as electrophysiological studies, none of these techniques can be recommended for routine diagnostic purposes because of lack of specificity. Similarly they do not have sufficient discriminative power to differentiate PD-D from DLB and AD.

#### **GENETIC ASPECTS OF PD-D**

The effect of genetic disposition as a risk factor has only been studied systematically for APOE genotypes, and the results have been conflicting. A positive correlation of E2 or E4 alleles with PD-D was reported in some studies,<sup>8,166,167</sup> whereas a negative association with E4 was found in a number of others.<sup>168–171</sup> Dementia has been reported in familial forms of PD such as PARK1<sup>172–174</sup> and PARK8.<sup>175</sup> Dementia is rare in PARK2, PARK6, and PARK7. There is some evidence for familial aggregation of dementia in PD<sup>176</sup> and increased frequency of dementia in the relatives of PD patients with dementia has been found in some,<sup>177</sup> but not all<sup>178,179</sup> studies.

#### **CLINICO-PATHOLOGICAL CORRELATIONS**

Studies describing clinico-pathological correlations in patients with PD-D can be broadly classified into three groups: those studies suggesting a correlation of dementia with nigral and brainstem pathology, those suggesting that limbic and cortical LB-type degeneration is the main correlate, and those suggesting co-incident Alzheimer type pathology as the main correlate of dementia. These studies and their main findings are tabulated in Table 3.

On the basis of the recent studies using  $\alpha$ -synuclein immunohistochemistry, and assessing several potential pathological correlates simultaneously, the main pathological correlate of dementia in PD seems to be the LB-type degeneration in cerebral cortex and limbic structures. AD-type pathology frequently co-exists, but it often does not reach a severity to justify pathological diagnosis of AD.

#### **CONCLUSIONS**

The prevalence of dementia in PD is close to 30%, and its incidence is increased by 4 to 6 times over the general age-appropriate population. Main risk factors are old age, severity of motor impairment, and already compro-

**TABLE 1.** *Features of dementia associated with Parkinson's disease***I. Core features**

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
  - Impairment in more than one cognitive domain
  - Representing a decline from premorbid level
  - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

**II. Associated clinical features**

1. Cognitive features:
  - Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
  - Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
  - Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
  - Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
  - Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
2. Behavioral features:
  - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
  - Changes in personality and mood including depressive features and anxiety
  - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
  - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
  - Excessive daytime sleepiness

**III. Features which do not exclude PD-D, but make the diagnosis uncertain**

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

**IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D**

- Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
  - Acute confusion due to
    - a. Systemic diseases or abnormalities
    - b. Drug intoxication
  - Major Depression according to DSM IV
- Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

**TABLE 2.** *Criteria for the diagnosis of probable and possible PD-D***Probable PD-D**

- A. Core features: Both must be present
- B. Associated clinical features:
  - Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
  - The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis
- C. None of the group III features present
- D. None of the group IV features present

**Possible PD-D**

- A. Core features: Both must be present
- B. Associated clinical features:
  - Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
  - Behavioral symptoms may or may not be present
- OR
- C. One or more of the group III features present
- D. None of the group IV features present



TABLE 3. Clinico-pathological correlation studies

Routine histology for Lewy bodies			
1979	Hakim and Mathieson (1979)	19/34 PD cases with dementia; ATP in 33/34 cases	Dementia in PD due to ATP.
1980	Boller et al. (1980)	29 PD; 9 severe and 7 mild dementia; ATP in 9/9 with severe and 3/7 with mild dementia	Dementia in PD due to ATP.
1982	Jellinger and Grisold (1982)	100 PD; 3 types—a) PD +ATP or AD; b) AD with normal SN; c) LB with ATP; dementia severity correlates with ATP	Dementia in PD due to ATP.
1984	Gaspar and Gray (1984)	18/32 PD with dementia; SN, LC and nbM pathology; loss and decreased ChAT correlate with dementia; increased ATP more in demented	Dementia in PD is heterogenous, and includes subcortical pathology and ATP.
1988	Yoshimura (1988)	37/56 PD with dementia; 3 types—a) pure PD; b) PD with ATP; c) PD with VaD	Dementia in PD is heterogenous. In some cases dementia in PD due to subcortical pathology.
1988	Kosaka et al. (1988)	35 LBD cases; 23 with dementia	Dementia in PD is heterogenous. In some cases dementia in PD due to ATP and in some subcortical pathology.
1989	Sudarsky et al. (1989)	4 PD with dementia; with SN and nbM pathology	Dementia in PD due to subcortical pathology.
1989	Rinne et al. (1989)	12 PD; dementia in PD correlated with medial SN neuronal loss	Dementia in PD due to subcortical pathology.
Ubiquitin immunohistochemistry for Lewy bodies (Kuzuhara et al., 1988)			
1993	Hughes et al. (1993)	44/100 PD with dementia; 29 AD; 4 diffuse cLBs; 6 limbic LB; 6 VaD	Dementia in PD is heterogenous, including cLBs, ATP, subcortical pathology, or VaD.
1993	Zweig et al. (1993)	13 PD with dementia without ATP; LC neuronal loss correlates with dementia	Dementia in PD due to subcortical pathology.
1993	Vermersch et al. (1993)	24 PD some with dementia; biochemical evidence of tau pathology in frontal cortex (relatively more than temporal cortex)	Dementia in PD due to ATP.
1997	Churchyard and Lees (1997)	27 PD with dementia; MMSE correlates with density of Lewy neurites in hippocampus and amygdala	Dementia due to LB (amygdala and hippocampus).
Alpha-synuclein immunohistochemistry for Lewy bodies (Spillantini et al., 1997)			
1998	Wakabayashi et al. (1998)	12/22 PD with dementia; more APOE e4; higher LB densities and amyloid plaques without NFT	Dementia due to LB (limbic and diffuse types).
1998	Mattila et al. (1998)	44 PD; cognitive impairment correlates with cLB and NFT	Dementia due to LB (especially if concurrent AD excluded).
1998	Brown et al. (1998)	12 PD with dementia; 6/12 minimal ATP; 6/12 LB	Dementia due to either ATP or LB or both.
2000	Hurtig et al. (2000)	22 PD with dementia; LB better correlate with dementia than ATP	Dementia due to LB.
2000	Mattila et al. (2000).	45 PD some with dementia; LB in 43/45; ATP in 18/45; APOE e4 cases had more LB; LB correlates best with dementia	Dementia due to LB.
2003	Apaydin et al. (2002)	12 PD with dementia; LB (limbic and diffuse) in dementia; mild ATP; 2 VaD	Dementia due to LB.
2003	Kovari et al. (2003)	22 PD with dementia; CDR scores correlate with LB and SP, not NFT	Dementia due to LB (limbic type).
2003	Colosimo et al. (2003)	276 PD; 67/276 diffuse LB and 50 limbic LB; 11 PD with dementia; 9 PD without dementia had diffuse or limbic LB	Dementia due to LB, but some cases with LB are not demented.
2004	Bertrand et al., (2004)	10/41 PD with dementia; dementia associated with hippocampal LB and cLB	Dementia due to LB.
2005	Braak et al. (2005)	88 PD some with dementia; MMSE correlates with ATP (NFT stage and SP); PD stage correlates with PD severity and dementia	Dementia due to LB, but some cases with advanced stage are not demented.
2005	Parkkinen et al. (2005)	32/106 LBD had dementia or parkinsonism; LB also in normals	Dementia due to factors other than LB.

TABLE 3. (Continued)

2005	Pletnikova et al. (2005)	21 PD some with dementia; LB density correlates with SP; not all PD with dementia have LB	Dementia due to factors other than LB.
2005	Aarsland et al. (2005)	18/22 PD with dementia; LB and Braak NFT stage correlate with dementia	Dementia due to LB.

PD, Parkinson disease; ATP, Alzheimer type pathology; SN, substantia nigra; LB, Lewy bodies; cLB, cortical Lewy bodies; LC, locus ceruleus; nbM, basal nucleus of Meynert; VaD, cerebrovascular disease; LBD, Lewy Body Disease; APOE, apolipoprotein E; NFT, neurofibrillary tangles; SP, senile plaques.

mised cognitive functions at baseline assessment. The clinical features of PD-D include insidious onset and slowly progressive course of cognitive impairments in attention, executive and visuospatial functions as well as memory, with relatively preserved core language functions. A dysexecutive profile predominates. Hallucinations, delusions, apathy, and mood changes are frequently associated behavioral features (Table 1). Dementia in PD is more commonly associated with the PIGD motor phenotype. Imaging studies demonstrate atrophy and hypometabolism, more prominent in the temporal and posterior areas. However, there is no single ancillary investigation which would help to diagnose individual patients. Retrospective as well as prospective clinical-pathological studies reveal that dementia in PD best correlates with LB pathology, so that PD-D can be designated as a LB-associated dementia.

The defining feature of PD-D is that dementia develops in the context of established PD. Hence, diagnosis of idiopathic PD before the development of dementia symptoms is the essential first step in the diagnosis. Diagnosis of dementia must be based on the presence of deficits in at least two of the four core cognitive domains (attention, memory, executive and visuo-spatial functions) as shown in clinical and cognitive examination, and be severe enough to affect normal functioning. Although there are some differences in the extent and profile of deficits in individual cognitive domains compared to patients with AD (more prominent memory impairment in AD, more prominent executive dysfunction in PD-D), these may vary from patient to patient and cannot be used as the sole basis of diagnosis. Neuropsychiatric and behavioral symptoms are frequent, but are not invariable. The profile of cognitive and behavioral symptoms in PD-D and DLB are very similar. There are several suggestive features which are found more frequently in PD patients with dementia, such as PIGD phenotype and RBD, but they lack specificity and are hence not included in the diagnostic criteria.

Based on the features described above, clinical diagnostic criteria for probable and possible PD-D are pro-

posed (Table 2). As there is no gold standard for diagnosis, the sensitivity and specificity of these criteria cannot be ascertained. Because the criteria are based on a comprehensive review of the existing literature, we propose that they be adopted and tested prospectively to assess their clinical utility, sensitivity, and specificity. Such prospective studies may provide the basis for future revisions.

## APPENDIX: INCLUSION CRITERIA FOR PUBLICATIONS

**Search Strategy:** Medline search, no time limit, in addition use of personal archives and reference list from relevant papers

**Evidence Sources:** As primary source: Full empirical papers published in English language journals.

As secondary source: Published abstracts of scientific meetings, or English abstracts of non-English journal publications that (1) meet other criteria below and (2) provide useful new information

**Diagnosis of PD:** Study used formal established clinical diagnostic criteria for idiopathic PD or

Study did *not* use formal established criteria, but provided sufficient details of inclusion/exclusion criteria to suggest patients had idiopathic PD

**Diagnosis of Dementia:** Diagnosis made at the time of the study by a Neurologist, Psychiatrist, or other specialist in dementia and

Study used formal criteria (DSM/ICD) for dementia following clinical examination (not retrospective case note examination) or

Study used operational definition based on appropriate age norm-referenced cognitive impairment measured using an *extended* mental status examination such as Mattis Dementia Rating Scale (NB: not MMSE alone). or

Operational definition based on the presence of significant impairment (appropriately defined relative to age-related normative data) in two or more separate domains of cognitive function.

**Presence of a Control Group:** A non-disease control group was not required for studies using standard neuropsychological measures with published age-related normative data, and those used norms to establish the presence/absence of cognitive impairment and its severity.

An age- and education-matched, non-disease control group was required for studies that used non-standard measures, or where the measures did not have adequate age-related normative data.

A disease control group was not necessary. However, the presence of a non-neurological patient group was considered to add weight to the interpretation of clinical evidence when factors such as motor impairment or mood may influence neuropsychological test performance.

**Minimum Number of Subjects per Group:** At least 10 subjects per group.

Greater evidential weight was given to studies using larger samples.

**Use of Accepted Scales/Test (for Neuropsychological Assessment):** Studies using standard version of published neuropsychological tests or established behavioral scales or

Studies which used non-standard versions of published tests/scales, or novel non-published tests, provided sufficient detail was given to allow an evaluation of the nature of the tests and any deficit identified and

Tests were appropriate for the population and tests were interpreted appropriately (e.g., inferences about cognitive impairment were not made on the basis of completion-time alone without appropriate controls).

**Statistics:** Details of test performance provided in the forms of tables or figures that showed both mean (or median) value, and a measure of variability (SD, SEM, IQR, 95%CI)

Studies which provided details of the statistical procedures employed to analyze the data and criteria for statistical significance ( $\alpha < 0.05$ ).

The nature of the analysis considered to be appropriate for the data (e.g., non-parametric tests for small samples, highly skewed distributions, ordinal data)

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