Pattern of brain atrophy rates in autopsy-confirmed dementia with Lewy bodies

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Abstract

Dementia with Lewy bodies (DLB) is characterized by preserved whole brain and medial temporal lobe volumes compared with Alzheimer’s disease dementia (AD) on magnetic resonance imaging. However, frequently coexistent AD-type pathology may influence the pattern of regional brain atrophy rates in DLB patients. We investigated the pattern and magnitude of the atrophy rates from 2 serial MRIs in autopsy-confirmed DLB patients (n = 20) and mixed DLB/AD patients (n = 22), compared with AD (n = 30) and elderly nondemented control subjects (n = 15), followed antemortem. DLB patients without significant AD-type pathology were characterized by lower global and regional rates of atrophy, similar to control subjects. The mixed DLB/AD patients displayed greater atrophy rates in the whole brain, temporoparietal cortices, hippocampus and amygdala, and ventricle expansion, similar to AD patients. In the DLB and DLB/AD patients, the atrophy rates correlated with Braak neurofibrillary tangle stage, cognitive decline, and progression of motor symptoms. Global and regional atrophy rates are associated with AD-type pathology in DLB, and these rates can be used as biomarkers of AD progression in patients with LB pathology.

1. Introduction

Pathologically, dementia with Lewy bodies (DLB) is characterized by unremarkable global brain atrophy on gross inspection, and microscopically by \(\alpha\)-synuclein aggregates (Spillantini et al., 1997) in Lewy bodies (LBs) (Kosaka, 1978; Lewy, 1912) and Lewy neurites. However, a frequent concomitant finding is varying degrees of Alzheimer’s disease (AD) type pathology, that is, \(\beta\)-amyloid in neuritic plaques and hyperphosphorylated tau in neurofibrillary tangles (NFT) (NIA-Reagan, 1997). This overlap between the 2 most common, yet distinct neurodegenerative dementias in terms of underlying pathology and clinical characteristics, often makes ante-mortem diagnosis challenging. This applies particularly to DLB patients with a high Braak NFT stage (Meredes et al., 2003) who are often misdiagnosed as having AD in the clinical settings (Schneider et al., 2007). Mixed DLB/AD dementia patients are of considerable interest because of the high frequency of the mixed pathology (Hamilton, 2000; Hansen et al., 1990; Schneider et al., 2007, 2009), their hypersensitivity to neuroleptics, and most important of all, their excellent response to acetyl-cholinesterase inhibitors (Graff-Radford et al., 2002).
et al., 2012; McKeith et al., 2004). Accessible, preferably noninvasive biomarkers, such as those derived from magnetic resonance imaging (MRI), would have an important role in differential diagnosis, tracking of disease progression, evaluation of treatment response, and designing clinical trials with disease-specific therapeutic agents or redesigning those with the currently available treatments in patients with DLB. Moreover, usage of longitudinal MRI measurements may reduce interindividual variability and provide a better insight into the biology of the disease than a single measurement.

Patients with AD are characterized by greater rates of whole brain and hippocampus atrophy, accompanied by greater ventricle expansion over time compared with control subjects in both clinically diagnosed and autopsy-confirmed cohorts (Fox et al., 2000; Jack et al., 2000, 2004; Whitwell et al., 2007a, 2007b). Atrophy rates on MRI have been used to assess treatment response in clinical trials on patients with AD and mild cognitive impairment (MCI) (Fox et al., 2000; Jack et al., 2003, 2008). Greater rates of atrophy on antemortem MRI have been positively associated with high Braak NFT stage and NFT density at autopsy (Josephs et al., 2008a; Silbert et al., 2003).

Relatively preserved medial temporal lobe volumes characterize patients with DLB compared with patients with AD; however, whether DLB patients have sufficient gray matter loss to be distinguished from normal control subjects, remained unclear in clinically diagnosed cohorts that likely included cases with mixed DLB/AD pathology (Barber et al., 2000; Burton et al., 2002, 2004; Harvey et al., 1999; Hashimoto et al., 1998). The involvement of frontal (Ballmaier et al., 2004; Barber et al., 2000, 2002; Whitwell et al., 2007a, 2007b), temporoparietal (Ballmaier et al., 2004; Harvey et al., 1999; Whitwell et al., 2007a, 2007b), and occipital cortices (Middelkoop et al., 2001; O’Donovan et al., 2013) has been observed in patients with DLB, although the findings have been inconsistent.

In autopsy-confirmed cohorts, medial temporal atrophy on cross-sectional MRI has been associated with mixed AD-type pathology in patients with DLB (Burton et al., 2009). Specifically, greater atrophy in the hippocampus and amygdala has been associated with a high Braak NFT stage (Kantarci et al., 2012) and tau-NFT density (Murray et al., 2013) in patients with LB pathology.

In longitudinal MRI studies, clinically diagnosed patients with DLB were reported to have greater whole brain atrophy rates than age-matched controls, similar to patients with AD and vascular dementia (O’Brien et al., 2001). However, greater whole brain atrophy and ventricle expansion rates were limited to patients with mixed DLB/AD pathology compared with control subjects in an autopsy-confirmed cohort (Whitwell et al., 2007a, 2007b). The differences across the studies can be attributed to different sampling schemes (clinical vs. autopsy-confirmed sample), and different methods used to measure the atrophy. Nevertheless, the regional pattern and magnitude of atrophy rates that characterize patients with autopsy confirmed DLB and mixed DLB/AD are unknown.

Our primary objective was to identify the regional pattern of gray matter atrophy rates on antemortem serial MRI in autopsy-confirmed DLB and DLB/AD compared with those with AD and elderly control subjects. We hypothesized that autopsy-confirmed patients with DLB would have similar rates of brain atrophy, compared with elderly control subjects, whereas those with mixed LB and AD-type pathology would be affected more in terms of topographic extent and magnitude of gray matter loss over the time. Our secondary objective was to correlate rates of atrophy with measures of cognitive decline and clinical progression in patients with DLB and DLB/AD; and finally, to report sample size estimates for a hypothetical clinical trial including patients with DLB only and for DLB/AD, using rates of atrophy as surrogate measures of outcome.

2. Methods

2.1. Participants

To be included in this study, participants had to have at least 2 serial 1.5 T brain MRIs approximately 2 years apart of sufficient technical quality and had to come to autopsy. We have chosen the participants exclusively based on the autopsy diagnosis and not the clinical syndrome. We included cases with LB pathology diagnosed as either high likelihood DLB (DLB group) or intermediate and low likelihood DLB (DLB/AD group) according to the Third Report of the DLB Consortium Criteria for DLB (McKeith et al., 2005). We also included cases with high likelihood AD with no LB pathology (AD group) and low likelihood AD with no LB pathology (control group) for comparison. Patients with amygdala-only Lewy bodies (n = 2) were included in the DLB/AD group as they had both LB and AD pathology. Patients were excluded if they had comitant neurologic illness at the time of either one of the MRIs or conditions known to interfere with cognition such as cortical infarcts, normal pressure hydrocephalus, subdural hematoma, or tumor. Those with lacunar infarcts or white matter hyperintensities were included.

Participants were recruited consecutively and followed prospectively until their death between 1999 and 2009 at the Mayo Clinic Alzheimer’s Disease Research Center (dementia clinic-based cohort) and Alzheimer’s Disease Patient Registry (community-based cohort) (Petersen et al., 1990) in Rochester, MN, USA. During life, participants underwent approximately annual clinical evaluations including standard measures of cognitive and functional performance such as Mini Mental State Examination (MMSE) (Folstein et al., 1975) that has been widely used in the field, the Dementia Rating Scale (DRS) (Mattis, 1988), which has greater dynamic range than MMSE. The severity of parkinsonism was quantified with the motor subtest of Unified Parkinson Disease Rating Scale (UPDRS) (Fahn et al., 1987). Progression of the disease was measured by subtraction of baseline from follow-up score and then annualized for consistency with imaging measures. Clinical diagnosis was established by the consensus of neurologists, neuropsychologists, and nurses. The diagnosis of probable AD was made according to NINCDS-ADRDA criteria for AD (McKhann et al., 1984). The diagnosis of probable DLB was made using the third report of the DLB Consortium criteria for DLB (McKeith et al., 2005), and diagnosis of MCI was based on Petersen criteria (Petersen, 2004). Informed signed consent was obtained from all individuals or their proxies antemortem, and study was approved by the Mayo Clinic Institutional Review Board.

2.2. Neuropathologic examination and diagnosis

Brains were processed, sectioned, and sampled using standardized methods (McKeith et al., 2005; Mirra et al., 1991). In all 87 cases, the examination and diagnosis were conducted by one of 2 experts (Dennis W. Dickson or Joseph E. Parisi) using standard staining and standard criteria (Braak and Braak, 1996), and also immunohistochemistry to determine the distribution and to semi quantitatively measure NFT density with corresponding Braak NFT stage. For Lewy body disease, cases were classified as brainstem-, limbic-, or neocortical-predominant according to the distribution and counts of LBs immunostained with monoclonal antibodies to α-synuclein. Based on the findings, we defined the study groups as follows: (1) cases with AD (n = 30) had high-probability AD according to the National Institute of Aging-Reagan criteria (NIA-Reagan, 1997). That is, the presence of frequent neuritic plaques corresponding to probable or definite AD according to Consortium to Establish Registry for Alzheimer’s Disease criteria for AD (Mirra et al., 1991), Braak NFT stage of V or VI and no LBs; (2) cases with DLB (n = 20) were
diagnosed according to the third report of the DLB Consortium criteria (McKeith et al., 2005) as high likelihood DLB. They had numerous transitional (limbic) or diffuse (neocortical) LBs, Braak NFT stage ≤ IV, and low to intermediate likelihood AD; (3) cases with mixed DLB/AD (n = 22) had both pathologies; however, not severe enough to meet criteria for high likelihood DLB. Mixed DLB/AD had intermediate or low likelihood DLB with limbic or neocortical LBs, Braak NFT stage ≥ V, and frequent neuritic plaques consistent with high likelihood AD. We did not have any cases with brainstem predominant LBs in our cohort. Two cases had LBs confined to the amygdala only and were included in the mixed DLB/AD group because of high likelihood AD pathology. Cases with atypical forms of AD were not observed in cases with LB pathology; (4) controls (n = 15) who had no LBs, they had low likelihood AD with Braak stage > III, and were non-demented at the time of MRIs. We have also assessed the presence of argyrophilic grain disease (AGD), a pathology frequently found in brains of cognitively healthy (Knopman et al., 2003) and nondemented elderly individuals (Barthof et al., 2007). This pathology has been known to be associated with aging (Ferrer et al., 2008; Saito et al., 2004) and has not been associated with a greater medial temporal gray matter loss in nondemented elderly individuals (Josephs et al., 2008b). Five controls, 5 DLB cases, and 1 mixed DLB/AD case had AGD. The relatively high number of AGD cases in our series may be because of our interest in and awareness of this entity, therefore we did not exclude cases with AGD.

2.3. Imaging studies

Brain MRIs were acquired at 1.5 T using 3-dimensional T1-weighted spoiled gradient echo recalled sequence (General Electric, Milwaukee, WI, USA) with following parameters: repetition time = 7 ms, echo time = 3 ms, inversion time = 900 ms, flip angle 8°, in-plane resolution of 1.0 mm, and slice thickness of 1.2 mm. The rates of whole brain atrophy and ventricle expansion were measured using the automated boundary shift integral algorithm (BSI) (Fox et al., 1996), modified in-house and described elsewhere (Gunter et al., 2003), and were reported as annualized percentage change from baseline volume (APC %). Regional gray matter loss across the entire brain was determined with automated, in-house developed Tensor Based Morphometry-Symmetric Diffeomorphic Image Normalization method (TBM-SyN) (Gunter et al., 2012), which uses symmetrical registration of serial MRIs (Ashburner and Ridgway, 2013), and computes 3-dimensional SyN deformations between each subject’s serial MRIs using preprocessed T1-weighted images. These deformations were averaged within the pathologic group and reported as annualized log Jacobian. Further, we visualized the TBM-SyN-derived differences in the regional gray matter atrophy rates in DLB and DLB/AD groups comparing them with the control and AD groups using Statistic Parametric Mapping package (SPM; version 5) (http://www.fil.ion.ucl.ac.uk/spm/), with 2-sided t-test at significance level p < 0.05, cluster extent threshold of 50 voxels, and correction for multiple comparisons with false discovery rate. To quantify the magnitude of atrophy rates in the hippocampus and amygdala, regions of interest (ROI) from an Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002), modified in-house to fit our template (Kantarci et al., 2010; Vemuri et al., 2008), were applied. Mean regional annualized log Jacobian measurements for these 2 ROIs were derived. Because LB or AD-related pathologies are not considered to affect preferentially one hemisphere over another, the ROI-based rates of atrophy were calculated as averages of right and left hemispheric ROIs. The hippocampus and amygdala were chosen for ROI analysis because these structures have received reasonable attention in the literature as proxies of AD and DLB on MRI (Burton et al., 2009, 2012; Kantarci et al., 2012; Murray et al., 2013; Vemuri et al., 2011; Whitwell et al., 2007a, 2007b) and can be consistently quantified with various softwares because of their distinct borders (Fischl et al., 2002; Patenaude et al., 2011).

2.4. Statistical analyses

Statistical analyses were performed with R statistical software package, version 2.14.0. (http://www.R-project.org) and SAS version 9.3, with 2-sided statistical significance set at type I error rate alpha < 0.05. For continuous variables, the means with standard deviations were reported along with the p-values from analysis of variance. For binary or categorical variables, the counts and proportions (%) were reported along with p-values from χ² tests. There were 2 specific normalizing transformations done to the data. The annualized DRS total had left skewness, so a constant number of 59 was first added to create a positive number where it was then cubed. The interval from MRI to death was transformed with a square root because of right skewness. To evaluate groupwise differences in the magnitude of atrophy rates derived from BSI and TBM-SyN methods, we used analysis of covariance, with pathologic diagnosis treated as the main effect, whereas the age at the time of second MRI and the interval from the second MRI to death were treated as adjustment covariates and used in the remaining analyses. We report adjusted Pearson correlations to assess the effect of NFT Braak stage on the atrophy rates within 2 global and 2 atlas-based regions, and to examine the association between atrophy rates and measures of the clinical or cognitive decline and progression of motor findings. Correlation analyses were performed exclusively within DLB and DLB/AD groups combined to see the dynamic range of values within patients having LB pathology, in keeping with our hypothesis and study objectives. Finally, we estimated the sample sizes needed per treatment group to power a hypothetical clinical trial using the annualized atrophy rates as the surrogate measures of outcome to detect standard effects of 25% and 50% in terms of hypothetical reduction or cessation of the gray matter loss that would be attributed to positive treatment response and would be clinically relevant, using a 2-sided 2-sample t-test with equal variances, type I error rate < 0.05, and power 80%.

3. Results

3.1. Subjects’ characteristics

Demographic and clinical characteristics of study participants at the time of the second MRI by group is provided in Table 1. The proportion of females (p = 0.19), years of education (p = 0.84), and inter scan interval (p = 0.20) were similar across the groups. Controls were older at the second MRI (p = 0.01) compared with pathologic groups of otherwise similar age, and the interval from the second MRI to death was also longer in controls than in the rest of sample (p = 0.01). Therefore, both age at second MRI and time from second MRI to death were used as covariates in statistical analyses. The duration of dementia was not different across the patient groups (p = 0.47). The decline in MMSE and DRS scores differed markedly across the groups (p < 0.001); patients with autopsy-confirmed DLB/AD and AD performed equally poorly on MMSE, and scored worse on DRS than other groups. As expected, patients with autopsy-confirmed DLB and mixed DLB/AD were characterized by a high frequency of clinical features associated with DLB such as visual hallucinations, fluctuations, REM sleep behavior disorder, and parkinsonism. Of these, only frequency of REM sleep behavior disorder distinguished DLB from the DLB/AD group (p = 0.03). The clinical diagnosis of DLB was present in 14 of 20 (70%) cases with autopsy-confirmed DLB and in 7 of 22 (32%) cases with DLB/AD. The breakdown of relevant medication type and
dosage is also reported in Table 1. Main autopsy findings by group are listed in Table 2.

### 3.2. Rates of whole brain and ventricle volume change

Global measures from BSI (Table 3) were available in 87 of the autopsied participants; however, 1 case from the mixed DLB/AD group was excluded from this analysis because of BSI failure. In patients with DLB, the whole brain atrophy rate was not different from that in controls \(p = 0.92\) but was lower than the rate in patients with mixed DLB/AD \(p = 0.01\) and AD \(p < 0.001\). In the mixed DLB/AD group, the whole brain atrophy rate was greater compared with controls \(p = 0.04\) and was similar to that seen in AD \(p = 0.36\). Similarly, the ventricle expansion rate in DLB group was consistent with the rate in control group but was lower compared with DLB/AD and AD groups \(p < 0.001\). Patients with DLB/AD were characterized by greater ventricle expansion compared with controls \(p = 0.003\), indistinguishable from those with AD \(p = 0.55\) (Fig. 1).

### 3.3. Regional pattern of the differences in cortical atrophy rates

Three participants (2 controls and 1 AD case) were excluded because of the failure of TBM-SyN analysis. Between-group differences in gray matter atrophy rates are displayed in Fig. 2. We did not...
find any differences in terms of increased gray matter loss between control and DLB or between the mixed DLB/AD and AD groups. These negative findings were consistent with the BSI-based whole brain atrophy and ventricle expansion rates as described above. Patients with DLB/AD had significantly greater atrophy rates in the temporoparietal neocortex (i.e., parahippocampal, middle and inferior temporal, inferior parietal, fusiform, and lingual gyrus), the hippocampus and amygdala as compared with control and DLB groups. Patients with DLB were characterized by generally preserved gray matter compared with DLB/AD and AD groups. The differences in atrophy rates within the hippocampus and amygdala ROIs by pathologic group are depicted in Fig. 3. In patients with DLB, the atrophy rate in the hippocampus was similar to control subjects \((p = 0.83)\), and was markedly lower compared with both DLB/AD \((p < 0.001)\) and AD \((p < 0.001)\) groups. In the mixed DLB/AD group, the atrophy rate was greater compared with controls \((p < 0.001)\) and was not different from that in AD group \((p = 0.71)\). Similarly, those with DLB did not differ from controls in the amygdala atrophy rate \((p = 0.23)\) and were characterized by preserved amygdala compared with AD \((p = 0.01)\). Greater atrophy rate in the amygdala distinguished DLB/AD group from both DLB \((p < 0.001)\) and controls \((p < 0.001)\), whereas DLB/AD and AD groups were affected similarly \((p = 0.09)\).

3.4. Atrophy rates and NFT Braak stage in patients with LB pathology

Greater atrophy rates in the whole brain, hippocampus, and amygdala, and expansion in the ventricle on antemortem MRI were associated with a higher Braak NFT stage at autopsy in patients with LB pathology (DLB and DLB/AD). The Pearson adjusted correlations between atrophy or expansion rates and Braak NFT stage are listed in Table 4.

3.5. Atrophy rates and measures of disease progression in patients with LB pathology

Adjusted Pearson correlations between atrophy rates and MMSE, DRS, and UPDRS as measures of cognitive decline and progression of motor impairment in patients with a range of LB pathology (DLB and DLB/AD combined) are displayed in Fig. 4. Greater whole brain atrophy rates were associated with a greater decline in cognitive function as measured by MMSE, \(r = 0.54\) (95% CI = 0.25, 0.73; \(p < 0.001\)) and with a greater progression of the motor impairment on UPDRS, \(r = -0.49\) (95% CI = -0.73, -0.13; \(p = 0.0091\)). There was borderline association with DRS, \(r = 0.38\), (95% CI = -0.03, 0.67; \(p = 0.063\)). Similarly, a greater atrophy rate in the
hippocampus was associated with a greater cognitive decline on MMSE, \( r = 0.61 \) (95% CI = 0.35, 0.77; \( p < 0.001 \)) and DRS, \( r = 0.55 \) (95% CI = 0.20, 0.77; \( p = 0.0036 \)); and also with progression of motor impairment, \( r = -0.69 \) (95% CI = -0.84, -0.41; \( p < 0.001 \)). Finally, the findings in the amygdala were consistent with the findings in the whole brain and the hippocampus; the amygdala atrophy rate correlated with decline in MMSE, \( r = 0.40 \) (95% CI = 0.09, 0.64; \( p = 0.012 \)), DRS, \( r = 0.57 \) (95% CI = 0.23, 0.78; \( p = 0.0022 \)) and the progression of motor impairment, \( r = -0.55 \) (95% CI = -0.77, -0.21; \( p = 0.0027 \)).

Neither measures of cognitive decline nor progression of motor impairment correlated with the ventricle expansion rate.

### 3.6. Sample size estimates for an hypothetical clinical trial

Global (the whole brain and ventricle), and regional (the hippocampus and amygdala) atrophy rates from autopsied patients were used to calculate sample size estimates per treatment group for a hypothetical clinical trial to detect an effect of 25% and 50% in terms of the reduction in rates of atrophy. The sample size estimates by fixed effect size and brain region are listed in Table 5. In DLB/AD group, the ventricle expansion rate followed by hippocampal atrophy rate required the smallest sample sizes to measure the desirable effect. For comparison, to detect a fixed effect size in the autopsy-confirmed AD group, rates of change in the hippocampus, followed by ventricle and the amygdala required smaller sample sizes than the whole brain atrophy rate. Because rates of atrophy (or ventricular expansion) were not different in DLB patients compared with normal control subjects, we did not report on sample size estimates for the DLB group.

### Table 4

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Pearson Correlation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain</td>
<td>-0.33 ( -0.58, -0.01)</td>
<td>0.041</td>
</tr>
<tr>
<td>Ventricle</td>
<td>0.43 (0.13, 0.65)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>-0.63 ( -0.79, -0.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amygdala</td>
<td>-0.49 ( -0.69, -0.20)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Key: CI, confidence interval; LB, Lewy body; MRI, magnetic resonance imaging; NFT, neurofibrillary tangles.

* The correlations are adjusted for the age at the second MRI and the time from the second MRI to death.

### 4. Discussion

In this study, we demonstrated the pattern and the magnitude of atrophy rates across the entire brain gray matter in a cohort of prospectively studied patients with autopsy-confirmed DLB and mixed DLB/AD as compared with those with AD patients and control subjects. Our findings showed that patients with DLB had rates of the whole brain atrophy and ventricle expansion similar to controls and did not display any region-specific increases in atrophy rates to be distinguishable from elderly controls. On the contrary, those with mixed DLB/AD had markedly greater rates of brain atrophy, and the topography of changes consistent with that seen in AD, affecting predominantly temporoparietal cortices, hippocampus, and amygdala. Greater atrophy rates not only correlated with high Braak NFT stage, but also with measures of disease progression in patients with LB pathology.

Our findings of minimal global atrophy rates in patients with DLB compared with normal control subjects are in agreement with previous longitudinal MRI study in a smaller sample of autopsy-confirmed DLB subjects from our group (Whitwell et al., 2007a, 2007b). In addition, we found no specific pattern of regional atrophy rates in patients with autopsy-confirmed DLB compared with normal controls, unlike the cross-sectional studies from clinically diagnosed patients with DLB (Ballmaier et al., 2004; Burton et al., 2002, 2004). In these cross-sectional studies, the hippocampus and the amygdala were atrophic in DLB patients compared with normal controls, although the atrophy in DLB was less prominent than in AD patients (Burton et al., 2002, 2004). Similarly, a greater atrophy was measured in temporal and parietal cortices in DLB compared with normal control subjects (Ballmaier et al., 2004). In this study, AD patients exhibited more atrophy in temporal and also orbitofrontal cortices than DLB patients which agreed with our results. Our findings also differ from reports on clinically diagnosed patients with DLB (O’Brien et al., 2001) who were found to have similar rates of whole brain atrophy compared to AD and other dementias groups. We attribute the differences largely to the fact these studies likely included cases with mixed DLB/AD pathology.

Both, global and regional atrophy rates in patients with mixed DLB/AD pathology were similar to patients with AD demonstrating that the presence of AD pathology probably drives the atrophy rates regardless of LB pathology. In keeping with this, we found greater atrophy rates in the mixed DLB/AD pathology group compared with
DLB. The mixed DLB/AD patients had higher rates of atrophy in temporoparietal regions, hippocampus, and amygdala compared with normal control subjects, a pattern consistent with the rates of atrophy in AD (Jack et al., 2004; Ridha et al., 2006; Scahill et al., 2002; Thompson et al., 2003), corresponding to the progression of neurofibrillary tangles (Braak and Braak, 1996). We found a positive correlation between greater global atrophy rates and a high Braak NFT stage in patients with a range of LB pathology (DLB and mixed DLB/AD), consistent with previous longitudinal MRI studies with pathologic confirmation (Josephs et al., 2008a; Silbert et al., 2003). These studies demonstrated that high NFT Braak stage and density have been associated with greater atrophy rates in patients with AD pathology. Similarly, in our study, greater atrophy rates in the hippocampus and amygdala positively correlated with higher Braak NFT stage in patients with a range of LB pathology (DLB and DLB/AD). Our results agree with previous cross-sectional findings in autopsy-confirmed DLB (Burton et al., 2009; Kantarci et al., 2012; Murray et al., 2013), indicating that greater medial temporal atrophy rates are associated with NFT pathology.

In patients with DLB who do not have sufficient and significant NFT pathology (low or intermediate likelihood AD and Braak stage up to IV in our cases), rate of cortical gray matter loss is minimal over the time, and appears not to be associated with α-synuclein...
accumulation, which likely has other deleterious effects on neuronal integrity. On the other hand, there may be a synergistic influence of tau-NFT and α-synucleinopathy, and perhaps also β-amyloid, particularly on clinical disease severity in patients with mixed DLB/AD (Jellinger et al., 2007; Horvath et al., 2013; Lashley et al., 2008). Given that the dementia duration was not different across the patient groups, differences in clinical measures between DLB and DLB/AD patients could be attributed to the synergistic effects the 2 underlying pathologies. However, we found a positive correlation between a greater cognitive decline measured by MMSE and DRD and greater atrophy rates in the hippocampus, the amygdala, and also the whole brain in the DLB and DLB/AD groups, which agrees with a previous study from our group in patients with MCI and AD (Jack et al., 2004), demonstrating the correlations between brain atrophy rates and cognitive decline.

Age-related ventricular expansion is observed in cognitively normal elderly individuals (Sowell et al., 2003), thus ventricular expansion may also be age-related in patients with LB pathology, explaining lack of a correlation between ventricular expansion rate and the disease progression in patients with LB pathology. However, an unexpected finding was the association of LB-related motor progression on UPDRS and rates of the whole brain, hippocampal, and amygdala atrophy in patients with DLB and DLB/AD. Potentially, the AD and LB-related pathologies can either independently progress, perhaps at similar rates, or can interact with each other influencing the disease progression. Our data suggest that the relationship between the atrophy rates, driven by AD-type pathology, and progression of motor impairment is an indirect association.

So far, structural MRI is not accepted as the primary outcome measure for monitoring effect size in clinical trials. However, in patients with AD, imaging measures may provide adequate power to considerable smaller sample sizes than are required when cognitive or functional measures are used (Fox et al., 2000; Hua et al., 2009; Jack et al., 2004). In the present study, we demonstrate that the pathologic underpinnings of atrophy rates on structural MRI are proxies of AD-type pathology, in particular tau-NFT pathology in patients with mixed DLB/AD pathology. The global and regional measures we suggested for powering the clinical trial are relatively well defined regions with distinct borders, measurable by various automated softwares (Fischl et al., 2002; Gunter et al., 2003; Patenaude et al., 2011) and different field strengths (Ho et al., 2010), therefore, these measures can be used as outcomes for AD-related treatment effects and should be sufficiently comparable across the trials. The sample sizes we calculated for patients with mixed DLB/AD were comparable with estimates for patients with AD both with regional and global measures, further supporting our findings that patients with mixed DLB/AD pathologies could be monitored by rates of atrophy in the clinical trials targeting AD-type pathology, which they may benefit from.

A major strength of the present study was the availability of serial MRIs in cases with pathologic diagnosis, clarifying the inconsistencies in the literature on whether or not patients with DLB are affected by marked brain atrophy rates. Usage of longitudinal measurement from serial scans with similar inter-scan interval, not requiring additional statistical adjustment was a strength as the inter-individual variability was lessened. The limitation to our study, as with most imaging-autopsy studies, was the interval between MRI and autopsy, which was approximately 2.5 years in patients and 4 years in control subjects. We assumed a linear relationship between atrophy rates and accumulation of brain pathology during this interval and controlled for this effect in statistical analysis. This was not a significant concern for control subjects who by definition had limited pathology; however, the assumption of linear progression of disease pathology may not be true in patients with dementia. Furthermore, we did not measure longitudinal change in dorsal midbrain or basal forebrain gray matter, the regions that are known to atrophy in patients with clinically (Brenneis et al., 2004; Hanuy et al., 2005; Vemuri, et al., 2011; Whitwell et al., 2007a, 2007b) or pathologically confirmed DLB (Kantarci et al., 2012). At this time, we were not able to conduct longitudinal measurement of these relatively small and deeply localized structures because of a high test-retest variability, and these analyses should be considered in future studies.

Overall, our findings have multiple clinical implications for using serial MRI as a tool in differential diagnosis of dementia, disease progression tracking, and designing clinical trials targeting specific pathologies that would use atrophy rates as the surrogate measures of outcome. The minimal change in volumes on structural MRI in autopsy-confirmed high-likelihood DLB reflects the fact that the pathologic progression of Lewy body pathology is not indexed by cortical gray matter volume loss, unlike AD and underscores the ongoing need for other biomarkers of disease progression for future trials in DLB. This implies that either the changes induced by α-synucleinopathy could be predominantly subcortical or cortical, but predominantly biochemical and not structural. On the contrary, structural MRI is useful in tracking progression of AD-related pathology and would be an appropriate biomarker in clinical trials targeting the co-existing AD-related pathology in patients with DLB.

Disclosure statement

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