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Amyloid-β deposition and regional grey matter atrophy rates in dementia with Lewy bodies

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Alzheimer's disease pathology frequently coexists with Lewy body disease at autopsy in patients with probable dementia with Lewy bodies. More than half of patients with probable dementia with Lewy bodies have high amyloid-β deposition as measured with ^{11}C-Pittsburgh compound B binding on positron emission tomography. Biomarkers of amyloid-β deposition precede neurodegeneration on magnetic resonance imaging during the progression of Alzheimer's disease, but little is known about how amyloid-β deposition relates to longitudinal progression of atrophy in patients with probable dementia with Lewy bodies. We investigated the associations between baseline ^{11}C-Pittsburgh compound B binding on positron emission tomography and the longitudinal rates of grey matter atrophy in a cohort of clinically diagnosed patients with dementia with Lewy bodies (n = 20), who were consecutively recruited to the Mayo Clinic Alzheimer's Disease Research Centre. All patients underwent ^{11}C-Pittsburgh compound B positron emission tomography and magnetic resonance imaging examinations at baseline. Follow-up magnetic resonance imaging was performed after a mean (standard deviation) interval of 2.5 (1.1) years. Regional grey matter loss was determined on three-dimensional T$_1$-weighted magnetic resonance imaging with the tensor-based morphometry-symmetric normalization technique. Linear regression was performed between baseline ^{11}C-Pittsburgh compound B standard unit value ratio and longitudinal change in regional grey matter volumes from an in-house modified atlas. We identified significant associations between greater baseline ^{11}C-Pittsburgh compound B standard unit value ratio and greater grey matter loss over time in the posterior cingulate gyrus, lateral and medial temporal lobe, and occipital lobe as well as caudate and putamen nuclei, after adjusting for age (P < 0.05). Greater baseline ^{11}C-Pittsburgh compound B standard unit value ratio was also associated with greater ventricular expansion rates (P < 0.01) and greater worsening over time in Clinical Dementia Rating Scale, sum of boxes (P = 0.02). In conclusion, in patients with probable dementia with Lewy bodies, higher amyloid-β deposition at baseline is predictive of faster neurodegeneration in the cortex and also in the striatum. This distribution is suggestive of possible interactions among amyloid-β, tau and α-synuclein aggregates, which needs further investigation. Furthermore, higher amyloid-β deposition at baseline predicts a faster clinical decline over time in patients with probable dementia with Lewy bodies.

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Introduction

Dementia with Lewy bodies (DLB) represents the second most common neurodegenerative form of dementia in the elderly, and is prevalent in up to 30% of all dementia cases in the community (Zaccai et al., 2005). The aggregation of aberrant α-synuclein in Lewy bodies and in Lewy neurites is the pathological hallmark of DLB, but it often coexists with the presence of Alzheimer's disease pathology at autopsy in the form of both tau neurofibrillary tangles and amyloid-β neuritic plaques (McKeith et al., 2005; Schneider et al., 2007). Little is known about how the evolution of Alzheimer's disease-pathology relates to α-synuclein formation (Wolozin and Behl, 2000; Harding and Halliday, 2001) and the temporal sequencing of Alzheimer's disease-related biomarkers in patients with DLB, many of whom will have pathologic and biomarker characteristics of Alzheimer's disease.

In the Lewy bodies disease spectrum of disorders, autopsy studies highlighted that co-occurrence of amyloid-β plaques and phosphorylated tau together with α-synuclein deposition are associated with greater cognitive decline (Kraybill et al., 2005; Nelson et al., 2009; Ferman et al., 2015; Howlett et al., 2015), and shorter survival (Kotzbauer et al., 2012; Graff-Radford et al., 2015) .

Amyloid PET labelling tracer ^{11}C-Pittsburgh compound B (PiB) is an in vivo biomarker of amyloid-β deposition in DLB (Fodero-Tavoletti et al., 2007; Burack et al., 2010; Driscoll et al., 2012; Kantarci et al., 2012c). Meta-analysis from multiple cohorts indicates that 68% of patients with probable DLB have abnormal PiB retention (Petrou et al., 2015). PiB retention is on average higher in patients with DLB than Parkinson's disease and Parkinson's disease dementia (Gomperts et al., 2008, 2012), but lower than patients with Alzheimer's disease (Kantarci et al., 2012b; Catafau and Bullich, 2015). Furthermore, PiB retention has been shown to be associated with older age, higher prevalence of APOE ε4 carriers (Maetzler et al., 2009), impaired cognitive performance (Gomperts et al., 2008, 2012; Maetzler et al., 2009) and lower PET glucose metabolism (Claassen et al., 2011) in patients with DLB.

Villemagne et al. (2011) suggested that greater amyloid-β deposition on PET is associated with a faster development of diagnostic clinical features after the onset of cognitive impairment in patients with DLB.

Atrophy in the limbic, temporal and parietal association cortices on structural MRI is a marker of neurodegeneration associated with tau neurofibrillary tangle pathology of Alzheimer's disease and DLB (Jack et al., 2004; Burton et al., 2009; Murray et al., 2013). In several studies, patients with probable DLB showed an Alzheimer's disease-like pattern of atrophy (Whitwell et al., 2007b; Sabattoli et al., 2008; Zhong et al., 2014) while autopsy confirmation later showed that the presence of tau neurofibrillary tangles and their Braak stage (Braak and Braak, 1991) of Alzheimer's disease primarily explained the cross-sectional (Burton et al., 2009; Kantarci et al., 2012a; Murray et al., 2013) and longitudinal (Nedelska et al., 2015) atrophy observed in the medial temporal structures.

Amyloid imaging with PiB retention and its relation to atrophy on MRI has been widely studied in Alzheimer's disease dementia (Archer et al., 2006; Jack et al., 2009; Chetelat et al., 2010), amnestic mild cognitive impairment and preclinical Alzheimer's disease (Andrews et al., 2013; Knopman et al., 2013; Petersen et al., 2013, 2016; Whitwell et al., 2013; Jack et al., 2014; Araque Caballero et al., 2015). Patients with probable DLB and Parkinson's disease dementia with high PiB retention have an Alzheimer's disease-like pattern of atrophy (Shimada et al., 2013) but longitudinal imaging studies investigating whether amyloid-β deposition influences rate of atrophy in patients with probable DLB are lacking.

The aim of this study is therefore to determine whether higher amyloid-β deposition at baseline measured by PiB-PET is associated with increased rates of atrophy in the limbic, neocortical regions and subcortical grey matter nuclei on MRI in patients with probable DLB. To pursue these goals, we analysed the longitudinal rates of atrophy on MRI in cortical and subcortical grey matter, with a customized atlas subdivision, which includes regions of interest involved in the pathophysiology of DLB and/or Alzheimer's disease such as basal ganglia, posterior cingulate gyrus and medial temporal lobe, temporal, occipital,

parietal and frontal neocortex (Minoshima *et al.*, 2001; Whitwell *et al.*, 2007*b*; Burton *et al.*, 2009; Teune *et al.*, 2010; Zhong *et al.*, 2014; McCleery *et al.*, 2015; Nedelska *et al.*, 2015; Mak *et al.*, 2016). Furthermore, we investigated whether amyloid-β deposition at baseline is associated with a faster cognitive and functional decline in patients with probable DLB.

Materials and methods

Subjects

Between November 2007 and August 2013, consecutive patients with a clinical diagnosis of probable DLB (*n* = 22) according to the Third Consortium Criteria for DLB (McKeith *et al.*, 2005) were recruited to the Mayo Clinic Alzheimer's disease Research Centre. Each patient underwent a baseline structural MRI and PiB-PET scans, and was followed longitudinally until a follow-up structural MRI scan was performed between 1 to 5 years from the baseline. Patients who had poor MRI scan quality for analysis at one of the time points were excluded (*n* = 2).

The diagnosis of probable DLB was made after a comprehensive neurological and neuropsychological evaluation, and confirmed in the setting of a consensus meeting composed of behavioural neurologists, neuropsychologists, and nurses who evaluated the patient. Standardized measures of cognitive and functional performance at baseline such as Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Scale, Sum of Boxes (CDR-SOB) were collected. Furthermore, the clinical characteristics of DLB at baseline were collected as follows: presence of parkinsonism was recorded, and the degree of extrapyramidal motor impairment was assessed through the Unified Parkinson's Disease Rating Scale part III (UPDRS-III); visual hallucinations were characterized by being fully formed, not restricted to a single episode and not related to another medical issue, treatment or advanced dementia; the fluctuations were considered to be present if they scored 3 to 4 on the Mayo Fluctuations Questionnaire (Ferman *et al.*, 2004); and probable rapid eye movement (REM) sleep behaviour disorder was defined as previously published (Boeve *et al.*, 2011). Data concerning acetylcholinesterase inhibitor (AChEI), atypical neuroleptics and dopaminergic treatments during the study period were collected by a neurology resident (L.S.) from each patient's chart, and further reviewed by a behavioural neurologist (J.G.R.). The daily dose of dopaminergic agents was expressed as levodopa equivalent dose (Tomlinson *et al.*, 2010).

Patients were excluded from this study if they had: a history of traumatic brain injury, hydrocephalus, or intracranial mass; neurological and psychiatric diseases other than probable DLB, history of chemotherapy, head radiation therapy or substance abuse. Patients were not excluded if they had a history of cerebrovascular disease, and none of them developed major cerebrovascular lesions during the study period.

The Mayo Clinic Institutional Review Board approved this study. All subjects provided written informed consent before participating in any research activity.

MRI acquisition

MRI examinations were performed at 3 T (GE Healthcare). A 3D high resolution magnetization prepared rapid gradient echo (MPRAGE) acquisition with repetition time/echo time/inversion time of 7/3/900 ms; flip angle of 8°; ~1 mm cubed resolution was performed for anatomical segmentation and labelling.

^{11}C-Pittsburgh compound B-PET acquisitions

A PET/CT scanner (DRX; GE Healthcare) operating in 3D mode was used to acquire PET images. A CT image was obtained for attenuation correction. Subjects were injected with PiB (mean, 596 MBq; range, 292–729 MBq). Following a 40-min PiB uptake period, a 20-min PiB scan consisting of four 5-min dynamic frames was obtained.

Structural MRI analysis

Regional grey matter loss across the entire brain was estimated with an automated, in-house developed implementation of tensor-based morphometry using symmetric diffeomorphic normalization (TBM-SyN) (Cash *et al.*, 2015). This method uses the symmetric diffeomorphic registration between serial MRIs (Avants *et al.*, 2008) to compute mappings between each subject's pair of serial preprocessed T$_1$-weighted MRI scans. The annualized log determinants of the Jacobians of these deformations were averaged within each cortical region of interest across both hemispheres, and assessed within the group in study (Cash *et al.*, 2015). Magnitude of atrophy rates from an Automated Anatomical Labelling atlas (Tzourio-Mazoyer *et al.*, 2002), customized and modified in-house to fit our template (Vemuri *et al.*, 2008) were applied to the annualized log Jacobian images. An additional region of interest to label the ventricles was created.

^{11}C-Pittsburgh compound B-PET image analysis

PiB-PET methods of analysis are consistent to what has been described in a previous study in probable DLB (Kantarci *et al.*, 2012*b*). Cerebellar uptake was used as an internal reference region of interest for PiB-PET uptake normalization. The global PiB retention standard uptake value ratio (SUVR) was obtained from the bilateral parietal (including posterior cingulate and precuneus), temporal, prefrontal, orbitofrontal, and anterior cingulate regions as previously described (Jack *et al.*, 2008; Lowe *et al.*, 2009).

Statistical analysis

All subjects were required to have data from two imaging visits that passed the quality control—one baseline scan plus one follow-up scan. We averaged regional atrophy rates from the in-house modified Automated Anatomical Labelling atlas to derive atrophy rates in 10 grey matter regions of interest plus the ventricles. Derived grey matter regions of interest included the following: posterior cingulate gyrus, medial temporal, temporal (excluding medial temporal), occipital, parietal

(excluding posterior cingulate gyrus) and frontal lobes, as well as putamen, caudate, pallidum and thalamus nuclei. We used separate linear regression models of global PiB SUVR at baseline on annualized log Jacobian, adjusting for age at baseline, to assess the relationship between global PiB SUVR and the rate of change in grey matter in each region of interest. Annualized log Jacobian $\times 100$ was used as an estimate of the annual per cent change in grey matter volume. The same was repeated to assess the relationship between global PiB SUVR and the rate of change in ventricular volume. To assess associations between baseline global PiB SUVR and annual per cent change in cognitive and functional measures such as MMSE and CDR-SOB, we first obtained annual per cent change by performing a linear regression on log of cognition for each subject using age as on the time scale. We used the transformation $100 \times [\exp(\text{slope}) - 1]$, which allows us to interpret the slope as an approximate annual percentage change. The next step was to calculate the Spearman rank correlations and associated P-values between annual percentage change in cognition and baseline global PiB SUVR. We fit a linear regression between annual percentage change in cognition and baseline global PiB SUVR to estimate the annualized change in cognition for a 1-unit decrease in PiB. To assess the relationship between baseline cognition and baseline PiB, as well as between change in cognition and change in grey matter volume, we again used Spearman's rank correlations and associated P-values. Analyses were performed using statistical software R v3.1.1.

Results

Subjects characteristics

Table 1 summarizes the characteristics of the 20 patients with probable DLB included in this study. Our sample had a mean baseline age of 70 years with a low frequency of females (15%), and a high frequency of visual hallucinations (80%), fluctuations (85%), parkinsonism (95%) and probable REM sleep behaviour disorder (95%). At baseline, mean MMSE score was 22 in our sample, while mean CDR-SOB was 4.0. APOE ε4 allele carrier frequency of was 40%. Average global PiB SUVR at baseline was 1.53.

The average time interval between the baseline and follow-up MRI scans was 2.5 years. During this period, all of the participants were exposed to AChEI treatment. In particular, 90% of the patients with DLB ($n = 18$) were continuously treated with AChEI for the whole study duration, while one subject (5%) who was only on dopaminergic therapy at baseline, was introduced to AChEI therapy during the inter-scan interval and remained on this therapeutic regimen without further discontinuations. Another subject (5%), who was on AChEI therapy at baseline, suspended treatment before the follow-up scan and started a dopaminergic therapy. Neither of the two abovementioned subjects behaved as outlier in the clinical or imaging data. Furthermore, 75% of patients with DLB ($n = 15$) were on dopaminergic therapy during the study period. Five of them

(25% of the sample) were not on dopaminergic drugs at baseline and initiated this therapy during the interscan interval. None of the patients suspended the dopaminergic therapy during the interscan interval. In our sample, the levodopa equivalent dose range at baseline was 180–800 mg, while the levodopa equivalent dose range at follow up was 180–1000 mg. Atypical neuroleptic drugs were administered to six (30%) patients during the study period (Table 1).

Baseline ^{11}C-Pittsburgh compound B-PET retention and rate of grey matter atrophy

After adjusting for age, an association between higher global PiB SUVR at baseline and greater decline in grey matter volume expressed as annualized log Jacobian percentage was found in the following cortical regions of interest: the posterior cingulate gyrus ($P = 0.02$), medial temporal lobe ($P = 0.01$) and temporal lobe (this region excludes the medial temporal region; $P < 0.05$), and occipital lobe ($P = 0.02$) but not the frontal ($P = 0.17$) nor parietal lobes (this region excludes the posterior cingulate gyrus; $P = 0.78$). A similar association of higher global PiB SUVR at baseline and higher grey matter atrophy rates was present also in subcortical grey matter regions such as the caudate ($P < 0.01$) and putamen ($P < 0.01$) nuclei but not in the globus pallidus ($P = 0.92$) or thalamus ($P = 0.20$) (Table 2). A graphical representation of these

Table I Demographic and clinical characteristics of patients with probable DLB at baseline

	Mean (SD) or count (%)
DLB included, n	20
Females, n (%)	3 (15)
Age at baseline MRI, years	70 (7.5)
Time between MRI scans, years	2.5 (1.14)
Education, years	15 (3.3)
APOE ε4 carriers, n (%)	8 (40)
CDR-SOB score	4.0 (1.6)
MMSE	22 (5)
UPDRS-III	9 (5)
Visual hallucinations, n (%)	16 (80)
Fluctuations, n (%)	17 (85)
Parkinsonism, n (%)	19 (95)
Probable RBD, n (%)	19 (95)
PiB ratio at baseline	1.53 (0.35)
Treatment with dopaminergic agent only, n (%)	1 (5)
Treatment with AChEI, n (%)	19 (95)
AChEI only, n (%)	10 (50)
AChEI + dopaminergic agent, n (%)	9 (45)
Treatment with atypical neuroleptics, n (%)	6 (30)

SD = standard deviation.

Table 2 Relationship between regional annualized log Jacobian and global PiB SUVR, controlling for age

	PiB SUVR estimate (SE)[a]	PiB SUVR P-value
Cortical grey matter regions		
Posterior cingulate gyrus	−0.0190 (0.008)	**0.023**
Medial temporal lobe	−0.0218 (0.008)	**0.012**
Occipital lobe	−0.0128 (0.005)	**0.016**
Temporal lobe	−0.0151 (0.007)	**0.047**
Frontal lobe	−0.0063 (0.004)	0.166
Parietal lobe	−0.0024 (0.009)	0.783
Subcortical grey matter regions		
Caudate	−0.0260 (0.008)	**0.007**
Putamen	−0.0189 (0.006)	**0.009**
Globus pallidus	0.0019 (0.018)	0.917
Thalamus	−0.0109 (0.008)	0.196
Ventricles	0.0487 (0.016)	**0.007**

SE = standard error.

[a]Estimate of the change in annualized log Jacobian for a 1-unit increase in PiB SUVR. We multiply by 100 to get approximate per cent change.

Annualized log Jacobian estimates × 100 can be interpreted as annualized percentage change in grey matter volume. Values in bold indicate $P < 0.05$.

associations is shown in Fig. 1. Removing the outliers for each analysis had an influence on the estimated effect by less than 1 standard error. Furthermore, an association between higher PiB retention at baseline and greater annual per cent increase in ventricular volume was observed ($P < 0.01$; Fig. 2). Figure 3 shows four patients with DLB who exemplify TBM-SyN findings of patients with high and low PiB retentions at different ages.

Baseline ^{11}C-Pittsburgh compound B-PET retention and global cognitive and functional measures

Higher PiB retention at baseline was not associated with MMSE (rho = −0.4, $P = 0.08$) or CDR-SOB (rho = −0.09, $P = 0.71$) scores at baseline. However, a correlation was found between higher global PiB retention at baseline and the annual per cent increase (i.e. worsening) in CDR-SOB scores (rho = 0.51; $P = 0.02$). No correlation was found between global PiB retention at baseline and MMSE (rho = −0.26; $P = 0.29$; data were missing at the second time point in one subject) annual per cent of change.

Brain atrophy rates and change in global cognitive and functional measures

Greater annual per cent of ventricles volume increase was associated with greater annual per cent increase (i.e. worsening) in CDR-SOB (rho = 0.54; $P = 0.01$). On the other hand, no correlation was found between the brain atrophy rates and annual changes in MMSE.

Discussion

In this study, higher PiB retention at baseline was associated with greater grey matter loss over time in regions such as the posterior cingulate gyrus, temporal lobe, occipital lobe and striatum, and with greater ventricular expansion over time. Furthermore, higher global PiB retention at baseline correlated with greater decline in CDR-SOB in patients with probable DLB.

Evidence from *in vivo* studies tracking biomarker trajectories during the progression of Alzheimer's disease supports the hypothesis that amyloid-β deposition on PET precedes atrophy on MRI (Jack *et al.*, 2013, 2016; Knopman *et al.*, 2013; Villemagne *et al.*, 2013). Assuming that Alzheimer's disease-related biomarkers would follow a similar trajectory in DLB, this study was designed to investigate the relationship between baseline PiB retention and atrophy progression on MRI in patients with a clinical diagnosis of probable DLB. Longitudinal MRI studies in patients with a spectrum of Alzheimer's disease and Lewy body disease pathologies at autopsy indicate that ante-mortem atrophy rates in the limbic and association neocortices (Nedelska *et al.*, 2015), as well as ventricular expansion rates (Whitwell *et al.*, 2007a; Nedelska *et al.*, 2015) are primarily driven by Alzheimer's disease pathology. Furthermore, longitudinal studies indicate that global atrophy (Mak *et al.*, 2015a) and cortical thinning rates (Mak *et al.*, 2015b) in patients with clinically diagnosed probable DLB are lower than patients with Alzheimer's disease dementia and not different from controls. These observations, along with our findings, suggest that patients with probable DLB, who have additional amyloid-β deposition, develop higher rates of ventricular expansion and higher rates of brain atrophy, with an Alzheimer's disease-like pattern.

Congruent with this interpretation, a cross-sectional analysis demonstrated that in patients within the Lewy body disease spectrum (probable DLB and Parkinson's disease dementia) with high PiB retention ($n = 6$), the pattern of atrophy overlapped with that observed in patients with Alzheimer's disease dementia ($n = 13$) by more than 95%, whereas patients with low PiB retention ($n = 9$) showed no cortical atrophy compared to cognitively normal and Alzheimer's disease subjects (Shimada *et al.*, 2013). Despite the small sample size and a cross-sectional design, the findings are consistent with the current study that there is an association between higher PiB retention at baseline and increased rates of cortical atrophy. Several longitudinal studies in non-demented older adults also support our finding that higher PiB retention at baseline is associated with greater atrophy rates (Chetelat *et al.*, 2012; Andrews *et al.*, 2013; Dore *et al.*, 2013; Araque Caballero *et al.*, 2015; Petersen *et al.*, 2016).

In addition to the higher rates of atrophy in the cortex, we also identified an association between higher PiB retention at baseline, and higher rates of atrophy in the striatum,
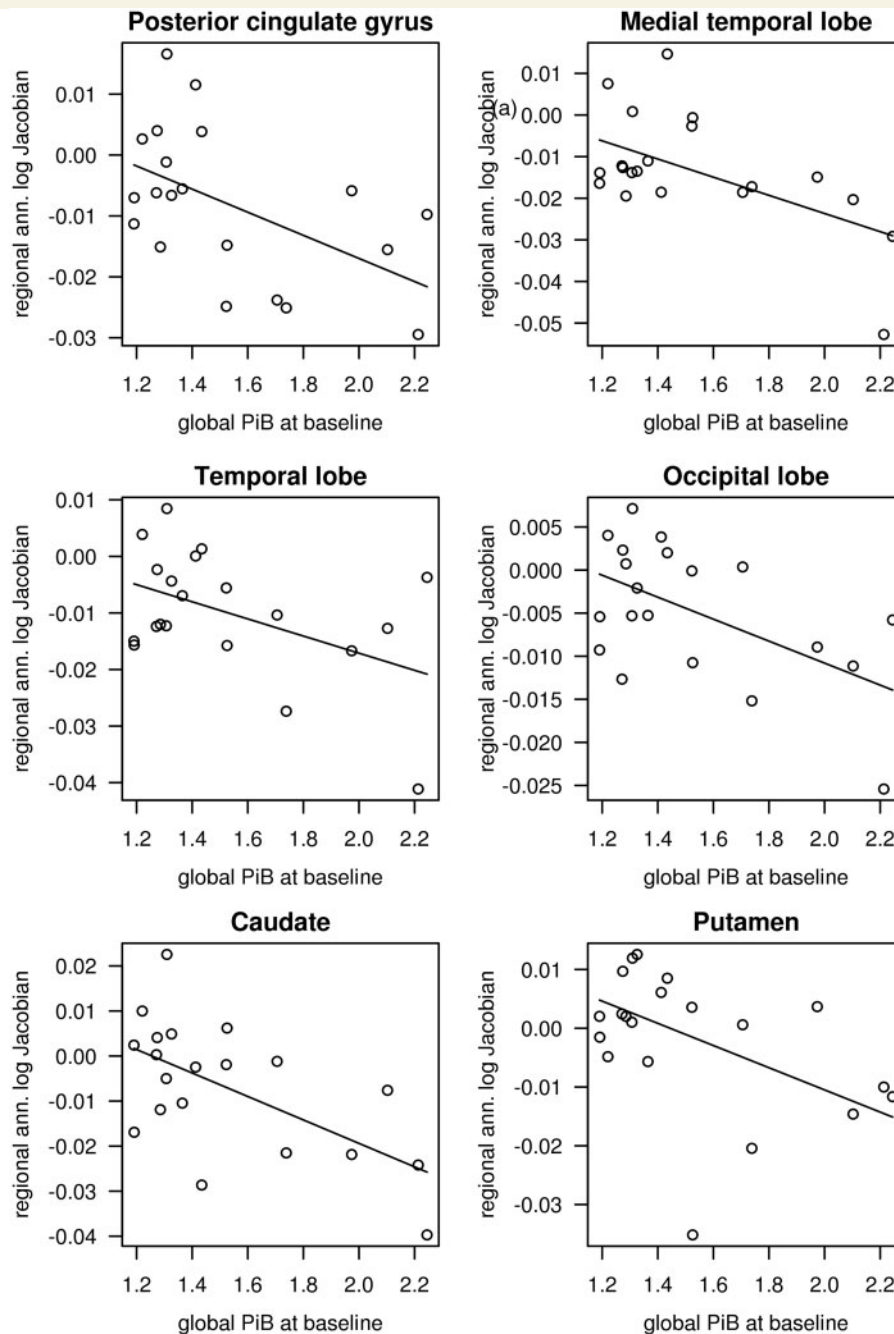
Figure 1 Associations between baseline PiB retention and grey matter atrophy rates. Linear regression model between baseline global PiB SUVR (*x*-axes) and regional grey matter annualized log Jacobian (*y*-axes) in patients with DLB, after adjusting for age. Only in the regions of interest with significant association ($P < 0.05$) are displayed. Regression line is shown for a 70-year-old.

which typically has reduced dopaminergic activity in DLB. *In vivo* striatum dopaminergic denervation with loss of presynaptic striatal dopamine transporter (DAT), as measured by single-photon emission tomography (SPECT) and PET, is a consistent finding among patients with probable DLB, compared to clinically normal controls and patients with Alzheimer's disease dementia (Walker *et al.*, 2002, 2004; O'Brien *et al.*, 2004; McKeith *et al.*, 2007). While the dopaminergic degeneration has been widely

documented to affect the striatum of patients with DLB (Walker *et al.*, 2004; Klein *et al.*, 2010), a cholinergic network alteration involving the striatum has been postulated in the Lewy body disease spectrum of disorders (Langlais *et al.*, 1993) but its mechanism is still poorly understood (Bohnen and Albin, 2011). In this setting, our finding of an association between higher PiB retention and higher atrophy rates in the caudate and putamen nuclei suggest an accelerated subcortical neuronal injury involving the
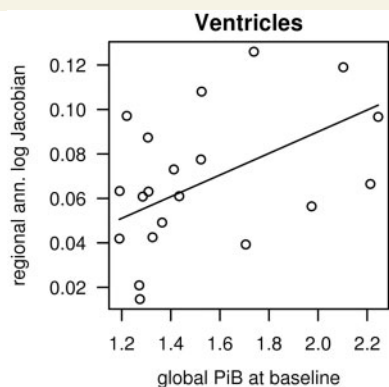
Figure 2 The association between baseline PiB retention and ventricular volume rate of change. Linear regression model between baseline global PiB SUVR (*x*-axis) and annualized log Jacobian in ventricular volume (*y*-axis) in patients with DLB, after adjusting for age, are shown. Regression line is shown for a 70-year-old.

dopaminergic and possibly the cholinergic system in patients with higher amyloid-β load. Higher burden of both α-synuclein (Duda *et al.*, 2002*a*; Jellinger and Attems, 2006) and amyloid-β deposition (Jellinger and Attems, 2006; Edison *et al.*, 2008; Kalaitzakis *et al.*, 2008) has been observed in the striatum of patients with DLB, suggesting a possible interaction between α-synuclein and amyloid-β aggregation. Furthermore, tau and α-synuclein deposits may be aggregating topographically in close proximity in synucleinopathies (Duda *et al.*, 2002*b*; Ishizawa *et al.*, 2003; Kotzbauer *et al.*, 2004), supporting direct cross-seeding between the two types of pathologies (Guo *et al.*, 2013), which could influence striatal degeneration in DLB patients.

Another finding in this study was the correlation between higher PiB retention at baseline and greater rates of functional disease progression on CDR-SOB, which also correlated with the ventricular expansion rates. Cognitive rating of disease progression using MMSE, in contrast, was not related to PiB retention at baseline. The simplest explanation may be attributed to reduced statistical power given the heterogeneity of DLB and the relatively small sample size. Cognitive test performance may be more sensitive to other factors that we could not account for, such as the influence of other pathologies (e.g. α-synuclein, tau) and other non-neurological factors (e.g. mood, frailty, pain, sleepiness). Although it may be argued that AChEI might mitigate the relationship between performance and grey matter volume by improving cognitive scores, this seems unlikely given that all patients had exposure to AChEI. Variability in the relationship between amyloid-β and disease severity is evidence in the literature with some studies showing higher amyloid-β deposition in those with lower CDR (Foster *et al.*, 2010) and MMSE scores (Compta *et al.*, 2011), while others show no such association (Compta *et al.*, 2011; Shimada *et al.*, 2013). The

relationship between disease progression and PiB may be suggestive of a more complex relationship between amyloid-β, tau and α-synuclein that is not easily disentangled by examining only amyloid-β. Furthermore, since PiB imaging does not distinguish between amyloid-β deposition of diffuse more than neuritic plaques (Kantarci *et al.*, 2012*c*), it is also not known whether this distinction may make a difference in the effects of amyloid protein aggregation in DLB, and may contribute to some of this variability. Overall our findings are in agreement with the hypothesis that patients with probable DLB with concomitant underlying Alzheimer's disease pathology could show a more aggressive clinical phenotype of the disease with increased atrophy rates and functional decline (Nelson *et al.*, 2009; Clinton *et al.*, 2010; Gomperts *et al.*, 2012; De Beer *et al.*, 2015; Ferman *et al.*, 2015; Graff-Radford *et al.*, 2015; Howlett *et al.*, 2015).

There are limitations to take into account, including potential bias related to the small sample size and ascertainment of subjects from a referral clinic-based cohort. Future studies that include ante-mortem imaging and post-mortem pathological analysis, as well as bigger sample sizes are needed to better understand PiB retention as a surrogate marker of amyloid-β deposition in DLB (Kantarci *et al.*, 2012*c*).

Current results, although preliminary, provide evidence for a faster rate of grey matter loss in DLB patients with high amyloid-β deposition. More work is needed to better establish whether amyloid-β deposition is also related to a high level of tau and α-synuclein aggregation, suggesting a synergistic or additive relationship, or if amyloid-β deposition provides a unique contribution to neuronal loss and grey matter atrophy. Also, our findings are a step forward towards understanding the variability of disease progression in DLB, and *in vivo* biomarkers for α-synuclein may provide further insight into the pathogenesis of this complex disease. Furthermore, *in vivo* demonstration of a relationship between higher amyloid pathology in patients with probable DLB and progression of neuronal damage and clinical decline provides a rationale for targeting the subset of DLB patients with significant amyloid burden, together with patients with Alzheimer's disease dementia, with emerging anti-amyloid agents.
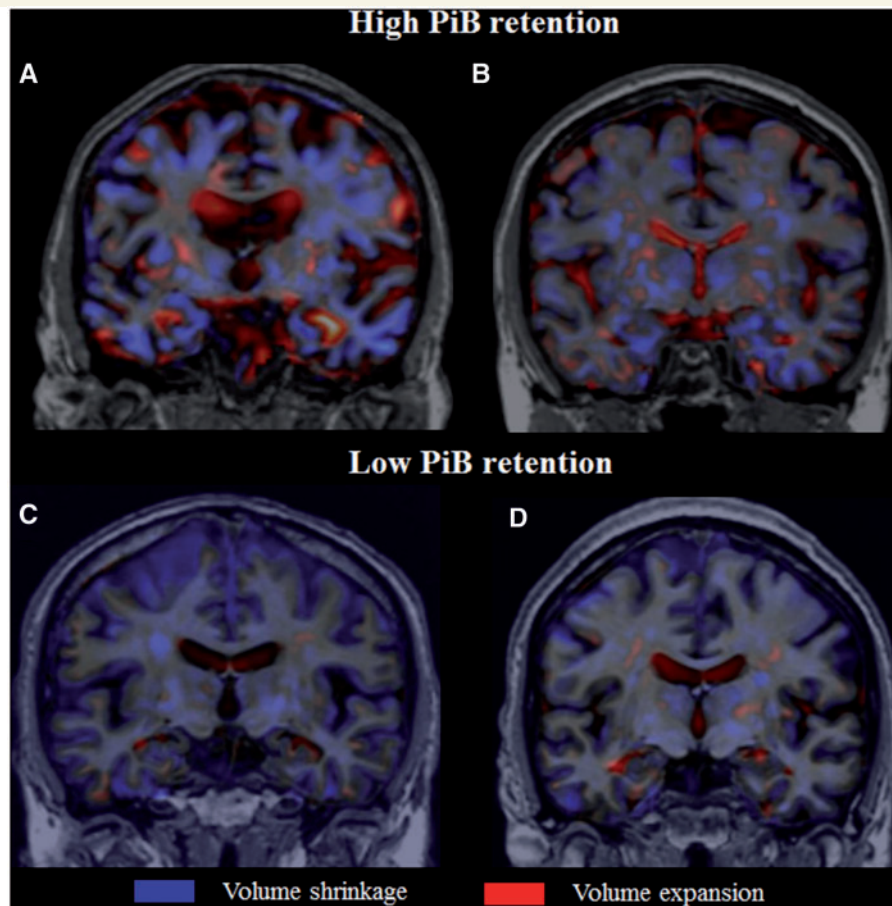
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Figure 3 TBM-SyN maps of four subjects included in the analysis. (A) Subject is a 79-year-old female, with high baseline global PiB retention (PiB SUVR = 2.2). During an inter-scan interval of 2 years, the annual percentage change (APC) in grey matter showed diffuse volume shrinkage in the cortex and basal ganglia. In particular, in the medial temporal lobe the APC grey matter loss was 5%, while the volume ventricle APC expanded by 6%. This can be seen in the figure where, in the medial temporal lobe, the hippocampi are coloured in blue (volume shrinking), while the ventricles are coloured in red (volume expansion). **(B)** Subject is a 62-year-old female with a high baseline global PiB retention (PiB SUVR = 2.1), and an inter-scan interval of 2 years. Grey matter volume loss was found diffusely in the cortical and subcortical structures, with 2% APC grey matter shrinkage (coloured in blue) in medial temporal lobe and a 12% APC of expansion (coloured in red) in the ventricles. **(C)** Subject is a 70-year-old male, with low baseline global PiB retention (PiB SUVR = 1.3), and an inter-scan interval of 3 years. Minimal grey matter volume shrinkage was found throughout the brain. In particular, no loss of volume was found in medial temporal lobe (APC = 0%; no/minimal blue colouring), while ventricles volume did show a volume expansion (APC = 6%; coloured in red). **(D)** Subject is a 53-year-old male, with low baseline global PiB retention (PiB SUVR = 1.2), and an inter-scan interval of 3 years. Minimal grey matter volume shrinkage was found throughout the brain. In particular, no loss of grey matter volume was found in medial temporal lobe (APC = 0%; no/minimal blue colouring), while ventricles volume expanded (APC = 9%; coloured in red).

access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest

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