Progressive cortical thinning and subcortical atrophy in dementia with Lewy bodies and Alzheimer's disease

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ABSTRACT

Patterns of progressive cortical thinning in dementia with Lewy bodies (DLB) remains poorly understood. We examined spatiotemporal patterns of cortical thinning and subcortical atrophy over 12 months in DLB (n=13), compared to Alzheimer's disease (AD) (n=23) and healthy controls (HC) (n=33). Rates of temporal thinning in DLB were relatively preserved compared to AD. Volumetric analyses subcortical changes revealed that the AD group demonstrated significantly increased hippocampal atrophy (-5.8%) relative to the HC (-1.7%; $p<0.001$) and DLB groups (-2.5%, $p=0.006$). Significant lateral ventricular expansion was also observed in AD (8.9%) compared to HC (4.3%; $p<0.001$), and DLB (4.7%; $p=0.008$) at trend level. There was no significant difference in subcortical atrophy and ventricular expansion between DLB and HC. In the DLB group, increased rates of cortical thinning in the frontal and parietal regions were significantly correlated with decline in global cognition (MMSE) and motor deterioration (UPDRS3) respectively. Overall, AD and DLB are characterized by different spatiotemporal patterns of cortical thinning over time. Our findings warrant further consideration of longitudinal cortical thinning as a potential imaging marker to differentiate DLB from AD.

Keywords: Dementia, Alzheimer's disease, Lewy bodies, MRI, neuroimaging, atrophy

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 [1–3]. Because low sensitivity for the diagnosis for DLB remains a problem [4] , there is a need for the development of reliable imaging markers to help distinguish DLB from other subtypes of dementia.

Cortical thickness is increasingly recognized as a more precise parameter of age-associated decline in grey matter compared to the voxel-based morphometry (VBM) technique [5,6]. In a previous study, we found a greater extent of cortical thinning in the AD group affecting predominantly temporo-parietal areas whereas DLB was characterized with cortical thinning in posterior structures [7]. This finding is consistent with a growing literature of reduced global atrophy in DLB compared to AD [8], while the preservation of the medial temporal lobe in DLB has been incorporated as a supportive feature in the revised criteria for the diagnosis of DLB [9].

As with our previous investigation, the majority of imaging studies in DLB has been cross-sectional, and no study to date has investigated the longitudinal progression of cortical thinning in DLB. To address this gap in the present literature, our aim in this study was to compare the progression of cortical thickness over a 12-month period in AD and DLB, and similarly aged healthy controls (HC). Based on earlier cross-sectional findings [8], we hypothesized that DLB would have significantly lower rates of cortical thinning compared to AD, particularly in the temporal lobe.

2. METHODS

2.1. Subjects, assessment and diagnosis

36 subjects with probable AD [10] and 35 with probable DLB [9] were recruited from a community dwelling population of patients referred to local Old Age Psychiatry, Geriatric Medicine or Neurology Services as previously described [11]. 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 caregivers felt they were too unwell and 9 subjects had died. However, there were no significant differences in age, gender, educational level, UPDRS III, NPI, or cognitive scores between the DLB subjects who dropped out and the DLB subjects who were included in the present study (Table 2). 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. At baseline and follow-up assessments, global cognitive measures included the Cambridge Cognitive Examination (CAMCOG) [12], which incorporates the Mini-Mental State Examination (MMSE) [13] in addition to a number of subscales assessing domains including orientation, language, memory, attention, praxis, calculation, abstract thinking and perception. Visuospatial memory was assessed with the Brief Visuospatial Memory Test (BVMT) [14]. Motor parkinsonism was

evaluated with the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) [15]. For subjects with dementia, neuropsychiatric features were examined with the Neuropsychiatric Inventory [16], and cognitive fluctuations were assessed with the cognitive fluctuation scale [17]. Functional ability was assessed with the Bristol Activities of Daily Living Scale (BADLS) [18].

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 3T MRI system using an 8 channel head coil (Intera Achieva scanner, Philips Medical Systems, Eindhoven, Netherlands). 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) x 240 (superior-inferior) x 180 (right-left); repetition time (TR) = 9.6ms; echo time (TE) = 4.6ms; flip angle = 8^{o}; SENSE factor = 2).

2.3. Image analysis

Cortical reconstruction and volumetric segmentation of MRI scans were processed on the same workstation using the Freesurfer 5.3 image analysis suite (http://surfer.nmr.mgh.harvard.edu/). The technical details are described previously [19,20]. The initial processing of T1w MRI images, for each subject and each time point, includes the following steps: removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures, intensity normalization, tessellation of the grey matter/white matter boundary, automated topology correction, and surface deformation to

optimally place the grey matter/white matter and grey matter/cerebrospinal fluid (CSF) boundaries. The cortical thickness is calculated as the closest distance from the grey/white matter boundary to the grey/CSF boundary at each vertex. All surface models in our study were inspected for accuracy and manual corrections were performed in the event of tissue misclassification / white matter errors. However, 3 subjects (2 AD, 1 DLB) still had extensive pial/white matter surface errors and were excluded. The dataset for all subsequent analyses comprised of 33 HC, 23 AD, and 13 DLB.

Subsequently, for the longitudinal processing, an unbiased within-subject template space [21] was created using robust, inverse consistent registration [22]. Several processing steps, such as skull stripping, Talairach transformations, atlas registration, as well as spherical surface maps and parcellations were then initialized with common information from the within-subject template, significantly increasing reliability and statistical power [23]. The cortical thickness maps were smoothed using a 15-mm full width at half maximum Gaussian kernel to reduce local variations in the measurements.

In addition, the following volumetric measures at both time-points were automatically obtained using Freesurfer: total intracranial volume, lateral ventricles, and 7 subcortical structures including the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and the nucleus accumbens.

2.4. Statistical analyses

Demographic and clinical measures

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. For each test statistic, a two-tailed probability value of < 0.05 was regarded as significant.

Cortical thickness comparisons

For each hemisphere, vertex-wise comparisons of percent change of cortical thickness (PcCTh) among the subject groups were performed using the longitudinal two stage general linear model in Freesurfer [23]. The PcCTh was the dependent factor and the diagnostic group was the independent factor. Additionally, we examined the correlations of PcCTh with cognitive decline (baseline score – follow-up score. To assess the involvement of PcCTH in disease severity, we assessed correlations with change scores of the UPDRS. In all imaging analyses, age and gender were included as nuisance covariates, and Family Wise Error (FWE) cluster-wise correction using Monte Carlo simulations with 10,000 iterations were applied to correct for multiple-comparisons [24].

Longitudinal atrophy of subcortical structures

To reduce the number of comparisons, we derived a total volume for each structure by combining the volumes from both hemispheres. For each subject, we first calculated the absolute difference in volumes between both times [(volume $_{\text{follow-up}}$ – volume $_{\text{baseline}}$)], before dividing by the volume at baseline [(volume $_{\text{follow-up}}$ – volume $_{\text{baseline}}$) /

volume $_{baseline}$] to quantify the amount of atrophy with respect to baseline, before multiplying by 100 to derive a percentage change score: [(volume $_{follow\text{-}up}$ – volume $_{baseline}$) / volume $_{baseline}$] * 100%. Subsequently, group differences in percentage change of subcortical volumes were tested with analysis of covariance (ANCOVA) controlling for age, gender, and the average of total intracranial volumes at both time-points. Post-hoc Tukey-Kramer pairwise comparisons were subsequently tested between each group.

3. Results

Subject characteristics

The demographic and clinical data for dementia and control subjects are summarized in Table 1. Subject groups were well matched for age, gender, and educational level, and there was no difference in inter-scan intervals among all subject groups (p=0.21). As expected, the DLB group had significantly higher UPDRS scores than the AD and HC groups at both time-points. Functional ability (BADLS) was similar in DLB and AD (p=0.23). Disease duration was comparable in both DLB (52.2 months) and AD (51.8 months; p=0.96), and the proportion of subjects on cholinesterase inhibitors was also similar (p=0.23). There were no significant differences in changes of NPI (p=0.50), CogFluct (p=0.52), between DLB and AD.

Longitudinal analyses of cognitive decline in DLB and AD

AD and DLB did not differ on global cognitive measures such as MMSE and CAMCOG at baseline or follow-up. Although both DLB and AD performed poorer over time, the decline in global cognition did not differ between groups. BVMT

scores were similar for both groups at baseline and follow-up, including change scores.

Comparisons of longitudinal cortical thinning: AD vs HC

Compared to HC, the AD subjects had significantly greater PcCTh in the bilateral frontal and temporo-parietal cortices: left precuneus, left rostral middle frontal gyrus, left isthmus cingulate, left temporal pole, left superior parietal gyrus, left superior frontal gyrus, left inferior parietal gyrus, left middle temporal gyrus, left caudal middle frontal gyrus left cuneus, right superior parietal gyrus, right precuneus, right superior frontal gyrus, right paracentral gyrus and right middle temporal gyrus. Compared to AD, no increased rates of cortical thinning was found in the HC group (Figure 1; Table e-1; FWE Monte Carlo cluster-wise corrected).

Comparisons of longitudinal cortical thinning: AD vs DLB

Compared to DLB, the AD subjects had significantly greater PcCTh in the left middle and superior temporal gyrus, extending to the left lingual gyrus. No increased progressive cortical thinning was found in the DLB group compared to AD (Figure 1; Table e-1; FWE Monte Carlo cluster-wise corrected).

Comparisons of longitudinal cortical thinning: DLB vs HC

There were no significant differences in PcCTh in any regional areas between the DLB and HC groups.

Clinical and cognitive associations of cortical thinning

The anatomical results for the vertex-wise correlational analyses are displayed in

Figure 2; Table e-2; controlled for age and gender and FWE Monte Carlo cluster-wise corrected. In the DLB group, increased PcCTH in the left frontal lobe was significantly correlated with decline in MMSE scores, CAMCOG Orientation and Expressive Language performances. Decline in UPDRS was also significantly correlated with increased rates of thinning in the right superior parietal region. In the AD group, increased PcCTH in the bilateral frontal regions were significantly correlated with decline in BVMT scores. No significant correlations between rates of cortical thinning and cognitive decline were demonstrated in the HC group.

Longitudinal comparisons of subcortical atrophy and ventricular expansion

Table 3 and Figure 3 show the percentage change in subcortical volumes between baseline and follow-up. After Bonferroni correction for multiple comparisons, the AD group demonstrated significantly increased longitudinal hippocampal atrophy (-5.8%) relative to the HC (-1.7%; $p<0.001$) and DLB groups (-2.5%, $p=0.006$). Significant lateral ventricular expansion was also observed in AD (8.9%) compared to HC (4.3%; $p<0.001$), and DLB (4.7%; $p=0.008$) at trend level. There was no significant difference in subcortical atrophy and ventricular expansion between DLB and HC.

4. Discussion

Previous longitudinal studies in DLB have focused on the assessment of global brain measures such as whole brain atrophy rates, yielding somewhat conflicting results. O'Brien and colleagues found no significant differences in whole brain atrophy rates between AD and DLB [25]. In contrast, another study with pathological confirmation of diagnosis revealed significantly greater global atrophy rates in AD compared to DLB [26]. To our knowledge, this is the first study to evaluate the topographical

differences in the progression of cortical thinning between DLB and AD. The main findings are: (i) DLB and AD are characterized by distinct spatial and temporal patterns of cortical thinning. Consistent with our *a priori* hypothesis, the temporal lobe showed significantly greater cortical thinning in AD compared to DLB over the follow-up period; (ii) regional cortical thinning over time was correlated with cognitive decline in both AD and DLB groups; (iii) significantly greater loss of hippocampal volume and lateral ventricular expansion over 1 year was also observed in the AD group.

Firstly, the present longitudinal findings should be interpreted in light of the baseline comparison [7]. Compared to similarly aged HC, we have previously reported that AD was characterized by cortical thinning in the temporo-parietal cortices extending into the frontal lobes while a milder degree of cortical thinning in the parietal regions was evident in DLB. Furthermore, cortical thickness of the left temporal lobe was relatively preserved in DLB compared to AD at baseline. As such, it is noteworthy that our present longitudinal study has revealed a similar spatial pattern of accelerated thinning in the cortical regions that were already thinner in AD compared to HC and DLB at baseline.

At present, the longitudinal progression of cortical thinning in DLB is relatively unknown. Moreover, the cellular mechanisms through which alpha-synuclein pathology – the characteristic hallmark of Lewy body disease – contributes to neurodegeneration remains poorly understood [27]. Increasing *in vitro* evidence also suggests that alpha-syunclein is not a direct causative factor of neurodegeneration. Rather, it triggers a series of secondary molecular processes that eventually leads to

neuroinflammation, disruption of neurotransmitters, and eventually cell loss [27,28]. Consistent with this view, we found no differences in the rates of regional cortical thinning between DLB and HC over 12 months. Although it is possible that our negative finding might represent a Type-II error due to the relatively small sample size of DLB (n=13) and short duration of follow-up (1 year), corroborative evidence have come from previous studies. A larger study has found similar global and regional brain atrophy rates in pathologically confirmed DLB (n = 20) and HC (n = 15) subjects over a long follow-up period of 2 years [29]. In addition, using a Boundary Shift Integral method, Whitwell and colleagues (2007) also reported minimal global atrophy rates in DLB (n = 9) compared to HC (n = 25). Similar patterns of atrophy rates have also been reported in subjects with Parkinson's disease (PD), another Lewy body disease [30,31]. These convergent findings, despite methodological differences and sampling (clinical and autopsy confirmation), support the view that alpha-synuclein pathology – a major constituent of Lewy bodies – has limited direct involvement in cerebral atrophy. 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 [32].

Compared to AD, DLB was characterized by a significantly slower rate of temporal thinning compared to AD. It is well-established that the relative preservation of the MTL in DLB compared to AD is recognized as the most consistent structural MRI finding at the cross-sectional level [8], and is in keeping with the different neuropsychological profiles of both groups. Considered with our baseline observation of reduced temporal thickness in AD [7], the present findings extend the literature by elucidating the differential trajectories of temporal thinning in both conditions over

time, thereby validating the inclusion of medial temporal lobe preservation as a supportive biomarker for the clinical diagnosis of DLB [9]. While the diagnostic value of FP-CIT for DLB has been established to be the "gold standard" in the clinical community [33], there are clinical benefits to be gained with multimodal imaging (i.e. integrating SPECT and MRI in conjunction). In terms of improving accuracy in differential diagnosis, MRI striatal volumetric data have been combined with occipital perfusion SPECT to distinguish subjects with mild DLB from subjects with mild AD with a high degree of sensitivity and specificity [34].

The clinical implications of cortical thinning in DLB are still poorly understood. Our correlational analyses of the UPDRS change scores among the DLB subjects revealed a significant association between increased thinning in the superior parietal cortex and greater motor deterioration. Our findings are in accord with recent VBM studies demonstrating significant atrophy of the parietal cortex in PD subjects presenting with freezing of gait compared to PD subjects without freezing symptoms [35,36]. In addition, white matter hyperintensities in the parietal lobe has been linked to impaired balance and postural support [37]. Taken together, these findings fits within the framework that the superior parietal lobe is part of the motor system involved in sensorimotor integration.

The frontal lobe was also involved with cognitive decline in the DLB group. Increased thinning in the superior frontal regions was associated with greater decline in MMSE, an index of global cognition. In addition, increased thinning in the left rostral middle frontal regions was correlated with both the orientation and language components of the CAMCOG assessment. Similarly, reductions in prefrontal volumes have been correlated with attentional deficits [38]. Despite the small sample size in

our study, the potential of the frontal lobe as a plausible biomarker for cognitive impairment in DLB should be established further in a larger cohort of DLB subjects.

Increased cortical thinning over 1 year in AD relative to HC was found in the temporo-parietal areas extending to the frontal regions. Our results are thus in agreement with earlier studies demonstrating that AD is associated with progressive loss of whole brain volumes, particularly in the medial temporal structures [25]. Increased rates of cortical thinning were also found in the precuneus and the isthmus of the cingulate gyrus. Both structures are involved in the default mode network, which has been found to be impaired in AD [39]. Indeed, the precuneus has been implicated in episodic memory [40] while the posterior cingulate projects strongly to the enthorinal and parahippocampal cortices, both of which are among the earliest sites of pathological changes in AD [41].

Consistent with the differential patterns of progressive cortical thinning in AD and DLB, our longitudinal analyses of subcortical changes also revealed significantly faster atrophy in the AD group, particularly in the hippocampus, and the thalamus albeit at trend level. The finding of increased ventricular expansion in AD compared to HC and DLB also agrees with previous studies [42].

The major strengths of the study include the comprehensive neuropsychological assessment and a well-characterized group of probable DLB and AD patients. In addition, all the groups were matched for age, gender, and educational level. The longitudinal design, a rarity in the DLB imaging literature, allowed us to address unanswered questions related to the progression and clinical implications of cortical

thinning in Lewy body dementia. 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 diagnosis using the consensus clinical diagnostic method adopted here [43]. Attrition of subjects is also a common drawback in longitudinal studies. Less than half (n=14) of the originally recruited DLB subjects (n=35) returned for a follow-up assessment due to disease progression including 9 deaths. 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 (Table 2). Finally, to minimize the number of comparisons between the DLB, AD and HC groups, we have summed the left and right hemispheric measures of each subcortical structure. Although there is no evidence to indicate systematic laterality of subcortical changes in AD and DLB, our combined volumes for each structure might have resulted in a loss of potential information about asymmetrical disease-related changes.

5. Conclusion

In accordance with our hypothesis, faster thinning over 1 year was found in the temporal lobe in AD relative to DLB. Besides validating the inclusion of the medial temporal lobe as a supportive biomarker in the revised diagnostic criteria for DLB, our findings also highlight the clinical utility of longitudinal cortical thinning as a complementary imaging marker to differentiate DLB from AD. Greater cortical thinning could exert deleterious effects on global cognitive decline and was associated with increasing motor severity in DLB. However, our finding of similar rates of

cortical thinning in DLB and HC underscores the ongoing need to develop other surrogate biomarkers of disease progression in DLB.

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Contributions

Elijah Mak formulated the research question, performed the statistical analyses, interpreted the results, and wrote the manuscript.

Li Su 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.

	HC	DLB	AD	p value
n	33	13	23	
Gender (m:f)	20:13	12:1	13:10	χ^2=5.28, 0.07[§]
Age (yrs)	76.7 ± 5.3	77.0 ± 8.3	76.5 ± 5.4	$F_{2,68}$=0.03, p=0.97[*]
Education (yrs)	11.8 ± 2.6	10.6 ± 1.9	11.3 ± 3.8	p=0.16[k]
Disease duration (mths)		52.2 ± 20.4	51.8 ± 26.5	p=0.96[†]
ChEI (%)		76.92	91.30	χ^2=1.44, p=0.23[§]
BADL		17.41 ± 10.17	14.09 ± 7.87	p=0.23 [w]
UPDRS				
Baseline	1.9 ± 1.8	27.7 ± 8.0	4.7 ± 4.1	p<0.01[k]
Follow-up	2.1 ± 2.0	32.6 ± 13.2	5.7 ± 4.8	p<0.01[k]
Change	-0.2 ± 2.0	-4.9 ± 8.4	-1.0 ± 2.4	p=0.09[w]
NPI Total				
Baseline		21.1 ± 16.8	19.4 ± 12.4	p=0.81[w]
Follow-up		24.8 ± 14.9	19.7 ± 15.0	p=0.30[w]
Change		-3.7 ± 17.4	-0.3 ± 11.8	p=0.50[t]
CogFluct				
Baseline		8.1 ± 3.4	2.8 ± 3.6	p<0.01[w]
Follow-up		7.8 ± 5.4	1.8 ± 3.3	p<0.01[w]
Change		-0.1 ± 4.4	1.0 ± 4.6	p=0.52[t]
MMSE				
Baseline	29.2 ± 0.9	21.3 ± 6.3	20.9 ± 4.0	p=0.80[†]
Follow-up	29.2 ± 0.9	19.8 ± 5.8	18.8 ± 4.2	p=0.60[†]
Change	-0.1 ± 1.0	2.6 ± 2.9	2.0 ± 3.2	P=0.63[†]
CAMCOG				
Baseline	97.8 ± 3.3	69.9 ± 18.0	69.2 ± 11.3	p=0.90[†]
Follow-up	98.6 ± 2.8	66.8 ± 17.9	62.2 ± 14.4	p=0.42[†]
Change	-0.8 ± 2.50	5.8 ± 10.8	7.0 ± 10.2	p=0.74[†]
BVMT-Total				
Baseline	18.9 ± 6.7	6.23 ± 6.7	4.2 ± 2.7	p= 0.51[w]
Follow-up	21.9 ± 5.8	7.8 ± 7.7	5.2 ± 2.6	p=0.51 [w]
Change	-3.0 ± 5.3	-0.1 ± 4.5	-1.0 ± 2.7	p=0.48[†]
Interscan interval (days)	370.9 ± 13.3	379.1 ± 18.8	379.6 ± 17.8	p=0.21[k]

Table 1. Demographics, clinical and neuropsychological measures.

Values expressed as Mean ± 1SD. [§] χ2– DLB, AD, Controls; *ANOVA – HC, DLB, AD. [k] Kruskal-Wallis test. [w] Wilcoxon rank-sum test – AD and DLB. † Student's t-test – AD and DLB. 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; BADLS = Bristol Activities of Daily Living Scale.

	DLB dropped-out	DLB returned	P value
n	21	14	
Gender (m:f)	14:7	13:1	χ^2=3.3, 0.07[§]
Age (yrs)	79.1 ± 6.2	77.2 ± 8.0	p=0.43[†]
Education (yrs)	11.0 ± 3.0	10.5 ± 1.9	p=0.69[w]
UPDRS	25.1 ± 12.3	27.2 ± 7.9	p=0.58[†]
NPI Total	21.4 ± 18.1	21.5 ± 16.1	p=0.70[w]
CogFluct	4.6 ± 3.3	8.4 ± 3.4	p<0.01[†]
MMSE	19.7 ± 4.7	21.2 ± 6.0	p=0.42[†]
CAMCOG	66.2 ± 14.0	69.9 ± 17.3	p=0.49[†]

Table 2. Demographics and clinical characteristics of DLB subjects.

Values expressed as Mean ± 1SD

[§] χ2– Chi-Square test; [w] Wilcoxon rank-sum test. † Student's t-test.

Abbreviations: DLB = dementia with Lewy bodies; 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.

Subcortical structures & lateral ventricle	Percentage of change [a]			Group comparisons of longitudinal subcortical atrophy [b]		
	HC	DLB	AD	AD vs HC	DLB vs HC	AD vs DLB
Thalamus	-0.87%	-2.01%	-2.41%	0.001*	0.06	0.82
Caudate	-1.47%	-3.77%	-3.20%	0.23	0.21	0.93
Putamen	-0.39%	-0.30%	-0.82%	0.80	0.99	0.82
Pallidum	-0.04%	-0.58%	0.20%	0.97	0.52	0.45
Hippocampus	-1.70%	-2.51%	-5.76%	<0.001**	0.90	0.006**
Amygdala	-2.41%	-6.25%	-4.80%	0.17	0.11	0.84
Accumbens	-0.33%	-1.00%	-2.05%	0.87	0.94	0.76
Lateral ventricle	+ 4.29%	+ 4.70%	+ 8.91%	<0.001**	0.990	0.008*

Table 3. Comparisons of longitudinal atrophy in subcortical structures and lateral ventricle expansion between groups.

[a] Percentage of change in volumes between baseline and follow-up, measured according to baseline.

[b] Group-comparisons were performed with ANCOVA, correcting for age, gender and the average total intracranial volume, followed by post-hoc Tukey-Kramer pairwise comparisons.

* Significant difference at standard threshold of $p < 0.05$ without correction for multiple comparisons.

** Significant difference between groups after Bonferroni correction for multiple comparisons.

Abbreviations: DLB, dementia with Lewy bodies; AD, Alzheimer's disease; HC, Healthy control.

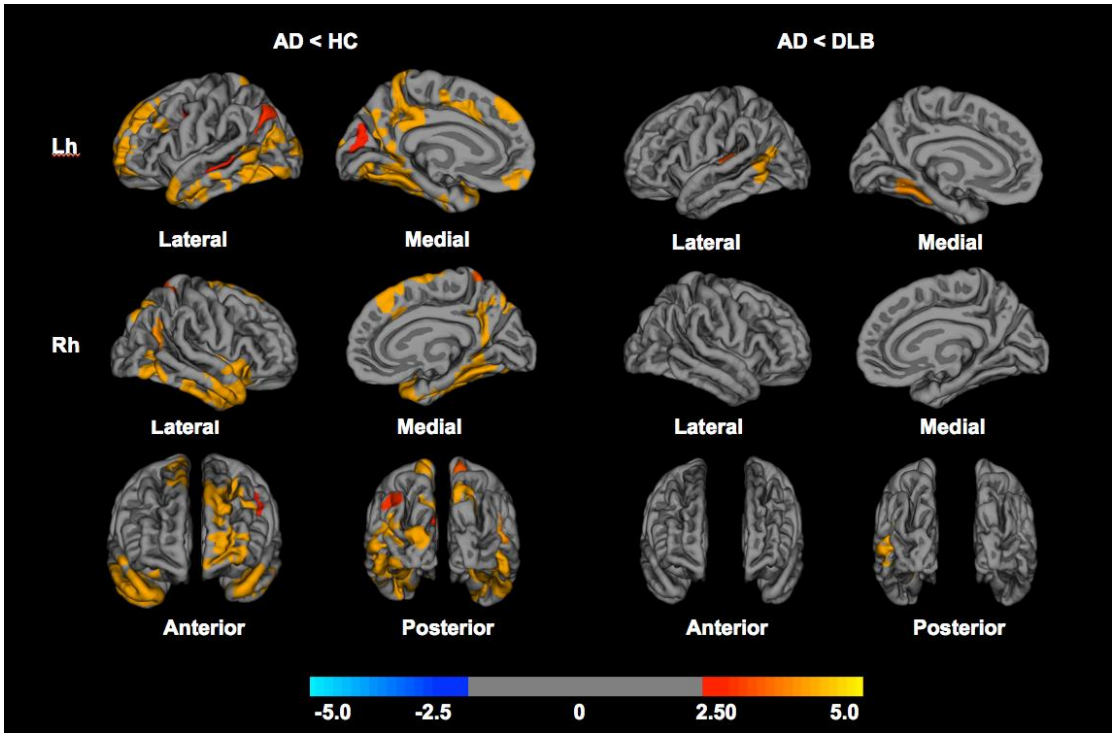

Figure 1. Vertex-wise comparisons of progressive cortical thinning between (A) AD and HC, (B) AD and DLB. Results were corrected using family-wise error correction with Z Monte Carlo simulation (10,000) iterations and thresholded at a corrected P value of 0.01 (Z=2.0). Age and sex were included as nuisance covariates. The color bar shows the logarithmic scale of p values ($-\log_{10}$).

Abbreviations: DLB = dementia with Lewy bodies; AD = Alzheimer's disease; HC = healthy controls; Lh = left hemisphere; Rh = right hemisphere.

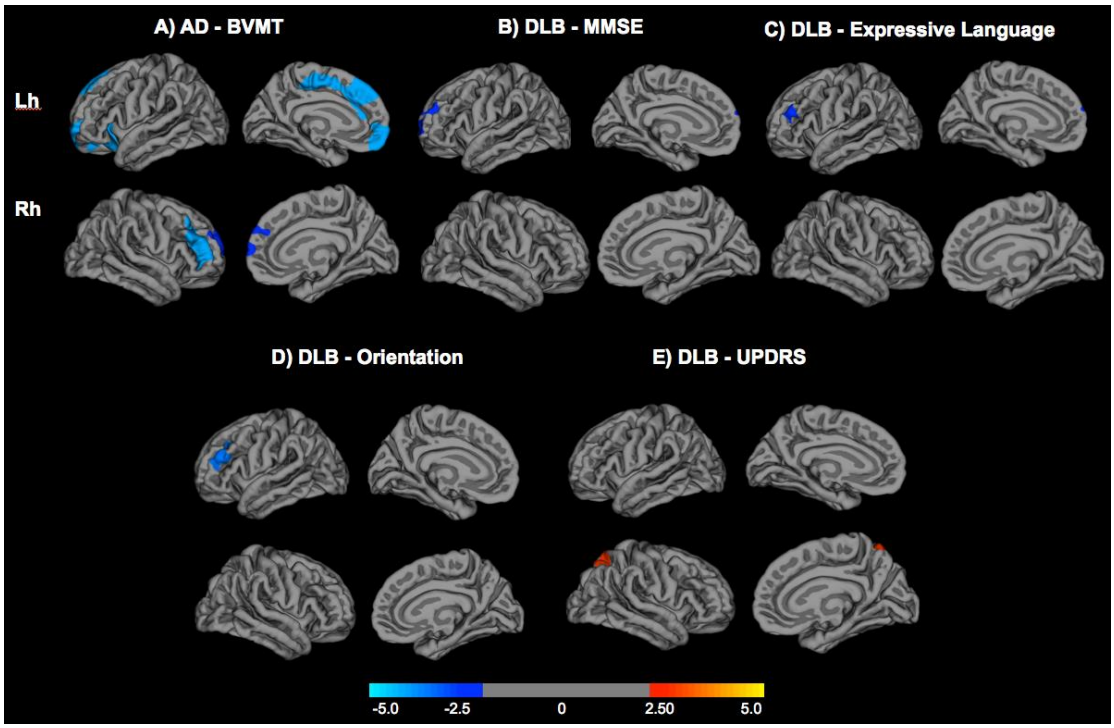

Figure 2. Vertex-wise correlations between percent of cortical thinning and longitudinal decline in (A) BVMT total scores in AD, (B) MMSE in DLB, (C) CAMCOG-Expressive Language in DLB, (D) CAMCOG-orientation scores in DLB, (E) UPDRS progression in DLB. Results were corrected using family-wise error correction with Z Monte Carlo simulation (10,000) iterations and thresholded at a corrected P value of 0.01 (Z=2.0). The color bar shows the logarithmic scale of p values ($-\log_{10}$). Abbreviations: DLB = dementia with Lewy bodies; AD = Alzheimer's disease; Lh = left hemisphere; Rh = right hemisphere; MMSE = Mini-Mental State examination; CAMCOG = Cambridge Cognitive Examination; BVMT = Brief Visuospatial Memory Test; UPDRS = Unified Parkinson's Disease Rating Scale.

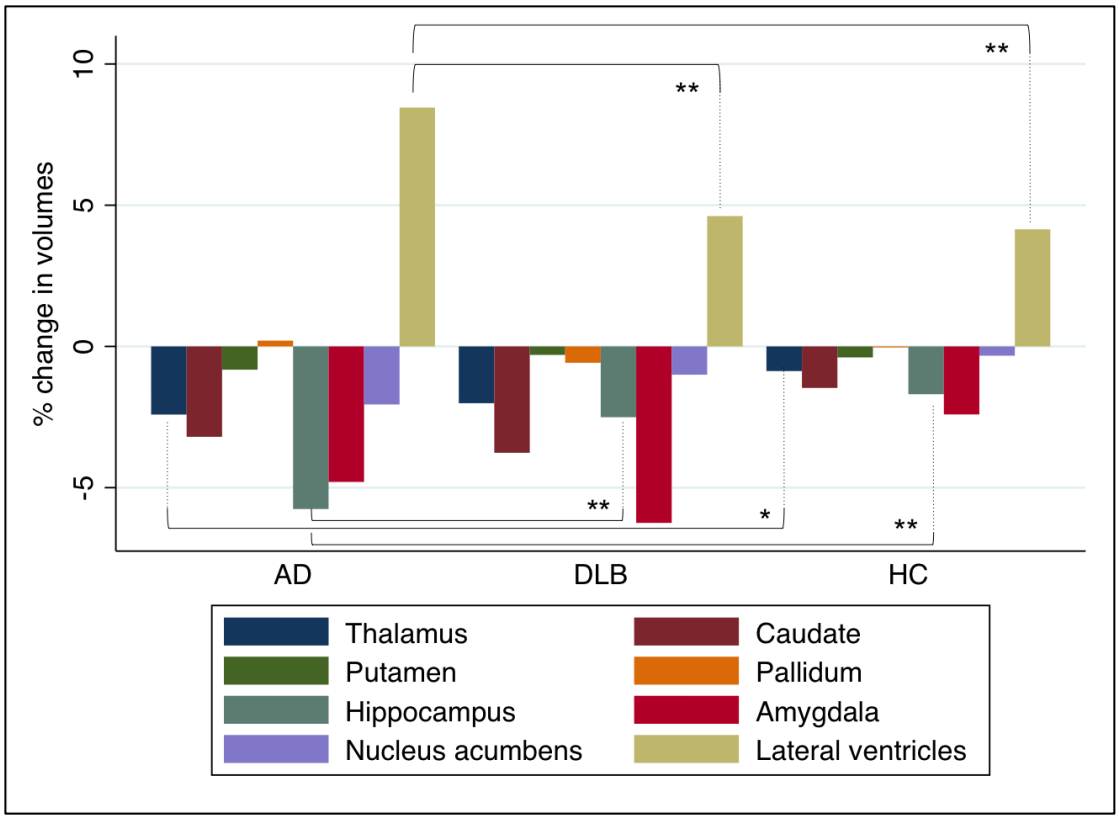

Figure 3. Longitudinal atrophy in subcortical structures and lateral ventricle expansion.

* Significant difference at standard threshold of $p < 0.05$ without correction for multiple comparisons.

** Significant difference between groups after Bonferroni correction for multiple comparisons.

Abbreviations: DLB, dementia with Lewy bodies; AD, Alzheimer's disease; HC, Healthy control.

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