Longitudinal assessment of global and regional atrophy rates in Alzheimer's disease and dementia with Lewy bodies

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ABSTRACT

Background & objective: Percent whole brain volume change (PBVC) measured from serial MRI scans is widely accepted as a sensitive marker of disease progression in Alzheimer's disease (AD). However, the utility of PBVC in the differential diagnosis of dementia remains to be established. We compared PBVC in AD and dementia with Lewy bodies (DLB), and investigated associations with clinical measures.
Methods: 72 participants (14 DLBs, 25 ADs, and 33 healthy controls (HCs)) underwent clinical assessment and 3 Tesla T1-weighted MRI at baseline and repeated at 12 months. We used FSL-SIENA to estimate PBVC for each subject. Voxelwise analyses and ANCOVA compared PBVC between DLB and AD, while correlational tests examined associations of PBVC with clinical measures.
Results: AD had significantly greater atrophy over 1 year (1.8%) compared to DLB (1.0%; p = 0.01) and HC (0.9%; p < 0.01) in widespread regions of the brain including periventricular areas. PBVC was not significantly different between DLB and HC (p = 0.95). There were no differences in cognitive decline between DLB and AD. In the combined dementia group (AD and DLB), younger age was associated with higher atrophy rates (r = 0.49, p < 0.01).
Conclusions: AD showed a faster rate of global brain atrophy compared to DLB, which had similar rates of atrophy to HC. Among dementia subjects, younger age was associated with accelerated atrophy, reflecting more aggressive disease in younger people. PBVC could aid in differentiating between DLB and AD, however its utility as an outcome marker in DLB is limited.

1. Introduction

Dementia with Lewy bodies (DLB) is the second leading cause of degenerative dementia in older people after Alzheimer's disease (AD), accounting for up to 15% of cases confirmed at autopsy (McKeith et al., 1996). DLB shares common clinical, neuropsychological and pathological features with other dementia subtypes such as AD and Parkinson's disease with dementia, making differentiation between these disorders challenging. Despite the development of consensus diagnostic criteria, the sensitivity for differential diagnosis of DLB in clinical practice remains low and many DLB patients could be misdiagnosed. In light of

this uncertainty, and with important implications for subsequent patient management, there is growing emphasis on the development of reliable imaging markers to help distinguish DLB from other subtypes of dementia.

The majority of imaging studies in AD and DLB have been cross-sectional, while there has been a paucity of longitudinal studies in DLB (O'Brien et al., 2001; Whitwell et al., 2007), which might be more sensitive to detect early pathological changes than measurements at a single time point (Smith et al., 2007). Furthermore, a longitudinal design can reduce the confounding effect of inter-individual morphological variability as each subject serves as his or her own control. The rate of whole brain atrophy on serial MRI is increasingly recognized as a sensitive and objective marker of disease progression in neurodegenerative diseases (Fox and Freeborough, 1997). Reported whole brain atrophy rates in AD range from 1% to 4% per year (Cover et al., 2011), while atrophy rates in similarly aged non-demented people range from 0.3% to 0.7% per year (Cover et al., 2011; Henneman et al., 2009; Sluimer et al., 2008). As such, longitudinal assessment of brain atrophy in

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different subtypes of dementia and healthy controls may allow us to distinguish pathological rates of brain atrophy from normal age-related changes. The clinical relevance of atrophy rates has been supported by previous studies showing the relationship with cognitive dysfunctions (Sluimer et al., 2008). In light of this evidence, global atrophy rates are used as a secondary outcome marker in phase III trials of potentially disease-modifying interventions in AD (Frisoni et al., 2010).

Previous studies using serial MRI to investigate atrophy rates in DLB have yielded conflicting findings, with some studies showing similar rates in subjects with DLB and AD (O'Brien et al., 2001), while slower atrophy rates in DLB have been reported (Whitwell et al., 2007). Thus, the clinical implications of whole brain atrophy rates in DLB remain poorly understood, and further studies are warranted.

The aims of the present study were to use serial MRI to investigate whole brain atrophy rates over a 12-month period in clinically diagnosed subjects with AD and DLB, and similarly aged HC, as well as to investigate the associations between percent brain volume change (PBVC) and clinical measures. Based on earlier cross-sectional findings of reduced whole brain atrophy and relative structural preservation of the medial temporal lobes (Mak et al., 2014; R. Watson et al., 2012a), we hypothesized that subjects with DLB would have significantly lower rates of whole brain atrophy compared to AD.

2. Methods

2.1. Subjects, assessment and diagnosis

At baseline, seventy one subjects with dementia over the age of 60 (36 subjects with probable AD (McKhann et al., 1984) and 35 with probable DLB (McKeith et al., 2005)) were recruited from a community dwelling population of patients referred to local Old Age Psychiatry, Geriatric Medicine or Neurology Services in the North East of England, UK, as previously described (R. Watson et al., 2012a). Consensus on diagnosis was made with 3 experienced clinicians. Subjects underwent clinical and neuropsychological evaluations at baseline and follow-up at 1 year. Thirty-five similarly aged control subjects were recruited from relatives and friends of subjects with dementia or volunteered via advertisements in local community newsletters.

For the purpose of the present study, we included only subjects with MRI assessments from both baseline and 1-year follow-up. Of the 36 AD subjects, 25 were included after 11 were unable to participate in the follow-up assessment. Of the 35 DLB subjects, 14 were included after 12 declined to participate as they or their carers felt they were too unwell and 9 subjects had died. Half the DLB subjects (n = 7) had abnormal dopamine transporter scans as part of the clinical work-up before entering the study. Of the 35 HC subjects, 33 were included in the present analyses after 2 declined to participate due to other reasons. The research was approved by the local ethics committee. All subjects or, where appropriate, their nearest relative, provided written informed consent. Assessment of global cognitive measures at both baseline and follow-up assessments, included the Cambridge Cognitive Examination (CAMCOG) (Huppert et al., 1995), which incorporates the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Motor parkinsonism was evaluated with the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003). For subjects with dementia, neuropsychiatric features were examined with the Neuropsychiatric Inventory (Cummings et al., 1994), and cognitive fluctuations were assessed with the cognitive fluctuation scale (Walker et al., 2000).

2.2. MRI acquisition

Subjects underwent both baseline and repeat MR imaging with a 12-month interval. At each time point, subjects underwent T1 weighted MR scanning on the same 3 T MRI system using an 8 channel head coil (Intera Achieva scanner, Philips Medical Systems, Eindhoven, Netherlands) within 2 months of the clinical assessments as previously described (R. Watson et al., 2012a). The sequence was a standard T1 weighted volumetric sequence covering the whole brain (3D MPRAGE, sagittal acquisition, 1 mm isotropic resolution and matrix size of 240 (anterior–posterior) × 240 (superior–inferior) × 180 (right–left); repetition time (TR) = 9.6 ms; echo time (TE) = 4.6 ms; flip angle = 8°; SENSE factor = 2). The acquired volume was angulated such that the axial slice orientation was standardized to align with the AC–PC line.

2.3. Image analysis

2.3.1. Estimation of whole brain atrophy rate

Whole brain atrophy rate was estimated with SIENA (Smith et al., 2001), part of the FSL software package (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Firstly, brain extraction was performed in acquired images at both of the two time points (Smith et al., 2002). For each individual subject, the baseline and follow-up brain images were aligned to each other (Jenkinson and Smith, 2001) using the skull images to constrain the registration scaling, and both brain images were then resampled into the space halfway. Next, tissue-type segmentation was carried out (Zhang et al., 2001) in order to find brain/non-brain edge points, and then perpendicular edge displacement (between the two time points) was estimated at these edge points. Finally, the mean edge displacement across the whole brain was converted into a global estimate of PBVC between the two time-points.

2.3.2. Voxel-wise assessment of atrophy over time

Next, we performed a voxelwise statistical analysis of atrophy across subjects using SIENAr, an extension of SIENA from the FSL package (Bartsch et al., 2004). Built upon the result of the previous SIENA analysis, the edge displacement image was dilated for each subject, transformed into MNI152 space, and masked by a standard MNI152-space brain edge image. In this way the edge displacement values were warped onto the standard brain edge. Next, voxelwise statistical analysis was performed on the resulting images from all subjects to test for significant differences in atrophy over time among the AD, DLB and HC groups. In all voxelwise comparisons, age and gender were included as covariates in the General Linear Model (GLM). The threshold free cluster enhancement (TCFE) algorithm (Nichols and Holmes, 2002) was used to correct for multiple comparisons across the whole brain at p < 0.05 based on permutation testing (5000 permutations for each contrast in order to build an empirically derived null distribution against which to compare observed effects). The anatomical locations of the significant cortical GM clusters were determined by using the standard Harvard–Oxford cortical structural atlas (see http://www.fmrib.ox.ac.uk/fsl/) containing 48 regions for each hemisphere.

2.4. Statistical analysis

Statistical analyses were performed with the STATA13 (http://www.stata.com) software. The distribution of continuous variables was tested for normality using the Skewness–Kurtosis test and visual inspection of histograms. Parametric data were assessed using either t-tests or analysis of variance (ANOVA) for continuous variables. For non-parametric data, Kruskal–Wallis was used. χ^2 tests were used to examine differences between categorical measures. Group effects in PBVC were tested with analysis of covariance (ANCOVA) controlling for age and gender, followed by post-hoc comparisons using the Tukey–Kramer tests. Associations of PBVC with clinical measures were evaluated with Spearman's rank order correlation coefficient or Pearson's correlations depending on the distribution of the data. These correlational tests were further adjusted by applying Bonferroni correction for multiple

Table 1
Demographics, clinical variables and PBVC.

	HC	DLB	AD	p value
n	33	14	25	
Gender (m:f)	20:13	13:1	15:10	$\chi^2 = 5.37$, 0.07^a
Age (years)	76.7 ± 5.3	77.2 ± 8.0	76.8 ± 5.5	$F_{2,69} = 0.04$, $p = 0.96^b$
Education (years)	11.8 ± 2.6	10.5 ± 1.9	11.4 ± 3.7	$p = 0.14^c$
UPDRS	1.9 ± 1.8	27.2 ± 7.9	4.8 ± 4.0	$p < 0.01^c$
NPI Total		21.5 ± 16.1	19.0 ± 11.9	$p = 1.00^d$
CogFluct		8.4 ± 3.4	2.6 ± 3.5	$p < 0.01^d$
MMSE				
Baseline	29.2 ± 0.9	21.2 ± 6.0	20.6 ± 3.9	$p = 0.70^e$
Follow-up	29.2 ± 0.9	19.7 ± 5.6	18.7 ± 4.0	$p = 0.54^e$
Change	+0.1 ± 1.0	−2.5 ± 2.8	−1.9 ± 3.1	$p = 0.58^e$
CAMCOG				
Baseline	97.8 ± 3.3	69.9 ± 17.3	69.5 ± 11.1	$p = 0.93^e$
Follow-up	98.6 ± 2.8	66.5 ± 17.1	63.0 ± 14.0	$p = 0.49^e$
Change	+0.8 ± 2.5	−5.8 ± 10.3	−6.6 ± 9.9	$p = 0.84^e$
Interscan interval (days)	370.9 ± 13.3	379.1 ± 18.8	379.6 ± 17.8	$p = 0.21^c$
PBVC	−0.9 ± 0.8	−1.0 ± 0.9	−1.8 ± 0.9	
				$F_{2,66} = 8.85$ $p < 0.01^f$ $p = 0.01^g$ $p < 0.00^h$ $p = 0.95^d$

Values expressed as Mean ± 1SD.

Abbreviations: DLB, dementia with Lewy bodies; AD, Alzheimer's disease; HC, healthy control; UPDRS III, Unified Parkinson's Disease Rating Scale, Part III; NPI Total, Neuropsychiatry Inventory; CogFluct, cognitive fluctuation scale; MMSE, Mini-Mental State Examination; CAMCOG, Cambridge Cognitive Examination; PBVC, percent whole brain volume change.

  [a] χ^2 — DLB, AD, and controls.
  [b] ANOVA — HC, DLB, and AD.
  [c] Kruskal–Wallis test.
  [d] Wilcoxon rank-sum test — AD and DLB.
  [e] Student's t-test — AD and DLB.
  [f] ANCOVA with age, gender and inter-scan interval as covariates — HC, DLB, and AD.
  [g] Post-hoc Tukey–Kramer test — AD and DLB.
  [h] Post-hoc Tukey–Kramer test — AD and HC; DLB and HC.

comparisons, where a probability value of $p < 0.003$ (0.05/15) was regarded as significant.

3. Results

3.1. Subject characteristics

The demographic and clinical data for patients and control subjects are summarized in Table 1. Subject groups were well matched for age and educational level, and there was no difference in inter-scan intervals among all subject groups ($p = 0.21$). There were more men in the DLB group and as expected, the DLB group had significantly higher UPDRS III scores than the AD and HC groups. There was no significant difference in age, gender, educational level, UPDRS III, NPI, or cognitive scores between the 21 DLB subjects who dropped out and the 14 DLB subjects who were included in the present study (Supplementary Table 1). AD and DLB did not differ on cognitive measures at baseline, follow-up, or annualized change scores.

3.2. Comparisons of PBVC

Global atrophy between baseline and follow-up was expressed as a negative PBVC. Mean (±SD) PBVC over 1 year was as follows: HC, −0.9% ± 0.8; DLB, −1.0% ± 0.9; and AD, −1.8% ± 0.9. ANCOVA revealed that PBVC over 1 year was significantly different between groups [$F(2,66) = 8.85$, $p < 0.01$] (Table 1). Post-hoc Tukey–Kramer tests revealed significantly greater PBVC over 1 year in AD compared to the DLB ($p = 0.01$) and HC ($p < 0.01$) groups, but the DLB group did not differ from HC ($p = 0.95$) (Fig. 1).

3.3. Voxelwise comparison of atrophy rate: AD vs. HC

The areas showing significantly accelerated atrophy in AD compared to HC are represented in Fig. 2A, $p < 0.05$, Family Wise Error (FWE) corrected. They include regions of the temporal, occipital and parietal
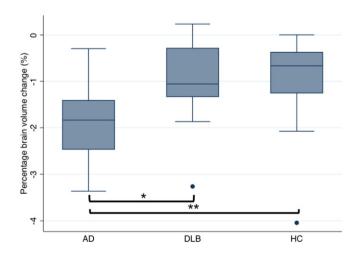

Fig. 1. Box-and-whisker plots showing rates of whole brain atrophy for all diagnostic groups. Negative rates represent a decrease in whole brain volume over time. The horizontal lines in the boxes represent the 25th, 50th (median) and 75th percentiles of the distributions. The vertical lines extending from the boxes stop at the most extreme data points within 1.5 interquartile ranges of the boxes. Differences between groups were assessed by using ANCOVA controlling for age, gender and inter-scan interval, with post-hoc Tukey–Kramer tests. * = $p < 0.05$, ** = $p < 0.01$. Abbreviations: ANCOVA, analysis of covariance; DLB, dementia with Lewy bodies; AD, Alzheimer's disease; HC, healthy control.
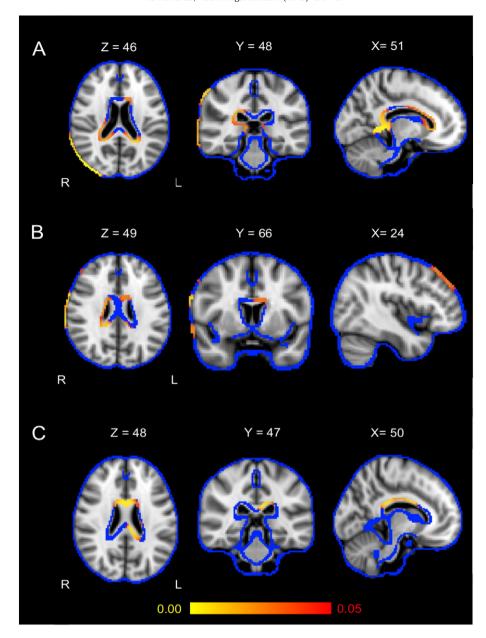
Fig. 2. Longitudinal voxelwise results. Areas of significant differences in atrophy rates between (A) AD and HC, (B) AD and DLB, and (C) correlation between atrophy rate and age in combined dementia group overlaid on the MNI152 standard template. Blue represents all the standard space brain edge voxels used for testing group differences in atrophy rates and associations with clinical measures. Red and yellow represent significant voxels, i.e. p values, FWE corrected. Abbreviations: DLB, dementia with Lewy bodies; AD, Alzheimer's disease; HC, healthy control; FWE, family wise error.

lobes. Significantly accelerated atrophy was also found around the periventricular regions. As expected, there was no region in the brain that showed significantly faster atrophy in HC compared with AD.

3.4. Voxelwise comparison of atrophy rate: AD vs. DLB

The areas of accelerated atrophy in AD compared to DLB are represented in Fig. 2B, p < 0.05, FWE corrected. They include regions of the temporal, frontal and parietal lobes, with atrophy also around the periventricular regions. We did not find any regions showing significantly faster atrophy in DLB compared to AD.

3.5. Voxelwise comparison of atrophy rate: DLB vs. HC

There was no significant difference in regional atrophy rates between DLB and HC after correction for multiple comparisons.

3.6. Association between PBVC and cognitive decline

To investigate the relationship between PBVC and cognitive decline, we assessed associations with global indices of cognition at baseline, follow-up, and annualized change scores. Across the whole sample, PBVC was significantly correlated with $MMSE_{(baseline)}$ ($r = 0.41$, $p < 0.01$), $MMSE_{(follow-up)}$ ($r = 0.37$, $p < 0.01$), $CAMCOG_{(baseline)}$ ($r = 0.40$, $p < 0.01$), and $CAMCOG_{(follow-up)}$ ($r = 0.44$, $p < 0.01$). However, when examined separately within a) the combined dementia group (AD and DLB) and b) HCs, PBVC was not associated either with any measures of global cognition at each time point, or with annualized change scores.

3.7. Association between PBVC and age

A mixed model ANOVA, with age as a within subject factor, diagnostic group (dementia vs. HC) as a between subject factor and gender as

covariate, showed that there was a significant main effect of group on PBVC, [$F(1,67) = 12.35$, $p < 0.01$], no significant main effect of age [$F(1,67) = 1.00$, $p = 0.32$] and a significant group × age interaction [$F(1,67) = 10.82$, $p < 0.01$]. To further investigate the association between age and PBVC, we performed an additional correlation analysis. Within the combined dementia group, PBVC was significantly correlated with age at baseline ($r = 0.49$, $p < 0.01$), suggesting that younger age at baseline is associated with higher rates of atrophy (Fig. 3). Extended voxelwise correlational tests further revealed significant positive correlations between age and atrophy rates in the periventricular region, $p < 0.05$, FWE corrected (Fig. 2D). No significant correlation between PBVC and age at baseline was found within the HC group ($r = -0.25$, $p = 0.16$).

4. Discussion

In this longitudinal study, we examined brain atrophy rates (at whole brain and regional levels) over 1 year in DLB and AD compared against similarly aged HC. We further investigated associations of atrophy rates with clinical and cognitive measures. As hypothesized, the rate of atrophy in the AD group was significantly higher in comparison to the DLB group, which showed a similar atrophy rate relative to HC. Furthermore, among dementia (AD and DLB) subjects, we found that earlier age at baseline was associated with a more aggressive rate of atrophy.

Our results confirm those of previous studies that showed increased whole brain atrophy rates in AD compared to HC (O'Brien et al., 2001; Sluimer et al., 2008; Whitwell et al., 2007). Our HC subjects had a PBVC of −0.9%, while the PBVC in AD subjects was −1.8%, approximately twice that of the controls. These rates of atrophy over 1 year are comparable with previous studies that have investigated clinical cohorts of subjects with AD (Cover et al., 2011; Henneman et al., 2009; O'Brien et al., 2001; Sluimer et al., 2008) with various methodologies. Although the majority of studies assessing atrophy rates in AD have done so over periods of 1 year or more, increased rates of atrophy in AD compared to HC have also been demonstrated at intervals as short as three to six months (Bradley et al., 2002; Schott et al., 2005), and accelerated atrophy is demonstrable several years prior to diagnosis in AD (Fox et al., 2001). Collectively, these findings support a growing body of evidence that rates of atrophy are good discriminators of AD from HC. In contrast, DLB showed a much slower rate of atrophy (−1%) relative to the AD

group. Our result, corroborated by a similar finding from a previous study (Whitwell et al., 2007), suggests that whole brain atrophy rates may be useful in distinguishing DLB from AD. However, a previous study using boundary shift integral to assess whole brain atrophy found no difference in rates between AD and DLB (O'Brien et al., 2001), as although the numerical values were lower in DLB (1.4%) than AD (2%), the relatively small sample size of that study (10 DLBs and 9 ADs) might have reduced the statistical power to detect a between-group difference.

Despite evidence of cognitive decline in the DLB group, atrophy rates were in similar in the DLB and HC groups over 12 months. Our findings are thus consistent with those from an earlier study with pathological verification (Whitwell et al., 2007). Furthermore, the rate of atrophy in non-demented Parkinson's disease has also been reported to be similar to that of HC (Burton et al., 2005). Thus, these convergent findings support the view that alpha-synuclein pathology – a major constituent of Lewy bodies – has limited involvement in neuronal loss (Whitwell et al., 2007). This notion is also consistent with evidence demonstrating a strong correlation between hippocampal atrophy and β-amyloid plaques and neurofibrillary tangles but not synuclein pathology (Burton et al., 2009). It is also interesting to note that cognitive decline was present in DLB compared to HC in the relative absence of atrophic changes over time. More studies will be needed to elucidate the temporal relationships between the onset of cognitive symptoms and structural changes in Lewy body diseases. Furthermore, increasing in vitro evidence also suggests that alpha-synuclein is not a direct causative factor of neurodegeneration. Rather, it triggers a series of secondary molecular processes that eventually leads to a host of processes including neuroinflammation, disruption of neurotransmitters, and eventually cell loss (Lashuel et al., 2013; Wolozin and Behl, 2000).

We also extended previous studies by performing a voxelwise analysis of atrophy rates in different brain regions. Compared to HC, accelerated atrophy was found predominantly in the temporal, parietal, and to a lesser degree, occipital lobes in AD. Our longitudinal findings thus provide further support to the characteristic pattern of atrophy in the medial temporal lobe and temporo-parietal cortices at the cross-sectional level (Whitwell et al., 2007).

Our voxelwise analysis did not reveal significantly higher atrophy rate in the DLB group when compared to the AD group in any brain
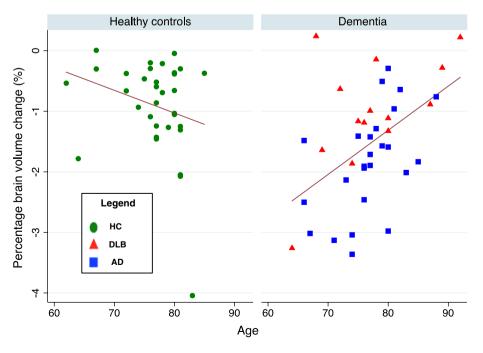

Fig. 3. Scatterplots of age at baseline by whole-brain atrophy rate.

region, while the reverse contrast (AD < DLB) showed accelerated atrophy affecting widespread areas including the temporal, frontal and parietal regions in the AD group. These longitudinal results are in keeping with a growing literature – albeit mostly cross-sectional – suggesting that DLB is typically characterized by less pronounced global atrophy than AD while the relative preservation of the medial temporal lobe in DLB has been the most consistent structural MRI finding (Mak et al., 2014). Similarly, we did not find atrophy of the temporal lobe in DLB compared to HC despite applying a relatively liberal threshold of p < 0.001 at an uncorrected level (data not shown). Although the mechanisms underlying cognitive decline in DLB and AD remain poorly understood, our finding of differential patterns of temporal lobe atrophy may also have implications for cognitive abnormalities associated with AD and DLB, such as the marked impairment of episodic memory in AD compared to DLB.

The involvement of frontal lobe deficits in DLB remains to be established. Ballmaier and colleagues have reported greater atrophy of the frontal areas in AD compared to DLB (Ballmaier et al., 2004), but other studies have reported no difference in frontal volumes between DLB and AD (Burton et al., 2002). Moreover, the relative preservation of the temporal lobe has led researchers to hypothesize that the frontal lobe could be less susceptible in DLB as the reciprocal connections with temporal regions would be affected to a lower degree (Ballmaier et al., 2004). Compared to DLB, our finding of accelerated atrophy in the frontal lobe in AD supports this hypothesis, and corroborates with baseline evidence of lesser white matter tract changes in frontal areas in DLB (Rosie Watson et al., 2012b).

Age is the strongest risk factor for dementia, yet the extent to which atrophy rates change with age in dementia remains to be clarified. We found that the effect of age on atrophy rates could be modulated by neurodegenerative pathologies, as evidenced by a significant group × age interaction. Consistent with a previous study in AD (Whitwell et al., 2007), we demonstrated that atrophy rates in the combined dementia group accelerated with younger baseline age. Furthermore, our voxelwise analysis extends previous findings by showing that the age–atrophy association was primarily driven by ventricular expansion over 1 year. Another cross-sectional study also demonstrated increased cortical thinning in younger AD patients (aged 60–75 years) compared to older AD patients (aged 80–91 years) despite similar degrees of global cognitive impairment (Stricker et al., 2011). Considered together, these findings corroborate previous research suggesting less severe pathological burden in late-onset AD, and would support the notion that the extent of pathological changes required to manifest cognitive deficits is markedly lower as people age (Marshall et al., 2007). Although we found a negative but non-significant correlation between age at baseline and PBVC for HC (increased atrophy rate with advancing years), a previous study in HC reported that the strongest negative correlations between age and percent annual change in regional volumes were found in the entorhinal cortex and the hippocampus — both of which are particularly vulnerable in the early stages of AD (Fjell et al., 2009).

Despite evidence suggesting that whole brain atrophy rates are associated with cognitive decline among AD subjects (Sluimer et al., 2008), we did not find any significant correlation of global atrophy rates with global cognitive measures in both AD and DLB. There are few possible reasons for this observation. As discussed, alpha-synuclein pathology in DLB might be more closely associated with synaptic dysfunction rather than cell loss (PBVC), which was reported to be minimal and comparable to HC. Another possible reason for a lack of correlation is the within-subject variability of such neuropsychological measurements. Furthermore, it is likely that capacities involved in the performance of MMSE and MOCA are underpinned by anatomically distinct brain regions.

The major strengths of the study include a well-characterized group of probable DLB and AD patients. In addition, all the groups were matched for age and educational level. Some potential limitations of this study include the lack of neuropathological verification of AD and DLB, as subject groups were based on clinical diagnosis, though this is an inherent limitation of all ante-mortem imaging studies. Furthermore,

we have previously demonstrated good agreement between clinical and pathological diagnoses using the consensus clinical diagnostic method adopted here (McKeith et al., 2000). However, we cannot exclude the possibility that, given their age, a proportion of HC subjects will also have preclinical disease, which would potentially reduce the sensitivity of between-group differences in atrophy rates. The high rate of attrition in the DLB group should also be considered when interpreting our findings. Less than half (n = 14) of the originally recruited DLB subjects (n = 35) returned for a follow-up assessment due to disease progression. While it is possible that differences in gender and mortality rates might have influenced our results, these observations are in keeping with previously established differences in gender ratios (Nelson et al., 2010) and mortality rates between AD and DLB (Williams et al., 2006). Although the present study found similar rates of atrophy in DLB and HC, it is worth noting that a previous voxel-based morphometry study of the same cohort at baseline demonstrated both cortical and subcortical atrophy in DLB compared to HC (R. Watson et al., 2012a). This raises the question as to whether the DLB subjects in the present study represent a more resilient sub-group of DLB. However, they did not differ from those who were unable to complete the 12 month assessment (n = 21) in age or measures of global cognition, neuropsychiatric features or motor parkinsonism. Lastly, our finding of a significant correlation between age and rate of atrophy in the periventricular regions should be considered with the caveat that the FSL-SIENAr technique might be more sensitive along ventricular boundaries that are smooth and well defined as opposed to the sulci.

5. Conclusions

Our results indicate a higher rate of global brain atrophy in AD compared to DLB, reflecting pathophysiological differences between Lewy body and AD and highlight the potential utility of longitudinal imaging to improve differential diagnosis. Our results also suggest that, unlike AD, whole brain atrophy rate over 1 year may not be useful as a potential outcome marker for putative disease modifying therapies in DLB, and other markers are needed.

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Author contributions

Elijah Mak formulated the research question, performed the statistical analyses, interpreted the results, and wrote the manuscript. Su Li and Guy Williams assisted with the interpretation of the results, and provided comments and additional suggestions for revisions of the draft.

Rosie Watson, recruited and assessed study participants, assisted with the interpretation of the results, and reviewed the manuscript.

Michael Firbank designed the imaging protocol, assisted with the interpretation of the results, and reviewed the manuscript.

Andrew Blamire obtained funding for the project, designed the imaging protocol, undertook routine quality assurance on the MR system, assisted with the interpretation of the results, and reviewed the manuscript.

John O'Brien obtained funding for the project, designed the imaging protocol, assisted with recruitment of study participants, assisted with the interpretation of the results, and reviewed the manuscript. All authors approved the final manuscript.

Disclosures

Elijah Mak has no conflict of interests. Li Su has no conflict of interests. Guy Williams has no conflict of interests. Rosie Watson has no conflict of interests. Andrew Blamire has no conflict of interests. Michael Firbank has no conflict of interests. John O'Brien has acted as a consultant for GE Healthcare, Lilly, TauRx and Cytox.

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References

Ballmaier, M., O'Brien, J.T., Burton, E.J., Thompson, P.M., Rex, D.E., Narr, K.L., McKeith, I.G., DeLuca, H., Toga, A.W., 2004. Comparing gray matter loss profiles between dementia with Lewy bodies and Alzheimer's disease using cortical pattern matching: diagnosis and gender effects. Neuroimage 23 (1), 325–335. http://dx.doi.org/10.1016/j.neuroimage.2004.04.02615325380.

Bartsch, A.J., De Stefano, N., Homola, G., Smith, S., 2004. Extending SIENA for a multi-subject statistical analysis of sample-specific cerebral edge shifts: substantiation of early brain regeneration through abstinence from alcoholism. Tenth Int. Conf. Funct. Mapp. Hum. Brain.

Bradley, K.M., Bydder, G.M., Budge, M.M., Hajnal, J.V., White, S.J., Ripley, B.D., Smith, A.D., 2002. Serial brain MRI at 3–6 month intervals as a surrogate marker for Alzheimer's disease. Br. J. Radiol. 75 (894), 506–51312124237.

Burton, E.J., Barber, R., Mukaetova-Ladinska, E.B., Robson, J., Perry, R.H., Jaros, E., Kalaria, R.N., O'Brien, J.T., 2009. Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. Brain 132 (1), 195–203. http://dx.doi.org/10.1093/brain/awn29819022858.

Burton, E.J., Karas, G., Paling, S.M., Barber, R., Williams, E.D., Ballard, C.G., McKeith, I.G., Scheltens, P., Barkhof, F., O'Brien, J.T., 2002. Patterns of cerebral atrophy in dementia with Lewy bodies using voxel-based morphometry. Neuroimage 17 (2), 618–630. http://dx.doi.org/10.1006/nimg.2002.119712377138.

Burton, E.J., McKeith, I.G., Burn, D.J., O'Brien, J.T., 2005. Brain atrophy rates in Parkinson's disease with and without dementia using serial magnetic resonance imaging. Mov. Disord. 20 (12), 1571–1576. http://dx.doi.org/10.1002/mds.2065216116613.

Cover, K.S., van Schijndel, R.A., van Dijk, B.W., Redolfi, A., Knol, D.L., Frisoni, G.B., Barkhof, F., Vrenken, H., neuGRID, Alzheimer's Disease Neuroimaging Initiative, 2011. Assessing the reproducibility of the SienaX and Siena brain atrophy measures using the ADNI back-to-back MP-RAGE MRI scans. Psychiatry Res. 193 (3), 182–190. http://dx.doi.org/10.1016/j.pscychresns.2011.02.01221764565.

Cummings, J.L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D.A., Gornbein, J., 1994. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 44 (12), 2308–23147991117.

Fjell, A.M., Walhovd, K.B., Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Holland, D., Brewer, J.B., Dale, A.M., 2009. One-year brain atrophy evident in healthy aging. J. Neurosci. 29 (48), 15223–15231. http://dx.doi.org/10.1523/JNEUROSCI.3252-09.200919955375.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12 (3), 189–1981202204.

Fox, N.C., Crum, W.R., Scahill, R.I., Stevens, J.M., Janssen, J.C., Rossor, M.N., 2001. Imaging of onset and progression of Alzheimer's disease with voxel-compression mapping of serial magnetic resonance images. Lancet 358 (9277), 201–205. http://dx.doi.org/10.1016/S0140-6736(01)05408-311476837.

Fox, N.C., Freeborough, P.A., 1997. Brain atrophy progression measured from registered serial MRI: validation and application to Alzheimer's disease. J. Magn. Reson. Imaging 7 (6), 1069–10759400851.

Frisoni, G.B., Fox, N.C., Jack, C.R., Scheltens, P., Thompson, P.M., 2010. The clinical use of structural MRI in Alzheimer disease. Nat. Rev. Neurol. 6 (2), 67–7720139996.

Henneman, W.J., Sluimer, J.D., Barnes, J., van der Flier, W.M., Sluimer, I.C., Fox, N.C., Scheltens, P., Vrenken, H., Barkhof, F., 2009. Hippocampal atrophy rates in Alzheimer disease: added value over whole brain volume measures. Neurology 72 (11), 999–1007. http://dx.doi.org/10.1212/01.wnl.0000344568.09360.3119289740.

Huppert, F.A., Brayne, C., Gill, C., Paykel, E.S., Beardsall, L., 1995. CAMCOG — a concise neuropsychological test to assist dementia diagnosis: socio-demographic determinants in an elderly population sample. Br. J. Clin. Psychol. 34 (4), 529–541.

Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med. Image Anal. 5 (2), 143–15611516708.

Lashuel, H.A., Overk, C.R., Oueslati, A., Masliah, E., 2013. The many faces of α-synuclein: from structure and toxicity to therapeutic target. Nat. Rev. Neurosci. 14 (1), 38–48. http://dx.doi.org/10.1038/nrn340623254192.

Mak, E., Su, L., Williams, G.B., O'Brien, J.T., 2014. Neuroimaging characteristics of dementia with Lewy bodies. Alzheimers Res. Ther. 6 (2), 1825031634.

Marshall, G.A., Fairbanks, L.A., Tekin, S., Vinters, H.V., Cummings, J.L., 2007. Early-onset Alzheimer's disease is associated with greater pathologic burden. J. Geriatr. Psychiatry Neurol. 20 (1), 29–33. http://dx.doi.org/10.1177/08919887062970861734176837.

McKeith, I.G., Ballard, C.G., Perry, R.H., Ince, P.G., O'Brien, J.T., Neill, D., Lowery, K., Jaros, E., Barber, R., Thompson, P., Swann, A., Fairbairn, A.F., Perry, E.K., 2000. Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology 54 (5), 1050–105810720273.

McKeith, I.G., Dickson, D.W., Lowe, J., Emre, M., O'Brien, J.T., Feldman, H., Cummings, J., Duda, J.E., Lippa, C., Perry, E.K., Aarsland, D., Arai, H., Ballard, C.G., Boeve, B., Burn, D.J., Costa, D., Del Ser, T., Dubois, B., Galasko, D., Gauthier, S., Goetz, C.G., Gomez-Tortosa, E., Halliday, G., Hansen, L.A., Hardy, J., Iwatsubo, T., Kalaria, R.N., Kaufer, D., Kenny, R.A., Korczyn, A., Kosaka, K., Lee, V.M., Lees, A., Litvan, I., Londos, E., Lopez, O.L., Minoshima, S., Mizuno, Y., Molina, J.A., Mukaetova-Ladinska, E.B., Pasquier, F., Perry, R.H., Schulz, J.B., Trojanowski, J.Q., Yamada, M., 2005. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65 (12), 1863–1872. http://dx.doi.org/10.1212/01.wnl.0000187889.17253.b116237129.

McKeith, I.G., Galasko, D., Kosaka, K., Perry, E.K., Dickson, D.W., Hansen, L.A., Salmon, D.P., Lowe, J., Mirra, S.S., Byrne, E.J., Lennox, G., Quinn, N.P., Edwardson, J.A., Ince, P.G., Bergeron, C., Burns, A., Miller, B.L., Lovestone, S., Collerton, D., Jansen, E.N., Ballard, C., de Vos, R.A., Wilcock, G.K., Jellinger, K.A., Perry, R.H., 1996. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. Neuroil. 47 (5), 1113–11248909416.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS–ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neuroil. 34 (7), 939–944. http://dx.doi.org/10.1212/wnl.34.7.9396610841.

Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Mov. Disord. 18 (7), 738–750. http://dx.doi.org/10.1002/mds.1047312815652.

Nelson, P.T., Schmitt, F.A., Jicha, G.A., Kryscio, R.J., Abner, E.L., Smith, C.D., Van Eldik, L.J., Markesbery, W.R., 2010. Association between male gender and cortical Lewy body pathology in large autopsy series. J. Neurol. 257 (11), 1875–1881. http://dx.doi.org/10.1007/s00415-010-5630-420563821.

Nichols, T.E., Holmes, A.P., 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum. Brain Mapp. 15 (1), 1–2511747097.

O'Brien, J.T., Paling, S., Barber, R., Williams, E.D., Ballard, C., McKeith, I.G., Gholkar, A., Crum, W.R., Rossor, M.N., Fox, N.C., 2001. Progressive brain atrophy on serial MRI in dementia with Lewy bodies, AD, and vascular dementia. Neurology 56 (10), 1386–138811376193.

Schott, J.M., Price, S.L., Frost, C., Whitwell, J.L., Rossor, M.N., Fox, N.C., 2005. Measuring atrophy in Alzheimer disease: a serial MRI study over 6 and 12 months. Neurology 65 (1), 119–124. http://dx.doi.org/10.1212/01.wnl.0000167542.89697.0f16009896.

Sluimer, J.D., van der Flier, W.M., Karas, G.B., Fox, N.C., Scheltens, P., Barkhof, F., Vrenken, H., 2008. Whole-brain atrophy rate and cognitive decline: longitudinal MR study of memory clinic patients. Radiology 248 (2), 590–598. http://dx.doi.org/10.1148/radiol.248207093818574133.

Smith, S.M., De Stefano, N., Jenkinson, M., Matthews, P.M., 2001. Normalized accurate measurement of longitudinal brain change. J. Comput. Assist. Tomogr. 25 (3), 466–47511351200.

Smith, S.M., Rao, A., De Stefano, N., Jenkinson, M., Schott, J.M., Matthews, P.M., Fox, N.C., 2007. Longitudinal and cross-sectional analysis of atrophy in Alzheimer's disease: cross-validation of BSI, SIENA and SIENAX. Neuroimage 36 (4), 1200–1206. http://dx.doi.org/10.1016/j.neuroimage.2007.04.03517537648.

Smith, S.M., Zhang, Y., Jenkinson, M., Chen, J., Matthews, P.M., Federico, A., De Stefano, N., 2002. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 17 (1), 479–48912482100.

Stricker, N.H., Chang, Y.-L., Fennema-Notestine, C., Delano-Wood, L., Salmon, D.P., Bondi, M.W., Dale, A.M., Alzheimer's Disease Neuroimaging Initiative, 2011. Distinct profiles of brain and cognitive changes in the very old with Alzheimer disease. Neuroil. 77 (8), 713–721. http://dx.doi.org/10.1212/WNL.0b013e31822b000421832223.

Walker, M.P., Ayre, G.A., Cummings, J.L., Wesnes, K., McKeith, I.G., O'Brien, J.T., Ballard, C.G., 2000. The clinician assessment of fluctuation and the One Day Fluctuation Assessment Scale. Two methods to assess fluctuating confusion in dementia. Br. J. Psychiatry 177, 252–25611040887.

Watson, R., Blamire, A.M., Colloby, S.J., Wood, J.S., Barber, R., He, J., O'Brien, J.T., 2012a. Characterizing dementia with Lewy bodies by means of diffusion tensor imaging. Neurology 79 (9), 906–914. http://dx.doi.org/10.1212/WNL.0b013e318266fc5122895591.

Watson, R., O'Brien, J.T., Barber, R., Blamire, A.M., 2012b. Patterns of gray matter atrophy in dementia with Lewy bodies: a voxel-based morphometry study. Int. Psychogeriatr. 24 (4), 532–540. http://dx.doi.org/10.1017/s104161021100217122126938.

Whitwell, J.L., Jack Jr., C.R., Parisi, J.E., Knopman, D.S., Boeve, B.F., Petersen, R.C., Ferman, T.J., Dickson, D.W., Josephs, K.A., 2007. Rates of cerebral atrophy differ in different degenerative pathologies. Brain 130 (4), 1148–1158. http://dx.doi.org/10.1093/brain/awm02117347250.

Williams, M.M., Xiong, C., Morris, J.C., Galvin, J.E., 2006. Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease. Neurology 67 (11), 1935–1941. http://dx.doi.org/10.1212/01.wnl.0000247041.63081.9817159097.

Wolozin, B., Behl, C., 2000. Mechanisms of neurodegenerative disorders: part 1: protein aggregates. Arch. Neurol. 57 (6), 793–796. http://dx.doi.org/10.1001/archneur.57.6.79310867775.

Zhang, Y., Brady, M., Smith, S., 2001. Segmentation of brain MR images through a hidden Markov random field model and the expectation–maximization algorithm. IEEE Trans. Med. Imaging 20 (1), 45–57. http://dx.doi.org/10.1109/42.90642411293691.