Dementia with Lewy bodies and Parkinson's disease dementia – the same or different and is it important?

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Abstract

Biological definitions of neurological diseases are now becoming a reality, although still in the research phase. This development will recategorize neurological diseases, providing objective diagnostics and the promise of therapeutics that target biological mechanisms, a similar strategy that has been proven successful in tumors and other conditions. We will discuss this development for dementias with dominant Lewy pathology, as there are now biological assays for this pathology that have sparked new interest in diagnosing all positive subjects as a single disease. Can α-synuclein assay alone be a specific criterion for a spectrum of clinical syndromes with Lewy pathology? Based on evidence, this seems unlikely. Will α-synuclein assay be a definitive diagnostic marker for Lewy body dementia? Based on the evidence, this too seems unlikely. We advocate that one biological assay will not reflect the complex spatiotemporal features of brain pathology. Diverse sequential mechanisms underpin the highly heterogeneous phenotypes of and clinicopathological processes found in Lewy body dementias. Disease modification, if possible, will be most effective when targeting the early underlying mechanisms, especially those leading to aggressive phenotypes, other than those at the irreversible pathological endpoint.

Keywords: Dementia with Lewy bodies, Parkinson's disease dementia, α-synuclein, Lewy pathology

Introduction

It has been decades since the first definition of dementia with Lewy bodies (DLB) and its later separation from Parkinson's disease dementia (PDD) by the arbitrary one-year rule. The two neurological syndromes have considerable similarities, inspiring debate on whether they should be considered a single disease entity. Note that by definition both have dominant Lewy pathology and dementia. The debate remains viral because, in the case of PDD, there is an extended movement disorder phase (PD without dementia) with various rates of cognitive decline. Strikingly, patients can have an extremely long PD phase (over two decades) and a low risk of developing dementia.[1] This refutes the opinion that dementia is an inevitable outcome of advancing PD. In DLB, the incidence of parkinsonism varies with its disease phenotypes, with many showing only traces in the prodromal phase.[2] The arbitrary one-year rule underscores different events that precipitate the spatiotemporal pathophysiology of these syndromes, and the presence and severity of additional pathologies also suggest dissimilar mechanisms at play in the subsequent dementia stage. While current clinical management may be similar, if disease modification for better care is the end goal, understanding the biological causes underpinning these different phenotypes is required. With their prodromal phases being clinically (and arguably mechanistically) diverse, targeting these different initiating mechanisms before dementia becomes irreversible or converts to an aggressive phenotype will require the separate identification of these Lewy body syndromes. Combining them into a single diagnostic category based on end-stage pathology is unlikely to improve the clinical management of different disease mechanisms.

1. Best practice for identifying disease mechanisms

Biological disease definitions have revolutionalized the diagnosis of tumors (Box 1) and allowed the development of curative therapies. Treatment breakthroughs are due to understanding the diverse biological factors that trigger the multistep process of tumorigenesis. A similar logic is being applied to other complex diseases, enriching clinical trials in Alzheimer's disease (AD) and other tissue disorders like cardiomyopathy. DLB and PDD accumulate pathological α-synuclein in neurons in association with neuronal loss and dysfunction (Box 1). The Lewy body form of α-synuclein is now detectable peripherally promising potential disease modification. However, DLB and PDD have known diverse molecular drivers (Box 1) consistent with genetic diversity (as well as similarities).[3] This

strongly implies that a single biological mechanism leading to Lewy body formation is unlikely, similar to tumors of the same cell type (Box 1).

Box 1 Biological mechanisms for tumors versus Lewy body dementias

- Tumors have similar clinicopathological properties - the abnormal growth of genetically changed cells causing pain due to tissue displacement, disruption, and dysfunctions - and were conventionally treated with surgical removal and radio/chemotherapy to confine the malicious growth of malignant cells. DLB and PDD also have similar clinicopathological properties - the abnormal proteinaceous α-synuclein aggregation in neurons impacting cognitive functions – with current treatments only symptomatic.
- For tumors, the disease trajectory in a single tissue type can differ markedly depending on the underlying type of malignant cells. For DLB and PDD, the prodromal and clinical disease trajectories differ markedly due to more poorly understood biological mechanisms that influence the regional distribution and severity of cell death and Lewy and other concomitant pathologies.
- Tumors involving a single cell type are now diagnosed and successfully treated according to their biology - e.g. breast tumors are differentiated by their production of HER2 protein and estrogen or progesterone receptors for treatment. DLB and PDD do not impact the same cell types at the same time – e.g. cortical versus dopaminergic neurons – with already known different molecular drivers – e.g. higher mortality in DLB with *APOE* ε4 genotype,[4] excitatory cortical neurons in PDD have less *SNCA*-expression and those in DLB have increased gene splicing,[5] longer telomers but more cellular senescence[6]– showing biological differences. Differentiating DLB and PDD will be required to identify their biological mechanisms for treatment.

2. DLB versus PDD – similarities and differences in symptoms

Both DLB and PDD have dementia as their main clinical feature, although the severity of dementia for a diagnosis differs (more severe for DLB, Table 1). Dementia in DLB must commence before or concurrently with parkinsonism,[7] with around 22% of DLB cases (at age <65) demonstrating motor deterioration preceding cognitive symptoms.[8] For PDD, cognitive deficits can present at any stage of PD, with some PD cases with mild cognitive impairment (MCI) rapidly dementing.[9,10]

There are consistently more males with PDD[8,11] compared to DLB (Table 1). Male DLB patients are more likely to have RBD and parkinsonism than female patients, with females older and more cognitively impaired at first visit and more likely to have neocortical tangles.[12,13] This suggests diverse biological mechanisms even within DLB.

<Table 1 to be here>

2.1 Predementia stages differentiate DLB from PDD

An international consensus group recently proposed three phenotypes for prodromal DLB in research settings (Table 1) which may last more than 15 years:[14] MCI with Lewy body (MCI-LB), delirium-onset, and neuropsychiatric-onset. In contrast, the predementia stage of PDD accounts for two phases (Table 1) that can be up to 15-40 years in duration:[9,15-17] PD that presents with heterogeneous motor and non-motor signs and manifestations and PD-MCI prior to dementia diagnosis (as reviewed).[9,14,18] The association with clinical PD indicates different pathophysiological mechanisms for PDD compared to DLB.

MCI-LB has a cognitive impairment pattern characterized by non-amnestic MCI or multidomain amnestic MCI (Table 1), whereas single-domain amnestic MCI is less frequent.[14,19] PD-MCI develops slower and is less severe (Table 1), but the cognitive impairment pattern is similar to MCI-LB.[20-22] Delirium-onset prodromal DLB refers to delirious episodes that precede the occurrence of cognitive decline or dementia without identifiable provoking triggers, such as cerebrovascular disease, high fever, and alcohol or psychopharmacologic drug withdrawal.[14,23] This differentiates prodromal DLB from prodromal PDD (Table 1), as delirium in a PDD context appears only late in severe conditions.[23,24] Psychiatric-onset prodromal DLB often presents major depressive disorder as the initial presentation,[25] as does prodromal PD but with more motor signs (Table 1).[15,26] Psychosis becomes more prevalent throughout the prodromal DLB phase (rising to ~83%, Table 1).[14,25] Prodromal DLB can also present cognitive fluctuations and visual hallucinations (VH, Table 1), though uncommon as initiation signs.[25] In contrast, VH is rare in prodromal PD (Table 1) and early *de novo* PD.[27,28] Hyposmia and autonomic dysfunction in predementia DLB and PDD have low diagnostic value since these senescence defects may not be reported by patients.[14]

Isolated rapid eye movement sleep behavior disorder (iRBD) is a well-recognized prodromal sign of α-synucleinopathies. Early onset (median onset age: 58.0 years) and late onset (median onset age: 70.0 years) iRBD represent different clinical profiles, with late onset associated with a higher risk towards probable DLB.[29] Considering the mean onset age of DLB (>70 years) and PD (~ 60 years),[30] this aligns with the fact that iRBD does not typically present as an initial sign in prodromal DLB, but it is the most specific marker of prodromal PD.[25,31,32] DLB patients with iRBD are inclined to develop non-tremor-predominant parkinsonism and autonomic dysfunction compared to patients without iRBD.[2] The presence

of iRBD may differentiate the degeneration patterns of PD with a higher disease burden and increased risk for PDD.[33]

3. DLB versus PDD – similarities and differences in neuropathologies

As DLB has a dominant dementia syndrome and PDD occurs in the setting of a dominant PD syndrome, the impact of neuropathologies on cortical versus brainstem pathologies differs. Diagnostic AD pathology is more prevalent and severe in DLB compared with PDD and the loss of dopaminergic neurons in the substantia nigra is more marked in PDD compared with DLB (Figure 1).[34] The pattern of dopaminergic loss also differs with PDD patients having more ventral tier loss (relates to motor PD) compared with DLB which affects the dorsal tier more (innervates the caudate).[35] Importantly, the severity of regional dopaminergic cell loss is unrelated to the distribution or density of Lewy pathology.[36] These basic differences highlight different spatiotemporal patterns of pathologies in DLB versus PDD that do not simply present as a continuum or gradient of neuropathological load. This is exemplified by DLB not beginning with PD/PDD and not always progressing to DLB with AD, or PD that does not always end with PDD.

<Figure 1 to be here>

3.1 The temporal pattern of Lewy pathology in different phenotypes

It is well known that Lewy (and other) pathologies do not occur everywhere in the brain, but initially concentrate in certain regions aligning with different phenotypes and progressing over different time scales to infiltrate more susceptible brain regions. For Lewy pathology, there are three temporospatial patterns now recognised (Figure 1) that relate to two types of PD (a slowly progressive earlier onset (average age 58y) group that initially impacts the noradrenergic locus coeruleus, and a later onset (average age 65y) group initially impacting the central lower brainstem and peripheral autonomic centres) and DLB (an older onset (usually >70y) more rapid/malignant group with limbic brain regions initially involved).[34,37,38] In PD, the later onset group is more likely to have dementia earlier in their disease course (an intermediate group), and those with dementia or cognitive impairment are more likely to have iRBD.[39]

The severity of Lewy pathology in the brain also differs between these three Lewy body groups with greater severity of Lewy pathology in the DLB group and the least severity in the slowly progressing PD group (which has the greatest dopaminergic cell loss).[34,40] The severity of entorhinal Lewy pathology correlates with the severity and duration of dementia

in these groups,[41] with the presence of Lewy pathology in the CA1 region of the hippocampus correlating with memory performance when controlling for other neuropathologies.[42] CA1 atrophy is the best predictor of episodic memory impairment in PD.[43] This data suggests that the severity of hippocampal Lewy pathology contributes to memory deficits in both PDD and DLB.

The differences in the severity of cortical Lewy pathologies in DLB versus PDD resemble the frequency of hallucinations between these groups (Table 1), with increased Lewy pathology in the amygdala and parahippocampal regions and other secondary visual pathways associating with visual hallucinations.[44,45] High Lewy pathology densities in parahippocampal and inferior temporal cortices (regions of ventral visual stream processing) are associated with early visual hallucinations,[44] with MRI identified atrophy in those regions associating with visual hallucinations (as well as iRBD and cognitive impairment) in PD.[39] This data supports the concept that it is the severity of Lewy pathology that impacts clinically and that neuropsychiatric onset dementia relates to increased Lewy pathology in the ventral visual stream of the temporal lobe.

3.2 Coexisting Alzheimer pathology in different phenotypes

In cases with Lewy pathology, early dementia with memory onset is also associated with diagnostic AD pathology.[34] DLB cases without iRBD have more AD pathology (particularly increased tau burden and hippocampal atrophy) compared to those with iRBD,[46] supporting the Lewy pathology as most relevant to iRBD. Autopsy studies in PDD show that approximately 50% have additional cortical Aβ, with two-thirds of these cases having sufficient tau pathology to be diagnosed with AD.[47] This differentiates the majority of PDD (only about a third with diagnostic AD pathology) from the majority of DLB (most with diagnostic AD pathology)(Figure 1).

The severity of AD pathology in the brain also differs between these groups with DLB having more Aβ in the striatum, entorhinal cortex, and amygdala compared to PDD.[35] The severity of AD pathology in frontal and temporal cortices are major determining factors in the development of dementia in Lewy pathology cases, with the severity of AD pathology also correlating with the severity and duration of dementia.[41,48]

3.3 Coexisting cerebrovascular pathologies in different phenotypes

There is a very high prevalence of cerebral amyloid angiopathy (CAA) which is associated with cognitive decline in DLB (82-91%) compared with PDD.[35,49-51] CAA is also more severe

in DLB compared with PDD, particularly in the parietal and occipital lobes,[49] and, like AD pathology, positively correlates with the severity of Lewy pathology.[52] White matter hyperintensities (WMH) are also more severe in DLB compared with PDD,[35] as may be expected by CAA reducing cerebral blood flow and regulation. The pattern of reduced perfusion in DLB largely spares the limbic and temporal lobe regions, consistent with the severity of coexisting CAA pathology, and parieto-occipital hypoperfusion has been incorporated into the cingulate island sign shown to be a potential biomarker for prodromal DLB.[53] In contrast, cerebral microbleeds have a similar low prevalence in both DLB and PDD.[54] The data support the suggestion that prominent concurrent small vessel cerebrovascular disease (CAA and WMH) is an additional pathological substrate of DLB.[49] A systematic review of neuroimaging studies in delirium identifies associations mainly with the consequences of small vessel cerebrovascular disease (WMH, impaired cerebral autoregulation, reduced blood flow and cerebral oxygenation, and glucose hypometabolism) as well as atrophy and dysconnectivity.[55] This prominent copathology may underlie delirium-onset dementia observed only in DLB.

4. DLB versus PDD – similarities and differences in biomarkers

While structural and vascular neuroimaging can assist in identifying brain regions involved, they are not pathology or neurochemically specific. Neurochemical imaging of dopaminergic denervation using the dopamine transporter (DAT) ligand has been used for over a decade and has proven particularly helpful in differentiating DLB from other dominant dementia syndromes or clarifying degenerative parkinsonism in patients with inconclusive clinical features, but not for identifying the underlying proteinopathy in parkinsonian patients.[56] More recently the development of neuromelanin-sensitive imaging has allowed the loss of both dopaminergic and noradrenergic neurons in the brainstem to be determined in research settings[57] and is equal to DAT scanning in diagnosing DLB.[58] In prodromal disease abnormalities in DAT scans are observed 5-10 years prior to abnormalities in neuromelanin imaging with a floor effect for DAT scans occurring earlier during the disease course.[59] A recent analysis has shown more significant loss of DAT in the posterior putamen in PDD compared with DLB (Table 2) as may be expected based on the regional differences in dopaminergic cell loss observed at postmortem (see above and Figure 1).

Biomarkers for brain proteinopathies have been in development for a similar time with neuroimaging success for highly prevalent protein depositions (as seen in AD, now recommended for biological diagnostics)[60] but not for less prevalent proteinopathies that are

more cell selective (α-synuclein and TDP43), although there has been recent advances in pathological α-synuclein neuroimaging.[61] The advantage of detecting pathological proteins by neuroimaging is the identification of regional and progressive brain changes, an advantage allowing their use in prognosis.[60] Significant disadvantages are the radiation exposure and their restricted availability, with these (and other) factors driving the development of more easily accessible peripheral biomarkers for brain proteinopathies. Peripheral fluid-based biomarkers are already quantitatively validated and in diagnostic use for AD pathologies (Figure 1).[60]

The recent development of α-synuclein seed amplification assays (SAA) shows great promise for detecting α-synucleinopathy (Table 2) even in the prodromal stage and may discriminate people with Lewy pathology.[62] While SAA assays are currently proposed as the cornerstone of a new biological diagnosis for Lewy pathologies,[63] SAA assays are more difficult to validate without good neuroimaging tools for brain α-synucleinopathy, and are not quantitative, so their sensitivity for detecting limited Lewy pathology and pathological progression is still to be established.[64,65] Importantly, both the site and quantity of Lewy pathology appear to be critical for different phenotypes and their prognosis so further work on additional biomarkers is warranted.

For both PDD and DLB where diagnostic differentiation is not problematic and Lewy pathology is substantial, prognostic biomarkers would seem to be of most value, particularly for the different subtypes with variable progression discussed above (Figure 1). The evaluation of biomarkers for coexisting AD and vascular pathologies would be of high value for the development of better prognostic staging for both PDD and DLB (Table 2). For the core biomarkers for AD,[60] the prevalence and amount of amyloid on PET scans is higher in DLB than PDD and correlates with more rapid clinical and cognitive decline.[66-69] The amyloid deposition appears when mild cognitive symptoms occur and not before,[69,70] and is associated with rapid disease in DLB but not PDD,[71] so this would appear to be a promising biomarker for progression. CSF tau and phospho-tau levels differentiate DLB even with mild dementia from PDD patients with the levels correlating with dementia severity,[71-73] while imaging data, as indicated above, show that concurrent small vessel cerebrovascular disease is an additional pathological substrate of DLB. Further analyses of the progressive impact of these biomarkers in the different Lewy body phenotypes are warranted for better prognosis (Figure 1).

<Table 2 to be here>

5. Identifying biological mechanisms for DLB and PDD

Following the hypothesis that pathological proteins are the dominant biological mechanism driving AD,[60] the accumulation of α-synuclein and its transmission within the nervous system is the unspoken dominant biological mechanism now considered for all Lewy pathologies. This is despite knowing that an alternate α-synucleinopathy (multiple system atrophy) has an entirely different biology, that the degeneration of dopaminergic cells can be driven by genes that can act independent of α-synuclein accumulation (*Parkin* and certain *LRRK2* mutations), and that the driving mechanisms for AD may influence at least DLB. The diversity of pathologies associated with α-synuclein accumulations that give the diversity of different clinical phenotypes is likely to have diverse as well as common biological mechanisms involved.

There has been considerable progress in understanding the progression but not the initiation of Lewy pathology in the brain. Neuronal type influences their capacity to take up pathological protein seeds, with hippocampal neurons having significantly higher seeding capacity in DLB compared with PD, while nigral dopaminergic neurons have significantly higher seeding capacity in PD compared with DLB.[74] This variance in neuronal seeding capacity in different clinical phenotypes suggests that, despite the same type of α-synuclein seed, other biological factors must influence its regional deposition in addition to differences between neuronal types. Neuronal distinctions that impact their seeding capacity are their transmembrane transporters and pathways involved in lipid metabolism, mitochondrial function, and the ubiquitin-proteasome system.[74,75] Even within the same neurons, local biological factors are likely to drive progression, as already observed in patients with rapid progression of PD having higher nigral dopaminergic neuronal seeding capacity than those with slower disease progression.[74] α-Synuclein pathology occurs following seeding due to the incorporation of what is thought to be an increase in intracellular α-synuclein levels. However, recent data show that the cellular buffering of α-synuclein is dependent on ionic concentrations and pH which modifies the concentrations required for aggregation.[76-78] This is more likely to be the mechanisms involved in both PDD and DLB as there is a reduction in the expression of *SNCA* in cortical excitatory neurons,[5] the neurons that concentrate Lewy bodies in PDD and DLB.[79] This suggests that the earliest changes leading to the initiation of pathogenic α-synuclein seeds are mechanisms changing intracellular buffering capacity,

including less researched roles in mRNA stability in membrane-less intracellular processing bodies.[80]

While it is expected that common biological pathways are important for both PDD and DLB (e.g. synaptic, metabolic, and inflammatory pathways)[81], multi-omics datasets have also identified mechanistic differences. Comparisons of bulk tissue and single-cell transcriptomics in the highly affected cingulate cortex revealed that there is a significant increase in oligodendroglial progenitors and vascular cells in DLB compared with PDD (consistent with selective cerebrovascular disease in DLB), with both groups having widespread dysregulation of different RNA splicing factors affecting protein translation in excitatory neurons only in DLB.[5] Analysis of RNA expression in frontal cortex found that glycerolipid metabolism and viral myocarditis were enriched in PDD, while B cell receptor signalling and one carbon pool by folate correlated with DLB.[82] Similar comparisons assessing telomere attrition, mitochondrial dysfunction and cellular senescence in PDD and DLB brain tissue show significantly higher loads of cellular senescence with low mitochondrial biogenesis in DLB.[6] The quantity of concurrent Aβ deposition elevates glial-associated matrisome proteins stratifying cases by the degree of amyloid burden.[81] These data emphasize that in patients with Lewy pathologies there are biological changes to diverse cell types (vascular cells and excitatory neurons in DLB) with cellular senescence and inflammatory pathways impacting DLB more than PDD. In addition to the focus on neuronal conditions and differences involved in α-synuclein pathologies, further research on the neighboring milieu these neurons operate in (aging factors, Aβ deposits, supporting cells, etc.) is likely to correlate with disease phenotypes and their diverse progression better than the sole identification of Lewy pathology.

Conclusions and future research directions

DLB and PDD have significant similarities in their clinical stages, although there are still substantial differences. The most distinguishing features of these different clinical phenotypes are found in their prodementia stages, which for DLB include an amnesic onset, a psychiatric onset, and a delirium onset, whereas for PDD, a motor onset (Table 1 and Figure 2). These phenotypes and their progression indicate that early diverse biological mechanisms are more likely to map to regional and neuronal factors and co-pathologies at the initial presence of Lewy pathology (Figure 2). While biomarker techniques now allow Lewy pathology to be identified in life, just identifying who may be at risk of Lewy pathology cannot determine their clinical phenotype, when the disease will occur, or how it will

progress. Unlike the pathological proteins in AD, for DLB and PDD it is the diversity in the regional quantity of α-synuclein as well as the co-pathologies involved that determine disease phenotype. Disease modification, if possible, will be most effective when targeting the early underlying mechanisms other than those at the irreversible pathological endpoint. The remaining challenges are developing tools for prodromal biomarkers and regional biology to identify and monitor subjects at high clinical risk. We strongly advocate expanding the biological construct beyond α-synuclein for divergent phenotypes of Lewy pathologies rather than considering them all on a similar path.

<Figure 2 to be here>

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Author contributions

Y.F.: Writing – original draft, Funding acquisition, Conceptualization. **G.M.H.**: Writing – original draft, review & editing, Funding acquisition, Conceptualization.

Competing interests

The authors claim that there are no competing interests.

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602 **Table 1**- Key clinical features and management

	Dementia with Lewy bodies	Parkinson's disease dementia
Sex[8,11]	Males or females	Mainly males
Age at death[35]	79.8	83.9
Disease duration[4,35]	4.2-6.7	4.0-5.0
Heritable component[7,83,84]	60%	16-36% for PD and unknown for PDD
Cognitive syndrome[85,86]	Initial pattern has greater deficiencies of attention and frontal/temporal-associated cognitive subsets, lower ratings in episodic verbal memory tasks. Attentional fluctuation is more frequent. Memory more impaired.	More impairment and fastest decline in executive function. Language decline is slower.
	Memory and language measures may be more sensitive for DLB; visuospatial and executive measures may be more sensitive for PDD.	
Neuropsychiatric syndrome[7,11,87,88]	Hallucination (76%) Anxiety (65%) Apathy (58%) Delusions (57%) Neuroleptic sensitivity (53%) Depression (49%)	Depression (58%) Apathy (54%) Hallucination (54%): often appear after dopaminergic therapy in 20% PDD patients Anxiety (49%) Neuroleptic sensitivity (39%) Delusions (29%)
	Difficult to differentiate but the incidence rank differs.	
Motor syndrome[85]	Parkinsonism – only need one motor feature (75%) o Rest tremor is less frequent.	Parkinsonism (essential diagnostic criteria requires two motor features)
Sleep disturbance[2,89]	Excessive daytime sleepiness (subjective): 11-100% Insomnia (26-75%) RBD (70-90%): RBD patients more likely to develop parkinsonism and autonomic dysfunction	Excessive daytime sleepiness (subjective): 83% Insomnia (72%) RBD (25-58%) in PD context, unknown incidence rate in PDD
Autonomic dysfunctions[85,90,91]	Frequent orthostatic hypotension	Valsalva ratio and response to isometric exercise most impaired. Mean arterial pressure standing ≤75 mmHg is strong predictor of cognitive decline.
	Autonomic dysfunction in PDD has important treatment implications.	
Predementia stage		
Mild cognitive impairment[14,19-22,92]	Non-amnestic MCI or amnestic MCI multidomain o Fluctuating cognition o Visuospatial skill and executive dysfunction	Non-amnestic MCI or amnestic MCI multidomain
#Delirium[14,23,27,28]	Prolonged or recurrent delirium o Recurrent VH	Rare
Psychiatric behaviour[14,25]	Depression, anxiety, apathy	Depression or anxiety
Motor signs[14,93]	o Psychomotor retardations (mimic bradykinesia) o Parkinsonism induced by antipsychotic medication (non-tremor)	Motor prodromes o Loss of dexterity in repetitive manual tasks (bradykinesia) o Still or stiff arm and fingers o Longstanding asymmetrical postural tremor o Subtle gait abnormalities and balance problems (*indicates high dementia risk in PD*)

Sleep disorders[14,26,94]	iRBD RBD o RBD may be induced by antidepressant medications Excessive daytime naps, waking during the night or too early	iRBD (*indicates high dementia risk in PD*) o Late onset: Aggressive, higher non-motor symptom burden o Early onset: Benign, longer disease duration Excessive daytime somnolence (*indicates high dementia risk in PD*), insomnia, obstructive sleep apnoea
Autonomic dysfunction[14,17]	Constipation, orthostatic dizziness, urinary incontinence, erectile dysfunction, increased sweating, or increased saliva	Constipation, orthostatic hypotension (*indicates high dementia risk in PD*), urinary dysfunction, erectile dysfunction, hyperhidrosis, salivary dysfunction
Others[95,96]	Anosmia, color discrimination	Anosmia, color discrimination (*both indicate high dementia risk in PD*)
Clinical management		
Acetylcholinesterase inhibitors[85,97]	Confirmed beneficial effects of donepezil and rivastigmine for cognitive and psychiatric symptoms in DLB and PDD	
Antipsychotics[85,97]	Clozapine and quetiapine are often selected for DLB and PDD	
Levodopa[85,97]	Less motor response in DLB than PD and may be associated with an increased risk of psychosis	
Disease-modifying therapies[85,97]	Emerging under the concept to target specific mechanisms with selection criteria	

603 DLB=dementia with Lewy bodies; (i)RBD=(isolated) rapid eye movement sleep behavior disorder; MCI=mild
604 cognitive impairment; PD(D)=Parkinson's disease (dementia); VH=visual hallucination.
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Table 2- Biomarkers currently use

	Dementia with Lewy bodies	Parkinson's disease dementia
α-synuclein biomarkers		
CSF SAA[98]	Excellent diagnostic performance for cortical Lewy body dementia. In amygdala- and brainstem-predominant cases, sensitivity is lower.	
CSF co-pathology protein levels[99,100]	A typical finding in DLB is decreased levels of $A\beta_{42}$ and α-synuclein, but higher $A\beta_{42}$, t-tau/$A\beta_{42}$, and α-synuclein in DLB than PDD.	
Skin and olfactory SAA[101]	NA	Only positive in the olfactory epithelium, suggestive of the brain-first subtype.
Neuroimaging biomarkers		
Dopaminergic imaging ([^{123}I]ioflupane SPECT)*[85]	Lower in caudate nucleus.	Greater asymmetry of uptake in the posterior putamen. Dopamine uptake in striatum is significantly lower in PDD compared to DLB.

*Only listed the method approved by the European Medicines Agency (EMA) and/or the US Food and Drug Administration (FDA) for clinical procedure guidance. DLB=dementia with Lewy bodies; PDD=Parkinson's disease dementia; SAA=alpha-synuclein seed amplification assay.

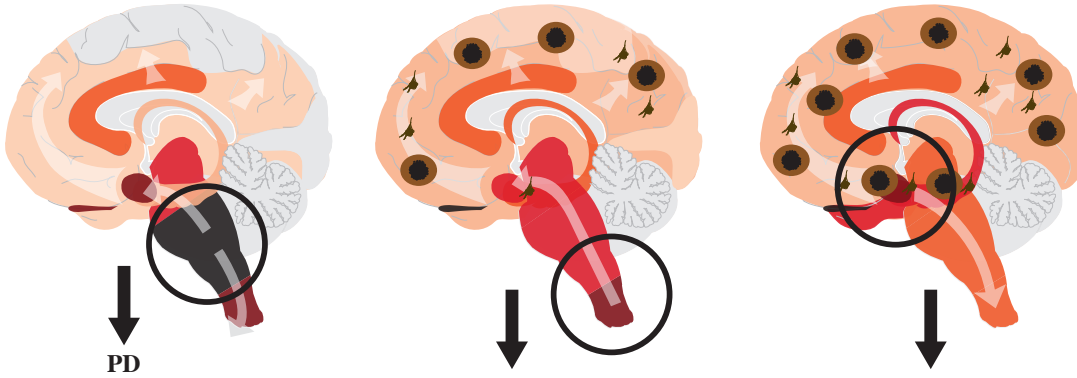
Figure Legends

Figure 1- Main neuropathologies in PDD and DLB and their biomarkers.
Three spatiotemporal patterns of Lewy pathologies have been identified with the initiating sites circled and the severity of regional Lewy pathology represented by colour intensity. Small cortical neurofibrillary tangles and cored amyloid plaques are overlayed. Other pathologies differentiating PDD and DLB are dopamine cell loss (greater in PDD than DLB) and cerebrovascular pathologies (found in DLB more than PDD). Biomarkers for the different pathologies are also given.
Abbreviations: AD=Alzheimer's disease, CAA=cerebral amyloid angiopathy, CSF=cerebrospinal fluid, DAT=dopamine transporter, DLB=dementia with Lewy bodies, LBD=Lewy body disease, PET=positron emission tomography, PD=Parkinson's disease, PDD=PD dementia, SAA=synuclein amyloid assay, VH=visual hallucinations, WMH=white matter hyperintensities

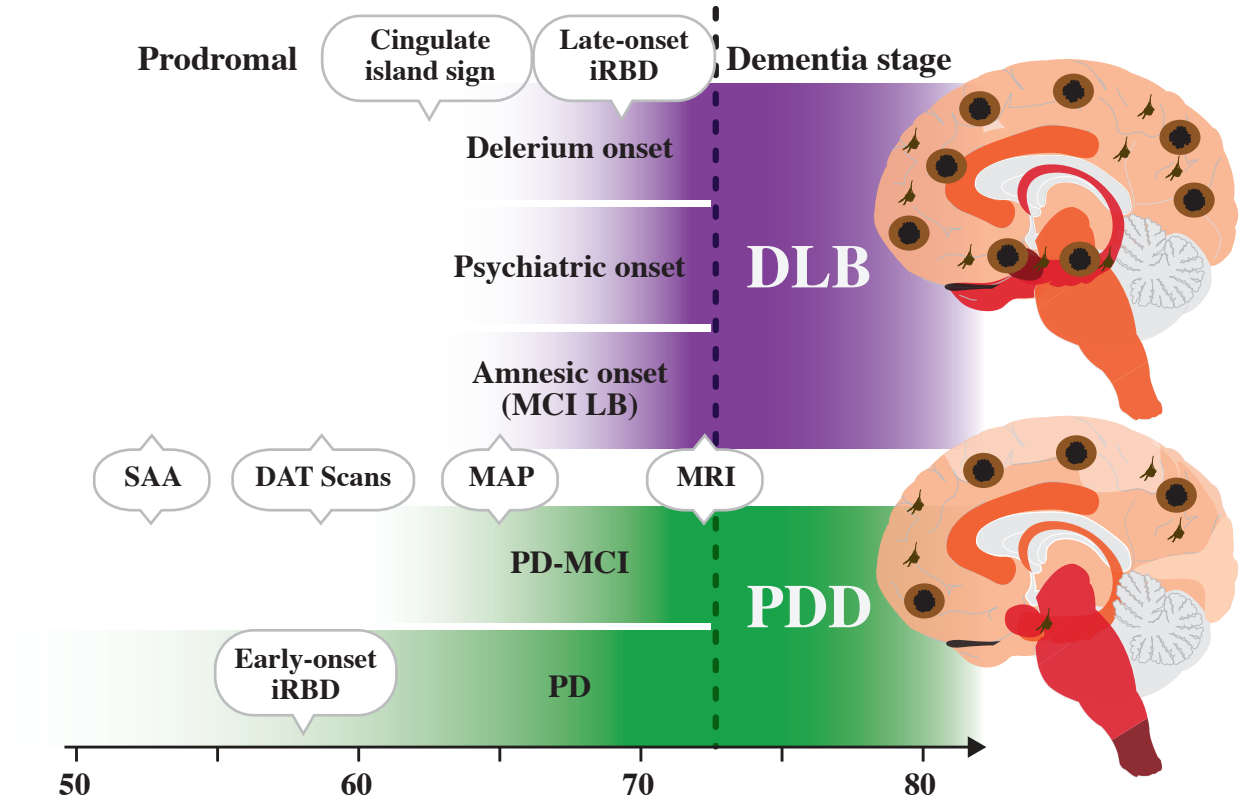
Figure 2- Overview of clinical trajectories and findings across disease stages.

DLB and PDD have similar dementia stage trajectories with the differences in regional end-stage neuropathologies indicated. These stages are observed at similar ages on average. The main substantive differences between DLB and PDD are found in the predementia stage where the considerable clinical differences are paralleled by differences in the presence and trajectories of diverse neuropathologies (see Figure 1).
Abbreviations: DAT=dopamine transporter, DLB=dementia with Lewy bodies, iRBD=isolated REM sleep behavior disorder, MAP=mean arterial pressure, MCI LB=mild cognitive impairment with Lewy bodies, MRI=magnetic resonance imaging, PD=Parkinson's disease, PDD=PD dementia, PD-MCI=PD with mild cognitive impairment, SAA=synuclein amyloid assay

3 temporospatial patterns of Lewy pathology progression



Biomarkers	PDD	DLB
alpha-Synuclein	**Lewy pathology**	
Peripheral SAA is sensitive for cortical LBD CSF α-synuclein levels were reduced in DLB and PDD	SN neurons - Highest SAA capacity Less Amygdala/parahipp -VH	Hipp neurons - Highest SAA capacity More Amygdala/parahipp - particularly psychiatric onset
Dopamine	**Dopamine cell loss**	
DAT scan Neuromelanin scan	Severe cell loss	Less cell loss - none - moderate
Amyloid/Tau	**AD pathology**	
PET Amyloid in DLB >PDD - correlating with more rapid clinical and cognitive decline CSF tau levels in DLB >PDD - correlating with dementia severity	Less AD path 50% have cortical Aβ 33% - reach AD criteria	More AD path - more Aβ in the striatum, entorhinal cortex, and amygdala Most cases reach AD criteria
Cerebrovascular Imaging	**Cerebrovascular pathology**	
Pathologies would be of high value for the development of better prognostic staging for both PDD and DLB	Less severe CAA Less WMH	More severe CAA - particularly parietal/occipital More severe WMH - particular in delirium onset


Prodromal
Cingulate island sign
Late-onset iRBD
Dementia stage
Delerium onset
Psychiatric onset
Amnesic onset (MCI LB)
DLB
SAA
DAT Scans
MAP
MRI
PD-MCI
PDD
Early-onset iRBD
PD
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