



Published in final edited form as:

*Mov Disord.* 2020 January ; 35(1): 5–19. doi:10.1002/mds.27867.

## Pathological Influences on Clinical Heterogeneity in Lewy Body Diseases

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### Abstract

Parkinson's disease (PD), Parkinson's disease with dementia (PDD) and dementia with Lewy Bodies (DLB) are clinical syndromes characterized by the neuropathologic accumulation of alpha-synuclein in the central nervous system that represent a clinico-pathological spectrum known as Lewy body disorders (LBD). These clinical entities have marked heterogeneity of motor and non-motor symptoms with highly variable disease progression. The biological basis for this clinical heterogeneity remains poorly understood. Previous attempts to subtype patients within the spectrum of LBD have centered on clinical features, but converging evidence from studies of neuropathology and ante mortem biomarkers including CSF, neuroimaging, and genetic studies suggest that Alzheimer's disease (AD) beta-amyloid and tau co-pathology strongly influences clinical heterogeneity and prognosis in LBD. Here, we review previous clinical biomarker and autopsy studies of LBD and propose that AD co-pathology is one of several likely pathological contributors to clinical heterogeneity of LBD, and that such pathology can be assessed *in vivo*. Future work integrating harmonized assessments and genetics in PD, PDD, and DLB patients followed to autopsy will be critical to further refine the classification of LBD into biologically distinct endophenotypes. This approach will help facilitate clinical trial design for both symptomatic and disease-modifying therapies to target more homogenous subsets of LBD patients with similar prognosis and underlying biology.

### Keywords

Parkinson's Disease; dementia with Lewy bodies; alpha synuclein; neuropathology; clinical heterogeneity

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HIH contributed to the organization, execution, and review and critique of the paper

Financial Disclosures:

Howard Hurtig has no financial disclosures

## INTRODUCTION

Parkinson's Disease (PD) is a common neurological disorder, affecting over 10 million people worldwide<sup>1</sup> and is marked by highly variable extra-pyramidal motor features of tremor, rigidity, and bradykinesia but also non-motor features of depression, autonomic dysfunction, and cognitive impairment. The reasons for this heterogeneity are unknown. Cognitive impairment and dementia are particularly strong predictors of poor prognosis<sup>2</sup>. Cognitive impairment is present in approximately 25% of patients in early stages of the disease and predicts faster progression to dementia<sup>3, 4</sup> which is likely inevitable but occurs at widely variable times after the onset of motor parkinsonism<sup>5, 6</sup>. Early efforts to create clinical subgroups were based on the observation in large cohort studies and clinical trials that disease progression was more benign in some patients with a particular set of motor symptoms than in others. Subsequent work has integrated new genetic markers, imaging characteristics, and CSF analytes in both hypothesis driven studies and data driven cluster analyses. However, robust, reproducible, clinical subgroups have been difficult to identify.

The diagnostic neuropathologic hallmark of PD is misfolded alpha-synuclein (SYN) aggregates that form intraneuronal Lewy bodies (LB) and Lewy neurites (LN) (collectively Lewy pathology: LP). The introduction of immunohistochemical staining for SYN increased the sensitivity to detect these aggregates in PD, and also revealed SYN accumulations in the neocortex of many patients previously diagnosed with Alzheimer's disease (AD)<sup>7, 8</sup>. The neuropathological terms to describe this mixed pathology varied in early literature, but many of these patients showed clinical features distinct from amnesic AD. The clinicopathologic syndrome of dementia with Lewy bodies (DLB),<sup>9-11</sup> was defined by consensus criteria in 1996, with core features of motor parkinsonism, visual hallucinations, fluctuations of alertness, and dementia. Criteria have been subsequently revised to include biomarkers to improve the sensitivity of clinical diagnosis<sup>12, 13</sup>. Historically, the onset of the dementia should either predate or occur within one year of the onset of the motor parkinsonism, the so-called '1-year rule', in order for a diagnosis of DLB to be considered. However, because the clinical features of DLB and PDD are similar<sup>13, 14</sup> and the two entities share genetic risk factors<sup>15-17</sup>, prodromal features<sup>18-20</sup>, and exhibit similar neuropathologic features at autopsy<sup>9, 21-23</sup>, the concept of a distinct separation between these overlapping conditions has been challenged by many investigators, who regard PD, PDD and DLB as a single disease, LBD, whose clinical features are spread across a spectrum<sup>9, 23, 24</sup>.

While SYN is the hallmark pathology of LBD, tau and beta-amyloid (A $\beta$ ) co-pathology is common (overall ~50% of all LBD have a secondary neuropathological diagnosis of medium to high level AD in most large autopsy series- see below)<sup>21, 24-28</sup>. Several converging lines of evidence indicate that AD co-pathology not only contributes to decreased survival and a shortened motor-dementia interval but also influences specific motor and cognitive features<sup>21, 25, 29-32</sup>. While *in vivo* SYN biomarkers are still being developed, methods to detect A $\beta$  and tau in living LBD patients are improving<sup>33-37</sup>. Here, we will review previous and ongoing efforts to connect LBD patient subtypes with ante mortem biomarkers and underlying neuropathology to improve understanding of the biological basis of LBD's clinical heterogeneity.

## The role of alpha synuclein in LBD pathogenesis

In 1997, a mutation in the *SNCA* gene coding for SYN was discovered in a Greek/Italian family with autosomal dominantly inherited PD. Later that year, SYN was reported to be the major constituent of Lewy bodies and Lewy neurites found in both PD and DLB<sup>7, 38</sup>. Landmark work by Braak and colleagues in 2003 proposed a conserved pattern of spread of LP in the brains of patients with PD, starting in the caudal brainstem and progressing rostrally through the upper brainstem, limbic regions, and finally the neocortex<sup>39</sup>. Other staging systems have emerged<sup>12, 40</sup>, and additional patterns of LP have been added to account for the frequent finding of LP in the amygdala and limbic regions of patients with AD<sup>41–43</sup>. Current hypotheses regarding why particular regions of the brain are affected selectively include the spread of pathology along functionally connected networks<sup>44</sup> and selective vulnerability of long unmyelinated axons<sup>45</sup>. LP in DLB is thought to ascend the neuroaxis in a similar caudo-rostral pattern<sup>12, 46</sup>; although, the prominence of early dementia with limited or no motor parkinsonism, rare patients without dopamine transporter deficits on SPECT imaging<sup>47</sup>, and rare autopsy cases with isolated neocortical SYN pathology without brainstem or limbic SYN<sup>48</sup>, suggests an alternative pattern of spread in some cases.

The observations of SYN Lewy-like pathology in transplanted mesencephalic grafts in PD patients<sup>49</sup> support a ‘prion-like’ mechanism of spread of misfolded SYN aggregates as central to disease pathogenesis. Moreover, recent experiments in cell and animal models use preformed SYN fibrils<sup>50, 51</sup> or brain homogenates from human LBD subjects<sup>52, 53</sup> to induce spread of SYN pathology that results neuron loss and dysfunction as well as motor phenotypes which further supports this theory. Most recently, separate SYN species have been identified that may have different ‘strain-like’ properties, with certain preparations being additionally capable of cross-seeding either tau<sup>54–56</sup> or A $\beta$ <sup>57</sup> and others leading to multiple systems atrophy type pathologies<sup>58–60</sup>. However, the core prion feature of infectivity has not clearly been demonstrated for LBD or AD in humans<sup>61</sup>.

Many autopsy studies have shown a correlation of LP with motor disease severity in PD<sup>43, 62</sup>. The majority of studies have found that PDD is associated with either limbic (transitional)<sup>13</sup> or neocortical (diffuse) stage LB pathology<sup>63–67</sup> with higher cortical LP density being observed than in non-demented PD<sup>2, 64–70</sup>. Neocortical LP is also associated with the onset of visual hallucinations<sup>70</sup> and hippocampal SYN pathology is associated with memory deficits even after controlling for age and co-occurring pathologies<sup>71</sup>. The current neuropathological assessment of DLB recognizes that cases with pure synucleinopathy without AD co-pathology are the most likely to exhibit core DLB features or visual hallucinations and fluctuations<sup>13</sup>. While LP is seen often at autopsy in asymptomatic individuals (Incidental Lewy Body Disease: ILBD)<sup>29, 72, 73</sup>, it is frequently less severe than the SYN pathology observed in DLB and PD<sup>74, 75</sup> and is associated with mild degrees of nigral neuron loss and tyrosine hydroxylase positive neuron loss suggesting that ILBD may be a preclinical state before motor symptoms of an LBD emerge<sup>76, 77, 75, 78</sup>. Some studies have not observed strong correlations between LP and neuronal loss in the substantia nigra<sup>75, 79</sup> or other brain regions<sup>26</sup>. These data could suggest that LP is an epiphenomenon rather than central to disease pathogenesis<sup>80</sup>; however, there are several alternative explanations. It is suggested that oligomeric SYN species, which predate LB formation, may

be more toxic than more mature species<sup>81, 82</sup> and may therefore result in cell death apart from visible LP post mortem. Synaptic dysfunction from these early SYN species may lead to neuronal dysfunction rather than frank cell death<sup>83, 84</sup>. Furthermore, as opposed to the extracellular pathology of tau neurofibrillary ghost tangles left behind from degenerated neurons, LP is cleared after cell death, leaving minimal “ghost” pathology detectable in highly degenerated regions<sup>85</sup>. Lastly, different methods and different antibodies used to detect SYN inclusions may show different degrees of pathology<sup>86, 87</sup>. While SYN pathology is diagnostic for LBD further understanding of the biological mechanisms of SYN aggregation and associated neurodegeneration are needed and it is possible that cell-autonomous factors may also influence the spread of pathogenic SYN to selectively vulnerable neurons with resultant neurodegeneration<sup>88</sup>.

### Alzheimer’s disease neuropathology

A $\beta$  plaques and tau positive neurofibrillary tangle pathology sufficient for a secondary neuropathological diagnosis of AD occurs in ~10% of PD, ~35% of PDD and ~70% of DLB patients (overall ~50% of all LBD)<sup>21, 24–28</sup>. In some studies, higher degrees of A $\beta$  plaques have been identified in neocortical, limbic, and striatal region in DLB than PDD<sup>89, 90</sup>, and striatal A $\beta$  plaques have also been shown to be more severe in PDD than non-demented PD patients<sup>91</sup>. While these group-wise differences exist between PDD and DLB, there are no neuropathological findings that reliably distinguish these clinical phenotypes on an individual patient level<sup>21, 22</sup>. Tau neurofibrillary tangle pathology is most often shown to have a similar distribution as seen in typical Alzheimer’s disease using conventional neuropathologic staging methods<sup>92</sup>, but more recent digital assessments suggest relative sparing of medial temporal lobe<sup>93</sup> and greater relative distribution in temporal neocortex in LBD versus AD<sup>94</sup>.

Several investigations of the neuropathology of LBD have shown that co-existent AD pathology may influence the onset of dementia in PD<sup>21, 25, 65, 66, 69, 95, 96</sup>. In patients with PDD, AD co-pathology is associated with older age, decreased motor- dementia interval, and decreased overall survival<sup>21, 25, 29, 97, 98</sup>. Two of these studies reported that tau and A $\beta$  pathology had a greater impact on the age of dementia onset than SYN alone<sup>32, 96</sup>. Studies differ on whether tau<sup>21</sup> or A $\beta$ <sup>99</sup> is the most significant contributor to dementia and shortened survival<sup>100</sup>. AD co-pathology has also been associated with a greater burden of neocortical deposition of SYN<sup>21, 65, 69, 94, 96, 99, 101, 102</sup>. These disparate conclusions may be in part due to the high correlation between these pathologies<sup>21, 94</sup> and relatively sparse sampling and qualitative ratings used on traditional autopsy studies.

Co-occurring tau and A $\beta$  pathology may affect specific clinical features in LBD as well overall prognosis. In DLB, several studies have reported that increasing levels of tau and A $\beta$  are associated with a decreased likelihood of visual hallucinations or attentional fluctuations<sup>30, 31, 103</sup>. These observations have resulted in alterations to the neuropathological assessment of DLB, whereby higher stages of tau are associated with a lower likelihood of patients exhibiting a ‘classic’ DLB phenotype<sup>13</sup>. Other studies have documented alterations in domain specific cognitive function in LBD patients with co-occurring tau and A $\beta$  pathology at autopsy<sup>94, 104, 105</sup>. In PD, patients with tau and A $\beta$  co

pathology are more likely to have a clinical phenotype of postural instability with little or no tremor (the “postural-instability-gait dysfunction or PIGD phenotype”) <sup>25, 32, 106</sup>. While co-occurring tau and A $\beta$  pathology is often associated with worse prognosis in LBD, several studies also describe small groups of patients with ‘pure’ synucleinopathy at autopsy with a fulminant course suggesting other potential biological sources of clinical heterogeneity <sup>95, 103, 107</sup>.

The studies listed above have relied on traditional neuropathologic assessments which use semi quantitative, subjective ordinal measurements and severity scales that tend to emphasize topography rather than density of pathology <sup>12, 108</sup>. Digital histologic measurements using image analysis techniques, offer a potential improvement over traditional methods by generating objective, finely grained, continuous measurements of pathologic burden, which in contrast to the traditional methodology, may improve the potential to make clinicopathologic correlations and relate pathologic burden to ante-mortem biomarker assessments. However, more work is needed to standardize methodology across labs <sup>93, 94, 100, 109</sup>. In our recent work using digital histology, we found that co-occurring tau and A $\beta$  pathology was related to a higher burden of neocortical SYN in patients with LBD. The degree of tau pathology was several fold less in LBD compared with age matched AD patients even when comparing subjects with similar Braak tau stages. We also found that tau in LBD occurred in a different distribution than in AD, with more relative temporal neocortical pathology. Lastly, we also found that regional tau burden was consistently related to worse cognitive performance both on measures of global cognition and domain-specific testing <sup>94</sup>. Another recent digital study of LBD found relative sparing of tau pathology in the hippocampus of LBD patients with AD co-pathology, compared to patients with clinical AD and mixed AD and SYN pathology <sup>93</sup>. Finally, others find similar correlation of mixed SYN, Tau and A $\beta$  pathology, with strong influence of neocortical SYN on overall survival in DLB <sup>100</sup>. Together, these studies highlight the ability of digital methods to enhance clinicopathological correlations and suggest that the distribution of tau in LBD may diverge from AD and influence clinical phenotype.

### Subtyping by Clinical Features

**Tremor Dominant vs Postural Instability Gait Disorder**—Early attempts to parse the clinical heterogeneity of PD centered on two motor subtypes: 1) predominant rest tremor (TD: tremor dominant) with relatively less bradykinesia, rigidity, postural instability, and a slower rate of progression compared with 2) PIGD with significant gait and postural dysfunction, and associated with older age of onset, more rapid progression and early onset of cognitive impairment <sup>110, 111–115</sup>. The notion of motor-based subtypes was first promoted in Hoehn and Yahr’s 1967 description of the clinical features of PD <sup>116</sup> and has been recapitulated in other publications since <sup>117, 118</sup>. Commonly used motor scales may be used to assign designations <sup>110, 119, 120</sup>. Non-motor symptoms such as depression and autonomic dysfunction <sup>121, 122</sup> have been reported with greater frequency and severity in PIGD patients than in TD patients <sup>123, 124</sup>. In addition, patients with a higher burden of PIGD signs have decreased survival when matched to other patients with similar age and disease duration <sup>125, 126</sup>. Patients with lower CSF A $\beta$  and higher CSF tau (i.e. findings indicative of underlying AD co-pathology) are more likely to have a PIGD phenotype <sup>127, 128</sup>. One of

these studies was a partial analysis of PD patients with new onset disease recruited to the Parkinson Progression Markers Initiative, a project sponsored by the Michael J. Fox Foundation, but a subsequent analysis failed to reproduce the earlier result<sup>34</sup>. Amyloid PET imaging has shown a greater likelihood of increased cortical tracer retention in PIGD versus TD<sup>129</sup>. There is minimal data directly comparing motor symptoms of DLB patients with and without co-occurring AD pathology, but majority of reported autopsy cases suggest less prominent rest tremor or a greater likelihood of PIGD phenotypes in DLB than PD<sup>112, 130</sup>, which aligns with the knowledge that DLB overall is more likely to harbor co-existing AD pathology than non-demented PD cases.

There are problems with TD and PIGD distinctions. Many patients in large cohorts have clinical features of both phenotypes and therefore fall into an ‘intermediate’ category of uncertain significance,<sup>124, 131</sup> and many patients will change designations, typically from TD to PIGD, over the course of their illness<sup>112, 131, 132</sup>. The designations are particularly unstable early in the disease course<sup>131</sup>.

**Age of Onset**—Age of onset is also a well-recognized predictor of progression. The Sydney Multi-Center Study followed 136 patients from onset of PD symptoms over the course of 20 years and has shown that a younger age of onset was associated with a longer course and also that an older age of onset was associated with decreased survival and greater likelihood of tau and A $\beta$  co-pathology<sup>5, 95</sup>. These observations are not surprising, since age is a risk factor for AD pathology, even in asymptomatic elderly individuals. Most subsequent studies have found that an older age of onset is associated with a greater burden of motor disease at diagnosis with a faster decline in motor scores, shorter motor-dementia interval, and a greater burden of PIGD scores<sup>110, 133–137</sup>. It is notable that the prognostic value of age of onset appears to be independent from disease duration<sup>137</sup> and from postmortem severity of AD pathology<sup>21</sup>.

### **Data Driven Patient Subtypes Using Cluster Analyses:**

More recently, many have used a group of statistical data driven methods known as cluster analyses to elucidate potential subtypes in different LBD populations. This type of approach is attractive given the data-driven approach rather than hypothesis-driven analyses. It is important to note that the clustering solutions and patient subtypes derived from these studies are, by definition, found in the specific population studied and are not always generalizable to other populations. Furthermore, the clustering solutions are derived from the variables that are collected a particular study. A review of the literature published after the year 2000 using PubMed and Medline using search terms “cluster analysis”, “Parkinson’s disease”, and “Dementia with Lewy Bodies” yielded eleven studies: ten in PD and one in DLB<sup>135, 138–147</sup>.

Many of the above studies have recapitulated an older age, rapid progression phenotype<sup>135, 138, 143, 144, 146, 148</sup> and some have shown groups with benign courses and tremor predominant phenotypes similar to previous studies<sup>138, 146</sup>. Others have found that groups with more PIGD-like phenotype are also marked by more severe motor deficits at onset, more non-motor symptoms and higher mortality<sup>125, 139, 140, 142</sup>. In studies where such



variables were included, non-motor symptoms often proved to be stronger determinants of cluster membership than motor features<sup>139, 141</sup>. Many of these studies have not attempted validation in other cohorts, and when it has been attempted, results have been disappointing<sup>140, 141, 145, 146</sup>. One of the above cluster analysis studies incorporated CSF tau and A $\beta$  levels into a post hoc analysis and found that patients with the “diffuse-malignant” phenotype who had worse motor scores, higher PIGD sub-scores, higher autonomic dysfunction, worse cognition, and faster disease progression had lower CSF A $\beta$  and higher tau than the other subtypes<sup>141</sup>. The details of the methods and results of these studies are detailed in Table 1. These purely clinical studies have not had pathologic validation, except one recent publication which performed a retrospective cluster analysis and found no difference in SYN or co-occurring tau and beta A $\beta$  pathology among their subgroups<sup>149</sup>.

### In Vivo Biomarker Associations with Patient Subtypes

**Cerebrospinal Fluid**—Cross sectional studies of CSF A $\beta$ 1–42, total tau and 181 phospho-tau in LBD show wide ranges of values with some patients having overlapping with healthy controls to others displaying pathologic levels similar to AD<sup>24, 150</sup>. In PD, most large studies find that CSF A $\beta$ 1–42 is lower than controls at diagnosis and is associated with worse memory impairment in more advanced disease<sup>4, 151–158</sup>. Low levels of CSF A $\beta$ 1–42 has also been linked to faster motor progression<sup>156</sup>. In DLB, AD-like CSF values are more likely than in PDD<sup>159</sup> and lower A $\beta$ 1–42 and higher tau levels were associated with a greater likelihood of admission to a long term care facility and higher mortality<sup>160</sup>. Total tau and 181 phospho-tau are reported to be either equivalent or lower than healthy controls in non-demented PD patients<sup>34, 128, 151, 152</sup>, but higher in PDD<sup>153, 161, 162</sup>. An analysis of the Deprenyl And Tocopherol Antioxidant Therapy of Parkinson’s (DATATOP) trial found that higher levels of CSF tau may be related to faster motor progression<sup>163</sup>. While postmortem validation studies in LBD are rare, CSF measurements of tau and A $\beta$ 1–42 relate to the severity of AD pathology in LBD<sup>35, 164</sup> as previously seen in AD<sup>165–167</sup>. Interestingly, low CSF A $\beta$ 1–42 may also relate to neocortical distribution of SYN pathology<sup>35</sup>. Further work is needed to elucidate the relationship between ante mortem AD CSF biomarkers and underlying neuropathology and to continue to collect longitudinal data on CSF measurements in well characterized cohorts<sup>168</sup>. Nevertheless, CSF tau and A $\beta$  biomarkers appear to have some prognostic value in LBD but further data is needed to clarify this association and longitudinal progression of these markers over time<sup>163, 169</sup>.

*In vivo* SYN detection remains a critical need to advance LBD research. Developing a reliable assay for CSF SYN assay has proven difficult, in part because CSF SYN is present in relatively low amounts and leakage of peripheral blood into CSF during lumbar puncture can contaminate measurements<sup>170</sup>. Most, but not all, studies have found CSF total SYN to be lower in PD compared to healthy controls<sup>157, 128, 171–174</sup>. Higher levels of CSF total SYN were associated with faster cognitive decline in the DATATOP study<sup>156, 175</sup>. A separate study reported lower levels of CSF SYN in patients with non-tremor phenotypes<sup>34</sup>. Assays for phosphorylated and oligomeric CSF SYN, both likely more specific for pathological SYN, have shown elevations in patients with PD in some studies, but replication between centers has proven difficult<sup>153, 175–178</sup>. Moreover, in AD there are elevated levels of SYN that may represent leakage from damaged synapses, suggesting underlying mixed AD co-

pathology could alter total SYN levels in LBD<sup>150</sup>. More recently, real-time quaking induced conversion (RT-QuIC) methods, which takes CSF samples containing pathogenic SYN and incubates them in substrate containing non aggregated SYN monomers and allows templating to happen in repeated cycles, allows for signal amplification of CSF SYN that may aid in demonstrating increases in PD and DLB patients over healthy controls<sup>179, 180</sup>. Two drawbacks to this technique are the occasional false negatives and the fact that it is largely a binary measure as detection is only currently possible after several amplification cycles<sup>180, 181</sup>. Nonetheless this is an emerging approach that utilizes the pathological aggregation of SYN from patient samples that may be beneficial to detect the presence of underlying synucleinopathy *in vivo*. The interaction of CSF SYN, tau, and A $\beta$  in LBD continues to be investigated, but dynamic changes over the course of the disease are expected.

**Positron Emission Tomography**—Amyloid PET imaging studies show a gradient in the proportions of cases with increased retention across the LBD spectrum with generally low retention seen in PD to higher uptake in PDD and DLB<sup>24, 182–186</sup>. <sup>11</sup>C-Pittsburgh compound B may be more specific for neuritic amyloid plaques rather than diffuse plaques and has been described to have greater neocortical retention in DLB than PDD<sup>187</sup>. The degree of amyloid tracer retention in patients with LBD is generally less than what is seen in AD<sup>188, 189</sup>. Some studies have demonstrated that amyloid PET positivity is related to the presence and severity of cognitive deficits in PD<sup>184, 186, 190, 191</sup>; however, this finding is not universal<sup>192</sup>. Several tau tracers have been developed including <sup>18</sup>F-flortaucipir (formerly AV1451), <sup>18</sup>F-THK523, <sup>18</sup>F-5105, <sup>18</sup>F-FDDNP, and <sup>11</sup>C-PBB3<sup>193</sup>, some of which have been studied in LBD<sup>37, 194, 195</sup>. <sup>18</sup>F-Flortaucipir uptake is elevated in some LBD patients compared to controls, often in patients who also have evidence of amyloidosis on PET imaging, and the degree of uptake is typically less than what is seen in AD<sup>37, 194, 195</sup>. Similar to rates of co-occurring tau and A $\beta$  neuropathology, patients with a DLB phenotype are more likely to have elevated <sup>18</sup>F-flortaucipir uptake than non-demented PD<sup>195, 196</sup>. Patterns of uptake in LBD have differed from AD by concentrating in posterior temporo-parieto-occipital regions<sup>37, 194</sup> with unique areas of uptake in the primary motor and sensory cortices<sup>195</sup>, as opposed to temporal and frontal lobes as seen in AD. These data show many similarities to our recently published post mortem work using digital histologic methods<sup>94</sup>. Increased <sup>18</sup>F-flortaucipir uptake in LBD is associated with cognitive deficits across PD, PDD and DLB<sup>37, 196</sup>. Post-mortem validation studies of <sup>18</sup>F-flortaucipir in LBD are needed to confirm these *in vivo* observations and further clarify the regional distribution and cognitive phenotypes associated with tau pathology in LBD. Nonetheless, these divergent patterns of uptake in LBD compared with AD could potentially be interpreted as consistent with the aforementioned model data suggesting cross-seeding of SYN, tau and A $\beta$  by specific alpha-synuclein strains<sup>54–57</sup>. Moreover, the intermediate degree of <sup>18</sup>F-flortaucipir uptake in LBD between healthy controls and AD is consistent with our observations using digital histologic measurements of tau pathology in LBD and AD<sup>94</sup>.

## Genetic Influences

Monogenic causes of LBD including mutations, duplications, and triplications of the *SNCA* gene as well as mutations in *PARKIN*, *PINK1*, *DJ-1*, and others are rare in PD and



DLB<sup>197–203</sup>. More common genetic risk factors for the development of LBD include the *MAPTH1* haplotype<sup>206–209</sup>, apolipoprotein epsilon  $\epsilon 4$  alleles (*APOE*  $\epsilon 4$ )<sup>210–215</sup>, and the glucocerebrosidase gene (*GBA*)<sup>17, 199</sup>, and leucine rich repeat kinase-2 (*LRRK2*)<sup>216, 217</sup>. *MAPTH1* haplotypes have been associated with greater risk of occurrence of PD and DLB<sup>218–220</sup>, dementia in PD<sup>221, 222</sup>, and may be associated with higher degree of SYN pathology at autopsy<sup>223, 224</sup>. Certain studies have not found an association of H1 haplotypes with DLB<sup>225</sup> and additionally one other study has documented decreased in AD co-pathology in DLB associated with H1 haplotypes<sup>226</sup>. *APOE*  $\epsilon 4$  alleles in LBD have been associated with higher likelihood of both tau and A $\beta$  co-pathology and also higher degrees of SYN<sup>16, 209, 227–229</sup>, a higher risk of developing dementia<sup>208, 230, 231</sup>, and altered cognitive performance on specific tests<sup>208</sup>. *GBA* mutations have been associated with earlier onset PD and a more rapidly progressive clinical course with a 6 fold higher risk of dementia<sup>17, 201, 232–234</sup>. Autopsy data shows relatively greater neocortical synucleinopathy burdens in patients with *GBA* mutations than sporadic PD with variable rates of AD co-pathology<sup>235–237</sup>. *LRRK2* mutations are not associated with a more aggressive clinical course of PD, although one study of young patients showed an association with the PIGD phenotypes<sup>186, 187</sup>. Post mortem studies of brains from patients with *LRRK2* mutations have found mixed SYN, tau, and TDP-43 neuropathologies<sup>216, 238</sup>. In some patients with *LRRK2* mutations and also in patients with other, more rare, monogenic causes of PD, SYN pathology can be absent even in the setting of severe clinical phenotypes<sup>238</sup>. Genome-wide association (GWAS) studies comparing statistical frequencies of single-nucleotide polymorphisms (SNPs) between disease and control populations are an important mechanism for discovery of novel common risk variants. Two recent GWAS in DLB had pathologic validation in a subsection of their subjects confirmed the strong effect of *APOE*  $\epsilon 4$  alleles, *GBA*, and *SNCA* genes in the occurrence of DLB<sup>209, 225</sup> similar to other studies in PD<sup>218, 220</sup>. SNPs in *SNCA* have been linked to increased *SNCA* gene expression in sporadic PD<sup>204</sup>. Interestingly, SNPs in the *SNCA* gene that associated with PD in previous studies were different than the ones implicated in the occurrence of DLB<sup>218, 225</sup>. Thus, there are both shared and distinct risk SNPs implicated in DLB compared to PD and AD, likely contributing to the clinicopathological spectrum of LBD. These GWAS studies have also highlighted potential roles for other genes coding for proteins related to antigen presentation (*HLA-DPA1/DPB1* and *DRB5*)<sup>218, 220, 239</sup>, tyrosine kinases (*GAK*)<sup>220, 240</sup>, cell adhesion molecules (*CNTN1*)<sup>225</sup>, lysosomal degradation (*SCARB2*, *TMEM175*)<sup>209, 241</sup>, synuclein processing (*SPTBN1*)<sup>239</sup>, vesicular transport (*SYT11*)<sup>220, 240</sup> and many others in the potential pathogenesis of LBD although their role in disease progression and neuropathology remains to be seen. Finally, emerging studies highlight SNP associations with cognitive and motor features in sporadic PD<sup>205, 208</sup>, suggesting common genetic variation may also influence clinical heterogeneity in LBD.

## Conclusion

LBDs comprise a complex spectrum of clinicopathologic entities with marked clinical heterogeneity and a common neuropathology of misfolded alpha-synuclein aggregating into Lewy bodies, Lewy neurites and variable amounts of tau and A $\beta$  pathology. Here we review multiple converging lines of evidence from CSF measurements, PET imaging, and

neuropathologic studies emphasize the importance of co-occurring tau and A $\beta$  pathology affecting the clinical features and course of LBD (Table 2). While lower in overall burden compared to AD, tau in particular appears to have a strong influence on dementia and survival. We are optimistic that detailed neuropathologic studies of SYN, A $\beta$  and tau, using increasingly sophisticated techniques will continue to improve the understanding of how the mixed neuropathology in LBDs can be accurately predicted by precisely measured ante-mortem biomarkers compared with the current strictly clinical system of classification. While the neuropathology in LBD is likely a spectrum, postmortem work reviewed here suggest those patients with moderate to high level AD neuropathologic change at death have a worse prognosis and altered clinical phenotypes. Such patients can be currently identified using emerging biomarkers and we propose that AD biomarker profiles be included in research categorization of LBD. This proposed formulation has the potential to put the assignment of patients participating in well-designed therapeutic or disease modifying clinical trials of the future on firmer molecular biological footing. Indeed, stratifying classical LBD clinical phenotypes (PD, PD-MCI, PDD and DLB) by the presence of absence of *in vivo* biomarkers of AD pathology, in a manner similar to those proposed in AD dementia<sup>242</sup> will improve prognostication and potentially improve statistical power of clinical trials for both symptomatic and disease-modifying therapies by providing more homogenous patient populations (Figure 1). Moreover, based on growing experimental and human pathology data suggesting synergistic association of AD and SYN pathology, it is possible LBD patients with mixed-pathology may benefit from AD-directed therapies as they are developed.

While neuropathology observed in LBD postmortem represents a spectrum of both SYN and AD pathology, the factors that influence the occurrence of these pathologies is unclear. Age, genetic influences, or potentially different strains of pathogenic alpha-synuclein may partially account for divergence in LBD patients who develop significant AD co-pathology and possibly the rate of progression of these pathologies. Factors that result in varying expression of these pathologies are also poorly understood. Longitudinal prospective studies of LBD patients, using multi-modal biomarkers followed to autopsy will aid in beginning to answer these questions. Other co-pathologies, including cerebrovascular disease and TDP-43 are likely to influence clinical features and progression in LBD as well<sup>243</sup>; however, require further study. The majority of existing LBD studies focus on either PD/PDD or DLB separately, based partly on separate referral patterns to movement disorders specialists and memory clinics respectively. We suggest that harmonized assessments of PD, PDD and DLB cohorts followed to autopsy are urgently needed to capture the full clinicopathological spectrum of LBD and further elucidate the underlying biological substrates for clinical heterogeneity.

## Acknowledgements:

We thank Dr. Andrew Siderowf for his comments and suggestions for the manuscript.

Acknowledgement statement (including conflict of interest and financial disclosures):

All authors have nothing to disclose.

Funding Sources:

Research reported in this publication was supported by funding from National Center for Advancing Translational Sciences TL1TR001880, NIA AG010124, and NINDS NS088341, NS053488. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

David Coughlin is partially funded by NIH grant TL1TR001880

David Irwin is funded through NIA AG010124, and NINDS NS088341, Penn Institute of Aging

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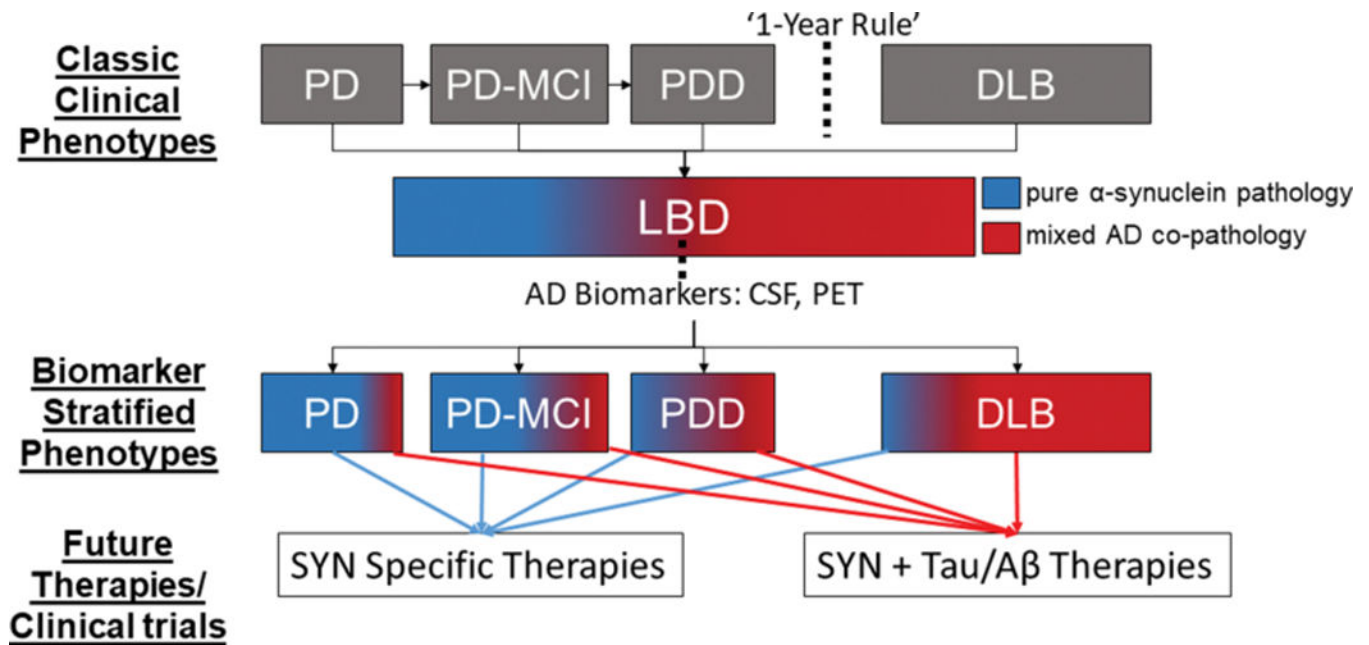


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**Figure 1.**

Current criteria separate LBDs into PD and DLB on the basis of the 1-year rule' (dashed-line). Within LBD, neuropathology ranges from pure synucleinopathy (SYN only: blue) to those with clinically significant AD co-pathology (SYN+AD: red). Emerging biomarker data suggests AD co-pathology may be accurately detected in living patients and we illustrate here a potential strategy to stratify clinical cohorts of LBD by the AD biomarker profiles (dashed lines) to improve clinical trials for SYN and Tau and/or A $\beta$  directed therapies during life for LBD patients (shaded clinical phenotype boxes represent relative frequency of pure SYN or mixed AD co-pathology in large autopsy series in PD, PDD, and DLB).

**Table 1:**

Cluster Studies in LBD

	Gasparoli et al., 2002 <sup>134</sup>	Dujardin et al., 2004 <sup>141</sup>	Lewis et al., 2005 <sup>137</sup>	Schrag et al., 2006 <sup>142</sup>	Post et al., 2008 <sup>143</sup>	Reijnders et al., 2009 <sup>145</sup>	Van Rooden et al., 2011 <sup>144</sup>	Fereshtehnejad et al., 2015 <sup>140</sup>	Erro et al., 2016 <sup>138</sup>	Fereshtehnejad et al., 2017 <sup>148</sup>	Morenas-Rodriguez et al., 2018 <sup>146</sup>
<b>Design and Inclusion</b>											
Patients, n	103	44	120	124	131	346	344	113	398	421	81
Inclusion	PD Dx <5y	PD Dx <3y	PD HY I-III	None	De Novo PD	None	PROPARK <sup>a</sup>	None	PPMI	PPMI	Probable DLB <sup>b</sup>
Age, mean years (SD)	NS	66 (median)	64.4 (9.3)	71.9 (11.0)	66.7 (10.4)	70.4 <sup>c</sup>	60.8 (11.3)	66.7 (8.9)	63.2 <sup>c</sup>	61.1 (9.7)	59.3 (48)
Disease Duration, mean years (SD)	NS	4 (median)	7.8 (5.4)	6.1 (4.4)	1.7 (0.9)	8.2	9.9 (6.2)	5.7 (4.2)	NS	0.5 (0.5)	5.0 (3.2)
Clustering Algorithm Type	NS	K-Means	K-means	K-Means	K-Means	K-Means	Model Based	K-means and agglomerative hierarchical	K-means	Agglomerative hierarchical	K-means
<b>Variables Included in Clustering Solution</b>											
<b>Demographics</b>											
Age of Onset											
Sex											
<b>Motor Features</b>											
UPDRSII											Motor Parkinsonism <sup>d</sup>
UPDRS III											Motor Parkinsonism <sup>d</sup>
Rate of Motor Progression											

	Gasparoli et al., 2002 <sup>134</sup>	Dujardin et al., 2004 <sup>141</sup>	Lewis et al., 2005 <sup>137</sup>	Schrag et al., 2006 <sup>142</sup>	Post et al., 2008 <sup>143</sup>	Reijnders et al., 2009 <sup>145</sup>	Van Rooden et al., 2011 <sup>144</sup>	Fereshtehnejad et al., 2015 <sup>140</sup>	Erro et al., 2016 <sup>138</sup>	Fereshtehnejad et al., 2017 <sup>148</sup>	Morenas-Rodriguez et al., 2018 <sup>146</sup>
Motor Phenotype											
Motor Complications (fluctuations, dyskinesias)											
<b>Non-Motor Features</b>											
Depression											
Anxiety											
Apathy											
Autonomic Dysfunction											
RBD											
Cognition											
Hallucinations											
<b>Clustering Solutions</b>											
N	2	2	4	2	3	4	4	3	3	3	3
Characteristics	Older age/rapid progression (39%) Younger age/slower progression (61%)	Worse motor and cognitive impairment (36%) Milder motor and preserved cognition (59%)	Young onset (41%) Tremor dominant (17%) Non-tremor dominant (26%) Rapid motor progression (17%)	Young onset more depression (36%) Older onset more rapid progression (64%)	Young onset (34%) Intermediate age onset (27%) Oldest age onset, more rapid progression (40%)	Young onset (29%) Tremor dominant (47%) Non tremor predominant with psychopathology (17%) Rapid disease progression (6%)	Young mild (49%) Youngest with non-motor complications (13%) Older and intermediately affected (30%) Diffuse and severely affected (8%)	Mainly motor (38%) Intermediate (27%) Diffuse malignant (35%)	Mild motor/slow progression (45%) Worse motor and non-motor burden (38%) Worse motor and non-motor burden (17%)	Mild motor predominant (52%) Intermediate (38%) Diffuse malignant (9%)	Cognitive predominant (57%) Neuro-psychiatric predominant (27%) Parkinsonism predominant (16%)

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Abbreviations: PD: parkinson's disease. Dx: diagnosis. HY: Hoehn and Yahr. PPMI: Parkinson's Progression Marker Initiative. NS: not stated. RBD: REM sleep behavior disorder (either reported of polysomnogram proven)

Grey boxes indicate variables used to determine clusters

<sup>a</sup> PROPARK Cohort from Verbaan D, Marinus J, Visser M, et al. Cognitive impairment in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry* 2007;78(11):1182-1187

<sup>b</sup> Probable DLB from McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005;65(12):1863-1872.

<sup>c</sup> Derived from cluster averages

<sup>d</sup> Motor parkinsonism derived from chart review, not UPDRS parts II and III



**Table 2.**

## Phenotypic Differences in LBD by Neuropathologic Subtype

	PD/PDD		DLB	
	SYN-AD	SYN+AD	SYN-AD	SYN+AD
<b>Age of Onset, (range of mean age)</b>	Younger (57–66)	Older (68–74) 21, 25, 94, 65, 69, 97	Similar (68–78)	Similar (70–85) <sup>21*</sup> , 29-94 <sup>*</sup>
<b>Motor Dementia Interval, (range of mean years)</b>	Longer (8–15) <sup>**</sup>	Shorter (2–10) <sup>21, 32, 69, 97***</sup>		NA
<b>Survival (range of mean years)</b>	Longer <sup>*</sup> (10–19)	Shorter (4.5–13) 21, 25, 65, 69, 97, 98	Longer (6–10)	Shorter (3–7) <sup>21*</sup> , 29-94 <sup>*</sup>
<b>Motor Phenotype</b>	More prominent rest tremor	Greater relative postural instability gait disorder 25, 32, 106	No clear data examining influence of AD co-pathology but overall DLB has less common rest tremor and more prominent postural instability <sup>114, 132</sup>	
<b>Hallucinations/Fluctuations</b>	No clear data comparing influence of AD co-pathology but hallucinations/fluctuations are common in PDD <sup>14</sup>		More frequent	Less frequent <sup>13, 31, 103</sup>
<b>Cognitive Dysfunction</b>	Executive, attention, visuospatial deficits	Additional episodic memory, naming deficits <sup>3, 105</sup>	Executive, attention, visuospatial deficits	Additional episodic memory, naming deficits <sup>94, 104, 105</sup>
<b>Genetic Associations</b>	<i>GBA</i> mutation carriers ++ APOE ε4 allele carriers +	<i>GBA</i> mutation carriers + <sup>221</sup> APOE ε4 allele carriers + <sup>16, 226, 227, 228</sup>	<i>GBA</i> mutation carriers ++, APOE ε4 allele carriers +	<i>GBA</i> mutation carriers +, <sup>214, 221</sup> APOE ε4 allele carriers ++ <sup>212, 226, 227, 228</sup>

\* not published data

\*\* some studies also describe small groups of patients with SYN-AD pathology and a more fulminant course<sup>69, 95, 103, 107</sup>

\*\*\* Several studies do not directly report motor dementia interval but rather cite that PDD patients are more likely to harbor SYN+AD pathology rather than SYN-AD (2, 25, 32, 66, 69).

SYN-AD: Synuclein neuropathology with no or low level AD co-pathology, SYN+AD: Synuclein pathology with moderate or high level AD co-pathology. NA: not applicable, DLB clinical syndrome defined by Motor dementia interval > 1 year.