Published in final edited form as:

Neurobiol Aging. 2015 January ; 36(1): 452–461. doi:10.1016/j.neurobiolaging.2014.07.005.

Pattern of Brain Atrophy Rates in Autopsy-Confirmed Dementia with Lewy Bodies

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Disclosure Statement:

Dr. Nedelska, Mr. Przybelski, Mr. Lesnick, Dr. Gunter, Dr. Senjem, Dr. Graff-Radford and Dr. Geda report no disclosures.

Dr. Ferman is funded by the NIH (Mayo Clinic Alzheimer's Disease Research Center/Project 1-P50-AG16574/P1 [Co-I]). Dr. Boeve has served as an investigator for a clinical trial sponsored by Cephalon, Inc. He has received honoraria from the American Academy of Neurology. He receives research support from the National Institute on Aging (P50-AG16574 [Co-I], U01 AG06786 [Co-I], R01-AG15866 [Co-I], and U24-AG26395 [Co-I]), and the Alzheimer's Association (IIRG-05-14,560 [PI]).

Dr. Murray is funded by P50-NS72187-03 (Co-I), and Robert H. and Clarice Smith and Abigail van Buren Alzheimer Disease Research Fellowship.

Dr. Vemuri is funded by NIH R00-AG37573.

Dr. Knopman serves as Deputy Editor for Neurology; served on a Data Safety Monitoring Board for Lilly Pharmaceuticals; served as a consultant to TauRx, was an investigator in clinical trials sponsored by Baxter, Elan Pharmaceuticals, and Forest Pharmaceuticals for the past 2 years; and receives research support from the NIH.

Dr. Smith is funded by the NIH (P50-AG16574).

Dr. Parisi receives publishing royalties for Principles & Practice of Neuropathology, 2nd edition.

Dr. Petersen serves on scientific advisory boards for Elan Pharmaceuticals, Wyeth Pharmaceuticals, and GE Healthcare and receives research support from the NIH (P50-AG16574 [PI] and U01-AG06786 [PI], R01-AG11378 [Co-I], and U01-24904 [Co-I]).

Dr. Dickson is funded by the NIH (P50-AG16574/Neuropathology Core [PI], P01AG017216 [PI], P50-NS072187 [PI], and R01-AG040042 [Co-I]).

Dr. Jack serves as a consultant for Janssen, Bristol-Meyer-Squibb, General Electric, Siemens, and Johnson and Johnson and is involved in clinical trials sponsored by Allon and Baxter, Inc. He receives research funding from the National Institutes of Health (R01-AG011378, R01-AG037551, U01-HL096917, U01-AG032438, U01-AG024904), and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation Family.

Dr. Kantarci serves on the data safety monitoring board for Pfizer Inc and Takeda Global Research & Development Center, Inc; and she is funded by the NIH (R01AG040042 [PI], R21 NS066147 [PI], P50 AG44170/Project 2 [PI], P50 AG16574/Project 1 [PI], and R01 AG11378 [Co-I]).

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Abstract

Dementia with Lewy bodies (DLB) is characterized by preserved whole brain and medial temporal lobe volumes compared to Alzheimer's disease dementia (AD) on MRI. 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 two serial MRIs in autopsy-confirmed DLB (n=20) and mixed DLB/AD patients (n=22), compared to AD (n=30) and elderly non-demented controls (n=15), followed antemortem. DLB patients without significant AD-type pathology were characterized by lower global and regional rates of atrophy, similar to controls. The mixed DLB/AD patients displayed greater rates in the whole brain, temporo-parietal 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 can be used as biomarkers of AD progression in patients with LB pathology.

Keywords

autopsy-confirmed dementia with Lewy bodies; Alzheimer's disease; serial MRI; atrophy rate; Braak neurofibrillary tangle stage; sample size estimate

1. Introduction

Pathologically, dementia with Lewy bodies (DLB) is characterized by unremarkable global brain atrophy on gross inspection, and microscopically by α -synuclein aggregates (Spillantini, et al., 1997) in Lewy bodies (LBs) (Kosaka, 1978; Lewy, 1912) and Lewy neurites. However, a frequent concomitant finding is varying degree of Alzheimer's disease (AD) type pathology, i.e. β -amyloid in neuritic plaques and hyperphosphorylated tau in neurofibrillary tangles (NFT) (NIA-Reagan, 1997). This overlap between the two most common, yet distinct neurodegenerative dementias in terms of underlying pathology and clinical characteristics, often makes antemortem diagnosis challenging. This applies particularly to DLB patients with a high Braak NFT stage (Merdes, 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., 2009, Schneider,

et al., 2007), their hypersensitivity to neuroleptics, and most important of all, their excellent response to acetyl-cholinesterase inhibitors (Graff-Radford, et al., 2012, McKeith, et al., 2004). Accessible, preferably non-invasive biomarkers, such as those derived from 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 re-designing those with currently available treatments in patients with DLB. Moreover, utilization of longitudinal MRI measurements may reduce inter-individual 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 to controls in both clinically diagnosed and autopsy-confirmed cohorts (Fox, et al., 2000, Jack, et al., 2004, Jack, et al., 2000, Whitwell, et al., 2007). 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., 2008, Jack, et al., 2003). 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 to patients with AD; however, whether DLB patients have sufficient gray matter loss to be distinguished from normal controls, remained unclear in clinically diagnosed cohorts that likely included cases with mixed DLB/AD pathology (Barber, et al., 2000, Burton, et al., 2004, Burton, et al., 2002, Harvey, et al., 1999, Hashimoto, et al., 1998). The involvement of frontal (Ballmaier, et al., 2004, Barber, et al., 2000, Burton, et al., 2002, Whitwell, et al., 2007), temporo-parietal (Ballmaier, et al., 2004, Harvey, et al., 1999, Whitwell, et al., 2007), 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 lobe 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 to controls in an autopsy –confirmed cohort (Whitwell, et al., 2007). The differences across the studies can be attributed to different sampling schemes (clinical versus 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 to those with AD and elderly controls. We hypothesized that autopsy-confirmed patients with DLB would have similar rates of brain atrophy, compared to elderly controls, 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.

Methods

2.1. Participants

In order to be included in this study, participants had to have at least two serial 1.5T brain MRIs approximately two 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 concomitant neurological 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 – 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. 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, and 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 as described below. 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 eighty-seven cases, the examination and diagnosis were conducted by one of two experts (D.W.D. or J.E.P.) 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, 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 AD/DLB group due to high likelihood AD pathology. Cases with atypical forms of AD were not observed in cases with LB pathology. 4. Controls (n=15) had no LBs, had low likelihood AD, 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 (Barkhof, 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 non-demented elderly (Josephs, et al., 2008b). Five controls, five DLB cases, and one mixed DLB/AD case had AGD. The relatively high number of AGD cases in our series may be due to 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 1.5T using three dimensional T1-weighted spoiled gradient echo recalled sequence (General Electric, Milwaukee, WI) with following parameters: TR = 7ms, TE = 3ms, TI = 900ms, 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 utilizes symmetrical registration of serial MRIs (Ashburner and Ridgway, 2013), and computes three 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 to the control and AD groups using Statistic Parametric Mapping package (SPM; version 5) (<http://www.fil.ion.ucl.ac.uk/spm/>), with two-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 two ROIs were derived. Since 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., 2012, Burton, et al., 2009, Kantarci, et al., 2012, Murray, et al., 2013, Vemuri, et al., 2011, Whitwell, et al., 2007), and can be consistently quantified with various softwares due to 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 χ^2 tests. There were two 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 due to right skewness. To evaluate group-wise 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 two global and two 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 two-sided two-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 to 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 (RBD), and parkinsonism. Of these, only frequency of RBD distinguished DLB from the DLB/AD group ($p=0.03$). The clinical diagnosis of DLB was present in 14 out of 20 (70%) cases with autopsy-confirmed DLB, and in 7 out 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 eighty-seven of the autopsied participants; however, one case from the mixed DLB/AD group was excluded from this analysis due to 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 to 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 to DLB/AD and AD groups ($p<0.001$). Patients with DLB/AD were characterized by greater ventricle expansion rate compared to controls ($p=0.003$), indistinguishable from those with AD ($p=0.55$) (Figure 1).

3.3. Regional Pattern of the Differences in Cortical Atrophy Rates

Three participants (two controls and one AD case) were excluded due to the failure of TBM-SyN analysis. Between-group differences in gray matter atrophy rates are displayed in Figure 2. We did not find any differences in 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 temporo-parietal neocortex (i.e. parahippocampal, middle and inferior temporal, inferior parietal, fusiform and lingual gyrus), the hippocampus and amygdala as compared to control

and DLB groups. Patients with DLB were characterized by generally preserved gray matter compared to DLB/AD and AD groups. The differences in atrophy rates within the hippocampus and amygdala ROIs by pathologic group are depicted in Figure 3. In patients with DLB, the atrophy rate in the hippocampus was similar to controls ($p = 0.83$), and was markedly lower compared to both DLB/AD ($p < 0.001$) and AD ($p < 0.001$) groups. In the mixed DLB/AD group, the atrophy rate was greater compared to 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 to 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's 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's 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 Figure 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 a 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. Since rates of atrophy (or ventricular expansion) were not different in DLB patients compared to normal controls, we did not report on sample size estimates for the DLB group.

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 to those with AD and controls. 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 temporo-parietal 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 to normal controls, are in agreement with previous longitudinal MRI study in a smaller sample of autopsy-confirmed DLB subjects from our group (Whitwell, et al., 2007). In addition, we found no specific pattern of regional atrophy rates in patients with autopsy-confirmed DLB compared to normal controls, unlike the cross-sectional studies from clinically diagnosed patients with DLB (Ballmaier, et al., 2004, Burton, et al., 2004, Burton, et al., 2002). In these cross-sectional studies, the hippocampus and the amygdala were atrophic in DLB patients compared to normal controls, even though the atrophy in DLB was less prominent than in AD patients (Burton, et al., 2002; Burton, et al., 2004). Similarly, a greater atrophy was measured in temporal and parietal cortices in DLB compared to normal controls (Ballmaier, et al., 2004). In this study, AD patients exhibited more atrophy in temporal and 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 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 presence of AD pathology is probably drives the atrophy rates regardless of LB pathology. In keeping with this, we found greater atrophy rates in the mixed DLB/AD pathology groups compared to DLB. The mixed DLB/AD patients had higher rates of atrophy in temporo-parietal regions, in the hippocampus and amygdala compared to normal controls, 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 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 two underlying pathologies. However, we found a positive correlation between a greater cognitive decline measured by MMSE and DRS 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 (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 current 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 to 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 current 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. Utilization 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 controls. 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 controls 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 atrophy in patients with clinically (Brenneis, et al., 2004, Hanyu, et al., 2005, Whitwell, et al., 2007, Vemuri, et al., 2011) or pathologically confirmed DLB (Kantarci, et al., 2012) due to high test-retest variability. At this time, we were not able to conduct longitudinal measurement of these relatively small and deeply localized structures, and these analyses should be considered in future studies.

Overall, our findings have multiple clinical implications for utilizing serial MRI as a tool in differential diagnosis of dementia, disease progression tracking, and for 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 could be 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 coexisting AD-related pathology in patients with DLB.

Acknowledgments

Study Funding:

The study was funded by the National Institutes of Health: P50-AG16574/P1 and R01AG040042 (to K.K.), R01-AG015866 (to T.J.F.), R01-AG11378 (to C.R.J.), P50-AG16574 (to R.C.P.); Mangurian Foundation; and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program.

Z. N. is supported by the CTSA Grant Number UL1 TR000135 from the National Center for Advancing Translational Science (NCATS), a component of the NIH. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH; by Grant Agency of Charles University in Prague (doctoral student grant 624012), and by European Regional Development Fund – Project FNUSA-ICRC CZ.1.05/1.1.00/02.0123 and project CZ.1.07/2.3.00/20.0117, European Social Fund and the State Budget of the Czech Republic.

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Web references

Statistical Parametric Mapping software. and documentation to be found at: <http://www.fil.ion.ucl.ac.uk/spm/> Recently viewed April 9, 2014

R statistical software to be found at: <http://www.R-project.org> Recently viewed April 9, 2014.

Highlights

- The global atrophy rates in autopsy-confirmed DLB were very low and similar to controls
- Medial temporal atrophy rates were lower in DLB compared to DLB/AD and AD patients
- The pattern of atrophy rates in mixed DLB/AD was similar to AD
- Atrophy rates correlated with Braak neurofibrillary tangle stage, cognitive decline and progression of motor symptoms in DLB and DLB/AD

Figure 1. Rates of the whole brain and ventricle volume change

Boxplots are depicting atrophy rate in the whole brain and expansion in the ventricle. Boxes indicate the lower quartile, the median, and the upper quartile of the distributions with whiskers extending to the furthestmost data point within the distance of 1.5 times the interquartile range.

Figure 2. Regional pattern of the differences in cortical atrophy rates

Voxel-level maps are showing the pattern of between-group differences in the annualized atrophy rates at $p < 0.05$, cluster extent threshold $k = 50$, and corrected for multiple comparisons with false discovery rate. Side T-score bars indicate magnitude of the differences. Pattern of greater atrophy rates in temporo-parietal regions characterizes AD compared to DLB group (left). Similar pattern with smaller magnitude of differences characterizes mixed DLB/AD compared to DLB group (middle). More subtle differences between DLB/AD group and controls control (right) are potentially due to smaller control sample size ($n = 13$) who were part of this analysis. No significant differences were found between DLB versus control and DLB/AD versus AD groups. R=right.

Figure 3. Atrophy rates in the hippocampus and the amygdala

Boxplots are depicting atrophy rates in the hippocampus and amygdala. Boxes indicate the lower quartile, the median, and the upper quartile of the distributions with whiskers extending to the furthestmost data point within the distance of 1.5 times the interquartile range.

Figure 4. Correlations between atrophy rates and measures of disease progression in patients with a range of LB pathology

Scatter plots show adjusted Pearson's correlations between annualized atrophy rates in the whole brain (top row), hippocampus (middle row), amygdala (bottom row), and annualized measures of cognitive decline on MMSE and DRS, and progression of motor findings on UPDRS. Correlation coefficient (ρ) and corresponding p-value is included within each scatterplot. Red triangles represent patients with DLB; blue squares represent patients with mixed DLB/AD.

Table 1

Subjects' characteristics at time of the second MRI (closer to the death).

	Controls n = 15	DLB n = 20	DLB/AD n = 22	AD n = 30	p-value ^d
No. of females (%)	10 (67)	6 (30)	10 (45)	15 (50)	0.19
MRI age, yr.	85.9 (6.8)	77.5 (7.1)	78.0 (9.4)	76.7 (10.7)	0.01
Education, yr.	14.7 (3.6)	14.5 (2.5)	13.9 (3.7)	13.9 (2.9)	0.84
Age at death, yr.	89.9 (7.0)	79.7 (7.6)	80.7 (9.3)	79.4 (10.9)	0.003
Time scan to death, yr.	4.0 (2.3)	2.2 (1.4)	2.7 (1.2)	2.7 (1.5)	0.01 ^b
Scan interval, yr.	2.3 (1.4)	1.7 (0.4)	1.8 (0.7)	1.9 (0.6)	0.20 ^b
Dementia duration, yrs.	-	5.3 (2.5)	6.2 (3.6)	6.5 (3.2)	0.47 ^a
MMSE	28.3 (2.2)	21.7 (5.6) ^c	15.0 (7.0) ^c	15.0 (5.8)	<0.001
DRS	135.1(5.0)	114.3 (19.1) ^c	99.9(21.3) ^c	87.7(26.4)	<0.001
Visual hallucinations [§] (%)	-	9 (45)	9 (41)	-	0.79
Fluctuations [§] (%)	-	7 (64)	2 (50)	-	0.63
RBD [§] (%)	-	14 (88)	6 (50)	-	0.03
UPDRS motor subscale	-	14.1 (7.7) ^c	12.4 (8.1) ^c	-	0.55
Clinical diagnosis (%)					
Cognitively normal	11 (73)	0 (0)	0 (0)	0 (0)	-
MCI	3 (20)	2 (10)	1 (5)	0 (0)	-
Probable DLB	0 (0)	14 (70)	7 (32)	0 (0)	-
Probable AD	0 (0)	4 (20)	14 (64)	28 (93)	-
Other [*]	1 (7)	0 (0)	0 (0)	2 (7)	-
Medication (%)					
ACHEI only	-	7 (35)	11 (50)	23 (76)	-
Dopaminergic agent only	-	3 (15)	1 (5)	0	-
No treatment	-	4 (20)	5 (22.5)	6 (20)	-
ACHEI+Dopaminergic agent	-	6 (30)	4 (17.5)	0	-
Memantine+ACHEI	-	0	1 (5)	1 (4)	-

Means (SD) are reported for continuous variables.

[§] A majority of control and AD subjects have not had clinical features associated with DLB assessed. The proportions (%) of these features are based on the available data which were incomplete due to the retrospective design and the disease severity limiting completion of certain tasks.

* One control subject was clinically diagnosed as uncertain (cognitively normal versus MCI), one patient with AD was clinically diagnosed as having probable corticobasal syndrome, and one patient with AD as having probable fronto-temporal dementia.

[†] Medication: The agents were administered in standard doses, i.e. acetyl-cholinesterase inhibitors (ACHEI) 10mg once a day; memantine 10mg up to twice a day, and dopaminergic agents titrated as needed.

^a From analysis of variance for the continuous variables and from a χ^2 test for differences in proportions.

^b Based on a square root transformation to normalize the distribution.

^c Missing data: MMSE was available in 18 DLB and 21 DLB/AD patients; DRS was available in 15 DLB and 13 DLB/AD patients; UPDRS was available in 15 DLB and 13 DLB/AD patients.

Table 2

Main autopsy findings.

	Controls n = 15	DLB n = 20	DLB/AD n = 22	AD n = 30	P-value ^a
Braak staging (% of cases)					<0.001
I	3 (20)	4 (20)	--	--	
II	4 (27)	6 (30)	--	--	
III	8 (53)	6 (30)	--	--	
IV	--	4 (20)	--	--	
V	--	--	5 (23)	2 (7)	
VI	--	--	17 (77)	28 (93)	
AD Likelihood* (% of cases)					<0.001
Low likelihood	15 (100)	16 (80)	--	--	
Intermediate likelihood	--	4 (20)	--	--	
High likelihood	--	--	22 (100)	30 (100)	

^a From a χ^2 test for differences in proportions.

* According to the NIA-Reagan criteria, 1997.

Table 3

Global rates of change with the mean (SD) for the annualized percentage change.

	Controls n = 15	DLB n = 20	DLB/AD n = 21	AD n = 30	ANCOVA p-value [‡]
Whole Brain	-0.3 (0.5)	-0.4 (0.5)	-1.1 (1.2)	-1.4 (0.9)	0.001
Ventricle	3.6 (1.4)	4.8 (3.3)	8.7 (3.5)	9.4 (4.4)	<0.001

[‡] p-values are from ANCOVA adjusting for age at the time of the second MRI and the time from the second MRI to death.
One patient with DLB/AD was excluded from this analysis due to the boundary shift integral algorithm failure.

Table 4

Correlations (95% CI) between rates of volume change and Braak NFT stage in subjects with a range of LB-pathology.

	Pearson's correlation^a	p-value
Whole Brain	−0.33 (−0.58, −0.01)	0.041
Ventricle	0.43 (0.13, 0.65)	0.006
Hippocampus	−0.63 (−0.79, −0.40)	<0.001
Amygdala	−0.49 (−0.69, −0.20)	0.001

^aThe correlations are adjusted for the age at the second MRI and the time from the second MRI to death.

Table 5

Sample size estimates (95% CI) per treatment group for a clinical trial.

	DLB/AD		AD	
	25%	50%	25%	50%
Whole Brain	274 (104, 1407)	70 (27, 354)	111 (62, 216)	29 (16, 54)
Ventricle	43 (27, 70)	12 (8, 18)	57 (34, 117)	15 (9, 28)
Hippocampus	69 (39, 145)	18 (10, 34)	47 (30, 99)	13 (8, 25)
Amygdala	81 (31, 283)	21 (8, 67)	53 (29, 135)	15 (9, 36)

Sample sizes are estimated to detect a fixed effect of 25% or 50% in reduction of atrophy or expansion rates based on a two-sided two-sample t-test with equal variances, $p < 0.05$, and 80% power.