Challenges in Predicting Cognitive Decline in Dementia with Lewy Bodies

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Abstract
Despite being the second most common form of neurodegenerative dementia, dementia with Lewy bodies (DLB) is under-recognized and carries a worse prognosis than other subtypes of the condition. Cognitive impairment is a cardinal feature of all types of dementia and DLB presents with a distinct profile with deficits in attention, executive function, and visuoperceptual abilities. This difference from Alzheimer’s disease and the common presence of neuropsychiatric symptoms may lead to challenges in predicting cognitive decline in this patient population. Firstly, the diagnosis of DLB is often delayed in clinical practice leading to variability from which time point in the disease course cognitive decline is measured. Secondly, the most frequently used measurement tools for cognitive difficulties focus on memory and naming rather than the domains affected by DLB. While there is now largely a consensus which tools are useful in diagnosing DLB, their validity in assessing deteriorating cognition is less clear. Thirdly, the presence of fluctuating cognition, the propensity to develop delirium episodes, as well as difficulties in distinguishing the two entities in clinical practice make it difficult to predict the disease course. Sleep disturbances are likely to influence cognitive decline but require further study in patients within established DLB. Fourthly, as in most cases of dementia, neuropathological comorbidities are frequently present in DLB. While the influence of Alzheimer’s pathology on cognitive decline in DLB is comparatively well understood, the impact of other pathologies remains unclear. The recent definition of research criteria for mild cognitive impairment in DLB could facilitate earlier diagnosis and more structured follow-up. Assessment tools measuring cognitive domains predominantly affected in DLB need to be more consistently used in longitudinal studies and clinical practice, as well as concurrent measures of fluctuations in cognition. Greater availability of biomarkers and digital healthcare solutions can play an important role in enabling more accurate monitoring and prediction of cognitive decline in DLB.

Introduction
Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia. While neuropathological case studies report incidences of 15–20% [1], this is considerably lower in routine clinical ser-
vices, often below 5%, with large geographical variations [2]. Compared to other forms of dementia, including Alzheimer’s disease (AD), DLB is known to have a less favourable prognosis in a number of domains including an almost 2 years earlier mortality, higher rates of hospitalisation and institutionalization, more frequent episodes of delirium, lower quality of life, and higher caregiver burden and healthcare costs [3–10]. Less certainty exists in relation to cognitive decline in DLB despite a progressive cognitive impairment being a cardinal feature of all dementias. Although several current studies [11, 12] suggest an accelerated cognitive decline compared to AD, the most recent meta-analysis found no difference between DLB and AD [13]. This review aims to outline challenges in predicting cognitive decline in DLB, to provide potential solutions for the practicing clinicians and to set future research directions (see Table 1 for an overview).

**Challenges due to a Delayed Diagnosis of Dementia with Lewy Bodies**

The prevalence of DLB amongst dementia subtypes diagnosed in memory services is about a quarter to one-third of what be expected from autopsy studies and DLB thereby seems substantially under-recognized [2]. A delay in DLB diagnosis is well-described in the literature: in the USA, more than 1 year was needed to establish the correct diagnosis of DLB for almost 50% of patients [14]. Similarly, in the UK, it took on average 1.2 years to arrive at a diagnosis of DLB from the initial appointment and more imaging and clinical assessments were needed than for patients with non-DLB diagnoses [15]. The impact of this delay in diagnosis on predicting cognitive decline is not clear. This, however, leads to the absence of a consistent point from which deterioration could be measured. Patients with DLB and AD are in most studies diagnosed

| Table 1. Overview of challenges, clinical considerations, and research directions |
|----------------|---------------------------------|---------------------------------|
| Challenge | Clinical considerations | Research directions |
| Delayed diagnosis of DLB | Proactively diagnose MCI and consider the possibility of Lewy body pathology | Prospective studies on how patients with MCI-LB progress to dementia |
| Tests used to diagnose DLB and to measure change over time | Use tools assessing cognitive domains predominantly affected in DLB (e.g., Montreal Cognitive Assessment (MoCA)) as screening tool and for follow-up assessments | Larger scale observational studies using the MoCA or a similar tool |
| Fluctuating cognition, delirium episodes, and sleep disturbances | When assessing cognition, simultaneously also assess for fluctuations, ideally using a structured tool (e.g. Clinician Assessment of Fluctuation scale or the Mayo Fluctuation Composite Score) | Develop a better understanding of the longitudinal course of fluctuations in DLB |
| Neurpathological co- and multi-morbidity | Establish clinical features of possible comorbid AD (using cognitive testing, CSF, or neuroimaging) | Larger clinico-pathological studies exploring the relative influence of amyloid-beta, tau, alpha-synuclein, cerebrovascular damage, TDP-43, and hippocampal sclerosis on cognitive decline and the general clinical picture |

DLB, dementia with Lewy bodies; AD, Alzheimer’s disease; MCI, mild cognitive impairment; MCI-LB, mild cognitive impairment with Lewy bodies; MoCA, Montreal Cognitive Assessment; REM, Rapid Eye Movement; CSF, cerebrospinal fluid.
with similar Mini-Mental State Examination scores (MMSE) [16], whereby scores in DLB patients are often slightly higher than in AD cohorts. A meta-analysis of survival data showed that differences in survival time were not explained by MMSE score at the time of diagnosis [8]. However, a study which measured survival from fixed MMSE score points of 20 and 17 showed that DLB had a shorter survival than AD when following up from each of these score points [17]. This could possibly indicate that at a higher MMSE score, the neurodegenerative process could already be further advanced in DLB. The variable ways in which DLB can present poses a challenge for clinical services. In a recent study of 251 patients diagnosed with DLB in a UK mental health and dementia care service, the most common early complaints were memory loss, but also hallucinations and low mood [18].

Early correct diagnosis of DLB remains an important challenge and an important step forward is the recent definition of research criteria for mild cognitive impairment (MCI) in DLB (MCI-LB) [19]. As in other already established diagnostic standards for MCI in neurodegenerative conditions, the triad of a subjective cognitive concern, an objective impairment in at least one cognitive domain, and largely preserved independent functioning needs to be met [20]. The cognitive impairment can be in any domain, but in the context of DLB, it is more likely to be associated with visuospatial, attentional, or executive deficits. For a diagnosis of MCI-LB, the authors propose that additional core features of DLB (fluctuating cognition, recurrent visual hallucinations, REM sleep behaviour disorder (RBD), at least one Parkinsonian motor sign) and/or proposed biomarkers (reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET, polysomnographic confirmation of REM sleep without atonia, and reduced meta-iodobenzylguanidine uptake on myocardial scintigraphy) need to be present [19]. Depending on the number of symptoms and biomarkers elicited, the research criteria support the diagnosis of either “probable” MCI-LB (at least 2 core features or one core feature and at least one biomarker present) or “possible” MCI-LB (only one core feature or biomarker present).

Another important concept is “mild behavioural impairment,” which was developed mirroring MCI to detect behavioural changes occurring in later life, which do not meet the criteria for a major psychiatric disorder or dementia [21]. Neuropsychiatric symptoms, even if mild and occurring in the absence of an obvious cognitive impairment, have been shown to be associated with an increased dementia risk [22, 23]. Although not formally operationalized, a psychiatric-onset DLB has been proposed [19], whereby more severe new-onset psychiatric presentations, as late-onset major depressive disorder and late-onset psychosis should raise the suspicion of underlying Lewy body pathology. In these presentations, cognitive testing and evaluation of the patient’s performance are challenging, both due to overlapping psychiatric symptoms and the propensity of patients with DLB to fluctuate in presentation. It has been shown that careful observation of the phenomenology (DLB presenting with more visual hallucinations and less paranoia than very-late-onset schizophrenia-like psychosis), and the neuropsychological profile (DLB presenting with prominent visuospatial deficits) can aid differential diagnosis between neurodegenerative and functional psychosis [24]. A higher frequency of hypersensitivity to any psychotropic medication and autonomic failure (ventilatory response to hyperventilation) can further predict DLB in those with late-onset depression [25]. In clinical reality, the use of biomarkers suggested as useful in MCI-LB, might supplement, or replace, these complex observations, but their clinical and economic value will need to be demonstrated [19, 26].

Overall, the variation of the time point and severity at which DLB is diagnosed makes it difficult to establish a clear baseline from which further decline can be monitored. The recent establishment of research criteria for MCI-LB and the increasing availability of biomarkers are important steps to facilitate earlier diagnosis and to improve monitoring of cognition. In cohorts which have been identified as at risk prior to receiving the diagnosis of dementia, there might be less heterogeneity between patients when the diagnosis is established. This should make it easier to synchronize cognitive trajectories and allow more coherent prediction of progression of cognitive decline [27].

Challenges with Structured Cognitive Tests Used to Diagnose Dementia with Lewy Bodies and to Measure Change Over Time

In contrast to AD, which is primarily characterised by impaired memory and language, there is a higher occurrence of difficulties in attentional, executive, and visuoperceptual domains in DLB [28]. As DLB and dementia in Parkinson’s disease (PDD) have an overlapping cognitive profile, recommendations regarding screening for PDD are likely to be useful for DLB. The Movement Disorder Society review committee recently endorsed...
The Montreal Cognitive Assessment (MoCA) [30], Mattis Dementia Rating Scale Second Edition (DRS-2) [31], and the PD-Cognitive Rating Scale (PD-CRS) [32] for cognitive screening in Parkinson’s disease. Not recommended were the scales most frequently used in clinical dementia services, the Mini-Mental State Examination (MMSE) [16] and the Adenbrooks’s Cognitive Examination (ACE-R/ACE-III) [33, 34]. The MMSE is considered unsuitable as it primarily tests cortical aspects of cognition, as memory and language, which are frequently preserved in PDD or DLB (also subsumed as Lewy body dementias; LBD), with insufficient testing of visuospatial and executive function [29]. The ACE-R/ACE-III [33] has good psychometric properties and assesses visuospatial function to a larger degree but has incomplete coverage of executive function, limited to only fluency tasks [29]. In contrast to the Mattis Dementia Rating Scale (DRS-2) and the MMSE, the MoCA has been shown to predict progression from MCI to PDD [35] as well as sensitivity to change over time in Parkinson’s disease without dementia [36]. In the latter longitudinal study of 102 patients with PD, lower MoCA scores, postural instability and gait disturbance, and depressive symptoms at baseline were associated with a higher risk of cognitive decline [36]. However, little is known how structured tests can evaluate cognitive decline in those with Lewy body disease who have already reached the dementia stage. The rate of cognitive decline in LBD has been assessed in a number of longitudinal studies, largely using the MMSE, and the latest meta-analysis found similar decline in LBD and AD [13]. It has been speculated that this lack of difference might be grounded in the MMSE being not sensitive enough in registering cognitive deficits specific to LBD [37]. Differences in the rate of change between MMSE and MoCA were evaluated over 1 year in fourteen patients with DLB: no significant difference between the decline on MMSE (0.98-point decline) and the MoCA (1.04-point decline) was detected, with a trend of MoCA being more sensitive in identifying cognitive decline in patients with a milder cognitive impairment [37]. This underlines that larger follow-up studies regularly applying MoCA over several years are needed to elucidate its usefulness for cognitive prognostication in DLB.

Visuospatial functioning has been identified as potential predictor of faster cognitive and functional decline in DLB [38, 39]. However, a more recent study of 67 patients with DLB followed for up to 4 years [40] found no significant association between low visuospatial scores at baseline and faster cognitive decline (measured by MMSE) or progression of dementia severity. The same study assessed cognitive decline on a number of domain-specific tests in patients with DLB comparatively to 119 patients with AD [40]. A difference in the rate of cognitive decline between DLB and AD was only detected in the Trail Making Test A (TMT-A), which assesses visual scanning, psychomotor speed, and attention by asking the participant to draw a line to connect consecutive numbers from 1 to 25 [41]. Older studies also identified that patients with DLB declined slower in recognition memory and recall, but more rapidly in verbal fluency than those with AD [42–44].

Overall, assessment of cognition in DLB should not rely on tests predominantly assessing language and memory, and the MoCA appears to be a useful tool to detect cognitive difficulties and progression to dementia. Larger scale evaluations are required in patients who have already been diagnosed with DLB, both to determine MoCA’s (or similar tests’) performance and domain-specific decline.

**Challenges due to Fluctuating Cognition, Delirium Episodes, and Sleep Disorders**

Fluctuations are one of the core features of DLB and present in the majority of patients [45]. The term is used to describe spontaneous variations of cognitive abilities, alertness, or arousal [28]. Importantly those periods of impaired cognition occur on a spectrum between very marked changes (often described as delirium-like) to mild episodes of reduced responsiveness and alternate with close-to-normal cognitive performance [46]. Periods of apparent lucidity may be triggered by a novel environment or formal assessment, for example, in an outpatient clinic, and this could lead to improved performance in cognitive testing. The duration and pattern of fluctuations can be highly variable, from very short (lasting minutes to hours) to longer episodes (lasting days). Hence, these are unlikely to be noted by the clinician during a single clinical encounter but could potentially lead to differing outcomes, and possibly improvements, in consecutive assessments. Fluctuations do not tend to follow a diurnal rhythm and several forms of fluctuations (both in terms of duration and severity) may occur in the same patient [46]. This is also reflected in the longitudinal assessment of cognition in patients with DLB over time. Patients with Lewy body pathology have been described to have a greater variation across annual mean cognitive decline [47], and in the largest clinical study assessing...
Cognitive Decline in DLB, recruiting more than 800 patients, 18% of patients had an improved MMSE score 2 years after baseline [12].

Delirium (or acute confusional state) has been described as an early feature of DLB, and delirium-onset DLB has been proposed in the research criteria for prodromal DLB [19, 48]. The authors suggest suspecting prodromal DLB when no adequate trigger for the delirium episode is found, when the delirium is recurrent or prolonged, and/or when the delirium leads to progressive cognitive decline [19]. While the higher occurrence of delirium in the early/prodromal/pre-diagnosis stage is well-described, recent research has also shown that patients with DLB remain at an increased risk of delirium compared to those with AD after a diagnosis of dementia is established [5]. This could reflect a misinterpretation of marked fluctuations (with clouding of consciousness and confusion) as delirium, DLB patients’ increased vulnerability for developing delirium episodes, or a combination of both factors [19].

In addition to potentially affecting the outcome of cognitive testing, delirium episodes occurring in those with established dementia are known to accelerate cognitive decline. Cognitive decline triggered by delirium has been shown to be more rapid than can be explained by the neurodegenerative disease or the processes driving the delirium alone [49]. However, patients with Lewy body pathology form a minority in studies examining the interaction between delirium and neurodegeneration, and their trajectory following delirium episodes remains unclear. It is important to recognize that a delirium episode might be in the context of (potentially undiagnosed) DLB, to apply caution when considering treatment with antipsychotic medications, which are associated with severe adverse outcomes in DLB [4, 19].

While disturbed sleep is an established risk factor for cognitive decline and development of dementia [50], and there appears to be a particularly increased risk for those with RBD to develop an alpha-synucleinopathy as DLB [51], less is known about how sleep disturbances affect prognosis in those with an established diagnosis of DLB [52]. In all-cause dementia, sleep disturbances are associated with a poorer prognosis, including a higher frequency of neuropsychiatric symptoms and worse quality of life, as well as more severe cognitive decline [52]. The association between dementia and sleep disturbances is considered bidirectional, whereby the brain pathology can lead to disturbed sleep, and the sleep disturbance to accelerated cognitive decline [52]. Considering the strong link between RBD and DLB [53], it is likely that these relationships with adverse outcomes are also relevant for DLB and proactive identification of difficulties sleeping is important in clinical practice [54]. However, studies explicitly assessing the effect of sleep disturbances in patients with established DLB are lacking. In addition to RBD, there would be value in evaluating the impact of insomnia and excessive daytime sleepiness. All 3 are common in alpha-synucleinopathies [55] but require differing treatments and might thereby lead to variations in cognitive trajectories [52].

Overall, delirium episodes, whether recognised or unrecognised, as well as potentially overlapping cognitive fluctuations, might contribute to the nonlinear, difficult-to-predict course of cognitive decline in DLB. Concurrently assessing cognition and fluctuations using a semi-quantitative scale (e.g., the Clinician Assessment of Fluctuation scale [56] or the Mayo Fluctuation Composite Score [57]) could make it easier to contextualize the cognitive scores and improve prediction of cognitive decline in patients with DLB. Sleep difficulties are likely to influence cognitive decline in DLB. It is important that those are recognised in routine practice and their impact on cognitive trajectories studied in cohorts of patients with established DLB.

**Challenges due to Neuropathological Co- and Multi-Morbidity**

Lewy body pathology is independently linked to cognitive decline [47, 58] and the distribution of Lewy bodies in different regions of the brain may influence their effect on cognition. Most relevant are probably limbic and neocortical Lewy bodies [47], but brain stem Lewy body pathology might also play a role [59]. It is now recognized that most patients with the clinical syndrome of dementia have mixed neuropathologies [60]. The impact of Lewy body pathology on cognitive loss varies at a person-specific level depending on additional brain pathologies present [58], whereby the most frequently occurring overlap with AD pathology (reported in at least two-thirds of cases of DLB) has an additional effect leading to accelerated cognitive decline. While earlier studies detected the AD pathological substrate post-mortem [61, 62], more recent work used cerebrospinal fluid (CSF) analysis [63]. An “Alzheimer’s” CSF pattern with higher total-tau and lower amyloid-beta-42 has been linked to worse performance in MMSE subtests assessing memory and orientation in patients with DLB [64]. Further, abnormal CSF amyloid-beta-42 has been shown to be more
common in those with medial temporal lobe atrophy on MRI scans [65, 66].

However, in Boyle and colleagues’ study [58] on mixed pathologies using the Religious Orders Study and the Memory and Aging Project, of 143 patients with cortical Lewy bodies, only 5 (4%) had pure Lewy body pathology (i.e. without additional neuropathologies). Besides AD, which was very common comorbidly with Lewy bodies (73%), other pathologies also occurred frequently, and at a similar rate to other studies [67, 68]. These included gross infarcts (34%), microinfarcts (26%), transactive response DNA-binding protein 43 (TDP-43, 41%), and hippocampal sclerosis (12%). These pathologies were often detected in combination and more than a third of the full cohort of more than 1,000 patients had 4 or more concomitant pathologies [58].

Overall, comorbid Alzheimer’s pathology has consistently been implicated in a more rapid cognitive decline in patients with DLB, and indicators of AD pathology are amnestic impairments in cognitive testing, an “Alzheimer’s” CSF patterns and medial temporal lobe atrophy. However, the impact of other pathologies on cognitive decline in DLB, especially in the context of multiple pathologies, remains unclear and requires further exploration in larger clinico-pathological cohorts [69].

**Conclusion**

Dementia is a multifactorial condition with highly variable disease progression, and this is particularly relevant for DLB [27]. During the disease course of DLB numerous complex processes interact and cognitive decline is often determined by several neurodegenerative pathologies as well as comorbid physical and mental health conditions [70, 71].

Challenges in relation to cognitive prognostication in DLB highlighted in this review are: making a timely diagnosis and establishing a consistent baseline from which decline can be measured, using tests sufficiently assessing domains affected by DLB to monitor decline, as well as continued awareness of other factors that can affect cognitive performance and considering the interplay between differing brain pathologies. Further, for patients with Parkinson’s spectrum disorders, as DLB, access to clinics for diagnosis and monitoring can be difficult due to motor or neuropsychiatric symptoms [72]. Hence, it has been highlighted that remotely collected data can reduce the need to commute for these patients while providing real-time insights into disease progression and treatment response [73]. These novel digital healthcare solutions could assist in addressing some of the challenges in relation to detecting DLB and monitoring cognitive decline [73, 74]. Of particular interest are fluctuations, visual hallucinations, and autonomic instability. Remote monitoring of thermoregulation or cardiovascular parameters, as hypotension, could feed into assessments leading to an earlier diagnosis. Remote EEG [75] could, besides aiding detection of visual hallucinations, also measure fluctuations [73], one of the main challenges in predicting cognitive decline. Further research is needed to validate tools like the MoCA [30] in longitudinal studies, to determine the influence of delirium episodes on the disease course of DLB, and to develop a more fine-grained definition of clinico-pathological phenotypes potentially diagnosable through biomarkers.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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