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Neuropsychological Characteristics of Dementia with Lewy Bodies and Parkinson's Disease with Dementia: Differentiation, Early Detection, and Implications for "Mild Cognitive Impairment" and Biomarkers

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Abstract Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB) are neurodegenerative conditions sharing a disorder of α-synuclein metabolism. Temporal differences in the emergence of symptoms and clinical features warrant the continued clinical distinction between DLB and PDD. While DLB and PDD groups' neuropsychological profiles often differ from those in Alzheimer's disease (AD), the diagnostic sensitivity, specificity, and predictive values of these profiles remain largely unknown. PDD and DLB neuropsychological profiles share sufficient similarity to resist accurate and reliable differentiation. Although heterogeneous cognitive changes (predominantly in memory and executive function) may manifest earlier and more frequently than previously appreciated in Parkinson's disease (PD), and executive deficits may be harbingers of dementia, the enthusiasm to uncritically extend the concept of mild cognitive impairment (MCI) to PD should be tempered. Instead, future research might strive to identify the precise neuropsychological characteristics of the prodromal stages of PD, PDD, and DLB which, in conjunction with other potential biomarkers, facilitate early and accurate diagnosis, and the definition of neuroprotective, neurorestorative, and symptomatic treatment endpoints.

Keywords Parkinson's disease · Lewy body dementia · Mild cognitive impairment · Biomarker · Prodrome · Neuropsychology

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Overview and History

From a pathological standpoint, Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB) are neurodegenerative conditions with a common disorder of α-synuclein metabolism. This commonality only came to be appreciated in the past decade when the critical role of α-synuclein in the pathophysiology of PD was discovered (Polymeropoulos et al. 1997). The opportunity to recognize a potential relationship between Lewy body pathology, dementia, and cognitive alterations in Parkinson's disease (PD) had presented itself early in the 20th century, but was not seized upon. Perhaps because many outside France were unconvinced of the existence of cognitive compromise in PD until the middle of the twentieth century (see Goetz 1992), little attention was devoted to the pathological basis of possible neurobehavioral change in PD. Even Lewy, whose name the eosinophilic inclusions described by him bear, did not ascribe neurobehavioral significance to these inclusion bodies initially observed in postencephalitic parkinsonian patients. Nor did he distinguish depression and dementia when he characterized PD (Lewy 1912, 1923), although one or both of these syndromes were present in the majority of subjects examined (see Schiller 2000).

Dementia associated with Lewy bodies was not recognized until the last 40 years of the twentieth century (Holdorff 2002). Two patients with parkinsonism and dementia with cortical Lewy-body like eosinophilic inclusions were described first in the early 1960s (Okazaki et al. 1961). Although these inclusion bodies lacked the distinctive halo of brainstem Lewy bodies, this group of investigators made an association between these cerebral inclusions and dementia. A case series of patients with clinical dementia and cortical, limbic, and brainstem Lewy

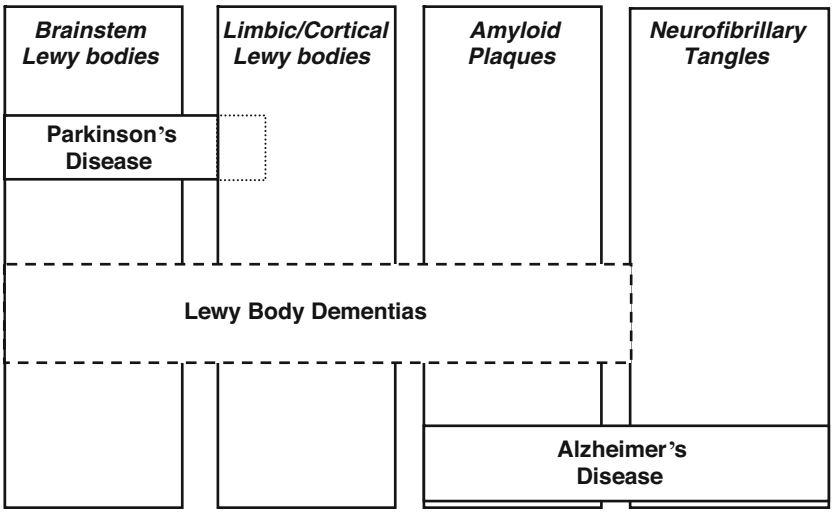

Fig. 1 Clinicopathologic relations among Alzheimer's disease and Lewy body disorders (Kaufer and Tröster 2008)

bodies was also described by Kosaka et al. (1980). By 1990, Kosaka and two independent groups of researchers described similar disorders of dementia in the context of parkinsonism and Lewy body pathology, but named the conditions differently: "diffuse Lewy body disease" (Kosaka 1990); "senile dementia of the Lewy body type" (SDLT; Perry et al. 1990); and "Lewy body variant of Alzheimer's disease" (LBV-AD; Hansen et al. 1990). Individuals with SDLT or LBV-AD had cortical and brainstem Lewy bodies and amyloid plaques (seen in Alzheimer's disease; AD). DLB encompassed three subtypes of Lewy body disease: a brainstem-predominant distribution of Lewy bodies defined PD, whereas additional Lewy body pathology in limbic and cortical regions defined LBV-AD and senile dementia of the Lewy Body type. The variable presence of amyloid plaques also formed the basis of two distinct pathological subtypes: the *Common* form (about 75% of cases) with mixed Lewy body and amyloid pathology, and the *Pure* form, with only Lewy body pathology. Figure 1 provides a schematic representation of the relationship between various pathologic features, the Lewy body diseases, and Alzheimer's disease.

One reason why a grasp of early terminology is important is that it is likely that variability in definitions, clinical diagnostic and pathologic ascertainment criteria and methods over time probably account for a substantial proportion of the inconsistency in neuropsychological contrasts between AD and DLB. The frequent overlap of Lewy body (PD) and amyloid (AD) pathology also clarifies why early neuropsychological studies sought to differentiate AD and DLB, whereas DLB vs. PDD comparisons are of much more recent origin, growing in number only since the biological commonality (i.e., an α-synucleinopathy) of DLB and PDD came to light. The change over time in diagnostic and pathologic criteria of DLB also needs to be borne in mind as a potential confound when reviewing prevalence and incidence estimates of the Lewy body dementias.

Diagnosis

Given the biological commonalities among DLB and PDD, yet variability and differences in clinical presentation, the DLB/PDD Working Group recently sought to clarify the preferred or recommended terminology (Lippa et al. 2007). Specifically, the group agreed to use the umbrella term *Lewy body disorders* to refer to PD, PDD, and DLB and to use the term *Lewy body dementias* to refer to PDD and DLB. While the group proposed that a single Lewy body disorder model is most useful for studying disease pathogenesis, it acknowledged that the use of PD, PDD, and DLB was warranted for clinical use.

The clinical distinction between PDD and DLB is also supported and facilitated by the recent revision of clinical diagnostic criteria for DLB (McKeith et al. 2005; Table 1) and the recent formulation of separate diagnostic criteria for PDD (Emre et al. 2007; Table 2). Probable criteria for PD have been proposed in various forms (Gelb et al. 1999), but the UK Parkinson's Disease Society Brain Bank (Queen Square) criteria (Hughes et al. 1992; Table 3) commonly used in research studies form the basis (a core feature) of the recent PDD criteria.

Epidemiology

Hospital-based clinic prevalence and incidence estimates of PDD and DLB predominate over community-based studies (which generally yield lower estimates), as do cross-sectional rather than longitudinal studies (meaning that many prevalence rates represent point-prevalence rather

Table 1 Revised clinical diagnostic criteria for DLB (from McKeith et al. 2005)

Criteria	Details
Central feature	Progressive cognitive decline that interferes with social and occupational function
Core features (any 2=probable DLB; any 1=possible DLB)	Fluctuating cognition
	Recurrent visual hallucinations
	Spontaneous motor parkinsonism
Suggestive features (1 or more+a core feature=Probable DLB, any 1 alone=Possible DLB)	REM sleep behavior disorder
	Severe neuroleptic sensitivity
	Decreased tracer uptake in striatum on SPECT dopamine transporter imaging or on MIBG myocardial scintigraphy
Supportive features (common but lacking diagnostic specificity)	Repeated falls and syncope
	Transient, unexplained loss of consciousness
	Systematized delusions
	Hallucinations in other modalities
	Relative preservation of medial temporal lobe on CT or MRI scan
	Decreased tracer uptake on SPECT or PET imaging in occipital regions
	Prominent slow waves on EEG with temporal lobe transient sharp waves

than period (or cumulative) prevalence estimates. A recent review of point prevalence rates considering the adequacy of the methodology of studies (Aarsland et al. 2005) found that among the soundest studies about 32% of PD patients have dementia, an estimate intermediate to those of 22% to 48% reported by subsequent studies (Athey et al. 2005; de Lau et al. 2005; Hobson et al. 2005). That review also observed that 3% to 4% of dementia cases were attributable to PDD and that the overall PDD prevalence among persons 65 years and older is about 0.5%.

Average point prevalence estimates for DLB are not meaningful given the strongly bimodal distribution of prevalence rates reported by the six methodologically most adequate studies. A review of those six studies noted a DLB prevalence ranging from 0% to 5% among the general population, and from 0% to 31% among dementia cases (Zaccai et al. 2005).

Two studies have provided cumulative prevalence estimates of PDD in patients followed from initial diagnosis of PD. One study reported that 26% and 28% of newly diagnosed PD patients had dementia after 3 and 5 years of follow-up, respectively (Reid et al. 1996). Aarsland et al. (2003a), in contrast, reported a prevalence of dementia of almost 80% among initially non-demented patients followed for 8 years. A more recent community-based study found that about 10% had developed dementia within a mean 3.5 year follow-up period (Williams-Gray et al. 2007). A study following patients with PD until death (and in whom autopsy was performed) found that 83% of patients developed dementia (Galvin et al. 2006).

Incidence of PDD varies by age, ranging from 3% among patients younger than 60 years, to 15% among PD patients older than 80 years (Biggins et al. 1992; Marder et al. 1995; Mayeux et al. 1990). Annual incidence figures from community studies fairly consistently indicate that about 10% of PD patients per year will develop dementia (Aarsland et al. 2001; Hobson et al. 2005; Marder et al. 1995), although a recent study reports a lower incidence among newly diagnosed patients followed 3 and 5 years (Williams-Gray et al. 2007). Incidence of DLB has been examined in only one study using formal criteria, and that study reported an incidence of about 3% among dementia cases and 0.1% in the population (Miech et al. 2002).

Neuropsychological Differentiation of Lewy Body Dementias (DLB, PDD) from Alzheimer's Disease

As noted in the historical overview, given the initial findings of overlap between AD and Lewy body dementia pathology, as well as the large prevalence of AD, early comparative studies of neuropsychological impairment in AD and Lewy body dementias focused on AD and DLB (and its variants) rather than DLB vs. PDD comparisons. For ease and brevity, this review separates AD vs. DLB or PDD and PDD vs. DLB comparisons, and highlights the conditions' neuropsychological profiles in broad brush strokes without close regard to whether DLB is represented in various studies by the pure or common forms of DLB. Readers interested in more detailed discussions of the neuropsychology of DLB, PDD, and PD are referred to recent chapters and reviews (Kaufer and Tröster 2008; Metzler-Baddeley 2007; Tröster and Fields 2008; Tröster and Woods 2005; Welsh-Bohmer and Warren 2006). In general, although these are not uniform findings, DLB manifests greater attentional, visuospatial, and executive impairments than AD, whereas AD involves more profound episodic memory impairment than DLB. Evidence with regard to remote memory, semantic memory, and language

Table 2 Clinical diagnostic criteria for PDD (from Emre et al. 2007)

Criteria	Details
Core features (both required for probable or possible PDD)	Diagnosis of Parkinson's disease per UK Parkinson's Disease Brain Bank (Queen Square) criteria Dementia of insidious onset and slow progression in the presence of PD, defined by: Impairment of more than one domain of cognition Impairment represents a decline from premorbid functioning Impairment in day-to-day functioning not ascribable to motor or autonomic dysfunction
Associated features (typical cognitive profile as outlined below in at least 2 of the 4 domains, and at least one of the behavioral symptoms required for diagnosis of probable PDD; atypical cognitive profile in one or more domains allows for diagnosis of possible PDD, in which behavioral disturbance may or may not be present)	Cognition Impaired attention which may fluctuate within or across days Impaired executive functions, e.g., planning, conceptualization, initiation, rule finding, set maintenance or shifting, bradyphrenia Preserved language, though word-finding and complex sentence comprehension deficits may be present Impaired memory, usually with benefit from cuing and better recognition than recall Behavior Apathy Changes in mood and personality, including features of depression and anxiety Delusions; commonly of the paranoid type Hallucinations; usually visual, complex and well-formed Excessive daytime sleepiness/somnolence
Features making the diagnosis of PDD uncertain (none of these features can be present when diagnosing probable PDD; one or both of these features can be present when diagnosing possible PDD)	Another abnormality capable of impairing cognition, but judged not to be the cause of the dementia (e.g., vascular disease on neuroimaging) Time interval between onset of motor and cognitive symptoms is unknown
Features suggesting another condition as causing the mental impairment (if present, PDD cannot be diagnosed)	Cognitive and behavioral abnormality occurs solely in the context of other conditions, such as confusional state due to systemic disease or intoxication, or major depressive disorder Features consistent with probable vascular dementia per NINDS-AIREN criteria

Table 3 UK Parkinson's disease society brain bank (Queen Square) criteria for diagnosis of Parkinson's disease

Criteria
Presence of parkinsonian syndrome evidenced by bradykinesia and at least one of: muscular rigidity, 4–6 Hz resting tremor, and postural instability not related to proprioceptive, vestibular, visual, or cerebellar dysfunction
Exclusion, by history, of: repeated strokes, repeated head injury, use of antipsychotic or dopamine depleting drugs, encephalitis, multiple affected relatives, no response to levodopa, sustained remission of symptoms, continued unilateral symptoms after 3 years, gaze palsy, early dementia, exposure to known neurotoxin, evidence on neuroimaging of tumor or communicating hydrocephalus, cerebellar signs, early dysautonomia, Babinski sign
Definite PD defined by at least three of the following supportive features: unilateral onset, persistence of symptom asymmetry, progression of symptoms, excellent response to levodopa, levodopa response sustained for 5 years, resting tremor, levodopa-induced dyskinesias, clinical course over 10 years

(naming and fluency) is more equivocal. Group differences between Lewy body dementias and AD are observable even on cognitive screening measures such as the Dementia Rating Scale (Mattis 2001) on which AD groups obtain a lower score on the Memory subtest, whereas DLB and PDD tend to perform more poorly on the Initiation/Perseveration and Constructions subtests (Aarsland et al. 2003b; Connor et al. 1998; Paolo et al. 1995).

Attention and Executive Functions

The compromise of attention in DLB is noteworthy because it may be the basis of fluctuating cognition, a characteristic of DLB (Walker et al. 2000). A range of experimental, cognitive screening, and clinical neuropsychological tests has been used to compare attention in AD and the Lewy body dementias, but the demonstration of greater attentional impairment in DLB or PDD than AD may require complex (sustained, selective, divided) attention tasks. In

addition, the demonstrability of greater attentional impairment and variability in reaction times in DLB compared to AD may be a function of the executive and visuospatial demands of the tasks (Bradshaw et al. 2006). Thus, while poorer performance by DLB than AD on simple attentional tasks, such as digit span, has been reported in a few studies (Hansen et al. 1990), the majority of studies using such tests fail to elicit differences (Connor et al. 1998; Gnanalingham et al. 1997; Salmon et al. 1996; Walker et al. 1997). In contrast, DLB subjects typically have been reported to be more impaired than AD patients on more demanding attentional tasks, such as the MMSE mental control tasks (Ala et al. 2001), visual search and set shifting (Sahgal et al. 1992) and the WAIS Digit Symbol test (Shimomura et al. 1998). On the Test of Everyday Attention (TEA; Robertson et al. 1996), DLB subjects have been reported to have deficits in visual but not auditory selective attention compared to AD, and to demonstrate greater impairment than AD on the TEA sustained attention and Stroop tests (Calderon et al. 2001). On cancellation tasks, regardless of whether letters or shapes are used, PDD and DLB perform more poorly than comparably demented AD patients (Noe et al. 2004).

Executive functions comprise a variety of cognitive operations (planning, abstraction, conceptualization, mental flexibility, insight, judgment, self-monitoring, and regulation) that are critical to adaptive, goal-directed behavior. Executive cognitive functions have generally been reported to be more impaired in DLB and PDD than AD (Collerton et al. 2003; Simard et al. 2000). Aarsland et al. (2003b) reported decrements of similar magnitude in PDD and DLB subjects compared to AD subjects on the Mattis DRS Initiation/Perseveration subtest, a finding consistent with a prior report of poorer Initiation/Perseveration performance in PDD than AD (Paolo et al. 1995). Additional studies have shown that DLB subjects are more susceptible to distraction, and have difficulty engaging in a task and shifting from one task to another, confabulation, and perseveration, all signs of executive dysfunction (Doubleday et al. 2002). DLB patients perform more poorly on Stroop, card sorting, and phonemic verbal fluency tasks than comparably demented AD patients (Calderon et al. 2001). In comparison to AD, PDD performance on card sorting tests tends to be more error-prone (Paolo et al. 1996).

The neural basis of the attentional and executive impairments in DLB and PDD requires further study, but it is likely that basal forebrain cholinergic system dysfunction is involved. Several lines of evidence support this proposal. Cholinergic neuronal loss and depletion of choline acetyltransferase are seen early in DLB (Tiraboschi et al. 2002) and administration of anticholinergics can disturb attention and precipitate hallucinations (Perry and Perry 1995) while cholinesterase inhibitors can improve cognition in DLB and PDD (Kaufer 2004; Leroi et al. 2006). A recent neuroimaging study's results further reinforce the connection between attention, working memory and executive impairment in PD/PDD and cholinergic dysfunction (Bohnen et al. 2006). In that study, global cortical acetylcholinesterase (AChE) activity measured by PET PMP imaging showed a greater reduction in PDD (21%) compared to PD without dementia (13%). Overall cortical AChE activity showed moderately strong correlations with performance on the WAIS-III Digit Span (r= 0.57), Stroop (r=0.46), and Trailmaking Part B–Part A (r= 0.44) tests. Although AChE was also correlated with performance on a visuospatial task (Judgment of Line Orientation test), it was not related to episodic memory test (California Verbal Learning Test) performance.

Visuoperceptual and Spatial Functions

Numerous studies have observed greater impairments in DLB compared to AD on visuospatial and constructional tasks (Collerton et al. 2003; Hansen et al. 1990; Noe et al. 2004; Simard et al. 2003). Even brief screening tasks, such as pentagon-copying from the Mini Mental Status Examination (MMSE; Folstein et al. 2001) have been reported to reveal greater impairment in DLB (Ala et al. 2001) or DLB and PDD (Cormack et al. 2004a) compared to AD. In the latter study, copying impairments in PDD and DLB were specifically related to disturbances in praxis and perceptual processing. Impairments on visuoconstructional tasks probably do not simply reflect the motor demands of the tasks and the motor impairment of PDD and DLB, since DLB and PDD are also more impaired than AD on the matching portion of the Benton Visual Retention Test (Noe et al. 2004) and DLB patients are more impaired than AD patients also on other tasks without significant motor demands. Specifically, on the Visual Object and Space Perception battery, DLB patients were more impaired than AD patients on three of five subtests (cubes, letters, and object decisions; Calderon et al. 2001).

Subjects with DLB have also been found impaired in both automatic (parallel) and controlled (serial) visual search (Cormack et al. 2004b), implicating also a preattentive perceptual impairment. Indeed, several studies have observed greater elementary visual perceptual deficits in DLB and/or PDD and linked these to visual hallucinations. Among DLB subjects those misidentifying a significant number of television personalities also performed much worse in size and form discrimination and visual counting compared to DLB subjects not making such misidentifications. Furthermore, the DLB subjects performed more poorly than an AD group in not only size and form discrimination and visual counting, but also in identifying overlapping figures (Mori et al. 2000). More-

over, DLB subjects with visual hallucinations performed significantly worse on the overlapping figures task. In similar vein, DLB and PDD subjects performed significantly worse than AD patients on tasks of object-form perception and space-motion perception, and among the DLB and PDD patients, those with visual hallucinations performed significantly worse than those without hallucinations on tasks of angle, object-form, and space–motion discrimination (Mosimann et al. 2004).

The fact visual perceptual disturbances in patients with DLB and PDD predispose them to visual hallucinations has an important clinical implication. First, because visual hallucinations are among the strongest diagnostic predictors of DLB and PDD (Galvin 2006; Tiraboschi et al. 2006), the neuropsychological assessment of visual perceptual and constructional functions is critical in suspected DLB and PDD, and their differentiation from AD. Indeed, visuoconstructional tasks, in combination with other tests, can differentiate DLB from normal aging and from AD with sensitivity in excess of 80% and specificity in excess of 90% (Ferman et al. 2006). Furthermore, poor performance on visuoperceptual and constructional tasks may indicate the need for more careful monitoring for development of hallucinations.

It is likely that occipital dysfunction is implicated in visuoperceptual abnormalities of DLB and PDD, and both the ventral occipito-temporal and dorsal occipito-parietal streams have been implicated (Calderon et al. 2001). Occipital lobe hypoperfusion on SPECT imaging has been reported to distinguish DLB from AD with a sensitivity of 65% and specificity of 87% (Lobotesis et al. 2001). A PET study of autopsy-confirmed AD and DLB subjects demonstrated that occipital hypometabolism distinguished DLB from AD with a sensitivity of 90% and specificity of 87% (Minoshima et al. 2001). Hallucinations in DLB have been related to posterior temporal lobe Lewy body counts (Harding et al. 2002), further supporting at least an overlap in the neuropathological basis of hallucinations and visuoperceptual deficits.

Memory

With regards to memory, in general, DLB subjects perform better on tests of episodic (declarative) memory than do AD patients, and this appears particularly true on tests of verbal rather than visual memory and on tests of recognition rather than recall, though most studies report better free recall performance in DLB and PDD than AD as well. Both DLB and PDD show relatively preserved memory performance compared to AD subjects on the Dementia Rating Scale (Aarsland et al. 2003b). Patients with AD generally also perform more poorly than DLB on the immediate and delayed recall portions of tests of word list learning such as the Selective Reminding Test (SRT; Noe et al. 2004) and the California Verbal Learning Test (CVLT; Simard et al. 2002), though one study found DLB to perform better than AD only on the recognition part of the CVLT (Hamilton et al. 2004), perhaps because some of the DLB subjects in that study may actually have had the Lewy body variant of AD. As on list learning, DLB subjects may show better prose passage (WMS-R Logical Memory) immediate and delayed recall than AD (Calderon et al. 2001). Only one study has reported comparably compromised recognition of words and faces (Recognition Memory Test) in AD and DLB (Calderon et al. 2001), although poorer performance by DLB and PDD than AD on the Benton Visual Retention Test in another study (Noe et al. 2004) suggests a possible dissociation between verbal and nonverbal memory in DLB and PDD. Further investigation is needed to determine to what degree elementary visual perceptual dysfunction may be contribute to visual memory impairment in DLB. Similarly, when proceeding from a pathological rather than clinical diagnostic standpoint, there is indication that patients with AD or combined AD and Lewy body pathology have more impaired memory than do patients with Lewy body pathology only (Kraybill et al. 2005).

The major pathological substrate of more severe amnestic deficits in AD relative to DLB and PDD likely reflects the burden of neurofibrillary tangles in the entorhinal cortex and surrounding medial temporal lobe regions in AD. Even with concomitant AD pathology associated with LBV-AD (Hamilton et al. 2004), DLB subjects appear to show more preserved consolidation and storage of verbal information than AD subjects. Although medial temporal lobe atrophy has been reported in DLB/PDD (Tam et al. 2005), it is not so pronounced as in AD. Furthermore, among neocortical and paralimbic regions the hippocampal region was the only one where the AChE activity was more severely decreased in AD than DLB and PDD subjects (Bohnen et al. 2003). Thus, lesser degrees of neuroanatomical and cholinergic compromise in the medial temporal regions may underlie the relatively better memory in DLB than AD.

Remote memory (recall of information from the remote past), unlike learning and retention of new information, is typically preserved in PD. However, patients with PD and dementia may have impairments in remote memory (Freedman et al. 1984; Huber et al. 1986; Leplow et al. 1997). In contrast to AD, in which the impairment is often characterized by a temporal gradient (revealing of greater impairment of recent than remote information), the memory loss in PD is equally severe for information across past decades. One study suggests that recognition of famous faces, a measure of remote memory, may be similarly compromised in AD and DLB (Gilbert et al. 2004). This similarity of DLB to AD in remote memory impairment may relate to the fact that this study evaluated patients with LBV-AD.

Language

Expressive language dysfunction in DLB is grossly similar to that of AD (Collerton et al. 2003; Simard et al. 2000), with early mild, and progressively more severe impairment in visual confrontation naming and verbal fluency, though some propose that naming is relatively preserved in DLB compared to AD and thus, of diagnostic significance (Ferman et al. 2006). Although some studies (Noe et al. 2004) reported similar performance on letter and category fluency tasks, others (Lambon Ralph et al. 2001) found DLB patients to have greater impairment on phonemic or letter fluency tasks compared to AD subjects. Different underlying mechanisms have been inferred from these findings—whereas AD patients have degraded semantic networks or retrieval problems selectively affecting semantic networks, DLB subjects are thought to have attentional and executive deficits that contribute to difficulty with word search and retrieval.

Two qualitative indices of fluency performance potentially illuminate the mechanisms underlying fluency deficits in Lewy body dementias, namely switching and clustering (Troyer et al. 1998). Switching refers to disengaging from one subcategory of words and moving onto another category that are related either semantically or phonemically. Clustering refers to the production of consecutive items from the same semantic or phonemic sub-category. The most efficient strategy likely involves retrieval of highly related words within one sub-category, followed by a switch to another sub-category where other highly-related words may be accessed. Switching impairments are more common in patients with PDD than in AD, while deficits in clustering are more pronounced in AD than PDD (Tröster et al. 1998; Troyer et al. 1998). Even when verbal fluency output is diminished in PD patients without dementia, clustering appears to be preserved (Heiss et al. 2001). These findings suggest that switching may be more dependent on intact executive or frontal-subcortical functions, which tend to be more compromised in PDD than in AD.

An error analysis system for the Boston Naming Test (Hodges et al. 1991) has been used to compare the performance of a normal control group to those of AD and PDD groups equated for overall severity of cognitive impairment (Tröster et al. 1996). Both AD and PDD subjects named fewer items than the control group, but AD subjects were more severely impaired than PDD subjects. The type of errors also differentiated the two dementia groups. The AD group made more phonemic errors, such as mispronunciations or distortions of the target, but sharing at least one syllable with it, and "don't know" responses than the control and PDD groups, which did not differ in the number of these errors. Both PDD and AD subjects made more semantic errors than the control group, but the PDD group made more semantic errors that were associative in nature. That is, PDD subjects tended to produce responses that were clearly related to the target, such as describing an associated action or function, a physical attribute, a contextual associate, or a subordinate or proper noun example of the target. These findings were interpreted to indicate that category knowledge in PDD is accessible to a limited extent, but insufficient to generate item names. By contrast, category knowledge is often unavailable in AD, consistent with the notion that AD involves a degradation of semantic networks (Martin and Fedio 1983).

Neuropsychological Differentiation of Dementia with Lewy Bodies (DLB) from Parkinson's Disease with Dementia (PDD)

By and large, the commonalities between the neuropsychological profiles of DLB and PDD outweigh the differences. Few studies have compared PDD and DLB using neuropsychological test batteries rather than less sensitive cognitive screening measures. Interpretation of the finding of more marked attentional and frontal/executive function impairments in DLB than PDD (Gnanalingham et al. 1997) is difficult because the DLB group's greater overall cognitive impairment confounds interpretation of the attentional findings. However, similar findings were reported in a study (Downes et al. 1998) that matched DLB and PDD groups for age, education, estimated premorbid IQ, and overall severity of cognitive impairment (MMSE score). DLB demonstrated more severe impairments than PDD on tasks involving attention and working memory (WAIS-R Arithmetic, Stroop), and verbal fluency (letter, category, and alternating fluency). Similarly, another study found DLB to be associated with poorer visual attention (Trailmaking test; Stroop test) and visual recognition (Delayed Matching to Sample - 48 test) than PDD (Mondon et al. 2007). It is possible that these greater impairments in attention in DLB than PDD reflect a breakdown of attentional inhibitory controls as demonstrable by evoked potentials, because these impairments in attention are observable independent of visuoperceptual impairments (Perriol et al. 2005). In contrast, a study using computerized simple and choice reaction time, and vigilance tasks failed to demonstrate differences in attention between DLB and PDD (Ballard et al. 2002).

Another group of investigators, using a wide ranging test battery (Noe et al. 2004) also failed to observe any neuropsychological differences between PDD and DLB groups equated for overall severity of dementia, although they did replicate others' findings of greater memory impairment in AD than DLB and PDD, and greater attention, visuoperceptual and constructional deficits in

DLB than AD. Studies have demonstrated comparably compromised pentagon copying (Cormack et al. 2004a), Brief Visual Retention Test stimulus-matching (Noe et al. 2004), visual cancellation (Noe et al. 2004), visual discrimination, space and object perception (Mosimann et al. 2004), clock drawing (Cahn-Weiner et al. 2003), figure drawing (Noe et al. 2004), and memory (Aarsland et al. 2003b; Noe et al. 2004) in DLB and PDD. When "cortical" (memory impairment) and "subcortical" patterns of impairment (attention, initiation and perseveration, and construction) are defined by Dementia Rating Scale subtest scores, both DLB and PDD are more likely to have a subcortical (55% and 56%, respectively) than cortical (26% and 30%) impairment pattern, the converse of the predilection of AD toward cortical impairment patterns (Janvin et al. 2006b). Of course, whether performance on a given DRS subtest is more susceptible to cortical vs. subcortical pathology remains a matter of debate.

Early Neuropsychological Detection of Lewy Body Dementias (DLB and PDD)

Basic Concepts, Definitions, and Approaches

Detection of a dementia in the earliest phase of neurodegeneration clearly has important clinical implications for treatment, because it is probable that potential neuroprotective or neurorestorative therapies and secondary prevention efforts might be expected to have their greatest impact in that early phase of the disease. Figure 2 illustrates for PD the various phases from pathology onset to diagnosis. The prediagnostic phase is the time period prior to diagnosis but it has no distinct early boundary. Whereas the prodrome is the period between onset of the earliest, non-specific symptoms and diagnosis, the pre-symptomatic phase is the time between pathology onset and emergence of the earliest, non-specific symptoms. In the case of PD, increasing reference has recently been made to the "premotor" phase of the disease during which, for example, sleep disturbance, olfactory dysfunction, mood disturbance, and signs of autonomic dysfunction (e.g., constipation) may manifest themselves before the classical motor symptoms of PD (Tolosa et al. 2007; Wolters and Braak 2006). Because the classic motor symptoms need to be present for PD (and PDD) diagnosis, and because the motor symptoms evolve gradually before diagnosis, the premotor phase, within the framework of Fig. 2, is best considered as beginning with onset of the non-specific symptoms and lasting a variable amount of time until one or more of the classic motor symptoms emerge in the pre-diagnostic phase.

Although the figure illustrates PD, it is readily applied to PDD and DLB. The convention of requiring a minimum of 12 months between motor symptom onset and emergence of dementia to diagnose PDD, even if somewhat arbitrary, has been recommended to be retained (Emre et al. 2007). Thus, the diagnosis of DLB is appropriate when onset of dementia precedes or occurs within a year of development of the motor symptoms. What remains less clear is how the concept of mild parkinsonian signs (Louis and Bennett 2007), the co-existence of mild cognitive impairment (MCI) and mild parkinsonism (Louis et al. 2005), and the finding that subtle cognitive dysfunction may already be detectable at the time of PD diagnosis in a sizeable subgroup (about 30%) of patients (Foltynie et al. 2004;

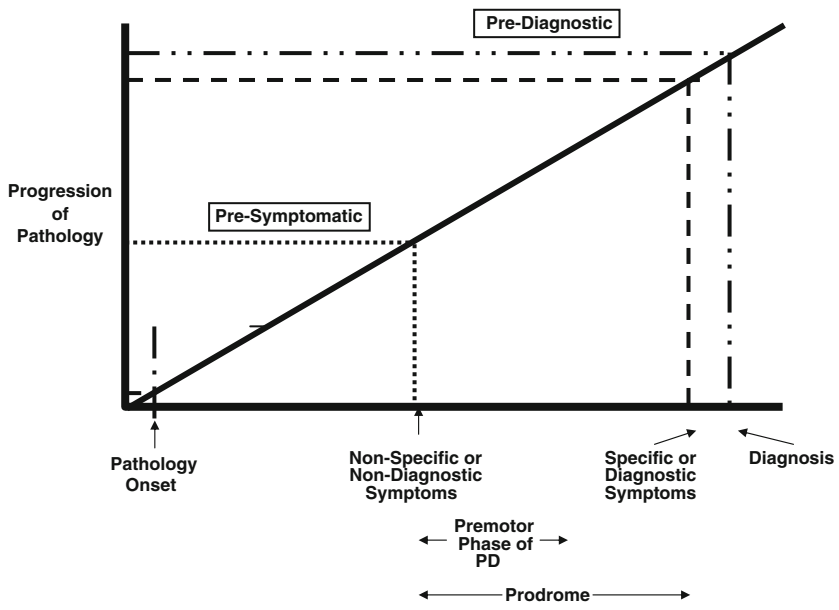

Fig. 2 Diagrammatic representation of pre-symptomatic and pre-diagnostic phases in Parkinson's disease. A *straight line* depicting increase in pathologic burden over time is shown only for ease of illustration, but the relationship is not linear

Muslimovic et al. 2005) will affect the definition of DLB and PDD and their prodromes. Indeed, PDD patients with parkinsonism for fewer than 9.5 years before dementia onset bear closer pathological resemblance to DLB than do those with parkinsonism longer than 9.5 years before dementia onset, who, relative to DLB patients, have fewer plaques, less cortical α-synuclein pathology, but greater cortical cholinergic abnormality (Ballard et al. 2006). In the following discussion, it must also be noted that the prodrome of PD is not necessarily that of PDD, and much more effort has been devoted to the early detection of PD (which itself has a years-long prodrome) than PDD. These efforts, however, may secondarily inform about cognitive dysfunction and its evolution in PDD.

Several demographic, disease, and neuropsychological variables (Table 4) have been associated with increased risk of dementia in PD, including, for example, education (Glatt et al. 1996), presence of REM sleep behavior disorder (Vendette et al. 2007), change in motor subtype from tremor-dominant to postural instability and gait difficulty (Alves et al. 2006), and poor performance on verbal fluency tasks (Jacobs et al. 1995). Two basic approaches have been taken to studying the neuropsychological prodrome of dementias. One approach involves defining a group of persons with mildly *impaired* cognition (or groups with different profiles of mildly impaired cognition) and then following the groups longitudinally. Some studies may also follow cognitively intact persons as a comparison group in this approach. After a pre-determined time, a determination is made which subjects reach a specific endpoint (e.g., dementia), and the cognitive (or other) baseline characteristics distinguishing those persons developing dementia from those free of dementia are identified. This approach is exemplified by studies that have, for example, examined conversion rates to dementia in persons with mild cognitive impairment (MCI). The second approach follows a group of *unimpaired* persons on whom detailed observations (including neuropsychological ones) are made over several timepoints. The characteristics associated with the endpoint (dementia) are then empirically identified and allow a detailed description of the evolution of symptoms during the prodrome.

The Concept of Mild Cognitive Impairment in Lewy Body Dementias

Mild cognitive impairment (MCI) is a transition state between normal, age-associated cognitive change and early dementia. The concept has attracted controversy and debate about its utility (Albert and Blacker 2006; Morris 2006; Petersen and O'Brien 2006). In brief, the initial conceptualization of MCI limited itself to mild memory impairment (Petersen et al. 1999), yet it has become clear that MCI can be quite heterogeneous in its expression, and that conversion rates to dementia and the stability of the MCI diagnosis are variable (and probably related to study setting, recruitment method and definition and ascertainment of MCI). While recent reformulations of MCI amnestic, non-amnestic, and single vs. multiple domain subtypes acknowledge cognitive heterogeneity, too limited data are available on non-amnestic MCI to judge whether MCI subtypes have clinical utility and validity.

Very little attention has been paid to the neuropsychological characterization of the prodrome of DLB, perhaps because the clinical and pathological diagnostic criteria for DLB themselves have been a matter of debate and continued refinement. Only few studies of MCI and AD have secondarily reported on the rate of conversion of MCI to DLB, and these data do not permit one to adequately address the potential value of MCI subtypes in predicting DLB. A recent community study of 141 persons with MCI and 440 cognitively-"healthy" followed for 30 months found "possible DLB" in ten subjects with AD. Of those 10, four had been cognitively normal at baseline, whereas four had non-amnestic MCI and two had amnestic MCI (Fischer et al. 2007). Another study, examining 34 persons who had amnestic MCI, converted to dementia, and came to autopsy (thus, introducing potential selection bias), reported that one patient had a final clinical diagnosis of DLB, and that three subjects received a neuropathologic diagnosis of Lewy body disease (Jicha et al. 2006).

There appears to be no study to date that has reported on the incidence of PDD among persons with MCI. However, the historical confluence of at least three events probably underlies recent attempts (Caviness et al. 2007; Fernandez et al. 2005; Janvin et al. 2006a) to extend the concept of

Table 4 Risk factors for dementia in Parkinson's disease (Tröster and Woods 2007)

Demographic variables	Disease variables	Neurobehavioral variables
Greater age	Later onset	Depression
Lower education	Disease duration	Poor performance on
Lower socioeconomic status	Disease severity	Executive/attention
Family history of Parkinson's dementia	Susceptibility to levodopa-induced psychosis or confusion	Verbal fluency
	REM sleep behavior disorder	Visuoperceptual
	Akinetic-rigid symptoms	List learning

Table 5 Braak staging of neuropathology in Parkinson's disease (Braak et al. 2003)

Stage	Primary brain region affected	Loci of pathology
1	Medulla	Dorsal IX/X motor nucleus and/or immediate reticular zone
2	Medulla and pontine tegmentum	Stage 1+caudal raphe nuclei, gigantocellular reticular nucleus and caeruleus-subcaeruleus complex
3	Midbrain	Stage 2+midbrain (esp. pars compacta of substantia nigra)
4	Basal prosencephalon and mesocortex	Stage 3+prosencephalon (confined to transentorhinal region and CA2-plexus)
5	Neocortex	Stage 4+high order sensory association areas of the neocortex and prefrontal cortex
6	Neocortex	Stage 5+first order sensory association neocortical areas and premotor areas; may be some mild changes in primary sensory areas and primary motor field

MCI to PD: the acknowledgement of cognitive heterogeneity in MCI and creation of subtypes of MCI (Petersen 2004), the detection at time of diagnosis in many PD patients of subtle cognitive (predominantly memory and/or executive) impairments resembling MCI subtypes (Foltynie et al. 2004; Muslimovic et al. 2005), and the neuropathologic staging of PD compatible with pre-diagnostic non-motor symptoms (Braak et al. 2003). Obviously, studying the cognitive characteristics of the PDD prodrome in persons with PD is more economical and efficient than studying persons with MCI since the current criteria for PDD require the presence of PD, and it is likely that only a small number of persons with MCI go on to develop PD. Nonetheless, studying the PDD prodrome will likely require considerable time because: a) the average disease duration until dementia is about 10 years (Aarsland et al. 2003a; Hughes et al. 2000), b) after 15 years, among surviving patients only about half may have dementia (Hely et al. 2005), and c) cognitive change in PD patients without dementia from year to year is quite small (Muslimovic et al. 2007; Tröster et al. 2007). The recent finding of cognitive changes in very early PD, coupled with a pathological staging system providing biological support for the notion that cognitive changes may occur in early PD, suggests that the PDD prodrome may coincide with the PD prodrome itself and thus require a new strategy for study (e.g., studying persons with mild cognitive impairment and/or mild parkinsonian signs).

The Braak staging system for PD (Table 5; Figs. 3 and 4) suggests that pathology begins in the medulla, pontine tegmentum, and olfactory structures (consistent with the observation of olfactory and taste alterations in early or pre-clinical PD (Lang et al. 2006; Tolosa et al. 2007), and then proceeds in the third and fourth stages to affect substantia nigra and basal mid- and forebrain nuclei when the disease itself becomes apparent. Neocortex is affected in the fifth and sixth stages. Although this staging system was recently critically re-evaluated (Braak et al. 2006a; Halliday et al. 2006), the finding that cognitive impairment is detectable even with the relatively insensitive MMSE in a subgroup of patients as early as stages 3 and 4 (Braak et al. 2006b, 2005) provides strong neurobiological support for the contention that a cognitive prodrome may begin around or even

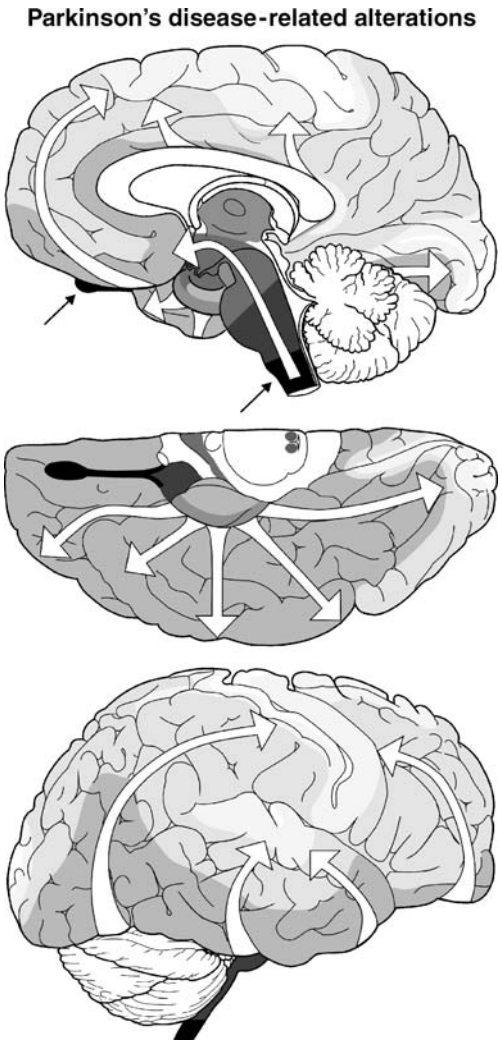

Fig. 3 Progression of pathology in Parkinson's disease according to the Braak staging system (from allocortex, through mesocortex to neocortex). Figure courtesy of Prof. Dr. Heiko Braak

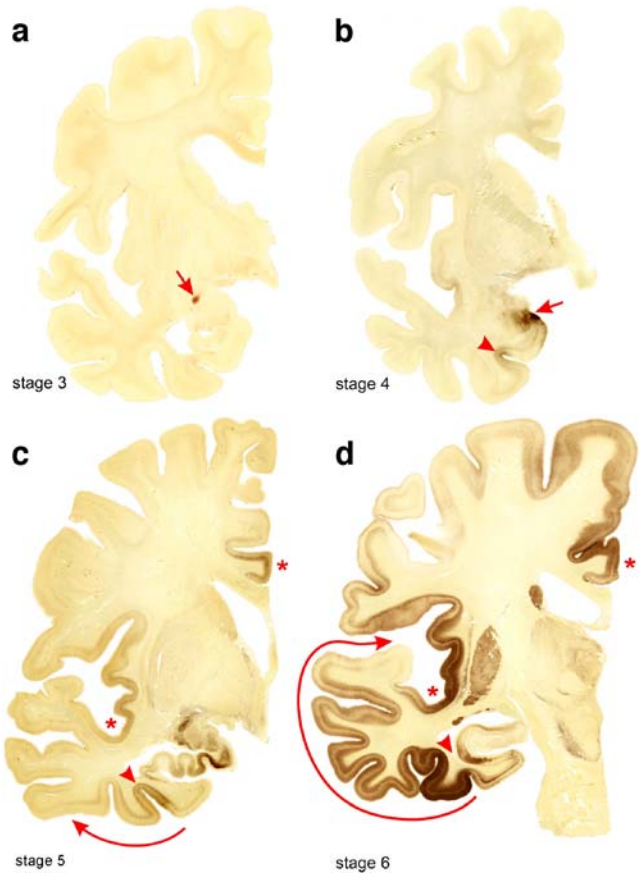

Fig. 4 Pathological changes indicated by alpha-synuclein staining in the Braak staging system for Parkinson's disease (stages 3–6). Amygdalar pathology in stage 3 (*arrow*) becomes more profound in stage 4, when anteromedial temporal mesocortex pathology (*arrowhead*) also becomes evident. In stage 5, additional lesions are evident in cingular and insular neocortex (*asterisks*), while a dense network of Lewy neurites emerges in the superficial anteromedial temporal neocortex and Lewy bodies are evident in the deeper projection neurons (*arrowhead*). In stage 6 pathological burden increases in extent and severity and, in advanced cases, affects primary neocortical fields such as in Heschl's gyrus (*arrow*). Figure courtesy of Prof. Dr. Heiko Braak

before the pathologic stages when PD becomes clinically diagnosable.

Only one study (Janvin et al. 2006a) has retrospectively defined MCI subgroups in PD and then examined subsequent conversion to dementia. In that community study of 72 nondemented PD subjects, 38 were diagnosed with MCI (six MCI-amnestic; 17 MCI-non amnestic, single domain; and 15 with MCI multiple domains (unspecified). Fifty-nine patients (82%) completed follow-up 4 years later, and more MCI (18; 62%) than initially cognitively normal subjects (six; 20%) became demented per DSM criteria. Single domain, non-memory MCI and multiple-domains MCI were associated with later development of dementia but amnestic MCI was not. Another study (Foltynie et al. 2004) found that 36% of newly diagnosed PD patients had cognitive impairment as defined by poor performance on one or more of the MMSE, Tower of London, and CANTAB pattern recognition tasks. Formal MCI subgroups were not identified, and a follow-up study of this sample (Williams-Gray et al. 2007) did not provide detailed analyses of whether subgroups with executive vs. memory vs. multiple deficits were more likely to develop dementia. The authors did, however, mention that preliminary analyses indicated that the cognitive subgrouping was *not* informative in dementia prediction. The report noted that poorer baseline performance on tests relatively more dependent on posterior cortical function (including pentagon copying, semantic fluency, and spatial recognition memory) was associated with more rapid cognitive decline over the ensuing 3 to 5 years.

A study retrospectively defining MCI in 86 PD patients consecutively enrolled over 5 years in a brain bank program, found that at baseline neuropsychological assessment 62% of patients were cognitively normal, 21% had MCI, and 17% had PDD (Caviness et al. 2007). These percentages unfortunately are not very meaningful because the groups differed significantly in disease duration, suggesting that the proportion of patients cognitively impaired at baseline is, not surprisingly, dependent on when in the disease course the baseline assessment is made and thus, sample dependent. The characterization of the type of MCI within the sample is probably of greater interest to neuropsychologists. The authors reported that of the PD-MCI subjects, 39% had single domain executive impairment, 22% single-domain amnestic impairment, 6% single domain language impairment, 22% multiple-domain MCI without an amnestic deficit, and 11% had multiple domain MCI with an amnestic deficit. Overall, executive impairment tended to be more common than amnestic deficit in PD-MCI. How MCI subtype might be related to subsequent dementia was not addressed in the study.

In essence, present data do not allow one to adequately evaluate the utility of MCI in PD. Two existing studies provide only suggestive, albeit, opposite findings about whether amnestic or non-amnestic cognitive deficits in PD are more strongly associated with later dementia. This state of knowledge suggests considerable caution is necessary in applying MCI to PD. There are several other reasons for this recommendation. First, one criticism of MCI is that this diagnosis hinders formulation of an accurate prognosis and timely treatment. While this objection does not apply to PD-MCI since PD will have been diagnosed when the diagnosis of MCI is made (Dubois 2007), it is unclear whether an MCI diagnosis in PD will aid treatment. Second, because some feel that MCI *is* early AD (Morris 2006), and because MCI, when converting to dementia, most often converts to AD, there is a danger that the diagnosis of MCI in PD will lead to confusion and perhaps an assumption among patients and physicians that the PD

patient will also develop AD. Third, MCI is heterogeneous and consequently it will be difficult to determine whether a given patient has PD-MCI or a form of MCI associated with another condition. While some (Petersen and O'Brien 2006) have suggested MCI might be an initial diagnosis, with a second step involving determination of the underlying etiology (much as is the case for dementia in the current DSM), it is unclear what value this approach adds since it is known the patient has PD. It seems preferable to reserve the use of MCI, as was originally done, to instances when there is no known neurologic or medical condition that can account for the cognitive syndrome, or alternatively, apply it only to cases of PD in which the cognitive syndrome is so atypical that another, as yet unidentified, etiology is suspected. Fourth, as others (Dubois 2007; Fernandez et al. 2005) have pointed out, the detection of MCI depends on how widely the assessment net is cast. In addition, there are at present no precise guidelines about which tests would be used to ascertain MCI, or about which of the multitudinous scores yielded by many tests would have to fall 1.5 standard deviations below the normative mean. Fifth, performance on neuropsychological tests can be affected by dopaminergic medications used to treat PD (Cools 2006), and especially in early PD, when one hemisphere may be preferentially affected by disease, overmedication of the relatively intact hemisphere can affect test performance (Tomer et al. 2007), making identification of MCI difficult. Sixth, depression (which is common in PD) can exacerbate cognitive impairment (Boller et al. 1998; Tröster et al 1995) and in practice it is difficult to distinguish with a single neuropsychological assessment whether cognitive impairment in PD reflects depression or MCI. Seventh, subtyping MCI into amnestic and non-amnestic types might be insufficient. For example, it is known that the memory impairment of PD is qualitatively heterogeneous and can resemble that seen in subcortical dementias such as Huntington's disease, or AD (Filoteo et al. 1997). Consequently, it is possible that gross subtypes of PD-MCI (e.g., amnestic) obscure the prognostic significance of more fine grained neuropsychological analyses. Finally, in multiple domain MCI in PD it might be challenging to determine whether a memory impairment is primary or secondary to executive dysfunction and thus whether there is a multiple or single domain MCI present.

Empirical Approaches to Identifying Cognitive Characteristics of Persons Developing Lewy Body Dementias

Studies utilizing an empirical approach to defining the prodrome to Lewy body dementias have generally looked at PDD rather than DLB. What emerges from these studies is a fairly consistent picture that tests placing a premium on a variety of executive functions appear to be the best predictors of PDD. Although one study of 87 patients (10 of whom became demented during 54 month follow-up) reported lower verbal intelligence and cognitive screening test scores among patients developing dementia than those not developing dementia, the results are difficult to interpret because it is unclear if the groups differed in intelligence premorbidly and whether the patients developing dementia might already have been in the early diagnosable stage of dementia at initial assessment (Biggins et al. 1992).

An early study showing the importance of frontal dysfunction in dementia prediction (Piccirilli et al. 1989) found that six of eight PD patients with (but only 1 of 22 without) "frontal dysfunction" on a Lurian task at baseline developed dementia at 4-year follow-up. In another study, notable for including 92 *newly-diagnosed* PD patients (15 of whom had dementia at diagnosis), a comparison of eight assessable patients who became demented over a 5-year follow-up and 39 assessable patients who did not develop dementia over that time revealed that the group developing dementia performed more poorly at baseline on tests of executive function (Raven Matrices or nonverbal reasoning and choice reaction time), simple reaction time, and verbal and nonverbal memory (Auditory Verbal Learning Test and Benton Visual Retention Test; Reid et al. 1996). What is not clear is whether the poor performances on tests of memory reflected true memory deficits or were secondary to executive dysfunction affecting encoding and retrieval processes. This issue was taken up in a recent study comparing the neuropsychological test performances of 18 PD patients developing PDD about 1 year after assessment and a group of 18 closely-matched patients not developing dementia (Woods and Tröster 2003). In that study, those patients developing dementia made more perseverative errors on the Wisconsin Card Sorting Test (Heaton et al. 1993) and performed more poorly on digit span backwards and on immediate recall and recognition discriminability on the California Verbal Learning Test (Delis et al. 2000). Given the absence of rapid rates of forgetting or impoverished delayed recall and the overall profile of deficits, the authors suggested that the poor performance on the verbal learning test was most parsimoniously explained by deficient executive processes controlling encoding and retrieval. The constellation of deficits also predicted well which patients developed dementia (although sensitivity was higher than specificity): impairment on at least two of the four variables had overall predictive power of 0.75.

In a study with a larger sample but not matched groups (23 PD patients developing dementia and 88 patients not developing dementia after a year), immediate recall on the Selective Reminding Test, category (semantic) and letter (phonemic or lexical) verbal fluency, and identification of

similarities and differences on the Dementia Rating Scale was poorer in the group developing dementia (Jacobs et al. 1995). After controlling for group differences in age, education, gender, severity of motor and depression symptoms, poorer performance on the verbal fluency tasks was associated with increased risk of dementia. Similar findings were obtained in yet another study (Mahieux et al. 1998) of 89 patients, of whom 81 were re-assessed about 3.5 years later and 19 of whom had developed dementia. The group developing dementia differed from the non-demenating group on numerous neuropsychological tests at baseline, but regression analyses revealed that only poorer performance on the Picture Completion subtest of the Wechsler Adult Intelligence Scale-Revised, the interference portion of the Stroop task, and letter verbal fluency were independently associated with dementia risk. Stroop task performance was also found to be an independent predictor of dementia after 4 years in an epidemiological study of 76 PD patients (Janvin et al. 2005), although the interpretability of that study's findings is limited by the very small range of tests administered (Benton Visual Retention test, multiple choice version, Judgment of Line Orientation, Mattis DRS, and Stroop task).

Biomarkers and Neuropsychology in Lewy Body Disorders

A biomarker is an objectively measurable characteristic indexing a normal or pathological biological process or response to therapy. Such markers can thus be used to facilitate identification of disease predisposition, diagnosis, monitoring of disease progression, and prediction and monitoring of treatment response. As has been noted by others (Michell et al. 2004), clinical tests, including neuropsychological ones, rely on the phenotypic expression of the disease and thus would not detect the very earliest pathological changes or be biomarkers thereof. Similarly, if a neuropsychological test were to have utility as a marker of treatment response, it would not be sensitive to disease progression by virtue of its sensitivity to symptomatic treatment. Neuropsychological tests may, however, prove helpful in detecting very early symptomatic changes associated with Lewy body dementias, as noted in the preceding section, and be helpful in monitoring treatment response. Indeed, in the case of dementia, one might argue that in order for biomarkers of treatment response to be useful, they would by necessity have to be related to improvement in neuropsychological test performance. If not, one would need to assume the biomarker indexes treatment effect on a biological process that is actually irrelevant or incidental to dementia. Considerable effort is being expended on a search for PD biomarkers, including biochemical, genetic, and neuroimaging tests (Dorsey et al. 2006; Lippa et al. 2007; Michell et al. 2004). Though numerous challenges remain, neuropsychological studies will be an important companion to biomarker studies. Such studies will be able to address whether neuropsychological test results have incremental validity when used in conjunction with biomarkers. For example, one recent study has suggested that performance on the Grooved Pegboard may be a marker of nigrostriatal degeneration as indexed by dopamine transporter imaging (Bohnen et al. 2007). It is likely that highly-specific biological processes indexed by biomarkers will likely account for only very small portions of variance in performance on complex cognitive tasks or tests. It is possible, however, that specific biological processes have a larger effect on more specific aspects of cognition. Detailed cognitive characterization of dementia prodromes will be necessary to address this possibility. Such studies might also improve our understanding of the molecular biologic basis of cognition in healthy persons.

Summary and Conclusions

Lewy body disorders share a disorder of α-synuclein metabolism. Whether DLB and PDD are the same disorder whose differences in symptom emergence are merely slave to the specific brain regions affected earlier and later in the disorders is controversial. Recently, there is greater consensus that clinical distinctions be maintained between these disorders even though they are pathologically similar. From a neuropsychological standpoint, DLB and PDD are more readily distinguished from AD than each other. Recent (re) formulation of diagnostic criteria for DLB and PDD and a pathological staging system for PD will facilitate investigation of potential subtle differences in pathology and neuropsychological phenotype, as well as the prodromes of DLB and PDD. More work has been done in characterizing the prodrome of PDD than DLB. The preponderance of the evidence suggests that executive dysfunction in PD may be the best predictor of subsequent PDD. Recent enthusiasm in extending the concept of MCI to PD needs to be tempered given the numerous challenges the definition and investigation of this construct faces in PD. However, it is anticipated that studies of those at risk for PD, and especially of persons with mild parkinsonian signs with or without MCI, might yield more fine grained characterization of the earliest cognitive changes in Lewy body disorders. If such changes can be reliably identified, they have the potential to be used in conjunction with biomarkers not only to diagnose these disorders earlier on, and to predict and monitor treatment response, but also to inform about the molecular neurobiol-

ogy of cognition. Neuropsychology will play a central role in these investigations.

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