Title

Pathological Influences on Clinical Heterogeneity in Lewy Body Diseases

Journal

Movement Disorders, 35(1)

ISSN

0885-3185

Authors

Coughlin, David G
Hurtig, Howard I
Irwin, David J

Publication Date

2020

DOI

10.1002/mds.27867

Peer reviewed

HHS Public Access

Author manuscript

Mov Disord. Author manuscript; available in PMC 2021 January 01.

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

David G Coughlin, MD[1,2,3], **Howard Hurtig**[1], **David J Irwin, MD MSTR**[1,2,3,4]

[1]University of Pennsylvania Health System, Department of Neurology

[2]Digital Neuropathology Laboratory

[3]Lewy Body Disease Research Center of Excellence

[4]Frontotemporal Degeneration Center, Philadelphia PA, USA 19104

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

Corresponding authors: David Irwin and Howard Hurtig, David Irwin MD MSTR, 3400 Spruce St, Philadelphia, PA 19104, And, Howard Hurtig MD, 330 S. 9th St, Philadelphia PA, 19107, phone and fax: 215 829 6500, 215 829 6606, dirwin@pennmedicine.upenn.edu hurtig@pennmedicine.upenn.edu.

Author Roles:

DGC contributed to the conception, organization, execution, writing of the first draft and critique of the paper.

DJI contributed to the conception, organization, execution, and review and critique of the paper.

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[1] 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[2]. Cognitive impairment is present in approximately 25% of patients in early stages of the disease and predicts faster progression to dementia[3, 4] which is likely inevitable but occurs at widely variable times after the onset of motor parkinsonism[56]. 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)[7, 8]. The neuropathological terms to describe this mixed pathology varied in early literature, but many of these patients showed clinical features distinct from amnestic AD. The clinicopathologic syndrome of dementia with Lewy bodies (DLB),[9–11] 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[12, 13]. 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[13, 14] and the two entities share genetic risk factors[15–17] , prodromal features[18–20], and exhibit similar neuropathologic features at autopsy[9, 21–23], 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[9, 23, 24].

While SYN is the hallmark pathology of LBD, tau and beta-amyloid (Aβ) co-pathology is common (overall ~50% of all LBD have a secondary neuropathological diagnosis of medium of high level AD in most large autopsy series- see below)[21, 24–28]. 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[21, 25, 29–32]. While *in vivo* SYN biomarkers are still being developed, methods to detect Aβ and tau in living LBD patients are improving[33–37]. 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[7, 38]. 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 [39]. Other staging systems have emerged[12, 40], 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[41–43]. Current hypotheses regarding why particular regions of the brain are affected selectively include the spread of pathology along functionally connected networks [44] and selective vulnerability of long unmyelinated axons[45]. LP in DLB is thought to ascend the neuroaxis in a similar caudo-rostral pattern[12, 46]; although, the prominence of early dementia with limited or no motor parkinsonism, rare patients without dopamine transporter deficits on SPECT imaging[47], and rare autopsy cases with isolated neocortical SYN pathology without brainstem or limbic SYN[48], suggests an alternative pattern of spread in some cases.

The observations of SYN Lewy-like pathology in transplanted mesencephalic grafts in PD patients[49] 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 [50, 51] or brain homogenates from human LBD subjects[52, 53] 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[54–56] or Aβ[57] and others leading to multiple systems atrophy type pathologies[58–60]. However, the core prion feature of infectivity has not clearly been demonstrated for LBD or AD in humans[61].

Many autopsy studies have shown a correlation of LP with motor disease severity in PD[43, 62]. The majority of studies have found that PDD is associated with either limbic (transitional)[13] or neocortical (diffuse) stage LB pathology[63–67] with higher cortical LP density being observed than in non-demented PD[2, 64–70]. Neocortical LP is also associated with the onset of visual hallucinations[70] and hippocampal SYN pathology is associated with memory deficits even after controlling for age and co-occurring pathologies[71]. 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[13]. While LP is seen often at autopsy in asymptomatic individuals (Incidental Lewy Body Disease: ILBD) [29, 72, 73], it is frequently less severe than the SYN pathology observed in DLB and PD[74, 75] 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 [76, 7775, 78]. Some studies have not observed strong correlations between LP and neuronal loss in the substantia nigra[75, 79] or other brain regions [26]. These data could suggest that LP is an epiphenomenon rather than central to disease pathogenesis[80]; 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[81, 82] 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[83, 84]. 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[85]. Lastly, different methods and different antibodies used to detect SYN inclusions may show different degrees of pathology[86, 87]. 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[88].

Alzheimer’s disease neuropathology

Aβ 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)[21, 24–28]. In some studies, higher degrees of Aβ plaques have been identified in neocortical, limbic, and striatal region in DLB than PDD[89, 90], and striatal Aβ plaques have also been shown to be more severe in PDD than non-demented PD patients[91]. 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[21, 22]. 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[92], but more recent digital assessments suggest relative sparing of medial temporal lobe[93] and greater relative distribution in temporal neocortex in LBD versus AD[94].

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

Co-occurring tau and Aβ pathology may affect specific clinical features in LBD as well overall prognosis. In DLB, several studies have reported that increasing levels of tau and Aβ are associated with a decreased likelihood of visual hallucinations or attentional fluctuations[30, 31, 103]. 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[13]. Other studies have documented alterations in domain specific cognitive function in LBD patients with co-occurring tau and Aβ pathology at autopsy[94, 104, 105]. In PD, patients with tau and Aβ 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)[25, 32, 106]. While co-occurring tau and Aβ 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[95, 103, 107].

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[12, 108]. 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[93, 94, 100, 109]. In our recent work using digital histology, we found that co-occurring tau and Aβ 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[94]. 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[93]. Finally, others find similar correlation of mixed SYN, Tau and Aβ pathology, with strong influence of neocortical SYN on overall survival in DLB[100]. 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[110111–115]. The notion of motor-based subtypes was first promoted in Hoehn and Yahr's 1967 description of the clinical features of PD [116] and has been recapitulated in other publications since[117, 118]. Commonly used motor scales may be used to assign designations[110, 119, 120]. Non-motor symptoms such as depression and autonomic dysfunction[121, 122] have been reported with greater frequency and severity in PIGD patients than in TD patients [123, 124]. In addition, patients with a higher burden of PIGD signs have decreased survival when matched to other patients with similar age and disease duration[125, 126]. Patients with lower CSF Aβ and higher CSF tau (i.e. findings indicative of underlying AD co-pathology) are more likely to have a PIGD phenotype[127, 128]. 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[34]. Amyloid PET imaging has shown a greater likelihood of increased cortical tracer retention in PIGD versus TD[129]. 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[112, 130], 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,[124, 131] and many patients will change designations, typically from TD to PIGD, over the course of their illness [112, 131, 132]. The designations are particularly unstable early in the disease course[131].

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 Aβ co-pathology[5, 95]. 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[110133–137]. It is notable that the prognostic value of age of onset appears to be independent from disease duration[137] and from postmortem severity of AD pathology[21].

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 [135, 138–147].

Many of the above studies have recapitulated an older age, rapid progression phenotype [135, 138, 143, 144, 146, 148] and some have shown groups with benign courses and tremor predominant phenotypes similar to previous studies[138, 146]. 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[125, 139, 140, 142]. In studies where such

variables were included, non-motor symptoms often proved to be stronger determinants of cluster membership than motor features[139, 141]. Many of these studies have not attempted validation in other cohorts, and when it has been attempted, results have been disappointing[140, 141, 145, 146]. One of the above cluster analysis studies incorporated CSF tau and Aβ 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 Aβ and higher tau than the other subtypes[141]. 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 Aβ pathology among their subgroups[149].

In Vivo Biomarker Associations with Patient Subtypes

Cerebrospinal Fluid—Cross sectional studies of CSF Aβ1–42, 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[24, 150]. In PD, most large studies find that CSF Aβ1–42 is lower than controls at diagnosis and is associated with worse memory impairment in more advanced disease[4, 151–158]. Low levels of CSF Aβ1–42 has also been linked to faster motor progression[156]. In DLB, AD-like CSF values are more likely than in PDD[159] and lower Aβ1–42 and higher tau levels were associated with a greater likelihood of admission to a long term care facility and higher mortality[160]. Total tau and 181 phospho-tau are reported to be either equivalent or lower than healthy controls in non-demented PD patients [34, 128, 151, 152], but higher in PDD [153, 161162]. 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[163]. While postmortem validation studies in LBD are rare, CSF measurements of tau and Aβ1–42 relate to the severity of AD pathology in LBD[35, 164] as previously seen in AD[165–167]. Interestingly, low CSF Aβ1–42 may also relate to neocortical distribution of SYN pathology[35]. 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[168]. Nevertheless, CSF tau and Aβ 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[163, 169]..

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[170]. Most, but not all, studies have found CSF total SYN to be lower in PD compared to healthy controls[157128, 171–174]. Higher levels of CSF total SYN were associated with faster cognitive decline in the DATATOP study[156, 175]. A separate study reported lower levels of CSF SYN in patients with non-tremor phenotypes[34]. 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[153, 175–178]. 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[150]. 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[179, 180]. 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[180, 181]. 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 Aβ 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[24, 182–186]. ^{11}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[187]. The degree of amyloid tracer retention in patients with LBD is generally less than what is seen in AD[188, 189]. Some studies have demonstrated that amyloid PET positivity is related to the presence and severity of cognitive deficits in PD[184, 186, 190, 191]; however, this finding is not universal[192]. Several tau tracers have been developed including ^{18}F- flortaucipir (formerly AV1451), ^{18}F-THK523, ^{18}F-5105, ^{18}F-FDDNP, and ^{11}C-PBB3[193], some of which have been studied in LBD[37, 194, 195]. ^{18}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[37, 194, 195]. Similar to rates of co-occurring tau and Aβ neuropathology, patients with a DLB phenotype are more likely to have elevated ^{18}F-flortaucipir uptake than non-demented PD[195, 196]. Patterns of uptake in LBD have differed from AD by concentrating in posterior temporo-parieto-occipital regions[37, 194] with unique areas of uptake in the primary motor and sensory cortices[195], 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[94]. Increased ^{18}F-flortaucipir uptake in LBD is associated with cognitive deficits across PD, PDD and DLB[37, 196]. Post-mortem validation studies of ^{18}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 Aβ by specific alpha-synuclein strains[54–57] . Moreover, the intermediate degree of ^{18}F-flortaupcipir uptake in LBD between healthy controls and AD is consistent with our observations using digital histologic measurements of tau pathology in LBD and AD[94].

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[197–203]. More common genetic risk factors for the development of LBD include the *MAPT* H1 haplotype[206–209], apolipoprotein epsilon *ε*4 alleles (*APOE ε4)*[210–215], and the glucocerebrocidase gene (*GBA)*[17, 199], and leucine rich repeat kinase-2 (*LRRK2)*[216, 217]. *MAPT* H1 haplotypes have been associated with greater risk of occurrence of PD and DLB[218–220], dementia in PD[221, 222], and may be associated with higher degree of SYN pathology at autopsy[223, 224]. Certain studies have not found an association of H1 haplotypes with DLB[225] and additionally one other study has documented decreased in AD co-pathology in DLB associated with H1 haplotypes[226]. *APOE ε4* alleles in LBD have been associated with higher likelihood of both tau and Aβ co-pathology and also higher degrees of SYN[16, 209, 227–229], a higher risk of developing dementia[208, 230, 231], and altered cognitive performance on specific tests[208]. *GBA* mutations have been associated with earlier onset PD and a more rapidly progressive clinical course with a 6 fold higher risk of dementia[17, 201, 232–234]. Autopsy data shows relatively greater neocortical synucleinopathy burdens in patients with *GBA* mutations than sporadic PD with variable rates of AD co-pathology[235–237]. *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[186, 187]. Post mortem studies of brains from patients with *LRRK2* mutations have found mixed SYN, tau, and TDP-43 neuropathologies[216, 238] . 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[238]. 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 ε4* alleles, *GBA,* and *SNCA* genes in the occurrence of DLB[209, 225] similar to other studies in PD[218, 220]. SNPs in *SNCA* have been linked to increased *SNCA* gene expression in sporadic PD[204]. Interestingly, SNPs in the *SNCA* gene that associated with PD in previous studies were different than the ones implicated in the occurrence of DLB[218, 225]. 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*)[218, 220, 239], tyrosine kinases (*GAK*)[220, 240], cell adhesion molecules (*CNTN1*)[225], lysosomal degradation (*SCARB2, TMEM175*)[209, 241], synuclein processing (*SPTBN1*)[239], vesicular transport (*SYT11*)[220, 240] 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[205, 208], 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 Aβ 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 Aβ 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, Aβ 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[242] 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[243]; 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

References:

1. Elbaz A, Carcaillon L, Kab S, Moisan F. Epidemiology of Parkinson's disease. Rev Neurol (Paris) 2016;172(1):14–26. [PubMed: 26718594]
2. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. Brain 2010;133(6):1755–1762. [PubMed: 20371510]
3. Muslimović D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 2005;65(8):1239–1245. [PubMed: 16247051]
4. Yarnall AJ, Breen DP, Duncan GW, et al. Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study. Neurology 2014;82(4):308–316. [PubMed: 24363137]
5. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 2008;23(6):837–844. [PubMed: 18307261]
6. Aarsland D, Andersen K, Larsen JP, Lolk A. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 2003;60(3):387–392. [PubMed: 12633150]
7. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. Nature 1997;388(6645):839–840. [PubMed: 9278044]
8. Hamilton RL. Lewy Bodies in Alzheimer's Disease: A Neuropathological Review of 145 Cases Using α-Synuclein Immunohistochemistry. Brain Pathol 2000;10(3):378–384. [PubMed: 10885656]
9. Lippa C, Duda J, Grossman M, et al. DLB and PDD boundary issues diagnosis, treatment, molecular pathology, and biomarkers. Neurology 2007;68(11):812–819. [PubMed: 17353469]
10. Hansen L, Salmon D, Galasko D, et al. The Lewy body variant of Alzheimer's disease A clinical and pathologic entity. Neurology 1990;40(1):1–1.
11. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47(5):1113–1124. [PubMed: 8909416]
12. 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. [PubMed: 16237129]
13. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017;89(1):88–100. [PubMed: 28592453]
14. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22(12):1689–1707. [PubMed: 17542011]
15. Nalls MA, Duran R, Lopez G, et al. A multicenter study of glucocerebrosidase mutations in dementia with lewy bodies. JAMA Neurol 2013;70(6):727–735. [PubMed: 23588557]
16. Tsuang D, Leverenz JB, Lopez OL, et al. APOE ϵ4 increases risk for dementia in pure synucleinopathies. JAMA Neurol 2013;70(2):223–228. [PubMed: 23407718]
17. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 2009;361(17):1651–1661. [PubMed: 19846850]
18. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord 2015;30(12):1600–1611. [PubMed: 26474317]
19. Boeve BF, Silber M, Ferman T, et al. REM sleep behavior disorder and degenerative dementia an association likely reflecting Lewy body disease. Neurology 1998;51(2):363–370. [PubMed: 9710004]

20. Donaghy PC, McKeith IG. The clinical characteristics of dementia with Lewy bodies and a consideration of prodromal diagnosis. Alzheimers Res Ther 2014;6(4):46. [PubMed: 25484925]
21. Irwin DJ, Grossman M, Weintraub D, et al. Neuropathological and genetic correlates of survival and dementia onset in synucleinopathies: a retrospective analysis. Lancet Neurol 2017;16(1):55–65. [PubMed: 27979356]
22. Ballard C, Ziabreva I, Perry R, et al. Differences in neuropathologic characteristics across the Lewy body dementia spectrum. Neurology 2006;67(11):1931–1934. [PubMed: 17159096]
23. Boeve BF, Dickson DW, Duda JE, et al. Arguing against the proposed definition changes of PD. Mov Disord 2016;31(11):1619–1622. [PubMed: 27492190]
24. Jellinger KA, Korczyn AD. Are dementia with Lewy bodies and Parkinson's disease dementia the same disease? BMC Med 2018;16(1):34. [PubMed: 29510692]
25. Jellinger K, Seppi K, Wenning G, Poewe W. Impact of coexistent Alzheimer pathology on the natural history of Parkinson's disease. J Neural Transm 2002;109(3):329–339. [PubMed: 11956955]
26. Irwin DJ, Lee VM-Y, Trojanowski JQ. Parkinson's disease dementia: convergence of [alpha]-synuclein, tau and amyloid-[beta] pathologies. Nat Rev Neurosci 2013;14(9):626–636. [PubMed: 23900411]
27. Kosaka K Diffuse Lewy body disease in Japan. J Neurol 1990;237(3):197–204. [PubMed: 2196340]
28. Marui W, Iseki E, Kato M, Akatsu H, Kosaka K. Pathological entity of dementia with Lewy bodies and its differentiation from Alzheimer's disease. Acta Neuropathol 2004;108(2):121–128. [PubMed: 15235805]
29. Wakisaka Y, Furuta A, Tanizaki Y, Kiyohara Y, Iida M, Iwaki T. Age-associated prevalence and risk factors of Lewy body pathology in a general population: the Hisayama study. Acta Neuropathol 2003;106(4):374–382. [PubMed: 12904992]
30. Lopez OL, Becker JT, Kaufer DI, et al. Research evaluation and prospective diagnosis of dementia with Lewy bodies. Arch Neurol 2002;59(1):43–46. [PubMed: 11790229]
31. Merdes A, Hansen L, Jeste D, et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. Neurology 2003;60(10):1586–1590. [PubMed: 12771246]
32. Compta Y, Parkkinen L, Kempster P, et al. The significance of α-synuclein, amyloid-β and tau pathologies in Parkinson's disease progression and related dementia. Neurodegener Dis 2014;13(2–3):154–156. [PubMed: 24028925]
33. Mollenhauer B, Locascio JJ, Schulz-Schaeffer W, Sixel-Döring F, Trenkwalder C, Schlossmacher MG. α-Synuclein and tau concentrations in cerebrospinal fluid of patients presenting with parkinsonism: a cohort study. Lancet Neurol 2011;10(3):230–240. [PubMed: 21317042]
34. Kang JH, Mollenhauer B, Coffey CS, et al. CSF biomarkers associated with disease heterogeneity in early Parkinson's disease: the Parkinson's Progression Markers Initiative study. Acta Neuropathol 2016;131(6):935–949. [PubMed: 27021906]
35. Irwin DJ, Xie SX, Coughlin D, et al. CSF tau and amyloid-beta predict cerebral synucleinopathy in autopsied Lewy body disorders. Neurology 2018.
36. McMillan CT, Wolk DA. Presence of cerebral amyloid modulates phenotype and pattern of neurodegeneration in early Parkinson's disease. J Neurol Neurosurg Psychiatry 2016;87(10):1112–1122. [PubMed: 27288043]
37. Gomperts SN, Locascio JJ, Makaretz SJ, et al. Tau positron emission tomographic imaging in the Lewy body diseases. JAMA Neurol 2016;73(11):1334–1341. [PubMed: 27654968]
38. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the α-synuclein gene identified in families with Parkinson's disease. Science 1997;276(5321):2045–2047. [PubMed: 9197268]
39. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24(2):197–211. [PubMed: 12498954]
40. Muller CM, de Vos RA, Maurage CA, Thal DR, Tolnay M, Braak H. Staging of sporadic Parkinson disease-related alpha-synuclein pathology: inter- and intra-rater reliability. J Neuropathol Exp Neurol 2005;64(7):623–628. [PubMed: 16042314]

41. Alafuzoff I, Ince PG, Arzberger T, et al. Staging/typing of Lewy body related alpha-synuclein pathology: a study of the BrainNet Europe Consortium. Acta Neuropathol 2009;117(6):635–652. [PubMed: 19330340]
42. Leverenz JB, Hamilton R, Tsuang DW, et al. Empiric refinement of the pathologic assessment of Lewy-related pathology in the dementia patient. Brain Pathol 2008;18(2):220–224. [PubMed: 18241240]
43. Beach TG, Adler CH, Lue L, et al. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. Acta Neuropathol 2009;117(6):613–634. [PubMed: 19399512]
44. Zeighami Y, Ulla M, Iturria-Medina Y, et al. Network structure of brain atrophy in de novo Parkinson's disease. Elife 2015;4.
45. Braak H, Ghebremedhin E, Rüb U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 2004;318(1):121–134. [PubMed: 15338272]
46. Marui W, Iseki E, Nakai T, et al. Progression and staging of Lewy pathology in brains from patients with dementia with Lewy bodies. J Neurol Sci 2002;195(2):153–159. [PubMed: 11897247]
47. Thomas AJ, Attems J, Colloby SJ, et al. Autopsy validation of 123I-FP-CIT dopaminergic neuroimaging for the diagnosis of DLB. Neurology 2017;88(3):276–283. [PubMed: 27940650]
48. Frigerio R, Fujishiro H, Ahn T-B, et al. Incidental Lewy body disease: do some cases represent a preclinical stage of dementia with Lewy bodies? Neurobiol Aging 2011;32(5):857–863. [PubMed: 19560232]
49. Kordower JH, Chu Y, Hauser RA, Freeman TB, Olanow CW. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat Med 2008;14(5):504–506. [PubMed: 18391962]
50. Luk KC, Kehm V, Carroll J, et al. Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science 2012;338(6109):949–953. [PubMed: 23161999]
51. Volpicelli-Daley LA, Luk KC, Patel TP, et al. Exogenous α-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. Neuron 2011;72(1):57–71. [PubMed: 21982369]
52. Recasens A, Dehay B, Bové J, et al. Lewy body extracts from Parkinson disease brains trigger α-synuclein pathology and neurodegeneration in mice and monkeys. Ann Neurol 2014;75(3):351–362. [PubMed: 24243558]
53. Masuda-Suzukake M, Nonaka T, Hosokawa M, et al. Prion-like spreading of pathological α-synuclein in brain. Brain 2013;136(4):1128–1138. [PubMed: 23466394]
54. Guo JL, Covell DJ, Daniels JP, et al. Distinct α-synuclein strains differentially promote tau inclusions in neurons. Cell 2013;154(1):103–117. [PubMed: 23827677]
55. Covell DJ, Robinson JL, Akhtar RS, et al. Novel conformation-selective alpha-synuclein antibodies raised against different in vitro fibril forms show distinct patterns of Lewy pathology in Parkinson's disease. Neuropathol Appl Neurobiol 2017;43(7):604–620. [PubMed: 28386933]
56. Giasson BI, Forman MS, Higuchi M, et al. Initiation and synergistic fibrillization of tau and alpha-synuclein. Science 2003;300(5619):636–640. [PubMed: 12714745]
57. Ono K, Takahashi R, Ikeda T, Yamada M. Cross-seeding effects of amyloid β-protein and α-synuclein. J Neurochem 2012;122(5):883–890. [PubMed: 22734715]
58. Woerman AL, Oehler A, Kazmi SA, et al. Multiple system atrophy prions retain strain specificity after serial propagation in two different Tg (SNCA* A53T) mouse lines. Acta Neuropathol 2019:1–18.
59. Woerman AL, Kazmi SA, Patel S, et al. MSA prions exhibit remarkable stability and resistance to inactivation. Acta Neuropathol 2018;135(1):49–63. [PubMed: 28849371]
60. Peng C, Gathagan RJ, Covell DJ, et al. Cellular milieu imparts distinct pathological α-synuclein strains in α-synucleinopathies. Nature 2018;557(7706):558. [PubMed: 29743672]

61. Irwin DJ, Abrams JY, Schonberger LB, et al. Evaluation of potential infectivity of Alzheimer and Parkinson disease proteins in recipients of cadaver-derived human growth hormone. JAMA Neurol 2013;70(4):462–468. [PubMed: 23380910]
62. Adler C, Beach T, Zhang N, et al. Unified Staging System for Lewy Body Disorders: Clinicopathologic Correlations (S27. 001). AAN Enterprises; 2018.
63. Braak H, Rüb U, Steur EJ, Del Tredici K, De Vos R. Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology 2005;64(8):1404–1410. [PubMed: 15851731]
64. Apaydin H, Ahlskog JE, Parisi JE, Boeve BF, Dickson DW. Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response. Arch Neurol 2002;59(1):102–112. [PubMed: 11790237]
65. Irwin DJ, White MT, Toledo JB, et al. Neuropathologic substrates of Parkinson disease dementia. Ann Neurol 2012;72(4):587–598. [PubMed: 23037886]
66. Compta Y, Parkkinen L, O'sullivan SS, et al. Lewy-and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain 2011;134(5):1493–1505. [PubMed: 21596773]
67. Tsuboi Y, Uchikado H, Dickson DW. Neuropathology of Parkinson's disease dementia and dementia with Lewy bodies with reference to striatal pathology. Parkinsonism Relat Disord 2007;13(3):70005–70001.
68. Hurtig H, Trojanowski J, Galvin J, et al. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology 2000;54(10):1916–1921. [PubMed: 10822429]
69. Jellinger KA, Attems J. Prevalence and impact of vascular and Alzheimer pathologies in Lewy body disease. Acta Neuropathol 2008;115(4):427–436. [PubMed: 18273624]
70. Harding AJ, Stimson E, Henderson JM, Halliday GM. Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease. Brain 2002;125(11):2431–2445. [PubMed: 12390970]
71. Adamowicz DH, Roy S, Salmon DP, et al. Hippocampal alpha-Synuclein in Dementia with Lewy Bodies Contributes to Memory Impairment and Is Consistent with Spread of Pathology. J Neurosci 2017;37(7):1675–1684. [PubMed: 28039370]
72. Parkkinen L, Pirttila T, Alafuzoff I. Applicability of current staging/categorization of alpha-synuclein pathology and their clinical relevance. Acta Neuropathol 2008;115(4):399–407. [PubMed: 18297293]
73. Zaccai J, Brayne C, McKeith I, Matthews F, Ince PG. Patterns and stages of alpha-synucleinopathy: Relevance in a population-based cohort. Neurology 2008;70(13):1042–1048. [PubMed: 18362284]
74. Coughlin DG, Petrovitch H, White LR, et al. Most cases with lewy pathology in a population-based cohort adhere to the braak progression pattern but 'failure to fit'is highly dependent on staging system applied. Parkinsonism Relat Disord 2019.
75. Milber JM, Noorigian JV, Morley JF, et al. Lewy pathology is not the first sign of degeneration in vulnerable neurons in Parkinson disease. Neurology 2012;79(24):2307–2314. [PubMed: 23152586]
76. Dijkstra AA, Voorn P, Berendse HW, et al. Stage-dependent nigral neuronal loss in incidental Lewy body and Parkinson's disease. Mov Disord 2014;29(10):1244–1251. [PubMed: 24996051]
77. van de Berg WD, Hepp DH, Dijkstra AA, Rozemuller JA, Berendse HW, Foncke E. Patterns of alpha-synuclein pathology in incidental cases and clinical subtypes of Parkinson's disease. Parkinsonism Relat Disord 2012;18 Suppl 1:S28–30. [PubMed: 22166446]
78. Dickson DW, Fujishiro H, DelleDonne A, et al. Evidence that incidental Lewy body disease is pre-symptomatic Parkinson's disease. Acta Neuropathol 2008;115(4):437–444. [PubMed: 18264713]
79. Tompkins MM, Hill WD. Contribution of somal Lewy bodies to neuronal death. Brain Res 1997;775(1–2):24–29. [PubMed: 9439824]
80. Espay AJ, Vizcarra JA, Marsili L, et al. Revisiting protein aggregation as pathogenic in sporadic Parkinson and Alzheimer diseases. Neurology 2019;92(7):329–337. [PubMed: 30745444]
81. Pountney DL, Voelcker NH, Gai WP. Annular alpha-synuclein oligomers are potentially toxic agents in alpha-synucleinopathy. Hypothesis. Neurotox Res 2005;7(1–2):59–67. [PubMed: 15639798]

82. Winner B, Jappelli R, Maji SK, et al. In vivo demonstration that α-synuclein oligomers are toxic. Proc Natl Acad Sci 2011;108(10):4194–4199. [PubMed: 21325059]
83. Kramer ML, Schulz-Schaeffer WJ. Presynaptic α-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies. J Neurosci 2007;27(6):1405–1410. [PubMed: 17287515]
84. Schulz-Schaeffer WJ. The synaptic pathology of α-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. Acta Neuropathol 2010;120(2):131–143. [PubMed: 20563819]
85. Lee HJ, Suk JE, Bae EJ, Lee SJ. Clearance and deposition of extracellular alpha-synuclein aggregates in microglia. Biochem Biophys Res Commun 2008;372(3):423–428. [PubMed: 18492487]
86. Beach TG, White CL, Hamilton RL, et al. Evaluation of alpha-synuclein immunohistochemical methods used by invited experts. Acta Neuropathol 2008;116(3):277–288. [PubMed: 18626651]
87. Beach TG, Corbille A-G, Letournel F, et al. Multicenter assessment of immunohistochemical methods for pathological alpha-synuclein in sigmoid colon of autopsied Parkinson's disease and control subjects. J Parkinsons Dis 2016;6(4):761–770. [PubMed: 27589538]
88. Surmeier DJ, Obeso JA, Halliday GM. Selective neuronal vulnerability in Parkinson disease. Nat Rev Neurosci 2017;18(2):101–113. [PubMed: 28104909]
89. Jellinger KA, Attems J. Does striatal pathology distinguish Parkinson disease with dementia and dementia with Lewy bodies? Acta Neuropathol 2006;112(3):253–260. [PubMed: 16804711]
90. Halliday GM, Song YJ, Harding AJ. Striatal beta-amyloid in dementia with Lewy bodies but not Parkinson's disease. J Neural Transm (Vienna) 2011;118(5):713–719. [PubMed: 21479514]
91. Kalaitzakis ME, Graeber MB, Gentleman SM, Pearce RK. Striatal beta-amyloid deposition in Parkinson disease with dementia. J Neuropathol Exp Neurol 2008;67(2):155–161. [PubMed: 18219254]
92. Gearing M, Lynn M, Mirra SS. Neurofibrillary pathology in Alzheimer disease with Lewy bodies: two subgroups. Arch Neurol 1999;56(2):203–208. [PubMed: 10025425]
93. Walker L, McAleese KE, Thomas AJ, et al. Neuropathologically mixed Alzheimer's and Lewy body disease: burden of pathological protein aggregates differs between clinical phenotypes. Acta Neuropathol 2015;129(5):729–748. [PubMed: 25758940]
94. Coughlin D, Xie SX, Liang M, et al. Cognitive and Pathological Influences of Tau Pathology in Lewy Body Disorders. Ann Neurol 2019;85(2):259–271. [PubMed: 30549331]
95. Halliday G, Hely M, Reid W, Morris J. The progression of pathology in longitudinally followed patients with Parkinson's disease. Acta Neuropathol 2008;115(4):409–415. [PubMed: 18231798]
96. Howlett DR, Whitfield D, Johnson M, et al. Regional Multiple Pathology Scores Are Associated with Cognitive Decline in L ewy Body Dementias. Brain Pathol 2015;25(4):401–408. [PubMed: 25103200]
97. Sabbagh MN, Adler CH, Lahti TJ, et al. Parkinson disease with dementia: comparing patients with and without Alzheimer pathology. Alzheimer Dis Assoc Disord 2009;23(3):295–297. [PubMed: 19812474]
98. Kotzbauer PT, Cairns NJ, Campbell MC, et al. Pathologic accumulation of alpha-synuclein and Abeta in Parkinson disease patients with dementia. Arch Neurol 2012;69(10):1326–1331. [PubMed: 22825369]
99. Ruffmann C, Calboli FC, Bravi I, et al. Cortical Lewy bodies and Aβ burden are associated with prevalence and timing of dementia in Lewy body diseases. Neuropathol Appl Neurobiol 2016;42(5):436–450. [PubMed: 26527105]
100. Ferman TJ, Aoki N, Crook JE, et al. The limbic and neocortical contribution of α-synuclein, tau, and amyloid β to disease duration in dementia with Lewy bodies. Alzheimer's & Dementia 2018;14(3):330–339.
101. Horvath J, Herrmann FR, Burkhard PR, Bouras C, Kövari E. Neuropathology of dementia in a large cohort of patients with Parkinson's disease. Parkinsonism Relat Disord 2013;19(10):864–868. [PubMed: 23746454]

102. Toledo JB, Gopal P, Raible K, et al. Pathological alpha-synuclein distribution in subjects with coincident Alzheimer's and Lewy body pathology. Acta Neuropathol 2016;131(3):393–409. [PubMed: 26721587]
103. Del Ser T, Hachinski V, Merskey H, Munoz DG. Clinical and pathologic features of two groups of patients with dementia with Lewy bodies: effect of coexisting Alzheimer-type lesion load. Alzheimer Dis Assoc Disord 2001;15(1):31–44. [PubMed: 11236823]
104. Peavy GM, Edland SD, Toole BM, Hansen LA, Galasko DR, Mayo AM. Phenotypic differences based on staging of Alzheimer's neuropathology in autopsy-confirmed dementia with Lewy bodies. Parkinsonism Relat Disord 2016;31:72–78. [PubMed: 27475955]
105. Kraybill ML, Larson EB, Tsuang D, et al. Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. Neurology 2005;64(12):2069–2073. [PubMed: 15985574]
106. Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, Lees AJ. A clinico-pathological study of subtypes in Parkinson's disease. Brain 2009;132(Pt 11):2947–2957. [PubMed: 19759203]
107. Geut H, Vergouw LJM, Galis Y, et al. Neuropathological and genetic characteristics of a post-mortem series of cases with dementia with Lewy bodies clinically suspected of Creutzfeldt-Jakob's disease. Parkinsonism Relat Disord 2019.
108. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol 2012;123(1):1–11. [PubMed: 22101365]
109. Neltner JH, Abner EL, Schmitt FA, et al. Digital pathology and image analysis for robust high-throughput quantitative assessment of Alzheimer disease neuropathologic changes. J Neuropathol Exp Neurol 2012;71(12):1075–1085. [PubMed: 23147505]
110. Jankovic J, McDermott M, Carter J, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 1990;40(10):1529–1534. [PubMed: 2215943]
111. van der Heeden JF, Marinus J, Martinez-Martin P, Rodriguez-Blazquez C, Geraedts VJ, van Hilten JJ. Postural instability and gait are associated with severity and prognosis of Parkinson disease. Neurology 2016;86(24):2243–2250. [PubMed: 27178702]
112. Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, McKeith IG. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2006;77(5):585–589. [PubMed: 16614017]
113. Williams-Gray C, Foltynie T, Brayne C, Robbins T, Barker R. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007;130(7):1787–1798. [PubMed: 17535834]
114. Williams LN, Seignourel P, Crucian GP, et al. Laterality, region, and type of motor dysfunction correlate with cognitive impairment in Parkinson's disease. Mov Disord 2007;22(1):141–144. [PubMed: 17089386]
115. Post B, Merkus MP, de Haan RJ, Speelman JD. Prognostic factors for the progression of Parkinson's disease: A systematic review. Mov Disord 2007;22(13):1839–1851. [PubMed: 17595026]
116. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17(5):427–442. [PubMed: 6067254]
117. Zetusky WJ, Jankovic J, Pirozzolo FJ. The heterogeneity of Parkinson's disease: clinical and prognostic implications. Neurology 1985;35(4):522–526. [PubMed: 3982637]
118. Mortimer JA, Pirozzolo FJ, Hansch EC, Webster DD. Relationship of motor symptoms to intellectual deficits in Parkinson disease. Neurology 1982;32(2):133–133. [PubMed: 7198740]
119. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. Mov Disord 2013;28(5):668–670. [PubMed: 23408503]
120. Schiess M, Zheng H, Soukup V, Bonnen J, Nauta H. Parkinson's disease subtypes: clinical classification and ventricular cerebrospinal fluid analysis. Parkinsonism Relat Disord 2000;6(2):69–76. [PubMed: 10699387]

121. Müller B, Larsen JP, Wentzel-Larsen T, Skeie GO, Tysnes OB. Autonomic and sensory symptoms and signs in incident, untreated Parkinson's disease: frequent but mild. Mov Disord 2011;26(1):65–72. [PubMed: 20925070]
122. Allcock LM, Kenny RA, Burn DJ. Clinical phenotype of subjects with Parkinson's disease and orthostatic hypotension: autonomic symptom and demographic comparison. Mov Disord 2006;21(11):1851–1855. [PubMed: 16958096]
123. Dissanayaka NN, Sellbach A, Silburn PA, O'Sullivan JD, Marsh R, Mellick GD. Factors associated with depression in Parkinson's disease. J Affect Disord 2011;132(1):82–88. [PubMed: 21356559]
124. Jankovic J, Kapadia AS. Functional decline in Parkinson disease. Arch Neurol 2001;58(10):1611–1615. [PubMed: 11594919]
125. de Lau LM, Verbaan D, Marinus J, van Hilten JJ. Survival in Parkinson's disease. Relation with motor and non-motor features. Parkinsonism Relat Disord 2014;20(6):613–616. [PubMed: 24679900]
126. Rajput AH, Pahwa R, Pahwa P, Rajput A. Prognostic significance of the onset mode in parkinsonism. Neurology 1993;43(4):829–830. [PubMed: 8469347]
127. Zuo LJ, Piao YS, Li LX, et al. Phenotype of postural instability/gait difficulty in Parkinson disease: relevance to cognitive impairment and mechanism relating pathological proteins and neurotransmitters. Sci Rep 2017;7:44872. [PubMed: 28332604]
128. Kang JH, Irwin DJ, Chen-Plotkin AS, et al. Association of cerebrospinal fluid beta-amyloid 1–42, T-tau, P-tau181, and alpha-synuclein levels with clinical features of drug-naive patients with early Parkinson disease. JAMA Neurol 2013;70(10):1277–1287. [PubMed: 23979011]
129. Wennberg AMV, Savica R, Hagen CE, et al. Cerebral Amyloid Deposition Is Associated with Gait Parameters in the Mayo Clinic Study of Aging. J Am Geriatr Soc 2017;65(4):792–799. [PubMed: 27869301]
130. Louis ED, Goldman JE, Powers JM, Fahn S. Parkinsonian features of eight pathologically diagnosed cases of diffuse Lewy body disease. Mov Disord 1995;10(2):188–194. [PubMed: 7753061]
131. Simuni T, Caspell-Garcia C, Coffey C, Lasch S, Tanner C, Marek K. How stable are Parkinson's disease subtypes in de novo patients: Analysis of the PPMI cohort? Parkinsonism Relat Disord 2016;28:62–67. [PubMed: 27132498]
132. Alves G, Larsen JP, Emre M, Wentzel-Larsen T, Aarsland D. Changes in motor subtype and risk for incident dementia in Parkinson's disease. Mov Disord 2006;21(8):1123–1130. [PubMed: 16637023]
133. Goetz CG, Tanner CM, Stebbins GT, Buchman AS. Risk factors for progression in Parkinson's disease. Neurology 1988;38(12):1841–1844. [PubMed: 3194061]
134. Ferguson LW, Rajput ML, Muhajarine N, Shah SM, Rajput A. Clinical features at first visit and rapid disease progression in Parkinson's disease. Parkinsonism Relat Disord 2008;14(5):431–435. [PubMed: 18321757]
135. Gasparoli E, Delibori D, Polesello G, et al. Clinical predictors in Parkinson's disease. Neurol Sci 2002;23 Suppl 2:S77–78. [PubMed: 12548352]
136. Jankovic J, Kapadia AS. Functional decline in Parkinson disease. Arch Neurol 2001;58(10):1611–1615. [PubMed: 11594919]
137. Pagano G, Ferrara N, Brooks DJ, Pavese N. Age at onset and Parkinson disease phenotype. Neurology 2016;86(15):1400–1407. [PubMed: 26865518]
138. Lewis SJ, Foltynie T, Blackwell AD, Robbins TW, Owen AM, Barker RA. Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. J Neurol Neurosurg Psychiatry 2005;76(3):343–348. [PubMed: 15716523]
139. Erro R, Picillo M, Vitale C, et al. Clinical clusters and dopaminergic dysfunction in de-novo Parkinson disease. Parkinsonism Relat Disord 2016;28:137–140. [PubMed: 27158121]
140. Fereshtehnejad SM, Romenets SR, Anang JB, Latreille V, Gagnon JF, Postuma RB. New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression: A Prospective Cohort Comparison With Other Phenotypes. JAMA Neurol 2015;72(8):863–873. [PubMed: 26076039]

141. Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. Brain 2017;140(7):1959–1976. [PubMed: 28549077]
142. Dujardin K, Defebvre L, Duhamel A, et al. Cognitive and SPECT characteristics predict progression of Parkinson's disease in newly diagnosed patients. J Neurol 2004;251(11):1383–1392. [PubMed: 15592735]
143. Schrag A, Quinn NP, Ben-Shlomo Y. Heterogeneity of Parkinson's disease. J Neurol Neurosurg Psychiatry 2006;77(2):275–276. [PubMed: 16421140]
144. Post B, Speelman JD, de Haan RJ. Clinical heterogeneity in newly diagnosed Parkinson's disease. J Neurol 2008;255(5):716–722. [PubMed: 18344057]
145. van Rooden SM, Colas F, Martinez-Martin P, et al. Clinical subtypes of Parkinson's disease. Mov Disord 2011;26(1):51–58. [PubMed: 21322019]
146. Reijnders JS, Ehrt U, Lousberg R, Aarsland D, Leentjens AF. The association between motor subtypes and psychopathology in Parkinson's disease. Parkinsonism Relat Disord 2009;15(5):379–382. [PubMed: 18977165]
147. Morenas-Rodriguez E, Sala I, Subirana A, et al. Clinical Subtypes of Dementia with Lewy Bodies Based on the Initial Clinical Presentation. J Alzheimers Dis 2018;64(2):505–513. [PubMed: 29889064]
148. Graham JM, Sagar HJ. A data-driven approach to the study of heterogeneity in idiopathic Parkinson's disease: identification of three distinct subtypes. Mov Disord 1999;14(1):10–20. [PubMed: 9918339]
149. De Pablo-Fernández E, Lees AJ, Holton JL, Warner TT. Prognosis and neuropathologic correlation of clinical subtypes of parkinson disease. JAMA Neurol 2019.
150. Hall S, Öhrfelt A, Constantinescu R, et al. Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or parkinsonian disorders. Arch Neurol 2012;69(11):1445–1452. [PubMed: 22925882]
151. Alves G, Bronnick K, Aarsland D, et al. CSF amyloid-beta and tau proteins, and cognitive performance, in early and untreated Parkinson's disease: the Norwegian ParkWest study. J Neurol Neurosurg Psychiatry 2010;81(10):1080–1086. [PubMed: 20547614]
152. Montine TJ, Shi M, Quinn JF, et al. CSF Aβ42 and tau in Parkinson's disease with cognitive impairment. Mov Disord 2010;25(15):2682–2685. [PubMed: 20818673]
153. Compta Y, Marti MJ, Ibarretxe-Bilbao N, et al. Cerebrospinal tau, phospho-tau, and beta-amyloid and neuropsychological functions in Parkinson's disease. Mov Disord 2009;24(15):2203–2210. [PubMed: 19795497]
154. Siderowf A, Xie SX, Hurtig H, et al. CSF amyloid {beta} 1–42 predicts cognitive decline in Parkinson disease. Neurology 2010;75(12):1055–1061. [PubMed: 20720189]
155. Alves G, Lange J, Blennow K, et al. CSF Abeta42 predicts early-onset dementia in Parkinson disease. Neurology 2014;82(20):1784–1790. [PubMed: 24748671]
156. Hall S, Surova Y, Ohrfelt A, Zetterberg H, Lindqvist D, Hansson O. CSF biomarkers and clinical progression of Parkinson disease. Neurology 2015;84(1):57–63. [PubMed: 25411441]
157. Parnetti L, Farotti L, Eusebi P, et al. Differential role of CSF alpha-synuclein species, tau, and Abeta42 in Parkinson's Disease. Front Aging Neurosci 2014;6:53. [PubMed: 24744728]
158. Compta Y, Pereira JB, Rios J, et al. Combined dementia-risk biomarkers in Parkinson's disease: a prospective longitudinal study. Parkinsonism Relat Disord 2013;19(8):717–724. [PubMed: 23643469]
159. van Steenoven I, Aarsland D, Weintraub D, et al. Cerebrospinal Fluid Alzheimer's Disease Biomarkers Across the Spectrum of Lewy Body Diseases: Results from a Large Multicenter Cohort. J Alzheimers Dis 2016;54(1):287–295. [PubMed: 27567832]
160. Lemstra A, de Beer M, Teunissen C, et al. Concomitant AD pathology affects clinical manifestation and survival in dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2017;88(2):113–118. [PubMed: 27794030]
161. Mollenhauer B, Trenkwalder C, von Ahsen N, et al. Beta-amlyoid 1–42 and tau-protein in cerebrospinal fluid of patients with Parkinson's disease dementia. Dement Geriatr Cogn Disord 2006;22(3):200–208. [PubMed: 16899997]

162. Liu C, Cholerton B, Shi M, et al. CSF tau and tau/Abeta42 predict cognitive decline in Parkinson's disease. Parkinsonism Relat Disord 2015;21(3):271–276. [PubMed: 25596881]
163. Zhang J, Mattison HA, Liu C, et al. Longitudinal assessment of tau and amyloid beta in cerebrospinal fluid of Parkinson disease. Acta Neuropathol 2013;126(5):671–682. [PubMed: 23644819]
164. Toledo JB, Brettschneider J, Grossman M, et al. CSF biomarkers cutoffs: the importance of coincident neuropathological diseases. Acta Neuropathol 2012;124(1):23–35. [PubMed: 22526019]
165. Tapiola T, Alafuzoff I, Herukka SK, et al. Cerebrospinal fluid beta-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. Arch Neurol 2009;66(3):382–389. [PubMed: 19273758]
166. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 2009;65(4):403–413. [PubMed: 19296504]
167. De Meyer G, Shapiro F, Vanderstichele H, et al. Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. Arch Neurol 2010;67(8):949–956. [PubMed: 20697045]
168. Mollenhauer B, Caspell-Garcia CJ, Coffey CS, et al. Longitudinal CSF biomarkers in patients with early Parkinson disease and healthy controls. Neurology 2017;89(19):1959–1969. [PubMed: 29030452]
169. Shi M, Bradner J, Hancock AM, et al. Cerebrospinal fluid biomarkers for Parkinson disease diagnosis and progression. Ann Neurol 2011;69(3):570–580. [PubMed: 21400565]
170. Mollenhauer B, Parnetti L, Rektorova I, et al. Biological confounders for the values of cerebrospinal fluid proteins in Parkinson's disease and related disorders. J Neurochem 2016;139:290–317. [PubMed: 26452984]
171. Hong Z, Shi M, Chung KA, et al. DJ-1 and alpha-synuclein in human cerebrospinal fluid as biomarkers of Parkinson's disease. Brain 2010;133(Pt 3):713–726. [PubMed: 20157014]
172. Shi M, Bradner J, Hancock AM, et al. Cerebrospinal fluid biomarkers for Parkinson disease diagnosis and progression. Ann Neurol 2011;69(3):570–580. [PubMed: 21400565]
173. Eusebi P, Giannandrea D, Biscetti L, et al. Diagnostic utility of cerebrospinal fluid α-synuclein in Parkinson's disease: A systematic review and meta-analysis. Mov Disord 2017;32(10):1389–1400. [PubMed: 28880418]
174. Mollenhauer B, Trautmann E, Taylor P, et al. Total CSF α-synuclein is lower in de novo Parkinson patients than in healthy subjects. Neurosci Lett 2013;532:44–48. [PubMed: 23149132]
175. Stewart T, Liu C, Ginghina C, et al. Cerebrospinal fluid alpha-synuclein predicts cognitive decline in Parkinson disease progression in the DATATOP cohort. Am J Pathol 2014;184(4):966–975. [PubMed: 24625392]
176. Park MJ, Cheon S-M, Bae H-R, Kim S-H, Kim JW. Elevated levels of α-synuclein oligomer in the cerebrospinal fluid of drug-naïve patients with Parkinson's disease. J Clin Neurol 2011;7(4):215–222. [PubMed: 22259618]
177. Wang Y, Shi M, Chung KA, et al. Phosphorylated α-synuclein in Parkinson's disease. Sci Transl Med 2012;4(121):121ra120.
178. Tokuda T, Qureshi M, Ardah M, et al. Detection of elevated levels of α-synuclein oligomers in CSF from patients with Parkinson disease. Neurology 2010;75(20):1766–1770. [PubMed: 20962290]
179. Fairfoul G, McGuire LI, Pal S, et al. Alpha-synuclein RT-Qu IC in the CSF of patients with alpha-synucleinopathies. Ann Clin Transl Neurol 2016;3(10):812–818. [PubMed: 27752516]
180. Groveman BR, Orrù CD, Hughson AG, et al. Rapid and ultra-sensitive quantitation of disease-associated α-synuclein seeds in brain and cerebrospinal fluid by αSyn RT-QuIC. Acta Neuropathol Commun 2018;6(1):7. [PubMed: 29422107]
181. van Rumund A, Green AJ, Fairfoul G, Esselink RA, Bloem BR, Verbeek MM. Alpha-synuclein RT-QuIC in the CSF of uncertain cases of parkinsonism. Ann Neurol 2019.
182. Foster ER, Campbell MC, Burack MA, et al. Amyloid imaging of Lewy body-associated disorders. Mov Disord 2010;25(15):2516–2523. [PubMed: 20922808]

183. Gomperts SN, Locascio JJ, Marquie M, et al. Brain amyloid and cognition in Lewy body diseases. Mov Disord 2012;27(8):965–973. [PubMed: 22693110]

184. Petrou M, Bohnen NI, Müller ML, Koeppe RA, Albin RL, Frey KA. Aβ-amyloid deposition in patients with Parkinson disease at risk for development of dementia. Neurology 2012;79(11):1161–1167. [PubMed: 22933741]

185. Petrou M, Dwamena BA, Foerster BR, et al. Amyloid deposition in Parkinson's disease and cognitive impairment: a systematic review. Mov Disord 2015;30(7):928–935. [PubMed: 25879534]

186. Mashima K, Ito D, Kameyama M, et al. Extremely Low Prevalence of Amyloid Positron Emission Tomography Positivity in Parkinson's Disease without Dementia. Eur Neurol 2017;77(5–6):231–237. [PubMed: 28285306]

187. Burack MA, Hartlein J, Flores HP, Taylor-Reinwald L, Perlmutter JS, Cairns NJ. In vivo amyloid imaging in autopsy-confirmed Parkinson disease with dementia. Neurology 2010;74(1):77–84. [PubMed: 20038776]

188. Edison P, Rowe CC, Rinne JO, et al. Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C] PIB positron emission tomography. J Neurol Neurosurg Psychiatry 2008;79(12):1331–1338. [PubMed: 18653550]

189. Villemagne VL, Ong K, Mulligan RS, et al. Amyloid imaging with 18F-florbetaben in Alzheimer disease and other dementias. J Nucl Med 2011;52(8):1210–1217. [PubMed: 21764791]

190. Donaghy P, Thomas AJ, O'Brien JT. Amyloid PET imaging in Lewy body disorders. Am J Geriatr Psychiatry 2015;23(1):23–37. [PubMed: 23831180]

191. Akhtar RS, Xie SX, Chen YJ, et al. Regional brain amyloid-beta accumulation associates with domain-specific cognitive performance in Parkinson disease without dementia. PLoS One 2017;12(5):e0177924.

192. Melzer TR, Stark MR, Keenan RJ, et al. Beta amyloid deposition is not associated with cognitive impairment in Parkinson's disease. Front Neurol 2019;10:391. [PubMed: 31105633]

193. Villemagne VL, Fodero-Tavoletti MT, Masters CL, Rowe CC. Tau imaging: early progress and future directions. Lancet Neurol 2015;14(1):114–124. [PubMed: 25496902]

194. Kantarci K, Lowe VJ, Boeve BF, et al. AV-1451 tau and β-amyloid positron emission tomography imaging in dementia with Lewy bodies. Ann Neurol 2017;81(1):58–67. [PubMed: 27863444]

195. Lee SH, Cho H, Choi JY, et al. Distinct patterns of amyloid-dependent tau accumulation in Lewy body diseases. Mov Disord 2018;33(2):262–272. [PubMed: 29168583]

196. Smith R, Schöll M, Londos E, Ohlsson T, Hansson O. 18F-AV-1451 in Parkinson's Disease with and without dementia and in Dementia with Lewy Bodies. Sci Rep 2018;8(1):4717. [PubMed: 29549278]

197. Singleton AB, Farrer M, Johnson J, et al. alpha-Synuclein locus triplication causes Parkinson's disease. Science 2003;302(5646):841. [PubMed: 14593171]

198. Zarranz JJ, Alegre J, Gomez-Esteban JC, et al. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol 2004;55(2):164–173. [PubMed: 14755719]

199. Morfis L, Cordato DJ. Dementia with Lewy bodies in an elderly Greek male due to alpha-synuclein gene mutation. J Clin Neurosci 2006;13(9):942–944. [PubMed: 17049244]

200. Ikeuchi T, Kakita A, Shiga A, et al. Patients homozygous and heterozygous for SNCA duplication in a family with parkinsonism and dementia. Arch Neurol 2008;65(4):514–519. [PubMed: 18413475]

201. Alcalay RN, Caccappolo E, Mejia-Santana H, et al. Frequency of known mutations in early-onset parkinson disease: Implication for genetic counseling: the consortium on risk for early onset parkinson disease study. Arch Neurol 2010;67(9):1116–1122. [PubMed: 20837857]

202. Rogaeva E, Johnson J, Lang AE, et al. Analysis of the PINK1 gene in a large cohort of cases with Parkinson disease. Arch Neurol 2004;61(12):1898–1904. [PubMed: 15596610]

203. Abou-Sleiman PM, Healy DG, Quinn N, Lees AJ, Wood NW. The role of pathogenic DJ-1 mutations in Parkinson's disease. Ann Neurol 2003;54(3):283–286. [PubMed: 12953260]

204. Mata IF, Shi M, Agarwal P, et al. SNCA variant associated with Parkinson disease and plasma alpha-synuclein level. Arch Neurol 2010;67(11):1350–1356. [PubMed: 21060011]

205. Cooper CA, Jain N, Gallagher MD, et al. Common variant rs356182 near SNCA defines a Parkinson's disease endophenotype. Ann Clin Transl Neurol 2017;4(1):15–25. [PubMed: 28078311]
206. Labbé C, Heckman MG, Lorenzo-Betancor O, et al. MAPT haplotype H1G is associated with increased risk of dementia with Lewy bodies. Alzheimer's & Dementia 2016;12(12):1297–1304.
207. Edwards TL, Scott WK, Almonte C, et al. Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease. Ann Hum Genet 2010;74(2):97–109. [PubMed: 20070850]
208. Mata IF, Leverenz JB, Weintraub D, et al. APOE, MAPT, and SNCA genes and cognitive performance in Parkinson disease. JAMA Neurol 2014;71(11):1405–1412. [PubMed: 25178429]
209. Bras J, Guerreiro R, Darwent L, et al. Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. Hum Mol Genet 2014;23(23):6139–6146. [PubMed: 24973356]
210. Krüger R, Menezes Vieira-Saecker AM, Kuhn W, et al. Increased susceptibility to sporadic Parkinson's disease by a certain combined α-synuclein/apolipoprotein E genotype. Ann Neurol 1999;45(5):611–617. [PubMed: 10319883]
211. Li Y, Hauser M, Scott WK, et al. Apolipoprotein E controls the risk and age at onset of Parkinson disease. Neurology 2004;62(11):2005–2009. [PubMed: 15184605]
212. Huang X, Chen PC, Poole C. APOE-ε2 allele associated with higher prevalence of sporadic Parkinson disease. Neurology 2004;62(12):2198–2202. [PubMed: 15210882]
213. Williams-Gray CH, Goris A, Saiki M, et al. Apolipoprotein E genotype as a risk factor for susceptibility to and dementia in Parkinson's disease. J Neurol 2009;256(3):493–498. [PubMed: 19308307]
214. Sabir MS, Blauwendraat C, Ahmed S, et al. Assessment of APOE in atypical parkinsonism syndromes. Neurobiol Dis 2019.
215. Singleton AB, Wharton A, O'Brien KK, et al. Clinical and neuropathological correlates of apolipoprotein E genotype in dementia with Lewy bodies. Dement Geriatr Cogn Disord 2002;14(4):167–175. [PubMed: 12411758]
216. Zimprich A, Biskup S, Leitner P, et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 2004;44(4):601–607. [PubMed: 15541309]
217. Healy DG, Falchi M, O'Sullivan SS, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol 2008;7(7):583–590. [PubMed: 18539534]
218. Nalls MA, Pankratz N, Lill CM, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet 2014;46(9):989–993. [PubMed: 25064009]
219. Labbe C, Heckman MG, Lorenzo-Betancor O, et al. MAPT haplotype H1G is associated with increased risk of dementia with Lewy bodies. Alzheimers Dement 2016;12(12):1297–1304. [PubMed: 27287057]
220. Nalls MA, Plagnol V, Hernandez DG, et al. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet 2011;377(9766):641–649. [PubMed: 21292315]
221. Williams-Gray CH, Mason SL, Evans JR, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry 2013:jnnp-2013–305277.
222. Evans JR, Mason SL, Williams-Gray CH, et al. The natural history of treated Parkinson's disease in an incident, community based cohort. J Neurol Neurosurg Psychiatry 2011;82(10):1112–1118. [PubMed: 21593513]
223. Colom-Cadena M, Gelpi E, Martí MJ, et al. MAPT H1 haplotype is associated with enhanced α-synuclein deposition in dementia with Lewy bodies. Neurobiol Aging 2013;34(3):936–942. [PubMed: 22819391]
224. Heckman MG, Kasanuki K, Brennan RR, et al. Association of MAPT H1 subhaplotypes with neuropathology of lewy body disease. Mov Disord 2019.

225. Guerreiro R, Ross OA, Kun-Rodrigues C, et al. Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. Lancet Neurol 2018;17(1):64–74. [PubMed: 29263008]
226. Wider C, Ross OA, Nishioka K, et al. An evaluation of the impact of MAPT, SNCA and APOE on the burden of Alzheimer's and Lewy body pathology. J Neurol Neurosurg Psychiatry 2012;83(4):424–429. [PubMed: 22291217]
227. Robinson JL, Lee EB, Xie SX, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. Brain 2018.
228. Josephs KA, Tsuboi Y, Cookson N, Watt H, Dickson DW. Apolipoprotein E ε4 is a determinant for Alzheimer-type pathologic features in tauopathies, synucleinopathies, and frontotemporal degeneration. Arch Neurol 2004;61(10):1579–1584. [PubMed: 15477512]
229. Dickson DW, Heckman MG, Murray ME, et al. APOE ε4 is associated with severity of Lewy body pathology independent of Alzheimer pathology. Neurology 2018;91(12):e1182–e1195. [PubMed: 30143564]
230. Tropea TF, Xie SX, Rick J, et al. APOE, thought disorder, and SPARE-AD predict cognitive decline in established Parkinson's disease. Mov Disord 2018;33(2):289–297. [PubMed: 29168904]
231. Monsell SE, Besser LM, Heller KB, Checkoway H, Litvan I, Kukull WA. Clinical and pathologic presentation in Parkinson's disease by apolipoprotein e4 allele status. Parkinsonism Relat Disord 2014;20(5):503–507. [PubMed: 24582705]
232. Gámez-Valero A, Prada-Dacasa P, Santos C, et al. GBA mutations are associated with earlier onset and male sex in dementia with Lewy bodies. Mov Disord 2016;31(7):1066–1070. [PubMed: 27027900]
233. Winder-Rhodes SE, Evans JR, Ban M, et al. Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. Brain 2013;136(Pt 2):392–399. [PubMed: 23413260]
234. Setó-Salvia N, Pagonabarraga J, Houlden H, et al. Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson's disease course. Mov Disord 2012;27(3):393–399. [PubMed: 22173904]
235. Neumann J, Bras J, Deas E, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain 2009;132(7):1783–1794. [PubMed: 19286695]
236. Clark LN, Kartsaklis LA, Gilbert RW, et al. Association of glucocerebrosidase mutations with dementia with lewy bodies. Arch Neurol 2009;66(5):578–583. [PubMed: 19433657]
237. Tsuang D, Leverenz JB, Lopez OL, et al. GBA mutations increase risk for Lewy body disease with and without Alzheimer disease pathology. Neurology 2012;79(19):1944–1950. [PubMed: 23035075]
238. Poulopoulos M, Levy OA, Alcalay RN. The neuropathology of genetic Parkinson's disease. Mov Disord 2012;27(7):831–842. [PubMed: 22451330]
239. Peuralinna T, Myllykangas L, Oinas M, et al. Genome-wide association study of neocortical Lewy-related pathology. Ann Clin Transl Neurol 2015;2(9):920–931. [PubMed: 26401513]
240. Sharma M, Ioannidis JP, Aasly JO, et al. Large-scale replication and heterogeneity in Parkinson disease genetic loci. Neurology 2012;79(7):659–667. [PubMed: 22786590]
241. Chang D, Nalls MA, Hallgrímsdóttir IB, et al. A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. Nat Genet 2017;49(10):1511. [PubMed: 28892059]
242. Jack CR, Bennett DA, Blennow K, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 2016;87(5):539–547. [PubMed: 27371494]
243. Buchman AS, Yu L, Wilson RS, et al. Progressive parkinsonism in older adults is related to the burden of mixed brain pathologies. Neurology 2019;92(16):e1821–e1830. [PubMed: 30894446]

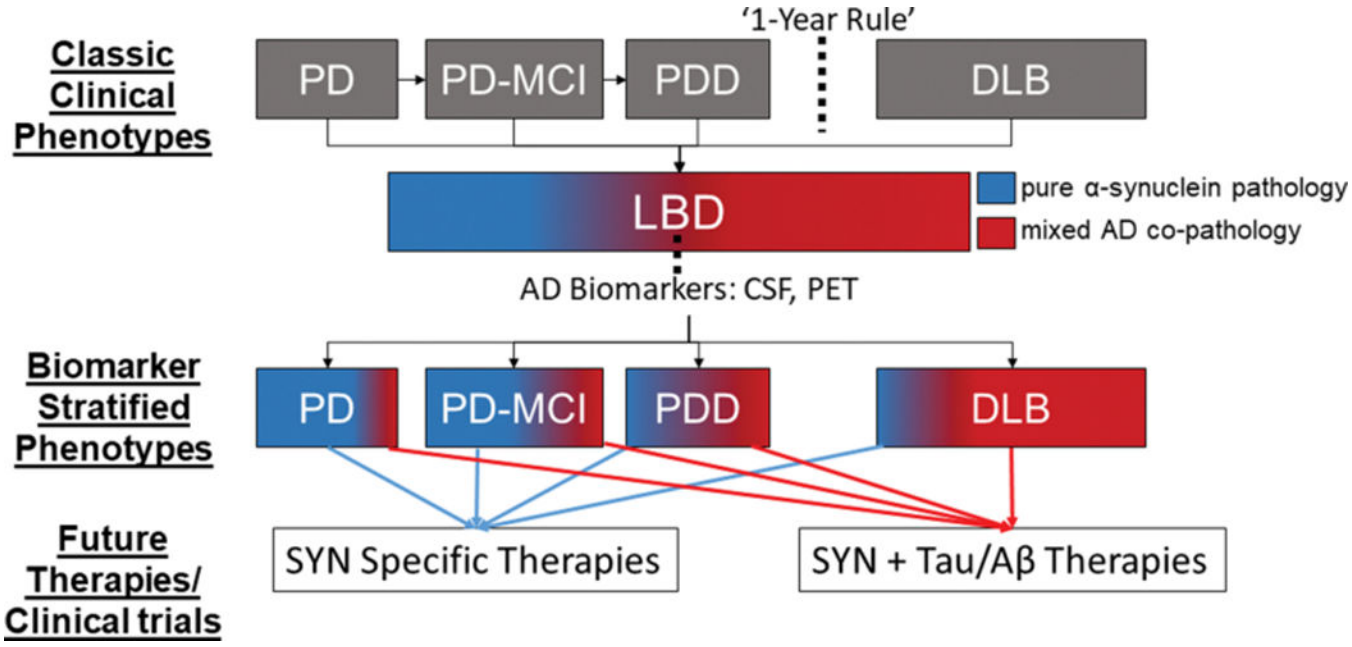


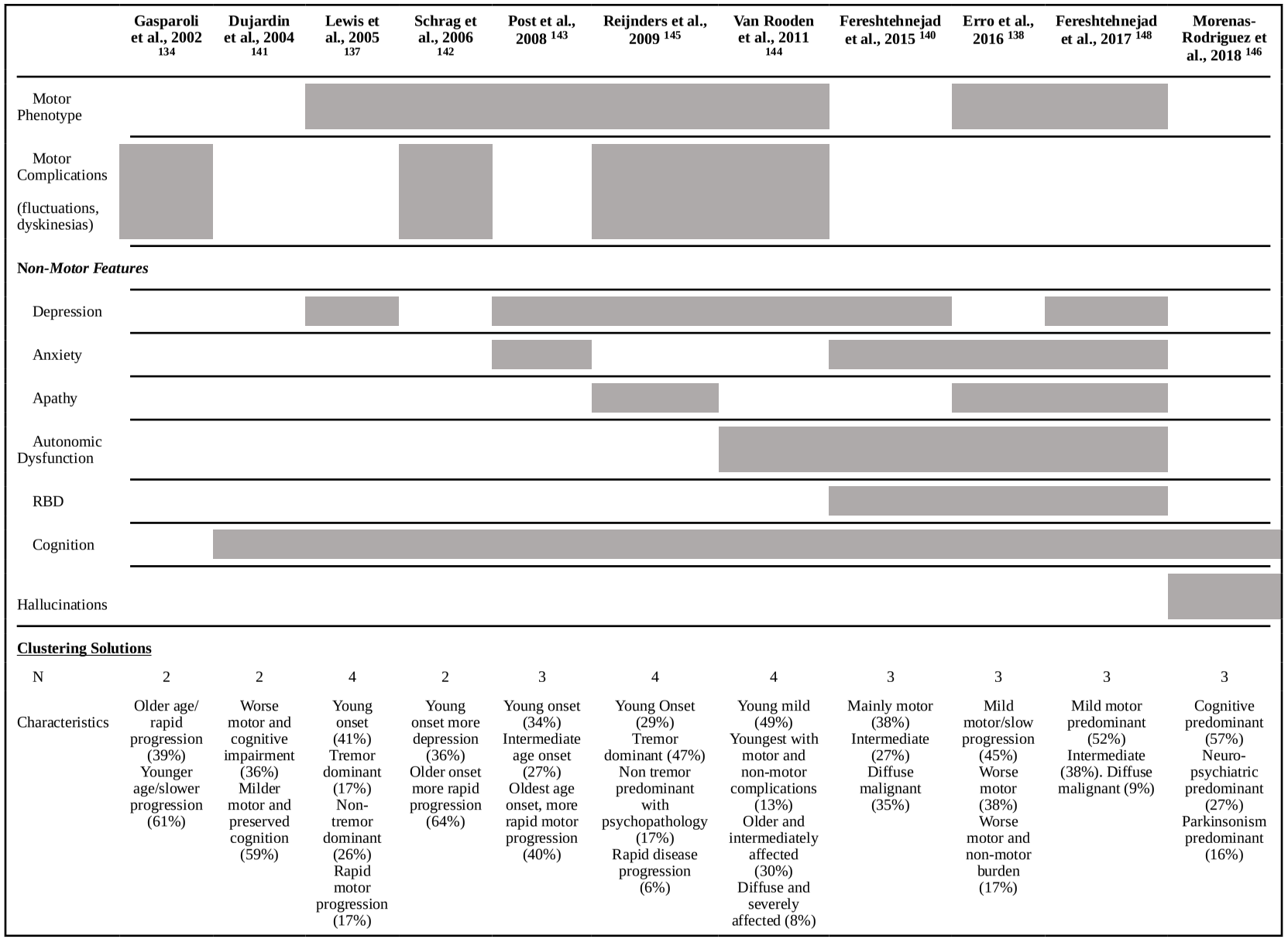
Figure 1.

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 Aβ 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 [134]	Dujardin et al., 2004 [141]	Lewis et al., 2005 [137]	Schrag et al., 2006 [142]	Post et al., 2008 [143]	Reijnders et al., 2009 [145]	Van Rooden et al., 2011 [144]	Fereshtehnejad et al., 2015 [140]	Erro et al., 2016 [138]	Fereshtehnejad et al., 2017 [148]	Morenas-Rodriguez et al., 2018 [146]
Design and Inclusion											
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[a]	None	PPMI	PPMI	Probable DLB[b]
Age, mean years (SD)	NS	66 (median)	64.4 (9.3)	71.9 (11.0)	66.7 (10.4)	70.4[c]	60.8 (11.3)	66.7 (8.9)	63.2[c]	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
Variables Included in Clustering Solution											
Demographics											
Age of Onset											
Sex											
Motor Features											
UPDRSII											Motor Parkinsonism[d]
UPDRS III											Motor Parkinsonism[d]
Rate of Motor Progression											



Mov Disord. Author manuscript; available in PMC 2021 January 01.

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

[a]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

[b]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.

[c]Derived from cluster averages

[d]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**
Age of Onset, (range of mean age)	Younger (57–66)	Older (68–74) [21, 25, 94, 65 ,69, 97]	Similar (68–78)	Similar (70–85) [21 *, 29, 94 *]
Motor Dementia Interval, (range of mean years)	Longer (8–15) **	Shorter (2–10) [21, 32, 69, 97] ***	NA	
Survival (range of mean years)	Longer * (10–19)	Shorter (4.5–13) [21, 25, 65, 69, 97, 98]	Longer (6–10)	Shorter (3–7) [21 *, 29, 94 *]
Motor Phenotype	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 [114, 132]	
Hallucinations/ Fluctuations	No clear data comparing influence of AD co-pathology but hallucinations/fluctuations are common in PDD [14]		More frequent	Less frequent [13, 31, 103]
Cognitive Dysfunction	Executive, attention, visuospatial deficits	Additional episodic memory, naming deficits[3, 105]	Executive, attention, visuospatial deficits	Additional episodic memory, naming deficits[94, 104, 105]
Genetic Associations	*GBA* mutation carriers ++ APOE ε4 allele carriers +	*GBA* mutation carriers + [221] APOE ε4 allele carriers + +[16, 226, 227, 228]	*GBA* mutation carriers ++, APOE ε4 allele carriers +	*GBA* mutation carriers +, [214, 221] APOE ε4 allele carriers ++ [212, 226, 227, 228]

* not published data

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

*** 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 ≤ 1year.