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Title Page

Amyloid PET imaging in Lewy body disorders.

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Key words: amyloid, imaging, dementia, Lewy bodies, Parkinson's disease, positron emission tomography

Abstract

Lewy body (LB) disorders, including Parkinson's disease (PD), Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are the second most common type of neurodegenerative dementia. Although the pathological hallmarks of LB disorders are Lewy bodies and Lewy neurites, cortical amyloid-beta ($A\beta$) deposition is also often seen. The relationship between $A\beta$ pathology and dementia in LB disorders is unclear. Recently, PET $A\beta$ ligands have been developed that enable *in vivo* imaging of $A\beta$. In this paper we review amyloid imaging studies in LB disorders.

LB disorders are associated with lower mean cortical $A\beta$ ligand binding compared with Alzheimer's Disease. In DLB and PDD many subjects have normal levels of cortical $A\beta$, though a subset show increased $A\beta$ ligand binding. Those with DLB show greater ligand binding than PDD; binding does not appear to be increased in PD without dementia. Cortical $A\beta$ deposition may be a factor in the development of cognitive impairment in some cases of dementia in LB disorders. Amyloid imaging is of limited use in the diagnosis of LB disorders but $A\beta$ deposition may predict the future development of dementia in PD. Reports of correlation between $A\beta$ deposition and symptom profile, severity and progression have been inconsistent. Some results suggest a synergistic interaction between $A\beta$ and α -synuclein.

Interpretation of the current evidence is hampered by differing methodologies across studies, and small sample sizes. Large, prospective longitudinal studies are needed to clarify the association of $A\beta$ with symptom development, progression, severity and treatment response in LB disorders.

Objective

Lewy body (LB) disorders include Parkinson's disease (PD) and the Lewy body dementias, dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD). Following Alzheimer's disease (AD), LB dementias are the second most common cause of neurodegenerative dementia, with DLB alone accounting for around 15% of cases at post-mortem (1) and 10% in clinical samples (2), and high rates of dementia observed in PD (3). DLB and PDD are both characterised by dementia syndromes with specific associated symptoms including parkinsonism, fluctuating cognition and visual hallucinations (3, 4). Based on international consensus, DLB is diagnosed when dementia develops without parkinsonism or within a year of the development of parkinsonism; PDD is diagnosed when parkinsonism precedes dementia by more than one year (3, 4). There are no other major clinical differences between DLB and PDD, and despite some controversy surrounding the 'one-year rule' they are generally recognised to be on a continuum of LB disease (5).

The pathological hallmarks of LB disorders are Lewy bodies and Lewy neurites, but many cases also display AD pathology (amyloid- β (A β) plaques and neurofibrillary tangles (NFTs)) post-mortem (6). The importance of AD pathology in LB disorders and its relationship to cognitive impairment is unclear. Post-mortem studies of confirmed DLB cases have reported that concurrent AD pathology measured by increased NFTs was associated with a lower likelihood of visual hallucinations and a lower chance of a DLB diagnosis during life (7, 8). A combination of AD and LB pathology in dementia is associated with a lower occurrence of parkinsonism and hallucinations compared with LB pathology alone (9). Greater cortical A β pathology has been associated with increased cognitive impairment (10) and a shorter time from onset of parkinsonian symptoms to cognitive impairment (11-13) in LB disorders. DLB has been associated with a greater A β burden than PDD and PD (12, 14, 15). It has been suggested that the co-occurrence of AD and LB pathology represents more than coincidence, and that there may be synergism, with A β increasing the propensity of α -synuclein to accumulate and aggregate (16).

Post-mortem studies are by their nature cross sectional and tend to report end-stage disease. Thus patients with initial 'pure Lewy body pathology' may be found post-mortem to have significant AD pathology, although this may not have been related to their initial presentation. PET amyloid imaging, initially with ^{11}C -PiB (Pittsburgh compound B) and now with ^{18}F labelled compounds, was developed to measure brain A β burden *in vivo* (17). Post-mortem studies have demonstrated that amyloid imaging with these ligands correlates well with A β deposition in the form of neuritic and diffuse plaques, and amyloid angiopathy (18-20). A β deposition *in vivo* is consistently elevated in AD, and also in some healthy control subjects (21, 22). The objective of this paper was to review all studies to date that have involved amyloid imaging in LB disorders to examine the contribution of A β pathology to these disorders.

Terminology in this research field has been a subject of some debate (5). In this paper we use the terminology accepted by recent consensus statements (3, 4). 'DLB' refers to dementia with Lewy bodies, where cognitive impairment emerged at the same time, or within a year of parkinsonian symptoms. 'PDD' refers to Parkinson's disease dementia, where cognitive impairment developed over a year after parkinsonian symptoms. 'LB dementias' refers to both DLB and PDD. 'LB disorders' refers to all LB pathologies (in this paper generally PD (+/- MCI), PDD and DLB).

Methods

A MEDLINE (Web of Knowledge; 1950-present) search was carried out in January 2013. The search algorithm used was: (“Amyloid”) AND (“Positron emission tomography” OR “PET”) AND (“Lewy” OR “Parkinson disease”). Each word was entered both as a ‘topic’ and ‘MeSH’ term; lemmatization was used. 82 English-language results were found. Titles and abstracts were then screened by two reviewers (PD and AT) to identify studies that performed amyloid brain imaging in patients with Lewy body disease. A total of 16 studies with original data were identified (Table 1 summarises these papers). Four papers reporting post-mortem findings in patients who had ante-mortem amyloid PET scans were also included. Two further ‘In Press’ studies available online came to the authors’ attention and were included. Reference lists from the selected articles were searched for any additional references not captured by the search, though none were found.

Results

Dementia with Lewy bodies

When compared with healthy controls, four studies found DLB to be associated with significantly greater cortical and subcortical ^{11}C -PiB binding on PET imaging (23-26). A 32% greater uptake was found in one study (23), although 6 controls with raised ^{11}C -PiB binding had been excluded from analysis, as the aim of the study was to examine patterns of raised A β deposition in LB disorders. Two studies failed to find a significant difference between DLB and controls in global or regional A β ligand binding (27, 28). In both, DLB displayed greater binding (mean cortical binding potential: 0.18 v. 0.08 (27); neocortex standardised uptake value ratio: 1.38 v. 1.26 (28)). It should be noted that these studies contained smaller DLB samples (n= 6 and n= 7 respectively) than those that found significant differences (n= 8-21 (23-26)).

Particular areas of increased A β ligand binding have included frontal, parietal and cingulate areas, along with the striatum (24-26, 29, 30), with relative sparing of the medial temporal lobe (24, 26, 30).

Four studies have compared amyloid brain imaging in DLB and AD. The largest study (n=42) found global ^{11}C -PiB retention ratio to be significantly lower in DLB (26). Two other studies have also found lower cortical A β ligand binding in DLB compared with AD (28, 30) (distribution volume ratio: 1.7 v. 2.0 (30); standardised uptake value ratio: 1.38 v. 1.93 (28)).

One study found no difference between DLB and AD, with very similar results in both groups in all cortical areas (24). In this study, the DLB group was on average 9 years older than the AD group, with significantly greater cognitive impairment, although results held after adjusting for age, though not cognition, in multivariate analysis.

Gomperts et al. (25) compared DLB with the other Lewy body disorders: PDD, PD with mild cognitive impairment (PD-MCI) and PD. The study compared precuneus ^{11}C -PiB retention, as retention was particularly high in this region and correlated very highly with global retention ($r=0.939$) (25). Mean precuneus ^{11}C -PiB distribution volume ratio was significantly higher in DLB than the other Lewy body disorders (DLB=1.49, PDD=1.28, PD-MCI=1.16, PD= 1.16). This echoed their earlier findings of higher global cortical ^{11}C -PiB retention in DLB (24). Edison et al. (23) also reported higher ^{11}C -PiB binding in DLB compared with PDD and PD, but did not report direct statistical testing between the groups. Another study comparing 3 DLB patients and 3 with multiple systems atrophy (MSA) found higher cortical ^{11}C -PiB binding in the DLB group (29).

Two studies found no difference in A β ligand binding between DLB and PD (28) (cortical standardised uptake value ratio: DLB=1.38, PD=1.14); or PD, PD with MCI and PDD (27) (mean cortical binding potential: DLB=0.18, PDD=0.11, PD-MCI=0.08, PD=0.04). In both studies, although not significant, A β ligand binding in the groups bore the same relationship to each other seen in studies that did find a significant difference (DLB>PDD>PD).

When present, the pattern of A β ligand binding in Lewy body disorders is similar to that seen in AD (24, 26, 30-34), although one study found occipital cortex binding relative to overall binding to be lower in AD (24).

Some studies divided each diagnostic group into A β positive and A β negative subgroups, based on a defined threshold of A β ligand binding. There was a consistent finding of higher rates of A β positive

subjects in AD than DLB, in DLB than PDD, and in PDD than controls or PD (Overall average: AD=78%, DLB=57%, PDD=35%, control=21%, PD=13%; Table 2). The findings of PD versus controls were variable, with some finding higher rates in PD (24, 27), others in controls (23, 28, 35).

Comparison across studies, and the amalgamation of data used here, should be treated with some caution as studies used different outcome measures (binding potential, distribution volume ratio, standardised uptake value ratio, visual inspection) and perhaps more importantly set different criteria for identifying cases as A β positive or negative (some looked at whole cortex average, in others increased A β in one cortical area sufficed). For example, 7 of the 8 total A β positive PD patients came from one study that accounted for only 18% of the total PD group (24).

Recruitment practices should also be taken into account. For example, some studies selected patients well known to the investigators with no sign of cognitive impairment (36) or patients with particularly characteristic symptoms (30). Whilst this is understandable, particularly in studies where sample sizes are likely to be low or where aetiopathological differences between disorders are being investigated and thus 'pure' cases are sought, it does mean that the samples may not necessarily be representative of the total population with that disease.

Parkinson disease dementia

All 6 studies comparing A β ligand binding in PDD and controls have found no significant difference between the two groups (23-25, 27, 31, 35). Foster et al. found a mean cortical binding potential of 0.11 in PDD compared with 0.08 in controls (27). In general PDD results were very similar to controls, with a tendency toward a small number of outliers in the PDD group with high levels of cortical A β (23, 25, 27, 33).

Maetzler et al. (31) compared PDD and AD after removing 2 PDD patients with markedly raised ¹¹C-PiB binding that they felt indicated a different disease entity to 'pure' PDD. The remaining PDD subjects demonstrated remarkably similar cortical A β binding to the control group and lower cortical and striatal binding than the AD group. The two high ¹¹C-PiB binding subjects had an 'AD-like' pattern of deposition. The only other study to compare PDD and AD found no outlying PDD subjects, with A β ligand binding significantly lower in PDD than AD (24).

Several studies have noted no significant difference in A β binding between PDD and PD (23-25, 27, 35) or PD with MCI (25, 37). However, PDD consistently has a greater proportion of A β positive subjects when groups are divided in a binary fashion as positive or negative (Table 2).

Relevant to this, Petrou et al. (32) identified 40 patients with PD at risk for dementia (with MCI/older age /long duration of PD/prominent gait or balance impairments). On further testing 5/40 subjects were diagnosed as having mild dementia. When the subjects underwent amyloid imaging 4/5 subjects with dementia had elevated ¹¹C-PiB binding on visual inspection, compared with 2/30 patients with PD-MCI and 0/5 with PD and some other risk factor for dementia. This finding of increased rates of A β positive subjects in PDD groups compared with PD or controls, without any difference in mean cortical A β ligand binding, may be accounted for by a subgroup of outlying PDD subjects with high A β binding (23, 25, 27, 33), or a different pattern of deposition in PDD that results in focal increases in binding without a significantly increased overall A β load (24).

Parkinson Disease

7 studies have compared amyloid imaging findings in PD and controls. One small study compared a group of PD patients with controls from a previous study and found the PD group had significantly lower ^{11}C -PiB binding in the frontal (^{11}C -PiB uptake/cerebellum: 1.10 v 1.30), parietal (1.15 v 1.35) and posterior cingulate (1.04 v 1.43) cortices (36). The PD subjects were well known to the investigators, with no evidence of cognitive impairment on routine assessment. It may be that they represented a subgroup of particularly cognitively healthy individuals.

Other studies have found no difference between PD and controls (23-25, 27, 28, 35), although mean cortical A β ligand binding was marginally lower in PD in some (25, 27, 28) (mean cortical binding potential: 0.04 v 0.08 (27), standardised uptake value ratio: 1.14 v 1.26 (28)). Edison et al. found similar ^{11}C -PiB uptake in all brain areas (0-4% higher in PD than controls) although 6 ^{11}C -PiB positive subjects were removed from the control group before analysis (23).

Three studies comparing PD with AD have all found lower brain A β ligand binding in PD (24, 28, 36).

Relationship between A β and clinical picture

Cognitive impairment and dementia severity

Two studies have found a significant correlation between MMSE score and A β ligand binding when analysing data across multiple disease groups (DLB, PDD, PD: $r=-0.5$, $p=0.01$, $n=26$ (24); DLB, PD, AD, MCI, FTLD, VaD, controls: $r=-0.49$, $p<0.0001$, $n=109$ (28)). However, over both studies, only the MCI group in Villemagne et al. (28) displayed the same correlation within the group ($r=-0.76$, $p<0.0001$, $n=20$).

Other studies have considered PDD/DLB as a single group for analysis. In such a group the A β positive subjects were found to have a significantly lower MMSE than the A β negative group, but this group was also older (33). Conversely, Foster et al. (27) were not able to identify differences between A β positive and negative PDD/DLB groups in MMSE, NPI or cognitive fluctuations. However, pooling the A β positive and A β negative PDD/DLB subjects ($n=21$) they found mean cortical and caudate A β binding correlated modestly with MMSE (cortical: $r=-0.47$, $p=0.04$; caudate: $r=-0.44$, $p=0.05$) and CDR global (cortical: $r=0.55$, $p=0.01$; caudate: $r=0.51$, $p=0.02$). No such correlation existed in PD or control groups. In PD with MCI, MMSE correlated strongly with caudate A β ($r=-0.82$, $p=0.007$, $n=9$) but not mean cortical A β ($p=0.52$).

In a population mostly consisting of PD-MCI, A β ligand binding was found to correlate with global cognitive scores ($r=-0.55$, $p=0.0006$, $n=40$) and Wechsler Adult Intelligence Scale score ($r=-0.54$, $p=0.0004$, $n=40$) (32). However these results may have been strongly influenced by 4 PDD subjects with high levels of brain A β and cognitive impairment.

In a DLB-only group, Gomperts et al. (25) found increased A β ligand binding to be associated with lower MMSE ($p<0.001$) scores and worse semantic memory ($p=0.001$). No such association was found in PDD, PD, PD-MCI or controls. Other studies have found no relationship between A β and MMSE (23, 34) or dementia severity measured by CDR (26) in DLB.

One longitudinal study in 46 PD subjects with either MCI or no cognitive impairment found that baseline increased precuneus ^{11}C -PiB binding was related to decline in executive function ($p=0.035$),

weakly related to decline in visuospatial function ($p=0.06$), and associated with a greater likelihood of transition to MCI or dementia ($p=0.035$) (37).

In summary, there is conflicting evidence surrounding the association of amyloid deposition with increased cognitive impairment in LB disorders. Where correlation has been reported, it has generally been modest, and often in samples containing disparate diagnostic groups. Further research is needed to clarify the association of amyloid deposition with cognitive impairment in each of the LB disorders.

Parkinsonism

In DLB and PDD, but not PD, higher relative A β ligand binding in the striatum (adjusted for overall binding) was associated in one study with better motor performance as measured by the UPDRS (DLB: $r=-0.87$, $p=0.01$, $n=8$; PDD: $r=-0.90$, $p=0.005$, $n=7$) (24). Other studies have found no correlation between global cortical (26, 27, 33, 34) or precuneus (25) A β binding and motor impairment. However, these studies did not report specifically assessing relative striatal binding. A longitudinal study found that baseline striatal or precuneus amyloid ligand binding in PD and PD-MCI did not predict future motor deterioration (37).

Hallucinations and visuospatial ability

In the two studies which have reported this, no relationship has been found between mean cortical (26) or occipital (24) A β binding and hallucinations.

In DLB, PDD and PD, but not AD or controls, relative parietal/posterior cingulate (but not occipital) binding was associated with impaired visuoperceptual ability as measured by the Benton visual form discrimination test (24).

Fluctuations

Fluctuations, measured using the Mayo Fluctuations Questionnaire, were not found to be associated with an increased A β ligand binding in DLB or PDD in two studies (26, 27).

RBD

No studies have reported investigating an association between RBD and A β ligand binding.

Disease onset, progression and treatment response

The first study of amyloid PET in DLB found that increased A β binding was correlated with a shorter time between the onset of cognitive impairment and diagnosis of DLB ($r=-0.75$, $p=0.01$, $n=10$), with no such relationship seen in AD (30).

Maetzler et al. (33) found that in a combined DLB and PDD group, A β positive patients had an older age at onset of parkinsonism and dementia and had lower MMSE scores. The authors suggested that this may be an effect of increasing A β with increasing age, or that cortical A β deposition is associated with different disease mechanisms resulting in an older age of onset and more rapid clinical progression.

In a small group of treatment naïve patients, Graff-Radford et al. (38) found that after treatment with acetylcholinesterase inhibitors A β positive patients (n=3) tended to remain stable or decline, whereas A β negative patients (n=4) tended to remain stable or improve.

Relationship with genetics, imaging findings and other biomarkers

An early study found the apolipoprotein E4 (ApoE4) genotype was associated with increased ^{11}C -PiB binding across groups (including relatively large groups of AD and controls) but not within diagnostic groups (30). Similarly, in a large study, Gomperts et al. (25) found that ApoE4 genotype and ^{11}C -PiB binding were correlated across the entire cohort (DLB, PDD, PD-MCI, PD, controls; $r=0.49$, $p<0.0001$). In a study involving DLB, PDD and PD subjects, the A β positive group (all of whom had dementia) were found to have increased rates of the ApoE4 allele and lower CSF A β -42 concentrations compared with A β negative patients (33). These results are consistent with findings in AD subjects, those with MCI and apparently healthy older controls, that the ApoE4 genotype is robustly associated with increased A β binding (39, 40).

In a recent study, Shimada et al. (34) examined the association between ^{11}C -PiB binding and cortical atrophy in a combined PDD/DLB group compared with AD and healthy controls. They found that of 6/15 PDD/DLB patients were ^{11}C -PiB +ve. Compared to ^{11}C -PiB –ve controls (^{11}C -PiB +ve controls were excluded) the ^{11}C -PiB +ve PDD/DLB group demonstrated significant cortical atrophy, particularly in temporal and parietal areas, whereas the ^{11}C -PiB –ve group did not. Using volume of interest analysis, the ^{11}C -PiB +ve PDD/DLB group had lower parahippocampal grey matter volume than ^{11}C -PiB –ve PDD/DLB subjects. There were no differences between the two groups in cognitive tests. Atrophy was not correlated with A β ligand binding in any group. The authors commented that A β deposition in PDD/DLB appeared to be associated with cortical atrophy in a pattern similar to that seen in AD, though the level of atrophy itself was not correlated with amyloid load and likely due to down-stream effects.

Three studies have compared amyloid imaging scans with ^{18}F -FDG PET in Lewy body disorders (26, 29, 35). Two studies in DLB and PDD reported brain hypometabolism (in areas such as the occipital and posterior parietotemporal lobes) in the absence of A β deposition and suggested that the two processes do not appear directly related, similar to the apparent dissociation between structural MR measures of atrophy and PET hypometabolism in DLB (41). One smaller study (n=3), found corresponding hypometabolism and amyloid deposition in several cortical areas (29).

Diagnostic utility

Some studies have investigated the diagnostic value of amyloid imaging in conjunction with other imaging methods. Burke et al. (42) used qualitative assessment of A β and dopamine transporter PET imaging in combination to diagnose patients with AD, DLB or FTD, and compared concordance with clinical diagnosis. The overall agreement was poor ($\kappa=0.39$; CI 0.18-0.61). The best agreement was for the diagnosis of DLB, and subjects were classified as such based solely on positive dopamine transporter PET results.

In a study of 21 DLB and 21 AD patients, a combination of hippocampal volume on structural MRI, cortical A β ligand binding and occipital lobe hypometabolism on PET could differentiate between AD and DLB with an accuracy of 98%, with each imaging technique contributing significantly to the

model used (26). Amyloid PET alone had an area under the receiver operating curve (AUROC) of 0.89 ($p < 0.001$).

Reviewing data from studies that provided data in the form of dot-plots (24, 28, 30), it is clear that even using post-hoc ideal thresholds to differentiate between AD and DLB based on amyloid ligand binding, specificity remains poor 50-71% (as a proportion of DLB cases have raised cortical amyloid), though sensitivity for AD can be up to 97% (as low amyloid in AD is rare).

Ossenkoppele et al. (43) performed ^{11}C -PiB and ^{18}F -FDG PET scans on 154 patients at a specialist memory clinic. Clinicians were asked to make a diagnosis following clinical assessment but before the scans, and to express their certainty in the diagnosis. Following the scan results the diagnosis was reassessed. Clinical diagnosis changed in 23% of cases. Clinicians reported that ^{11}C -PiB PET contributed to the diagnosis in 86% of patients, mostly as a test that may rule out AD.

Reports of post-mortem examination after amyloid PET imaging

The first post-mortem report of a patient with DLB who had had an amyloid PET scan was by Bacsikai et al. (44). They found that amyloid imaging findings corresponded to post-mortem A β levels in brain homogenates measured using enzyme-linked immunosorbent assays. Much of the A β burden on imaging was due to cerebral A β angiopathy.

Burack et al. (45) examined 3 patients with PDD, 2 of whom had extensive cortical ^{11}C -PiB uptake in PET scans before death. Both were found to have abnormal levels of cortical A β (predominantly diffuse plaques) post-mortem. All cortical areas with PET mean cortical binding potential greater than 0.2 had severe plaque burden post-mortem. The case with no raised A β binding had minimal A β plaques but abundant cortical Lewy bodies, suggesting there is no significant binding of ^{11}C -PiB to LBs during amyloid PET scans.

Kantarci et al. (26) reported 3 cases of DLB with ante-mortem amyloid imaging. One had raised cortical ^{11}C -PiB binding (^{11}C -PiB retention ratio >1.6) and two had borderline binding (^{11}C -PiB retention ratio 1.4-1.6). The case with raised ^{11}C -PiB had sparse neuritic plaques but frequent diffuse plaques. The two borderline cases had sparse or moderate neuritic plaques (the level of diffuse plaques was not mentioned).

The case with raised ^{11}C -PiB underwent quantitative comparison of amyloid deposition measured by ^{11}C -PiB PET and post-mortem image analysis of immunostains of corresponding regions (46). There was a strong correlation between ^{11}C -PiB retention (18 months ante-mortem) and post-mortem A β density in the 17 ROIs analysed ($r=0.899$; $p < 0.0001$). Lewy body and tau density did not correlate with ^{11}C -PiB retention.

Ikonomovic et al. (47) examined a case of probable DLB with a negative ^{11}C -PiB PET scan. Although post-mortem examination did identify A β plaques, they were infrequent and primarily diffuse rather than neuritic. The authors commented that the level of amyloid deposition necessary to elicit a positive ^{11}C -PiB PET scan is not yet clear. Post-mortem A β_{42} concentration in brain homogenates correlated with ^{11}C -PiB retention in the ante-mortem PET scan ($r=0.72$, $p=0.009$), corroborating the finding of Kantarci et al. (26) above.

Conclusions

Differences between diagnostic groups

In summary, all Lewy body disorders are generally associated with lower mean cortical A β ligand binding than AD. DLB is usually associated with higher mean cortical A β binding than PDD, PD or controls. There are no significant differences between PDD, PD and controls. When A β is present, the pattern of deposition in LB disorders is similar to that seen in AD, with deposition in frontal, parietal and cingulate areas, along with the striatum. Only one study used an ^{18}F -labelled tracer (Florbetaben) (28), all other studies used ^{11}C -PiB. The pattern of cortical binding with ^{18}F -Florbetaben was almost identical to that of ^{11}C -PiB, though to a slightly lesser degree (28).

Some differences between diagnostic groups only become evident when subjects are classified as A β positive or negative based on a defined threshold. In most studies directly comparing rates of A β positive subjects in each diagnostic group (Table 2), AD had higher rates than DLB, which in turn had higher rates than PDD, which had higher rates than PD or controls. Between PD and controls there was more variability, with controls having higher rates of A β positive subjects in 3 of 5 studies in which they were directly compared. From these findings we can conclude that whilst A β deposition in itself is neither necessary nor sufficient for the development of dementia in LB disorders, the presence of A β is more common in those with dementia, and relatively rare in those without dementia. These findings mirror results from post-mortem studies that have found greater A β deposition in DLB than PDD or PD (11, 12, 48, 49), and higher deposition in PDD than PD (48, 50, 51).

High levels of cortical A β are unusual in PD. Petrou et al. (32) found that most of the small number of patients with A β positive PET scans in a PD cohort identified for being at risk of dementia actually, on closer examination, already had dementia. Similarly, in a post-mortem study of 129 cases of PD, 17 of 20 of patients that had A β plaque pathology rated CERAD (52) grade B or C had dementia (85% v. 54% in the overall group) (53). In another neuropathological study of 200 patients with an initial diagnosis of PD, higher CERAD scores were found almost exclusively in patients who developed dementia (CERAD scores PD: B=3%, C=0%; PDD: B=51%, C=33%) (54).

Diffuse neocortical or limbic Lewy body pathology is generally seen as the main substrate of dementia in LB disorders (3, 51, 55). The findings above suggest that the presence of A β confers a higher risk for the development of dementia in LB disorders. A possible explanation for this is that the combination of cortical A β and Lewy body pathology may have synergistic effects. Some post-mortem studies have found that increased A β is associated with increased α -synuclein levels in the brain in Lewy body disorders and AD (16, 50, 56), although other studies have contradicted this (55, 57)

Interestingly, A β promotes the formation of α -synuclein oligomers and polymers *in vitro* (58). Experiments in transgenic mice expressing human A β , tau and α -synuclein peptides have shown that the presence of A β increases the formation of α -synuclein neuronal inclusions (58) and α -synuclein increases the deposition of both A β and tau (59).

Thus, in LB disorders, the presence of significant A β may lead to a synergistic interaction with α -synuclein, resulting in widespread deposition of α -synuclein and A β , leading to cognitive impairment. This hypothesis may help explain the infrequency of significant A β deposition in PD without cognitive impairment and the increased rates of A β seen in DLB compared with PDD, as DLB

by definition demonstrates dementia (an indicator of widespread neurodegeneration) earlier in the disorder. The apparent synergistic interaction between A β and α -synuclein is a possible target for therapeutic intervention, given our ability to identify the subset of Lewy body disease sufferers with A β deposition using PET imaging.

Relationship of A β to clinical picture

In imaging studies cognitive impairment has correlated positively with A β ligand binding across diagnostic groups (24, 28). This may simply reflect that A β burden is high in AD and DLB and low in PD and controls. More interestingly, A β binding may be correlated with cognitive impairment in Lewy body dementia only-groups (27, 33) and may predict cognitive decline in PD and PD-MCI (37). Some pathological studies support these findings. Patients with a combination of DLB and AD pathology post-mortem have been found to have had worse cognitive function (10), more severe dementia (60) and a faster rate of cognitive decline (61) than those with 'pure' DLB pathology. A correlation between cognitive impairment and A β deposition in PD and PDD groups has been found (48, 50, 62), although this link did not survive regression modelling in some studies (62). Conversely, other studies have found no correlation of MMSE with CERAD score in PD with or without cognitive impairment (55, 63), and AD pathology in PDD has been found not to affect performance on MMSE or other neuropsychological tests (64).

Imaging studies have found suggestive links between increased A β ligand binding and older onset of motor impairment and dementia (33), and a shorter interval between the onset of motor impairment and cognitive impairment (30). There have been various, often contradictory pathological findings about the association of A β deposition with disease onset and progression in LB disorders.

Increased A β burden post-mortem has been associated with older age of onset and shorter survival in DLB, PD and PDD (54); and shorter duration of parkinsonism prior to the onset of dementia in PDD and DLB (11-13, 50, 57). Other studies found no correlation between A β burden age of onset, disease duration and age of death in DLB (10, 57) or PD (56); rate of decline in PD or PDD (55); or the interval between motor and dementia symptoms in PDD (51). Some even found increased A β to be associated with longer disease duration in PD, although with higher dementia scores (62). A large epidemiological study (65) found that the occurrence of dementia in PD was a function of age, and age of onset had no effect above this. Thus, in some studies (12, 50) the shorter duration of parkinsonism before dementia observed in A β positive patients could simply be a function of their older age.

Findings from amyloid imaging studies can drive hypotheses that should then be tested in other imaging studies as well as pathological studies. Similarly, pathological findings (from which most of our current knowledge of the A β in LB disorders derives) will drive hypotheses in future imaging studies. Some other positive findings from these early imaging studies that should be tested in future studies include the links between striatal A β and Parkinsonism; parietal/posterior cingulate A β and visuo-perceptual ability; and A β ligand binding, ApoE genotype and CSF A β -42. Further studies are also needed to corroborate the finding that the other core symptoms of DLB, visual hallucinations and fluctuating cognition, are not related to A β deposition.

Based on current data it is not possible to make any firm conclusions on the influence of A β pathology on disease progression and clinical phenotype in Lewy body disorders. There are a few reasons for this. A β imaging studies have thus far, with two exceptions, been cross sectional rather than longitudinal. Studies vary in image acquisition, processing and analysis; clinical and imaging outcome measures used and cut off points for A β positive and negative cases; recruitment source (i.e. movement disorder or memory clinics); entry criteria for subjects; and processing of results (e.g. the removal of control/PDD subjects with raised amyloid from analysis (23, 31, 34)). Few studies have tested the same hypotheses using comparable outcome measures. Many studies also suffered from low sample sizes, and sub-optimal measures such as the MMSE, which may not be sensitive to cognitive changes in LB disorders. These problems, and a tendency in some studies to report the results of statistical tests without summary data, prevented any quantitative meta-analysis of the results. Large-scale, prospective studies are needed to properly investigate the effect of A β burden on the onset, progression, severity and character of symptoms in LB disorders.

Neuropathological studies suffer from similar inconsistencies (e.g. in the use of grading rather than fully quantitative measures to assess brain pathology). Comparison between imaging and pathological studies is difficult as amyloid PET measures both diffuse and neuritic plaques, as well as amyloid angiopathy, whereas most pathological studies focus solely on neuritic plaques. Although ^{11}C -PiB has higher affinity for neuritic plaques, diffuse plaques account for most of the *in vivo* binding in LB disorders (45, 46).

Some authors have questioned the ability of PET amyloid imaging to adequately quantify amyloid burden, highlighting problems with current PET amyloid imaging technology including partial volume effects and non-specific binding of amyloid radioligands (66).

PET imaging has a relatively low resolution compared with MRI. This results in a relatively large voxel size. Given the thinness of the cerebral cortex, partial volume effects (where a voxel contains signal from both grey and white matter, or grey matter and CSF, for instance) are possible (66). This is further complicated by the presence of significant cortical atrophy in a proportion of subjects with cognitive impairment. Although this problem is by no means unique to PET amyloid imaging, it does raise doubts about the ability of PET imaging to accurately quantify amyloid burden in dementia and highlights the importance of the use of correction measures for partial volume effects (67). Few of the studies reviewed here used such correction measures (Table 1).

Amyloid radioligands, particularly ^{18}F -labelled ligands, have high non-specific white-matter binding (17). Studies comparing PiB binding (*in vitro* and *in vivo*) with amyloid burden measured by immunohistochemistry have demonstrated that PiB does not give a direct quantitative measure of cortical amyloid burden (44, 68). Similarly, a study comparing *in vivo* PiB binding with amyloid burden post-mortem found cases where the precuneus was observed to have the highest PiB retention, despite other brain areas having markedly greater amyloid burden quantified by stereological assessment (69). It should be noted that, despite this, there was a strong correlation between ^{11}C -PiB binding and post-mortem amyloid burden in the precuneus, anterior cingulate and posterior cingulate, though not the hippocampus or orbitofrontal cortex (69). Thus, although ligand retention and amyloid burden are correlated in different brain areas within one subject (46) and between subjects (19, 69), amyloid PET cannot be said to precisely quantify amyloid burden in each particular brain area. These issues should be borne in mind when interpreting and discussing amyloid PET findings.

Clinical use and diagnostic utility

The large variability in A β binding found in DLB and PDD limits the use of A β imaging in isolation in the diagnosis of dementia. However, it may improve accuracy when used in conjunction with other biomarkers such as structural MRI and FDG-PET (26). A β imaging has negative predictive value in the diagnosis of AD, positive predictive value for the development of dementia in MCI and clinicians find it of use in the diagnosis of dementia, particularly where diagnostic confidence is low (43, 70). Given that A β deposition is uncommon in PD compared with PDD, amyloid imaging in PD may be useful to identify cognitively normal or sub-syndromal patients who will later go on to develop dementia. This test may be expected to have a high positive predictive value but a low sensitivity, given the frequent occurrence of PDD in the absence of significant A β pathology. In one study, 2/3 PD subjects with a high amyloid ligand binding later developed MCI (37). Further prospective studies are required to investigate this.

Neuropathological studies have found that NFT pathology in DLB may be associated with a clinical picture more similar to AD than classical DLB (57, 71). The degree to which high A β binding is also associated with a less classical DLB clinical phenotype is of interest; such patients may have a different prognosis, different levels of neuroleptic sensitivity and a different response to treatment. There is a relative paucity of NFT pathology in LB disorders (63), but when present it is a reliable correlate of dementia (51, 54). Although no imaging ligands for tau are yet available, there are imaging correlates of tau pathology. Brain atrophy on MRI, particularly in the medial temporal lobe has been found to be associated with post-mortem tau pathology, measured quantitatively with tau antibody and image analysis or semi-quantitatively using Braak NFT staging (72-74). A recent study has found brain atrophy in amyloid positive, but not amyloid negative PDD/DLB subjects (34), despite this, atrophy was not correlated with PiB binding. This may be because atrophy is the result of downstream effects, either of tau, α -synuclein, a combination of both, or another factor. A combination of amyloid imaging and MRI measures of atrophy (as a surrogate measure of tau pathology) may be important in any study wishing to investigate the influence of AD pathology in LB disorders.

To conclude, amyloid imaging studies have demonstrated that significant A β deposition is present in a proportion of DLB and PDD patients. Significant A β deposition appears to be relatively rare in PD. Dementia often occurs in the absence of A β , but there is some evidence that amyloid may be related to the onset or progression of cognitive symptoms in these disorders, though current results are not conclusive. Large scale, prospective amyloid imaging studies may resolve some of these unanswered questions and clarify the importance of A β in LB disorder

Table 1. Summary of PET amyloid imaging studies excluding neuropathological case studies

Study	Population	Source	Scans, ligand	Amyloid PET acquisition and image analysis	Regions reported	Major findings
Rowe et al. 2007 (30)	10 DLB 17 AD 9 MCI 6 FTD 27 HC	AD/DLB: memory disorders and neurobehavioural clinics. Controls: from a separate longitudinal study known to have normal cognitive function.	MRI ¹¹ C-PiB PET	90 min acquisition. ROI ¹¹ C-PiB DVR v. cerebellum. Logan graphical analysis method.	16 cortical and subcortical areas including overall cortex.	PiB burden AD>DLB>HC. PiB burden correlated with shorter time from onset of symptoms to diagnosis in DLB. ApoE4 genotype linked to Aβ burden across groups.
Edison et al. 2008* (23)	13 DLB* 12 PDD 10 PD 41 HC	Multicentre study (UK, Finland, Australia).	MRI ¹¹ C-PiB PET	60-90 min ¹¹ C-PiB uptake ratio; ROI v. cerebellum. Voxel based comparison with threshold p<0.001.	6 cortical areas, striatum, thalamus and whole cortex.	DLB more likely to show raised Aβ burden compared with PDD or PD.
Gomperts et al. 2008 (24)	8 DLB 7 PDD 11 PD 15 AD 37 HC	Movement and memory units. AD and HC collected separately in another longitudinal study.	¹¹ C-PiB PET	60 min DVR v cerebellum. Logan graphical analysis method.	6 cortical areas, striatum, whole cortex.	PiB binding DLB>PDD/PD/HC. PiB binding in DLB comparable to AD. In LBD (DLB+PDD) relative striatal binding was associated with improved performance on UPDRS.
Johansson et al. 2008 (36)	5 PD 16 AD 6 HC	AD and HC from previous study. PD: not stated.	¹¹ C-PiB PET ¹¹ C-L-DOPA PET	40-60 min regional uptake volume of interest v. cerebellum.	5 cortical areas, subcortical white matter, pons, striatum.	PiB retention was greater in AD than PD in all cortical areas and striatum. Lower in PD than control in frontal, parietal and cingulate areas.
Maetzler et al. 2008 (31)	10 PDD 6 AD 11 HC	Not stated	¹¹ C-PiB PET	42-72 min ROI SUVR v. cerebellum.	Frontal cortex, posterior cingulate, striatum, thalamus, brainstem, cerebellum, white matter	2/10 PDD had 'AD-like' pattern of amyloid deposition. Brainstem:posteriorcingulate DVR: PDD>control, AD, 'AD-like' PD.
Maetzler et al. 2009 (33)	9 DLB 12 PDD 14 PD	Ward/OP dept. in Neurodegenerative Dept. of a University Hospital	¹¹ C-PiB PET	42-72 min ROI SUVR v. cerebellum.	5 cortical areas, whole cortex, striatum	PiB +ve patients had lower CSF Aβ ₄₂ , higher ApoE4 allele rate, all had dementia. Within dementia, PiB +ve had lower MMSE scores.
Jokinen et al. 2010 (35)	11 PDD 8 PD 24 HC	University Hospital	¹¹ C-PiB PET ¹⁸ F-FDG PET MRI	60-90min ¹¹ C-PiB uptake ROI v. cerebellum.	5 cortical areas, caudate, putamen	No significant difference between groups in any cortical area. PDD more likely to show 1+ cortical areas with increased PiB uptake.
Foster et al. 2010 (27)	6 DLB 15 PDD 9 PD-MCI 8 PD 9 HC	Movement disorders centre	¹¹ C-PiB PET MRI	60 min dynamic scan. Binding potentials of ROIs and MCBP. Logan graphical analysis, cerebellum as reference.	5 cortical areas, caudate, mean cortex	No differences in MCBP or regional BPs between groups. Correlation between caudate BP/MCBP and MMSE in some groups.
Burke et al. 2011 (42)	14 DLB 36 AD 25 FTD	Cognitive disorders clinic	¹¹ C-PiB PET ¹¹ C-DTBZ PET	80 min scan. ROI DVR v. cerebellum. Subjective visual assessment.	Frontal cortex : white matter DVR ratio	Only moderate concordance between clinical diagnosis and diagnosis based on scan results.

Claasen et al. 2011 (29)	3 DLB 3 MSA 12 HC	Neurology clinic	¹¹ C-PIB PET ¹⁸ F-FDG PET MRI	40-60 min acquisition. ROI v. cerebellum.	7 cortical areas and caudate.	Higher binding found in DLB in all areas. Most marked in prefrontal, parietal, temporal and precuneus.
Villemagne et al. 2011 (28)	7 DLB 5 PD 30 AD 20 MCI 11 FTD 4 VaD 32 HC	Memory disorders service, movement disorders clinics	¹⁸ F-Florbetaben PET MRI	90-110 min acquisition. ROI SUVR v. cerebellar cortex	9 cortical areas, total cortex, 6 non-cortical areas.	AD and MCI had higher neocortical and striatal binding than controls. No other significant differences between groups.
Gomperts et al. 2012 (25)	18 DLB 12 PDD 14 PD-MCI 29 PD 85 HC	Movement disorders and memory disorders units. HCS from separate study.	¹¹ C-PIB PET	60 min dynamic acquisition. Logan graphical analysis method. ROI DVR v. cerebellum. SPM analysis corrected for multiple comparisons (false discovery rate).	Precuneus Voxel-wise comparison	DLB exhibited higher binding than other groups, particularly in frontal and parietal areas. No differences found between non-DLB groups. PiB burden increased in ApoE4 genotype across entire cohort. In DLB increased PiB binding was associated with decreased MMSE score and poorer semantic memory.
Graff-Radford et al. 2012 (38)	7 DLB (of 54 DLB)	AD research centre (retrospective study of pts. involved in longitudinal study)	¹¹ C-PIB PET MRI	40-60 min. ROI v. cerebellum. Partial volume correction.	Global cortical retention.	Both subjects who declined were PiB +ve; all 3 subjects who improved were PiB -ve.
Kantarci et al. 2012 (26)	21 DLB 21 AD 42 HC	DLB recruited from AD research centre. AD and HC from a longitudinal cohort.	¹¹ C-PIB PET ¹⁸ F-FDG PET MRI	40-60 min acquisition. ROI v. cerebellum. Voxel based comparison using FWE correction. Partial volume correction.	Global cortical retention Voxel-wise comparison	DLB PiB binding was significantly lower than AD but significantly higher than controls. No relationship found between global PiB and motor impairment, dementia rating, visual hallucinations or duration of symptoms.
Petrou et al. 2012 (32)	40 PD at risk for dementia	University based movement disorders subspecialty clinic	¹¹ C-PIB PET ¹¹ C-DTBZ PET MRI	80 min acquisition. Logan graphical analysis method. DVR v. cerebellum.	Mean cortical PiB DVR. Visual assessment.	Cortical PiB was inversely correlated with overall cognitive score and WAIS score.
Ossenkoppele et al. 2012 (43)	66 AD 30 MCI 15 SMC 18 FTD 5 DLB 20 other	Specialist memory disorder clinic. Patients mostly attending for second/third opinion.	¹¹ C-PIB PET ¹⁸ F-FDG PET MRI	90 min dynamic scan. ROI BP v. cerebellum. For 12 patients 60-90 min SUVR ROI v cerebellum.	Visual assessment.	¹¹ C-PIB PET contributed to diagnostic process in 86% of patients, mainly used to rule out AD.

Shimada et al. 2012 (34)	8 DLB 7 PDD 13 AD 22 HC	Not stated	¹¹ C-PiB PET MRI	90 min dynamic scan. Logan graphical analysis method. VOI DVR v. cerebellum.	Mean cortical PiB DVR. 4 cortical areas.	PiB positive LBD subjects demonstrated cortical atrophy compared with HC; greater atrophy in parahippocampal regions than PiB –ve LBD subjects.
Gomperts et al. 2013 (37)	35 PD 11 PD-MCI	Not stated	¹¹ C-PiB PET	60 min dynamic scan. Logan graphical analysis method. DVR v. cerebellum.	Precuneus, frontal cortex and striatum.	Higher PiB retention at baseline associated with progression to MCI or dementia and with deterioration in executive function. Motor deterioration not linked to baseline striatal or precuneus amyloid burden.

*Includes 10 DLB patients from Rowe et al. (30).

DLB = dementia with Lewy bodies; PD(D) = Parkinson's disease (dementia); AD = Alzheimer's disease; MSA = multisystem atrophy; FTD = frontotemporal dementia; VaD = vascular dementia; MCI = mild cognitive impairment; HC = healthy controls; SMC = subjective memory complaint.

PET = positron emission tomography; MRI = magnetic resonance imaging; PiB = Pittsburgh compound B; DTBZ = dihydrotetrabenazine; FDG = fluorodeoxyglucose; ROI = region of interest; SUVR = standardised uptake value ratio; MCBP = mean cortical binding potential; DVR = distribution volume ratio; SPM = statistical parametric mapping; FWE = family-wise error.

Table 2. Cortical amyloid burden classification (positive or negative) by diagnostic group

Study	DLB		PDD		PD		PD-MCI		AD		Control		Method of classification
	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	
Edison et al. 2008* (23)	11	2	2	10	0	10	-	-	-	-	6*	41	PiB uptake ratio >2SD above control mean in 1 or more cortical regions
Gomperts et al. 2008 (24)	7	1	7	0	7	4	-	-	15	0	19	18	DVR >1.3 in 50+ cortical voxels
Maetzler et al. 2008 (31)	-	-	2	8	-	-	-	-	6	6	0	11	Visual inspection
Maetzler et al. 2009 (33)	4	5	4	8	0	14	-	-	-	-	-	-	SUVr >1.45/<1.38
Jokinen et al. 2010 (35)	-	-	3	8	0	8	-	-	-	-	2	22	Cortical SUVr >1.5 in 1 or more cortical regions
Foster et al. 2010 (27)	2	4	4	11	1	7	1	8	-	-	1	8	MCBP $\geq$ 0.2
Villemagne et al. 2011 (28)	2	5	-	-	0	5	-	-	29	1	5	27	SUVr >1.4
Graff-Radford et al. 2012 (38)	3	4	-	-	-	-	-	-	-	-	-	-	Global cortical PiB retention ratio >1.5
Kantarci et al. 2012 (26)	11	10	-	-	-	-	-	-	19	2	9	33	Global cortical PiB retention ratio >1.5
Petrou et al. 2012 (32)	-	-	4	1	0	5	2	28	-	-	-	-	Visual inspection
Ossenkoppele et al. 2012* (43)	4	1	-	-	-	-	-	-	40	26	-	-	Visual inspection
Shimada et al. 2012 (34)	4	4	2	5	-	-	-	-	13	0	5*	17	DVR >2 SD above HC mean in one or more cortical region.
Total	48	36	28	51	8	53	3	36	122	35	47	177	
% +ve	57		35		13		8		78		21		

*Includes control subjects that were excluded from analysis because of high cortical A β ligand binding

PiB=Pittsburgh compound-B; DVR=distribution volume ratio; MCBP=mean cortical binding potential; SUVr=standard uptake volume ratio

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