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NEUROIMAGING (N PAVESE, SECTION EDITOR)

Molecular Imaging and Updated Diagnostic Criteria in Lewy Body Dementias

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Abstract
Purpose of Review The aims of the study were to review recent advances in molecular imaging in the Lewy body dementias (LBD) and determine if these may support the clinical but contested temporal profile distinction between Parkinson disease (PD) with dementia (PDD) versus dementia with Lewy bodies (DLB).
Recent Findings There do not appear to be major regional cerebral metabolic or neurotransmitter distinctions between PDD and DLB. However, recent studies highlight the relative discriminating roles of Alzheimer proteinopathies. PDD patients have lower cortical β-amyloid deposition than DLB. Preliminary tau PET studies suggest a gradient of increasing tau binding from cognitively normal PD (absent to lowest) to cognitively impaired PD (low) to DLB (intermediate) to Alzheimer disease (AD; highest). However, tau binding in DLB, including the medial temporal lobe, is substantially lower than in AD.
Summary Alzheimer-type proteinopathies appear to be more common in DLB compared to PDD with relative but no absolute differences. Given the spectrum of overlapping pathologies, future α-synuclein ligands are expected to have the best potential to distinguish the LBD from pure AD.

Keywords Acetylcholine · β-Amyloid · Dementia with Lewy bodies · Diagnostic criteria · Dopamine · Parkinson disease with dementia

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Abbreviations

AD	Alzheimer disease
DAT	Dopamine transporter
DLB	Dementia with Lewy bodies
FDG	Fluorodeoxyglucose
MCI	Mild cognitive impairment
MIBG	Metaiodobenzylguanidine
MMSE	Mini-mental state examination
PCA	Posterior cortical atrophy
PD	Parkinson disease
PDD	Parkinson disease with dementia
RBD	REM sleep behavior disorder

Introduction

Lewy Body Dementia Pathology

Parkinson disease with dementia (PDD) and dementia with Lewy bodies (DLB) together comprise the Lewy body dementias (LBD) and share a common pathological substrate of α-

synucleinopathy, which is manifested by deposits in neuronal somal Lewy bodies and nerve terminal neurites [1]. Lewy body pathology has been found to be variably associated with Alzheimer disease (AD)-characteristic β-amyloid and neurofibrillary tau pathology depositions in LBD [2–7]. Furthermore, proteinopathy in subcortical projection systems may result in neurotransmitter changes, including dopaminergic and cholinergic systems, that may also contribute to cognitive impairments in LBD [8–11].

Updated Clinical Diagnostic Criteria: PD Dementia Versus DLB

Lewy body dementias have a spectrum of cognitive, motor, and neurobehavioral symptoms in common. The clinical distinction of DLB and PDD is based on the temporal manifestations of cognitive and motor symptoms. This temporal difference has been operationalized using the so-called 1-year rule [12]. According to this rule, PDD is diagnosed if dementia begins after 1 year of parkinsonism and DLB if dementia begins within 1 year of the onset of parkinsonism. Recently updated criteria for PD (including associated dementia) and DLB disagree on the 1-year rule with the first one not including it and the second upholding it [13, 14]. The new Movement Disorder Society Clinical Diagnostic Criteria do not consider dementia as an exclusion criterion for the diagnosis of PD, regardless of when it occurs in relation to parkinsonism onset. Patients with dementia who are already diagnosed with the DLB label can be classified as "PD dementia with Lewy bodies subtype" in the new PD diagnostic criteria [13]. In contrast, recently updated consensus diagnostic criteria for DLB uphold the 1-year rule [14]. Major changes in the updated DLB criteria include the inclusion of REM sleep behavior disorder (RBD) as a core clinical feature. Furthermore, molecular imaging biomarkers of striatal [^{123}I]ioflupane SPECT dopamine transporter (DAT) and cardiac [^{123}I]metaiodobenzylguanidine (MIBG) sympathetic myocardial scintigraphy are now used as indicative biomarkers. If one of these indicative biomarkers is present, only one of the four core clinical features is needed to establish a diagnosis of probable DLB [14].

It is apparent that the updated clinical diagnostic criteria for PD (dementia) and DLB are insufficient to identify and distinguish pathological mechanisms underlying the dementia syndrome. It is possible that the pathologic overlap of DLB and PDD represents confluence of separate initial pathological mechanisms at the time of emergence of dementia. Alternatively, it is conceivable that DLB and PDD represent phenotypic variations of the identical underlying disease process [15]. Furthermore, the clinical heterogeneity that can be observed among patients with either DLB or PDD may reflect distinct pathological mechanisms that may be present in some patients across both clinically defined groups, i.e., the 1-year rule may be suboptimal or even inappropriate for distinguishing subtypes of dementia pathologies in α-synucleinopathies [15].

This review will provide an overview of recent advances in molecular imaging in LBD and how these relate to the PDD and DLB subtypes based on the clinically defined 1-year rule. Although there do not appear major differences in neurotransmitter (dopaminergic and cholinergic) systems between PDD and DLB, there is emerging evidence for relative differences in non-Lewy (β-amyloid and tau) proteinopathies between these two clinical entities.

Metabolic Imaging Changes in the Lewy Body Dementias

Prospective evaluation of [^{18}F]fluorodeoxyglucose (FDG) metabolic changes have shown that incident dementia in PD initially may present as a predominant hypometabolic posterior cortical pathology involving the visual cortex, the precuneus, and the posterior cingulum [16]. Subsequent progression to PDD is associated with mixed subcortical, including the caudate nuclei and the thalami, and progressive cortical changes that also include the frontal lobes [16]. In both PDD and DLB, topographic metabolic changes appear to be similar [17], including marked deficits in occipital regions. These findings emphasize the significant pathophysiological overlap between these two conditions [18].

Clinically, AD and DLB may also be difficult to distinguish, especially if cognitive impairment manifests before parkinsonism in DLB. Several metabolic changes, however, appear to differentiate DLB from AD. For example, bilateral medial occipital glucose hypometabolism has been associated with severity of visual hallucinations in DLB [19] and is not a characteristic of AD. Relative metabolic or perfusion preservation of the mid- or posterior cingulate gyrus (so-called cingulate island sign) distinguishes DLB from AD [20, 21]. Prominent manifestation of the cingulate island sign was associated with lower Braak neurofibrillary tangle stage in autopsy cases [22•], which typically would be higher in AD. The presence of the cingulate island sign is also inversely associated with atrophy of the medial temporal lobe in DLB [23].

Occipital lobe hypometabolism and the cingulate sign are not specific for DLB, however, as they can also be seen with posterior cortical atrophy (PCA), a variant of AD [24•]. Clinically, DLB may share some visual and visuospatial impairment with PCA. Rather than becoming more granular, however, recent diagnostic consensus criteria for PCA now allow for the diagnosis of the so-called PCA-plus syndrome where patients meeting additional diagnostic criteria for either DLB or corticobasal syndrome can be classified within the PCA disease spectrum [25]. DLB and PCA showed overlapping areas of glucose hypometabolism, including the lateral

occipital lobe, lingual gyrus, precuneus, cuneus, posterior cingulate, inferior parietal lobe, supramarginal gyrus, thalamus, and basal ganglia [24•]. In contrast, DLB showed more severe hypometabolism in the medial occipital, anterior temporal, and orbitofrontal regions as well as the caudate nucleus than PCA. Conversely, PCA demonstrated more asymmetric hypometabolic patterns compared to DLB. The cingulate island sign was present in both PCA and DLB, although it was more asymmetric in PCA [24•]. A different FDG PET study found more right-hemispheric (lateral temporo-occipital) changes in PCA versus predominant left (medial) occipital changes in DLB [26].

Neurotransmission Imaging in the Lewy Body Dementias

Dopaminergic and Cholinergic System Imaging

The utility of striatal dopamine nerve terminal imaging in distinguishing DLB from AD is well established [27–29]. Dual ligand dopaminergic nerve terminal and β-amyloid imaging provides better diagnostic post-mortem confirmed classification of LBD, AD, and fronto-temporal dementia compared to consensus clinical assessment [30]. Normal striatal DAT binding has been reported in autopsy-confirmed DLB [31], however, and thus cannot be an absolute exclusion criterion for this disorder.

Striatal and limbofrontal dopaminergic denervation affects specific cognitive functions in PD [32], but nigrostriatal and limbofrontal dopaminergic losses are insufficient to fully explain the presence of dementia in PD [33]. Severe cholinergic losses are a consistent finding in PDD and DLB compared to PD and could provide an explanation for more severe cognitive impairment [33, 34]. The dual syndrome cognitive hypothesis posits that the high frequency of fronto-striatal executive changes in PD relates to dopaminergic changes and that the emergence of dementia is associated with posterior cortical and more widespread changes secondary to additional pathologies, such as cholinergic deficits [35, 36]. In agreement with this hypothesis, we recently reported that cortical cholinergic and caudate nucleus dopaminergic deficits may contribute to cognitive decline in PD both additively and multiplicatively [37]. An imbalance of synergistic function of the cholinergic and dopaminergic transmitter systems in cognitive pathways might lead to impaired cognitive processing [38]. For example, cholinergic deficits may aggravate striatal-frontal dysfunction due to loss of compensatory cortical attentional functions, and thereby perhaps exacerbating dysfunctional cortico-striate signaling [39]. Future studies using vesicular acetylcholine transporter ligands, such as [^{18}F]FEOBV (Fig. 1), may allow more precise assessment of not only cortical but also subcortical cholinergic regions in Lewy body disorders.

Cardiac Sympathetic Nerve Terminal Imaging

The autonomic nervous system is susceptible to α-synuclein pathology, which may be a mechanistic factor underlying autonomic dysfunction [40]. Severe cardiac sympathetic degeneration occurs in PD, PDD, and DLB, but not in AD, making it a suitable diagnostic biomarker. Indeed, recently updated diagnostic criteria for DLB provide increased diagnostic weighting to cardiac [^{123}I]MIBG noradrenergic sympathetic myocardial scintigraphy as an indicative biomarker. In these new diagnostic criteria, the presence of this biomarker abnormality in combination with only one of the clinical core features justifies a probable DLB diagnosis [14]. MIBG myocardial sympathetic imaging demonstrates good sensitivity (68.9%) and specificity (89.1%) to differentiate probable DLB from probably AD [41]. In a different study, combined use of MIBG cardiac scintigraphy and DAT SPECT imaging enabled more accurate differentiation between DLB and AD (sensitivity and specificity of 96.1 and 90.7%, respectively) compared with either DAT SPECT or MIBG myocardial scintigraphy alone [42]. As expected, there was a significantly higher frequency of motor parkinsonism in the group with abnormal dopamine nerve terminal imaging compared to those with a normal scan.

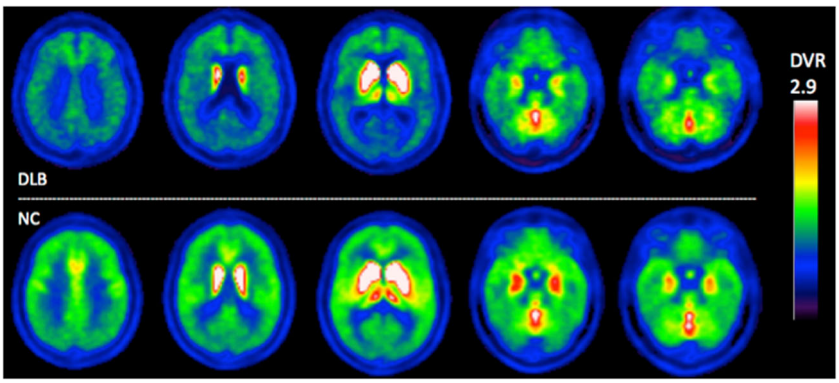

Fig. 1 [^{18}F]FEOBV vesicular acetylcholine transporter images in patients with DLB ($n = 4$, upper row) and healthy controls ($n = 7$, lower role). Prominent reductions in neocortical, archicortical (hippocampus), and subcortical structures (basal ganglia, thalamus) are present in DLB compared to normal control subjects. Figure courtesy of Robert Koeppe, PhD

Conversely, RBD was more frequently present in patients with abnormal MIBG binding compared to the normal MIBG group. These findings emphasize the potential utility of myocardial scintigraphy in the diagnosis of LBD, especially when the differential diagnosis versus AD is difficult to make or dopamine transporter imaging findings are normal or equivocal.

Fibrillary β-Amyloid PET Imaging in Lewy Body Dementias

The putative role of β-amyloid depositions in cognitive impairment is well described in the AD literature. However, both the prevalence and the functional significance of β-amyloid depositions are less well described in LBD. A recent literature review on in vivo β-amyloid PET imaging findings in LBD found suggestive evidence that PD patients both without and with mild cognitive impairment (MCI) have a lower incidence of AD-range β-amyloid deposition (average 6 and 11%, respectively) compared to elderly normal subjects (average 15%), and that PDD patients have a lower incidence of β-amyloid deposition (average 27%, range 0 to 80%) than do patients with DLB (average of 57%, range 33 to 100%) [15]. A recent [^{18}F]florbetapen β-amyloid PET study confirmed these observations of very low AD-range amyloidopathy in mild PD without dementia (0/33) based on visual assessment [43]. As in AD, the degree of amyloidopathy may be modified by ApoE ε4 allele genotype status [44].

With respect to clinical manifestations of amyloidopathy in LBD, a recent review concluded inconsistent correlations between β-amyloid deposition and cognitive function, at least in cross-sectional analyses [44]. However, prospective cohort analyses have shown that precuneus amyloidopathy is associated with faster progression to cognitive impairment and dementia in PD [45, 46]. Furthermore, most in vivo β-amyloid PET imaging studies have focused on cortical deposition only. Neuropathological studies, however, suggest a significant role for amyloidopathy in the basal ganglia, as striatal β-amyloid deposition is significantly greater in PDD compared to PD without dementia [47–50]. We recently investigated the relative correlates of striatal and cortical β-amyloid deposition to cognitive impairment in PD subjects with risk factors for PDD, such as older age, postural imbalance, or cognitive changes [51]. Elevated striatal amyloidopathy was present in about half of the patients with concomitant increased cortical binding. We found significantly lower cognitive performance in subjects with combined cortical and striatal β-amyloid deposition compared to those with abnormal cortical binding only. These findings suggest that amyloidopathy, especially in the striatum, may play a role in cognitive impairment in the LBD. Future studies investigating the role of amyloidopathy in cognitive impairment in LBD should include striatal regions.

Tau PET Imaging in Lewy Body Dementias

Tau proteinopathies are becoming an important imaging target in LBD. A [^{18}F]AV-1451 tau PET imaging study in a small number of seven DLB patients found that AV-1451 uptake was mildly increased in the inferolateral temporal and parietal/precuneus regions compared to control subjects [52•]. Greater AV-1451 uptake in the inferior temporal gyrus and precuneus in a combined group of DLB and cognitively impaired PD patients was associated with increased cognitive impairment as measured with the mini-mental state examination (MMSE) and the Clinical Dementia Rating scale [52•]. Shorter duration of disease was associated with greater AV-1451 uptake in the inferior temporal gyrus and precuneus in the DLB group. A subsequent larger [^{18}F]AV-1451 tau PET imaging study found that AV-1451 uptake was substantially more severe and extensive in AD compared to DLB patients [53••]. Medial temporal uptake completely distinguished AD dementia (highest) from probable DLB (lowest). Probable DLB patients had higher inferior, middle, and superior occipital; lingual, angular, fusiform, middle and inferior temporal gyri; and precuneus and cuneus AV-1451 uptake compared to normal control subjects [53••]. These investigators did not find, however, a significant correlation between posterior temporo-parietal and occipital AV-1451 uptake and clinical measures, including cognition, visual hallucinations, motor parkinsonism, or presence of RBD. Higher [^{11}C]PIB β-amyloid binding was associated with higher AV-1451 uptake in these regions suggesting an atypical pattern of tau deposition in probable DLB patients [53••]. Overall, there appears to be a gradient of increasing tau binding from cognitively normal PD (absent to lowest) to cognitively impaired PD (low) to DLB (intermediate) to AD (highest) (Table 1) [52•, 54].

Neuroinflammation Imaging in the Lewy Body Dementias

Neuroinflammation may be a key factor in the pathogenesis of dementing disorders, including LBD [55]. PET markers of mitochondrial translocator protein (TSPO) expression, performed initially with [^{11}C]PK11195, can be used for the in vivo assessment of microglial and astrocytic activation. Glial activation was shown in the putamen and substantia nigra in both DLB and PD patients using [^{11}C]PK11195 PET [56]. In contrast, DLB patients also showed increased uptake in the caudate and an extended glial activation pattern in several cortical regions and the cerebellum, suggesting possible evidence of a disease propagation pattern [56]. In PDD, glial activation (using

Table 1 In vivo tau PET imaging studies in PD (cognitive impairment), DLB, and AD. Findings suggest a gradient of increasing tau binding from cognitively normal PD (absent to lowest) to cognitively impaired PD (low) to DLB (intermediate) to AD (highest)

Ligand	Study population	Major findings
[^{18}F]AV-1451 tau PET (Hansen et al. [54])	PD (n = 26) without or with mild cognitive impairment; healthy controls (n = 23)	Tau pathology, as detected by AV-1451, is uncommon in PD with mild cognitive impairment and shows no significant correlation with cognitive dysfunction at this stage.
[^{18}F]AV-1451 tau PET (Gomperts et al. [52•])	DLB (n = 7) and PD cognitively impaired (n = 8) or cognitively normal (n = 9)	AV-1451 uptake was mildly increased in the inferolateral temporal and parietal/precuneus regions compared to control subjects. Greater AV-1451 uptake in the inferior temporal gyrus and precuneus in a combined group of DLB and cognitively impaired PD patients was associated with increased cognitive impairment as measured with the MMSE and the Clinical Dementia Rating scale. Shorter duration of disease was associated with greater AV-1451 uptake in the inferior temporal gyrus and precuneus in the DLB group.
[^{18}F]AV-1451 tau PET (Kantarci et al. [53••])	AD (n = 18); DLB (n = 15); controls (n = 90)	AV-1451 uptake was more severe and extensive in AD compared to DLB patients. Medial temporal uptake completely distinguished AD dementia from probable DLB. Probable DLB patients had higher inferior, middle, and superior occipital; lingual, angular, fusiform, middle and inferior temporal gyri; and precuneus and cuneus AV-1451 uptake compared to normal control subjects. No significant cognitive or clinical correlations of AV-1451 binding.

[^{11}C]PK11195 PET) was observed in the anterior and posterior cingulate, striatum and frontal, temporal, parietal, and occipital cortical regions [57]. Increased tracer binding was more extensive in PDD compared to PD. There was also a significant correlation between cognitive scores (MMSE) and glial activation, suggesting that microglial or astrocytic activation may be associated with neuronal damage in PDD [57]. Multi-modal imaging studies have found inconsistent relationships between the extent of glial activation and glucose metabolic or amyloidopathy changes in LBD [56–59].

Significant glial activation may be a factor in driving the disease process in LBD. It should be noted, however, that neuroinflammatory mechanisms are complex and not well understood, and inflammation could also be neuroprotective under certain conditions and stages of the neurodegenerative process [60]. Novel neuroinflammation imaging techniques, based on next-generation radiotracer probes, may be better able to disentangle the effects of inflammation in different stages of the neurodegenerative processes as they relate to clinical deterioration and may help in development of more effective interventions [61].

Discussion

Proteinopathy and Neurotransmitter Changes in the Lewy Body Dementias: Incremental and Threshold Effects?

Combined multi-ligand PET analysis in PD patients who were recruited based on risk factors for PDD (older age, imbalance, cognitive changes) showed evidence of independent cognitive contributions of not only individual neurotransmitter changes (dopamine, acetylcholine) but also β-amyloidopathy [51]. Triple-ligand analysis showed that global composite cognitive z-scores were best predicted by cortical cholinergic activity and global (cortical and striatal) β-amyloid binding. Verbal learning cognitive domain z-scores were predicted by cortical β-amyloid and cortical cholinergic activity. Attention cognitive domain z-scores were predicted by striatal β-amyloid uptake and caudate nucleus dopaminergic activity. Executive function cognitive domain scores were predicted by cortical cholinergic activity [51]. These data provide supportive evidence that neurotransmitter and proteinopathy changes have independent and incremental contributions to cognitive impairment in PD at risk of PDD. Likewise, variable presence and combinations of proteinopathies and neurotransmitter changes may define endophenotypes within the cognitive impairment syndrome of the LBD [62].

We reported previously that even low levels of cortical β-amyloidopathy associated with cognitive changes in PD patients at risk of dementia [63]. Interestingly, a number of cognitively normal elderly subjects in our study manifested higher levels of amyloidopathy than observed in our PD population. This suggests that, along with the observation that subjects with AD have a much higher amyloidopathy threshold to manifest cognitive changes, there may be a lower threshold for manifestation of β-amyloid associated cognitive impairment in PD [15]. In PD, however, β-amyloid deposition occurs in the setting of Lewy proteinopathy and multiple neurotransmitter system changes. The presence of multiple

pathologies in PD likely reduces the cerebral capacity to adapt to additional β-amyloid burden and thereby may lower its symptomatic threshold for cognitive or clinical symptom manifestation of this proteinopathy. This is in keeping with accumulating post-mortem evidence, which indicates that the presence of two proteinopathies (α-synucleinopathy and β-amyloidopathy) in PDD may exert additive or even synergistic detrimental interactions [64]. For example, comorbid cerebral β-amyloidopathy in PDD is associated with more severe clinical outcome, faster conversion to dementia, and shorter survival compared to PDD patients with more "pure" Lewy body pathology [5, 65]. It is conceivable that the presence of tau proteinopathy also may become symptomatic at low levels in the setting of multiple pathologies in LBD, but further studies are needed to confirm this hypothesis.

Imaging of Brain Network Disruption in the Lewy Body Dementias

Pathological and neurotransmitter system changes ultimately affect brain networks in PD [66–68]. Spatial covariance mapping has shown a distinct PD cognition-related network pattern (PDCP) characterized by FDG metabolic reductions in the parietal association, medial prefrontal, and premotor regions, with relative increases in the dentate nuclei and vermis [69]. Interestingly, PDCP expression was correlated with more severe losses of dopamine transporters in the caudate nucleus [70] and greater executive function rather than memory deficits [71]. Furthermore, PDCP network is largely spatially and functionally distinct from metabolic network changes seen in AD [71]. Spatial covariance mapping of regional cerebral perfusion changes using [^{99m}Tc]HMPAO SPECT in DLB found evidence of a cognitive-motor network pattern characterized by bilateral relative increases in the striatum, cerebellum, and supplementary motor areas and widespread bilateral reductions in parietal areas [72]. Interestingly, this perfusion pattern correlated with poorer cognitive performance, including attention, and fluctuations in cognitions.

Apart from dopaminergic modulation of cerebral networks, there is also evidence of cholinergic network modulation in PDD. An M1/M4 subtype muscarinic receptor brain SPECT study using the [^{123}I]QNB ligand found evidence of decreasing binding in basal forebrain, temporal cortex, striatum, insula, and anterior cingulum in PDD, implicating decreased signal detection capacity in limbic-paralimbic and salience cholinergic networks [73]. Regional cerebral blood flow findings using [^{99m}Tc]exametazime SPECT in these patients demonstrated relative hypoperfusion in temporo-parietal and prefrontal cortical regions and nodes of the frontoparietal and default mode networks. The muscarinic receptor pattern that correlated with cognitive improvement after donepezil administration coincided with the default mode network and frontoparietal networks [73]. These findings provide supportive evidence for the presence of several dysfunctional cholinergic networks in PDD. Collectively, these data show the presence of functional cognitive brain networks that can be altered in PDD or DLB and may be modulated by dopaminergic or cholinergic neurotransmitter changes.

Differential Molecular Imaging Diagnostic Approaches to Distinguish LBD from AD: Are We Ignoring the Presence of Overlapping Pathologies?

Molecular imaging studies have shown the utility of distinguishing LBD from AD based on dopaminergic nerve terminal imaging with good diagnostic accuracy [30, 74]. However, a normal pattern of striatal dopamine nerve terminal activity is insufficient to exclude LBD as a small number of subjects may have normal uptake [31]. This may be of particular relevance in the absence of motor parkinsonism. Cardiac sympathetic nerve terminal imaging is now defined as an indicative biomarker to distinguish DLB from AD [14] but studies also show the presence of subsets of patients with normal cardiac sympathetic nerve terminals [42, 72]. Hence, a normal cardiac sympathetic nerve terminal scan does not fully exclude DLB.

Proteinopathy imaging studies confirm the spectrum nature of overlapping pathologies in neurodegenerative disorders [52•, 53••, 72]. Recent FDG PET imaging studies also demonstrate overlapping metabolic changes between DLB and the PCA variant of AD [24]. These observations suggest that attempts to distinguish neurodegenerative disorders based on their clinical phenotype may ignore shared pathobiological mechanisms. Ultimately, it may be expected that with the introduction of novel molecular therapeutics in the clinic, imaging biomarkers that have specific binding to such therapeutic targets will be used for the identification of a specific pathobiology (and subsequent monitoring of treatment response) rather than establishing a clinically defined diagnostic entity.

Conclusions

Although Lewy bodies or neurites are the primary pathology, the etiology of cognitive decline in LBD is heterogeneous. Molecular imaging studies in LBD have targeted neurotransmitter systems, non-Lewy proteinopathies, and glucose metabolic or perfusion changes. Metabolic changes appear to show similar topographic changes in both DLB and PDD, including marked deficits in occipital regions and relative sparing of the medial temporal lobe compared to AD confirming the significant overlap between these two clinical conditions. Nigrostriatal denervation is another shared pathophysiology of LBD though normal striatal dopamine nerve terminal activity can occasionally be seen in DLB.

More recent studies highlight the role of Alzheimer proteinopathies, including β-amyloid and tau, where there is increasing evidence of relative differences between DLB and PDD. PDD patients have a lower incidence of cortical β-amyloid deposition (average 27%) than do patients with DLB (average of 57%). Striatal amyloidopathy may be a critical driver of cognitive impairment rather than isolated cortical deposition, at least in PD at risk of dementia. Tau PET studies demonstrate significantly lower uptake in DLB compared to AD, but higher than in PD and PDD. In particular, medial temporal uptake in DLB was below the lower range of uptake seen in AD and could be used as discriminatory marker.

Molecular imaging studies confirm the heterogeneous etiology underlying the cognitive impairment syndrome in LBD, where neurotransmitter and proteinopathy changes may have incremental and possibly interactive effects. Variable presence and combinations of proteinopathies and neurotransmitter changes may define endophenotypes within the cognitive impairment syndrome of LBD. Future molecular imaging studies targeting α-synuclein proteinaceous deposits are expected to shed further insights in the pathogenesis of LBD. As there is increasing recognition of a spectrum of overlapping pathobiology, future molecular imaging studies may shift away from providing diagnostic biomarkers for clinically defined entities. Rather, molecular imaging may identify the presence of specific molecular pathologies and may play an increasingly important role in guiding treatment of neurodegenerative disorders rather than establishing a clinical diagnosis.

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Compliance with Ethical Standards

Conflict of Interest Nicolaas I. Bohnen and Martijn L.T.M. Müller report grants from NIH, Department of Veterans Affairs, Michael J. Fox Foundation, Axovant Sciences, and Chase Pharmaceuticals.

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Human and Animal Rights and Informed Consent All reported studies/experiments with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- • Of importance
- •• Of major importance

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