Journal of Neurochemistry

JOURNAL OF NEUROCHEMISTRY | 2019 | 150 | 467–474 doi: 10.1111/jnc.14698

REVIEW

Clinical and neuropathological differences between Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies – current issues and future directions

Lauren Walker*, Leonidas Stefanis†‡ and Johannes Attems*

*Institute of Neuroscience, Campus for Ageing and Vitality, Newcastle University, Newcastle-upon-Tyne, UK

†First Department of Neurology, National and Kapodistrian University of Athens Medical School, Athens, Greece

‡Biomedical Research Foundation of the Academy of Athens, Athens, Greece

Abstract

Lewy body diseases share clinical, pathological, genetic and biochemical signatures, and are regarded as a highly heterogeneous group of neurodegenerative disorders. Inclusive of Parkinson's disease (PD), Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), controversy still exists as to whether they should be considered as separate disease entities or as part of the same disease continuum. Here we discuss emerging knowledge relating to both clinical, and neuropathological differences and consider current biomarker strategies as we try to improve our diagnostic capabilities and design of disease modifying therapeutics for this group of debilitating neurodegenerative disorders.

Keywords: clinical heterogeneity, dementia with Lewy bodies, neuropathology, Parkinson's disease, Parkinson's disease dementia.

J. Neurochem. (2019) **150**, 467–474.

This article is part of the Special Issue "Synuclein".

Clinical aspects

Clinically, both dementia with lewy bodies (DLB) and Parkinson's disease dementia (PDD) share the core features of Lewy body dementias: cognitive decline, parkinsonism (which is required by definition in PDD, but does not always occur in DLB), fluctuating level of cognition and alertness and visual hallucinations; of note, Rapid eye movement (REM) Sleep Behaviour Disorder has recently been included in the core features of DLB (McKeith *et al.* 2017), and is frequently present in PDD as well. What differentiates the two conditions on clinical grounds is the '1 year rule'; if dementia occurs in the setting of established Parkinson's disease (PD), at least after 1 year of the onset of parkinsonism, this is deemed to be PDD; if, on the other hand, dementia precedes, or occurs concurrently or within a year of the onset of parkinsonism, this is deemed to be DLB. This rather arbitrary definition has been criticized, but nevertheless is useful clinically. A number of studies have attempted to compare the clinical profiles of the two conditions, using the above definition. The overall conclusion is that DLB is generally a more severe condition than PDD, especially with regard to the cognitive and possibly neuropsychiatric domain (Bougea *et al.* 2018). It is difficult or impossible however to differentiate a single patient with parkinsonism as PDD or DLB based on a single examination, without regard to the temporal sequence of events. With progression of the disease, the two conditions appear even more alike, as most

Received January 18, 2019; revised manuscript received March 13, 2019; accepted March 14, 2019.

Address correspondence and reprint requests to Dr Lauren Walker, Institute of Neuroscience, Campus for Ageing and Vitality, Newcastle University, NE4 5PL, UK. E-mail: lauren.walker1@ncl.ac.uk

Abbreviations used: AD, Alzheimer's disease; Aβ, amyloid-β; CERAD, consortium to establish a registry for Alzheimer's disease; CSF, cerebrospinal fluid; DLB, dementia with lewy bodies; $HP\text{-}_T$, hyperphosphorylated tau; LBD, lewy body disease; NFT, neurofibrillary tangle; PDD, Parkinson's disease dementia; PD, Parkinson's disease; RBD, REM sleep behaviour disorder; TMA, tissue microarray; α-syn, α-synuclein.

neurodegenerative afflictions do, while with time there is also an increasing influence of other comorbidities. Indicatively, mortality rates for PDD and DLB do not differ in a recently published study from Sweden, and are approximately three times higher than the general population, underscoring their severity (Larsson *et al.* 2018). In an effort to examine similarities and differences between the two conditions, attempts have been made to compare the groups at their earliest stages. MCI-DLB cases are more affected cognitively than MCI-PD in domains such as frontal executive function, verbal and non-verbal memory and visuospatial abilities, which are the core cognitive domains that are affected in LBDs (Yoon *et al.* 2014). This reflects mostly a quantitative, rather than a qualitative difference between the two groups, and could result from case selection bias. On the other hand, in cases with an overall similar degree of mild dementia (defined as MMSE > or = 24), DLB cases had a slightly worse performance on tests of attention-executive function, and were severely affected in tests of visuospatial abilities, especially the intersecting pentagon test, compared to PDD (Petrova *et al.* 2015). This suggests that visuospatial function may be disproportionally affected in DLB compared to PDD, possibly related to the higher degree of parietal atrophy seen in DLB compared to PDD; however, temporal and occipital atrophy were also more pronounced in DLB (Beyer *et al.* 2007). Naturally, parkinsonism is more severe in these earlier stages of the conditions in PDD, despite higher use of dopaminergic medications (Petrova *et al.* 2015). This includes classical resting tremor, which is considered uncommon in DLB.

Neuropathological considerations

Despite the differences in temporal sequence of emerging clinical symptoms in PD, PDD and DLB, they share a neuropathological hallmark lesion assumed to be the causative substrate for motor symptoms observed in PD, and extrapyramidal symptoms and cognitive impairment in PDD and DLB (Spillantini *et al.* 1998; Hurtig *et al.* 2000; Braak *et al.* 2003; Mori 2005; Tsuboi and Dickson 2005; Ballard *et al.* 2006; Galvin *et al.* 2006; Tsuboi *et al.* 2007; Compta *et al.* 2011; Irwin *et al.* 2012). α-synuclein (α-syn) is a small protein 140aa in length, and under pathological conditions aggregates into β-sheet-rich oligomers and fibrils predominantly in neuronal cells and their processes (termed Lewy bodies and Lewy neurites respectively (Fig. 1a) (Spillantini *et al.* 1997; Serpell *et al.* 2000). The pathological delineation of PD compared to PDD/DLB lies in the stage of progression of pathology through the brain; PD patients have inclusions restricted to the brainstem and limbic regions, whilst in PDD and DLB patients Lewy body pathology extends to the neocortex. Based on the neuropathological observations at *post-mortem* examination, distinguishing between PDD and DLB is a universal challenge and confounded by the common pathologies shared by both. Primarily classed a synucleinopathies, Lewy bodies and neurites are central to the neuropathological diagnosis of PD, PDD and DLB, with the progression of these lesions to the limbic and neocortical structures providing a robust correlate for clinical dementia in PDD and DLB (Braak *et al.* 2003; McKeith *et al.* 2017). In a cohort of 52 Lewy body disease (LBD) cases (inclusive of PD, PDD, and DLB), 80% of PD cases were classified as the limbic transitional stage according to McKeith criteria, whilst both PDD and DLB cases were classified as neocortical LBD (with a slightly higher percentage of DLB cases fulfilling criteria for neocortical LBD compared to PDD cases 97% vs 90%) Fig. 2a. This finding has been reported previously (Jellinger 2018), and supports clinical data regarding the pronounced onset of cognitive impairment in relation to extrapyramidal symptoms in DLB compared to PDD, whilst it has also been reported that striatal α-syn is increased in PDD in relation to DLB, consistent with PDD being principally a motor disorder (Tsuboi *et al.* 2007). Furthermore, DLB cases seem to have a higher burden of Lewy bodies/neurites in limbic and neocortical regions, specifically the temporal lobe, and the CA2 region of the hippocampus compared to PDD cases (Fig. 1), whilst dopaminergic cell loss in the substantia nigra is reportedly higher in PDD and PD (mainly affecting the dorsolateral regions), compared to DLB (where medioventral regions are most affected) (Mori 2005; Tsuboi and Dickson 2005; Kovari *et al.* 2009; Jellinger 2018).

Although primarily classed as synucleinopathies, LBDs are heterogeneous disorders with pathologic substrates including synaptic degeneration, vascular pathology, neuronal loss and basal forebrain cholinergic degeneration. AD-related pathologies are also a common feature of PD, PDD and DLB, with hyperphosphorylated tau ($HP\text{-}_T$) and amyloid-β (Aβ) thought to contribute to the cognitive decline observed in DLB and PDD. DLB cases exhibit concurrent AD-related pathology at more advanced stage compared to PDD cases (Braak neurofibrillary tangle ≥IV, 38% vs 20%; Thal phase ≥ 4, 63% vs 50%; consortium to establish a registry for Alzheimer's disease B/C, 50% vs 30%) (Fig. 2c and d). Of note 28% of DLB and 10% PDD cases had sufficient pathology for a secondary neuropathological diagnosis of AD. This has been consistently demonstrated in multiple studies, as Aβ plaques are reportedly observed more in the entorhinal cortex, amygdala and putamen (Hepp *et al.* 2016), in addition to Aβ burden being significantly higher in cortical and subcortical regions in DLB compared to PDD (Jellinger and Attems 2006; Edison *et al.* 2008; Halliday *et al.* 2011; Walker *et al.* 2015; Hepp *et al.* 2016).

The presence of concomitant pathologies are also reflected in the clinical phenotype of DLB and PDD as the burden of additional pathologies has been associated with a more rapid decline in cognition, and a shorter survival time from the

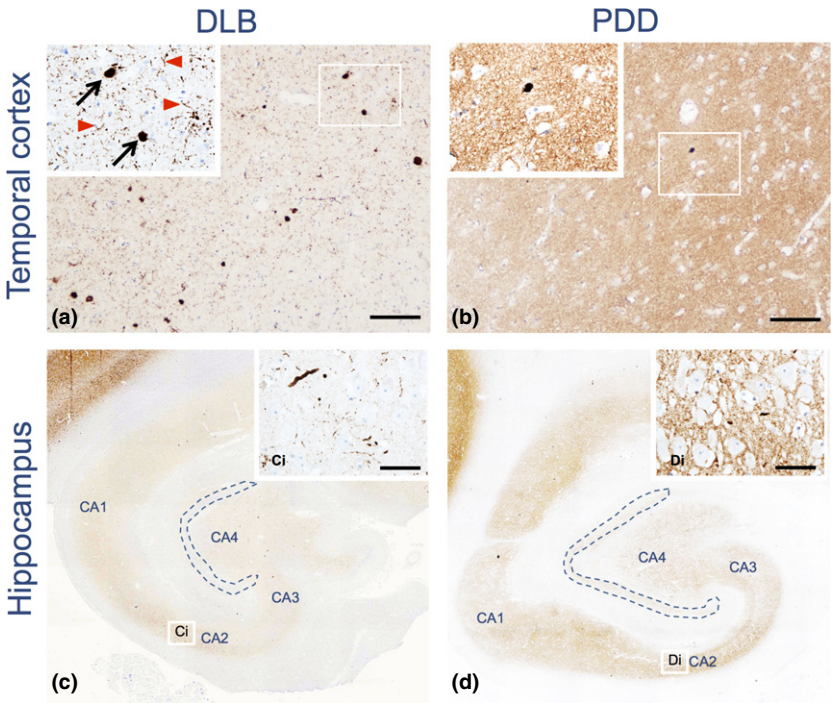

Fig. 1 Examples of Lewy body pathology: Lewy bodies, black arrows (a), and Lewy neurites, red arrow heads (b) in the temporal cortex and hippocampus of DLB and PDD cases. DLB cases appear to have more α-syn positive Lewy bodies and Lewy neurites in both the temporal lobe and CA2 of the hippocampus (a and c) compared to PDD cases (b and d). Blue dashed lines highlight the dentate gyrus. Scale bars represent 100 μm in (a) and (b), and 50 μm in (c) and (d). Abbreviations: DLB, dementia with lewy bodies; PDD, Parkinson's disease dementia; CA, Cornu Ammonis.

onset of clinical symptoms compared to 'pure' LBD groups (Olichney *et al.* 1998; Serby *et al.* 2003; Kraybill *et al.* 2005). In particular, the additive effect of AD-related pathologies to the clinical phenotype has been well documented; however, the relative contribution of each pathology to the clinical course of LBD is still unclear, as both concomitant HP-$_T$ pathology and Aβ burden have been associated with a shorter latency between the onset of motor symptoms and development of dementia in LBD cases (Ruffmann *et al.* 2016; Irwin *et al.* 2017). Although many studies into PDD and DLB can be longitudinal, *post-mortem* investigations are by nature cross-sectional, therefore making it challenging to decipher the exact contribution of individual pathologies to the individual clinical phenotype of DLB or PDD as onset of accumulation of such neuropathological lesions may appear years before they are clinically relevant. Numerous studies report conflicting results as to the relative contribution to each clinical disorder. It has been suggested that the occurrence of the DLB clinical syndrome is positively related to the presence of α-syn and negatively related to the severity of HP-$_T$ pathology, whilst Aβ has no effect (Tiraboschi *et al.* 2015), with regional HP-$_T$ scores relating to cognitive performance in LBD (Coughlin *et al.* 2019). In addition, PDD cases with greater AD-related pathology have a clinical phenotype similar to DLB, with a shorter time to dementia (Hely *et al.* 2008; Irwin *et al.* 2013), whilst other studies suggest Aβ and α-syn are strongly correlated with survival and timing of dementia (Ferman *et al.* 2018). This is currently a major challenge as there is no reliable neuropsychological testing to identify co-existent AD-related pathology in an LBD context, although work in our laboratory has suggested the presence of complex visual hallucinations in AD patients indicates the presence of concomitant LBD (Thomas *et al.* 2018).

It is therefore perhaps a combination of multiple pathologies that is detrimental to cognition in patients with DLB or PDD. Indeed, it has been shown that in both DLB and PDD that exhibit α-syn, HP-$_T$ and Aβ, the additive effect of all the three pathologies is a better predictor of dementia compared to one single pathology (Compta *et al.* 2011; Howlett *et al.* 2015).

The neuropathological staging of α-syn in LBD has been suggested to follow a caudal-rostral progression as outlined by Braak and colleagues progressing from the brainstem, through the limbic structures to the neocortex (Braak *et al.* 2003). However, as there is a current lack of validated-imaging biomarkers for α-syn, it is impossible to distinguish differences in protein propagation patterns between DLB and PDD. Of note, a recent study conducted by Irwin and colleagues reported 18% of neuropathologically confirmed DLB cases did not develop a motor disorder as part of their disease course, but the majority exhibited intermediate/high AD-related neuropathologic change, as assessed by National Institute on Ageing – Alzheimer's Association guidelines (Montine *et al.* 2012; Irwin *et al.* 2017). This may suggest that Lewy body formation in the limbic system and neocortex may occur without involvement of the brainstem, and may be triggered or exacerbated in vulnerable brain regions already subjected to pathological insults by the accumulation of HP-$_T$ and/or Aβ. The staging criteria proposed by Beach and

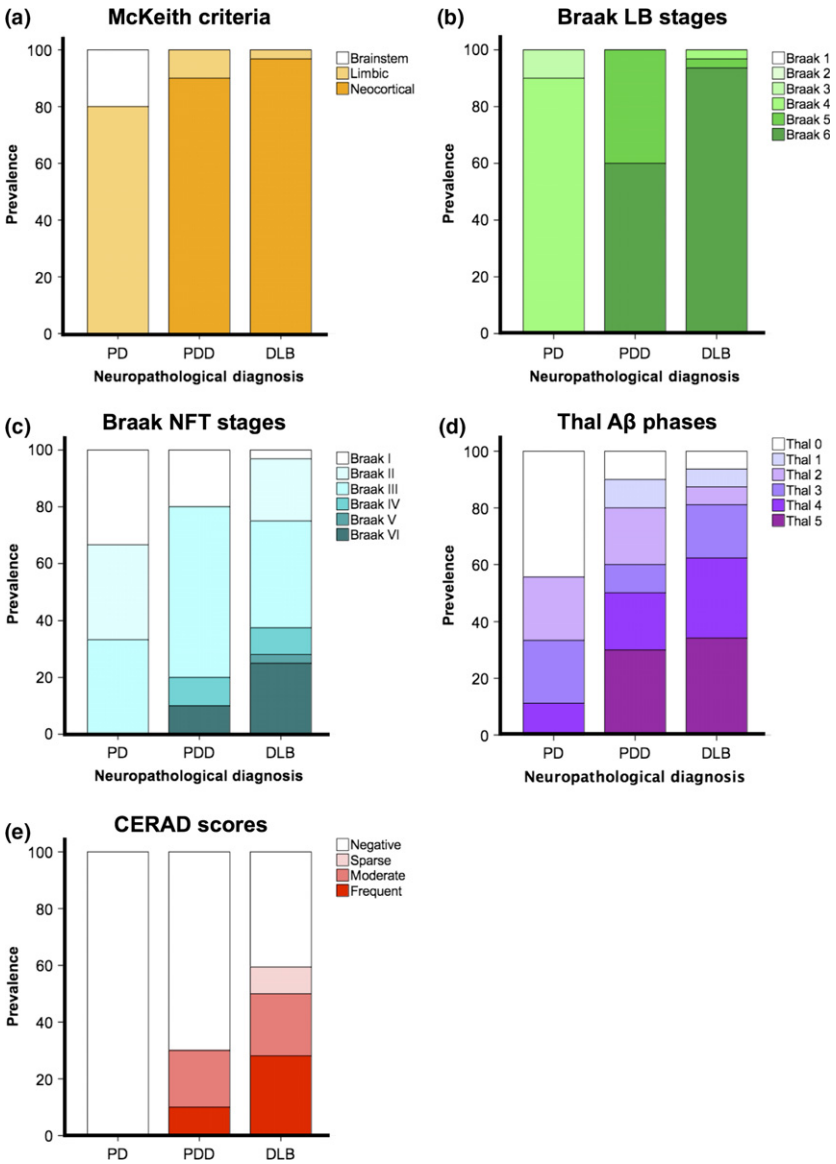

Fig. 2 The frequency of DLB cases that have α-syn progression to the neocortex as classified by McKeith criteria (a) and Braak LB staging (b) is higher than PDD and PD. AD-related pathology pathology also appears more advanced in DLB compared to PDD, and PD as classified by neurofibrillary tangle (NFT) Braak stage (c), Thal Aβ phase (d), and consortium to establish a registry for Alzheimer's disease (CERAD) score for neuritic plaque pathology (e). Abbreviations: DLB, dementia with Lewy bodies; LB, Lewy body; PDD, Parkinson's disease dementia; PD, Parkinson's disease; NFT, neurofibrillary tangle; CERAD, Consortium to Establish a Registry for Alzheimer's disease.

colleagues, where 10% of DLB cases were categorized as limbic predominant, without involvement of the brainstem, supports this observation (Beach *et al.* 2009). The colocalization of α-syn and HP-$_T$ has been demonstrated in human *post-mortem* tissue (Colom-Cadena *et al.* 2013), and potential interactions between pathological protein aggregates (α-syn, HP-$_T$ and Aβ) have been described in human and transgenic animals (Giasson *et al.* 2003; Clinton *et al.* 2010; Badiola *et al.* 2011).

Perhaps difficulties facing researchers in deciphering differences between these heterogeneous disorders stem from inconsistencies in experimental approaches. Historically, pathological lesions were assessed using semi-quantitative methodologies (utilizing mild, moderate, severe and very severe categories for HP-$_T$ and α-syn (Alafuzoff *et al.* 2008; McKeith *et al.* 2005)). This has the inherent problem of a subjective scoring between individual raters. Although semi-quantitative evaluation is extremely valuable when classifying neurodegenerative diseases, it lacks the accuracy to detect subtle differences in pathology loads, particularly in the later stages of disease when pathology burden is considerable. For, example the amount of HP-$_T$ can differ by up to 100% between cases that are classified as having severe pathology when assessed semi-quantitatively (Attems and Jellinger 2013). The introduction of quantitative neuropathological assessment, such as slide scanning with digital pathologic image analysis, or automated microscopy [for more details see (Attems *et al.* 2014; Walker *et al.* 2017)], will greatly add to our ability to potentially detect discrete clinic-pathological phenotypes of DLB and PDD, similar to what has been described in AD (Murray *et al.* 2011). As a result of financial and time restrictions, many

studies to date select a limited number of brain regions to investigate a particular component of disease e.g. burden of pathological protein aggregates, or degeneration of synapses. However, to tease out the global differences between DLB and PDD, increased number of brain regions and potential disease components should be encouraged. Tissue microarray provides an excellent platform for such studies as it allows the study of multiple components of disease to be studied in serial sections across 35 brain regions (Walker *et al.* 2017).

Genetic characteristics

Another approach in examining whether the two conditions are ends of a spectrum is to examine their genetic underpinnings. A number of studies have now confirmed that ApoE4 is a genetic risk factor for both DLB and, perhaps less so, PDD. In particular, regarding DLB, a recent Genome wide association studies (GWAS) and previous more targeted approaches have definitively shown that ApoE4 allele status is linked to an increased risk of DLB, even after considering only pathologically proven cases (Bras *et al.* 2014; Guerreiro *et al.* 2016, 2018). Despite earlier controversy, it appears clear that an ApoE4 allele also confers a higher risk of developing PDD. This was confirmed in a meta-analysis of case–control studies (Sun *et al.* 2019) and is evident also in neuropathological series (Tsuang *et al.* 2013). The fact of this association in LBDs could be taken to indicate the influence of concomitant AD pathology, but robust neuropathological data now indicate that, even in cases without such pathology, ApoE4 confers an increased risk for more widespread synucleinopathy and dementia, across the full spectrum of LBDs (Tsuang *et al.* 2013; Dickson *et al.* 2018). Two other major GWAS hits that emerged from the recent DLB study (Guerreiro *et al.* 2018), the loci for Glucocerebrosidase (GBA) and α-synuclein (SNCA) had also been previously ascertained as risk loci for DLB based on targeted approaches. GBA mutations were identified to strongly increase the risk of developing DLB (Nalls *et al.* 2013), and are known to increase the risk of developing PDD (Brockmann *et al.* 2015). Thus, GBA mutations may lead to either PDD or DLB, but whether there is a difference in the particular causal mutations has not been rigorously assessed. The SNCA locus of course is also the main hit in GWAS in PD (Nalls *et al.* 2011), but whether it is associated with an increased risk of developing PDD is not known. SNCA point mutations such as the originally identified p.A53T led usually to PD-PDD (Papadimitriou *et al.* 2016), but cases with a DLB presentation have been described (Morfis and Cordato 2006), underscoring again the fact that, like in GBA-PD, the same genetic defect may lead to either PDD or DLB. In an earlier focused study, the SCARB2 gene encoding for LIMP2, a transporter for the product of the GBA gene Glucocerebrocidase, was also shown to be marginally associated with DLB (Bras *et al.* 2014). This gene locus is also associated with PD (Nalls *et al.* 2011; Michelakakis *et al.* 2012). Interestingly, the exact location within the SCARB2 and SNCA loci was different in PD versus DLB, suggesting that there could be particular factors, perhaps operating in a region-specific manner that could differentially alter the transcriptional regulation of these genes, and therefore cause region-specific alterations. Overall, GWAS indicate that, even without taking into account the strong ApoE signal, DLB genetically resembles both AD and PD, probably in equal measures, whereas PD and AD are genetically distinct (Guerreiro *et al.* 2016). It would be interesting to perform such GWAS on 'pure' DLB in the absence of AD pathology to examine whether the association with AD risk genes still occurs; if so, this would suggest the existence of the same genetic factors that could contribute either to synucleinopathy or to HP-$_T$/Aβ pathology, with the end clinical result of dementia. As mentioned, ApoE4 appears to be such a factor.

Cerebrospinal fluid (CSF) biomarkers showing an AD profile are common in DLB, ranging from 25 to 50%, with an even higher percentage showing only low beta-amyloid (Schoonenboom *et al.* 2012; van Steenoven *et al.* 2016; Bougea *et al.* 2018). This is lower than the percentages of cases found on autopsy with AD pathology, and this likely reflects the accumulation of AD pathology with ageing and within the DLB condition. CSF biomarker data are quite consistent with imaging studies, showing overall about 50% of DLB cases with positivity on Aβ PET imaging (Ossenkoppele *et al.* 2015). Percentages of AD CSF biomarkers are much lower in PDD, but still above controls or PD, providing *in vivo* data for a smaller contribution of AD pathology to PDD as well (van Steenoven *et al.* 2016). Interestingly, levels of AD CSF biomarkers in GBA-PD were not different from controls and were not associated with the development of dementia, suggesting that in this defined genetic cohort AD-type pathology was not a determinant of PDD (Lerche *et al.* 2017). Whether this would be true in a cohort of GBA-DLB cases as well remains to be determined.

In conclusion, PDD and DLB both represent rather heterogeneous conditions. It is clear from neuropathological, biomarker and imaging studies that AD-type pathology is more of a determinant factor in DLB compared to PDD. The vast majority of PDD cases have dementia in the absence of significant AD pathology, indicating that the synucleinopathy *per se* is the major cause of the cognitive decline. The same is true for at least a large proportion of DLB cases. Genetic data suggest that DLB can be viewed rather as a combination of PD and AD in terms of pathogenetic mechanisms. The recent finding that ApoE4 is a risk factor for widespread synucleinopathy and consequent dementia regardless of AD pathology suggests that specific genetic factors may contribute to worse cognitive function and more widespread aberrant protein deposition in the context of both AD and pure LBDs. In addition, genetic differences within

the particular loci identified to be shared between PD and DLB may be responsible for the differential regional affectation by the synucleinopathic process in the case of DLB compared to PD. Six missense mutations have been identified in the *SNCA* gene in PD whilst to date only two have been associated with diffuse neuropathological Lewy body disease (Rosborough *et al.* 2017; Orme *et al.* 2018). In addition, gene-based mutation analyses of DLB and PDD has identified three missense mutations in *PSEN1* and *PSEN2* (three in DLB and one in PDD) (Meeus *et al.* 2012). These findings underscore the need to clearly define the separate nosological entitities within the LBD spectrum, taking into account concomitant biomarker, imaging and genetic data. Such approaches in the future may hold promise for more personalized treatments based on the individual profile of each patient within the LBD spectrum.

Acknowledgments and conflict of interest disclosure

Data in this manuscript are original and were generated for the purpose of this study. Photomicrographs were taken from tissue provided by the Newcastle Brain Tissue Resource, which is funded in part by a grant from the UK Medical Research Council (G0400074), by Brains for Dementia research, a joint venture between Alzheimer's Society and Alzheimer's Research UK and by the NIHR Newcastle Biomedical Research Centre awarded to the Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University. DLB research is supported by NIHR Newcastle Biomedical Research Centre in Ageing and Long-Term Conditions. LW is funded by the Alzheimer's Society. The authors have no conflicts of interest to declare.

References

Alafuzoff I., Arzberger T., Al-Sarraj S. *et al.* (2008) Staging of neurofibrillary pathology in Alzheimer's disease: a study of the BrainNet Europe Consortium. *Brain Pathol. (Zurich, Switzerland)* **18**, 484–496.

Attems J. and Jellinger K. (2013) Neuropathology, in *Oxford Textbook of Old Age Psychiatry*, (Dening T. T. and Alan Thomas J. ed.), pp. 87–105. Oxford Unversity Press, New York.

Attems J., Neltner J. H. and Nelson P. T. (2014) Quantitative neuropathological assessment to investigate cerebral multimorbidity. *Alzheimer's Res. Therapy* **6**, 85.

Badiola N., de Oliveira R. M., Herrera F. *et al.* (2011) Tau enhances alpha-synuclein aggregation and toxicity in cellular models of synucleinopathy. *PLoS ONE* **6**, e26609.

Ballard C., Ziabreva I., Perry R., Larsen J. P., O'Brien J., McKeith I., Perry E. and Aarsland D. (2006) Differences in neuropathologic characteristics across the Lewy body dementia spectrum. *Neurology* **67**, 1931–1934.

Beach T. G., Adler C. H., Lue L. *et al.* (2009) Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. *Acta Neuropathol.* **117**, 613–634.

Beyer M. K., Larsen J. P. and Aarsland D. (2007) Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies. *Neurology* **69**, 747–754.

Bougea A., Stefanis L., Paraskevas G. P., Emmanouilidou E., Efthymiopoulou E., Vekrelis K. and Kapaki E. (2018) Neuropsychiatric symptoms and alpha-Synuclein profile of patients with Parkinson's disease dementia, dementia with Lewy bodies and Alzheimer's disease. *J. Neurol.* **265**, 2295–2301.

Braak H., Del Tredici K., Rub U., de Vos R. A., Jansen Steur E. N. and Braak E. (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* **24**, 197–211.

Bras J., Guerreiro R., Darwent L. *et al.* (2014) Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. *Hum. Mol. Genet.* **23**, 6139–6146.

Brockmann K., Srulijes K., Pflederer S., Hauser A. K., Schulte C., Maetzler W., Gasser T. and Berg D. (2015) GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. *Mov. Disord.* **30**, 407–411.

Clinton L. K., Blurton-Jones M., Myczek K., Trojanowski J. Q. and LaFerla F. M. (2010) Synergistic Interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline. *J. Neurosci.* **30**, 7281–7289.

Colom-Cadena M., Gelpi E., Charif S., Belbin O., Blesa R., Marti M. J., Clarimon J. and Lleo A. (2013) Confluence of alpha-synuclein, tau, and beta-amyloid pathologies in dementia with Lewy bodies. *J. Neuropathol. Exp. Neurol.* **72**, 1203–1212.

Compta Y., Parkkinen L., O'Sullivan S. S. *et al.* (2011) Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? *Brain* **134**, 1493–1505.

Coughlin D., Xie S. X., Liang M. *et al.* (2019) Cognitive and pathological influences of Tau pathology in lewy body disorders. *Ann. Neurol.* **85**, 259–271.

Dickson D. W., Heckman M. G., Murray M. E. *et al.* (2018) APOE epsilon4 is associated with severity of Lewy body pathology independent of Alzheimer pathology. *Neurology* **91**, e1182–e1195.

Edison P., Rowe C. C., Rinne J. O. *et al.* (2008) Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. *J. Neurol. Neurosurg. Psychiatry* **79**, 1331–1338.

Ferman T. J., Aoki N., Crook J. E. *et al.* (2018) The limbic and neocortical contribution of alpha-synuclein, tau, and amyloid beta to disease duration in dementia with Lewy bodies. *Alzheimer's Dem.* **14**, 330–339.

Galvin J. E., Pollack J. and Morris J. C. (2006) Clinical phenotype of Parkinson disease dementia. *Neurology* **67**, 1605–1611.

Giasson B. I., Forman M. S., Higuchi M., Golbe L. I., Graves C. L., Kotzbauer P. T., Trojanowski J. Q. and Lee V. M. (2003) Initiation and synergistic fibrillization of tau and alpha-synuclein. *Science* (New York, N.Y.) **300**, 636–640.

Guerreiro R., Escott-Price V., Darwent L. *et al.* (2016) Genome-wide analysis of genetic correlation in dementia with Lewy bodies, Parkinson's and Alzheimer's diseases. *Neurobiol. Aging* **38**, 214.e217–214.e210.

Guerreiro R., Ross O. A., Kun-Rodrigues C. *et al.* (2018) Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. *Lancet Neurol.* **17**, 64–74.

Halliday G. M., Song Y. J. and Harding A. J. (2011) Striatal beta-amyloid in dementia with Lewy bodies but not Parkinson's disease. *J. Neural. Transm.* (Vienna, Austria : 1996) **118**, 713–719.

Hely M. A., Reid W. G., Adena M. A., Halliday G. M. and Morris J. G. (2008) The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov. Disord.* **23**, 837–844.

Hepp D. H., Vergoossen D. L., Huisman E., Lemstra A. W., Berendse H. W., Rozemuller A. J., Foncke E. M. and van de Berg W. D. (2016) Distribution and load of amyloid-beta pathology in Parkinson disease and dementia with lewy bodies. *J. Neuropathol. Exp. Neurol.* **75**, 936–945.

Howlett D. R., Whitfield D., Johnson M. *et al.* (2015) Regional multiple pathology scores are associated with cognitive decline in lewy body dementias. *Brain Pathol. (Zurich, Switzerland)* **25**, 401–408.

Hurtig H. I., Trojanowski J. Q., Galvin J. *et al.* (2000) Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. *Neurology* **54**, 1916–1921.

Irwin D. J., White M. T., Toledo J. B. *et al.* (2012) Neuropathologic substrates of Parkinson disease dementia. *Ann. Neurol.* **72**, 587–598.

Irwin D. J., Lee V. M. and Trojanowski J. Q. (2013) Parkinson's disease dementia: convergence of alpha-synuclein, tau and amyloid-beta pathologies. *Nat. Rev. Neurosci.* **14**, 626–636.

Irwin D. J., Grossman M., Weintraub D. *et al.* (2017) Neuropathological and genetic correlates of survival and dementia onset in synucleinopathies: a retrospective analysis. *Lancet Neurol.* **16**, 55–65.

Jellinger K. A. (2018) Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. *J. Neural. Transm (Vienna)* **125**, 615–650.

Jellinger K. A. and Attems J. (2006) Does striatal pathology distinguish Parkinson disease with dementia and dementia with Lewy bodies? *Acta Neuropathol.* **112**, 253–260.

Kovari E., Horvath J. and Bouras C. (2009) Neuropathology of Lewy body disorders. *Brain Res. Bull.* **80**, 203–210.

Kraybill M. L., Larson E. B., Tsuang D. W., Teri L., McCormick W. C., Bowen J. D., Kukull W. A., Leverenz J. B. and Cherrier M. M. (2005) Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. *Neurology* **64**, 2069–2073.

Larsson V., Torisson G. and Londos E. (2018) Relative survival in patients with dementia with Lewy bodies and Parkinson's disease dementia. *PLoS ONE* **13**, e0202044.

Lerche S., Schulte C., Srulijes K. *et al.* (2017) Cognitive impairment in Glucocerebrosidase (GBA)-associated PD: not primarily associated with cerebrospinal fluid Abeta and Tau profiles. *Mov. Disord.* **32**, 1780–1783.

McKeith I. G., Dickson D. W., Lowe J. *et al.* (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* **65**, 1863–1872.

McKeith I. G., Boeve B. F., Dickson D. W. *et al.* (2017) Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology* **89**, 88–100.

Meeus B., Verstraeten A., Crosiers D. *et al.* (2012) DLB and PDD: a role for mutations in dementia and Parkinson disease genes? *Neurobiol. Aging* **33**, 629.e625–629.e618.

Michelakakis H., Xiromerisiou G., Dardiotis E. *et al.* (2012) Evidence of an association between the scavenger receptor class B member 2 gene and Parkinson's disease. *Mov. Disord.* **27**, 400–405.

Montine T., Phelps C., Beach T. *et al.* (2012) National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol.* **123**, 1–11.

Morfis L. and Cordato D. J. (2006) Dementia with Lewy bodies in an elderly Greek male due to alpha-synuclein gene mutation. *J. Clin. Neurosci.* **13**, 942–944.

Mori H. (2005) Pathological substrate of dementia in Parkinson's disease–its relation to DLB and DLBD. *Parkinsonism Relat. Disord.* **11**(Suppl 1), S41–S45.

Murray M. E., Graff-Radford N. R., Ross O. A., Petersen R. C., Duara R. and Dickson D. W. (2011) Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet Neurol.* **10**, 785–796.

Nalls M. A., Plagnol V., Hernandez D. G. *et al.* (2011) Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet* **377**, 641–649.

Nalls M. A., Duran R., Lopez G. *et al.* (2013) A multicenter study of Glucocerebrosidase mutations in dementia with lewy bodies. *JAMA Neurol.* **70**, 727–735.

Olichney J. M., Galasko D., Salmon D. P., Hofstetter C. R., Hansen L. A., Katzman R. and Thal L. J. (1998) Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. *Neurology* **51**, 351–357.

Orme T., Guerreiro R. and Bras J. (2018) The genetics of dementia with lewy bodies: current understanding and future directions. *Curr. Neurol. Neurosci. Rep.* **18**, 67.

Ossenkoppele R., Jansen W. J., Rabinovici G. D. *et al.* (2015) Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA* **313**, 1939–1949.

Papadimitriou D., Antonelou R., Miligkos M. *et al.* (2016) Motor and nonmotor features of carriers of the p. A53T alpha-synuclein mutation: a longitudinal study. *Mov. Disord.* **31**, 1226–1230.

Petrova M., Mehrabian-Spasova S., Aarsland D., Raycheva M. and Traykov L. (2015) Clinical and neuropsychological differences between mild Parkinson's disease dementia and dementia with lewy bodies. *Dement Geriatr. Cogn Dis. Extra* **5**, 212–220.

Rosborough K., Patel N. and Kalia L. V. (2017) Alpha-synuclein and Parkinsonism: updates and future perspectives. *Curr. Neurol. Neurosci. Rep.* **17**, 31.

Ruffmann C., Calboli F. C., Bravi I. *et al.* (2016) Cortical Lewy bodies and Abeta burden are associated with prevalence and timing of dementia in Lewy body diseases. *Neuropathol. Appl. Neurobiol.* **42**, 436–450.

Schoonenboom N. S., Reesink F. E., Verwey N. A. *et al.* (2012) Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort. *Neurology* **78**, 47–54.

Serby M., Brickman A. M., Haroutunian V., Purohit D. P., Marin D., Lantz M., Mohs R. C. and Davis K. L. (2003) Cognitive burden and excess Lewy-body pathology in the Lewy-body variant of Alzheimer disease. *Am. J. Geriatric Psychiatry* **11**, 371–374.

Serpell L. C., Berriman J., Jakes R., Goedert M. and Crowther R. A. (2000) Fiber diffraction of synthetic alpha-synuclein filaments shows amyloid-like cross-beta conformation. *Proc. Natl Acad. Sci. USA* **97**, 4897–4902.

Spillantini M. G., Schmidt M. L., Lee V. M., Trojanowski J. Q., Jakes R. and Goedert M. (1997) Alpha-synuclein in Lewy bodies. *Nature* **388**, 839–840.

Spillantini M. G., Crowther R. A., Jakes R., Hasegawa M. and Goedert M. (1998) alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. *Proc. Natl Acad. Sci. USA* **95**, 6469–6473.

van Steenoven I., Aarsland D., Weintraub D. *et al.* (2016) Cerebrospinal fluid Alzheimer's disease biomarkers across the spectrum of lewy Body diseases: results from a large multicenter cohort. *Journal of Alzheimer's disease : JAD* **54**, 287–295.

Sun R., Yang S., Zheng B., Liu J. and Ma X. (2019) Apolipoprotein E polymorphisms and Parkinson disease with or without dementia: a meta-analysis including 6453 participants. *J. Geriatr. Psychiatry Neurol.* **32**, 3–15.

Thomas A. J., Mahin-Babaei F., Saidi M., Lett D., Taylor J. P., Walker L. and Attems J. (2018) Improving the identification of dementia with Lewy bodies in the context of an Alzheimer's-type dementia. *Alzheimer's Res. Therapy* **10**, 27.

Tiraboschi P., Attems J., Thomas A. *et al.* (2015) Clinicians' ability to diagnose dementia with Lewy bodies is not affected by beta-amyloid load. *Neurology* **84**, 496–499.

Tsuang D., Leverenz J. B., Lopez O. L. *et al.* (2013) APOE epsilon4 increases risk for dementia in pure synucleinopathies. *JAMA Neurol.* **70**, 223–228.

Tsuboi Y. and Dickson D. W. (2005) Dementia with Lewy bodies and Parkinson's disease with dementia: are they different? *Parkinsonism Relat. Disord.* **11**(Suppl 1), S47–S51.

Tsuboi Y., Uchikado H. and Dickson D. W. (2007) Neuropathology of Parkinson's disease dementia and dementia with Lewy bodies with reference to striatal pathology. *Parkinsonism Relat. Disord.* **13** (Suppl 3), S221–S224.

Walker L., McAleese K. E., Thomas A. J., Johnson M., Martin-Ruiz C., Parker C., Colloby S. J., Jellinger K. and Attems J. (2015) Neuropathologically mixed Alzheimer's and Lewy body disease: burden of pathological protein aggregates differs between clinical phenotypes. *Acta Neuropathol.* **129**, 729–748.

Walker L., McAleese K. E., Johnson M., Khundakar A. A., Erskine D., Thomas A. J., McKeith I. G. and Attems J. (2017) Quantitative neuropathology: an update on automated methodologies and implications for large scale cohorts. *J. Neural. Transm (Vienna)* **124**, 671–683.

Yoon J. H., Lee J. E., Yong S. W., Moon S. Y. and Lee P. H. (2014) The mild cognitive impairment stage of dementia with Lewy bodies and Parkinson disease: a comparison of cognitive profiles. *Alzheimer Dis. Assoc. Disord.* **28**, 151–155.