Differential Atrophy of Hippocampal Subfields: A Comparative Study of Dementia with Lewy Bodies and Alzheimer Disease

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Objectives: *Dementia with Lewy bodies (DLB) is characterized by relative preservation of the medial temporal lobe compared with Alzheimer disease (AD). The differential involvement of the hippocampal subfields in both diseases has not been clearly established, however. We aim to investigate hippocampal subfield differences in vivo in a clinical cohort of DLB and AD subjects.* **Methods:** *104 participants (35 DLBs, 36 ADs, and 35 healthy comparison [HC] subjects) underwent clinical assessment and 3T T1-weighted imaging. A Bayesian model implemented in Freesurfer was used to automatically segment the hippocampus and its subfields. We also examined associations between hippocampal subfields and tests of memory function.* **Results:** *Both the AD and DLB groups demonstrated significant atrophy of the total hippocampus relative to HC but the DLB group was characterized by preservation of the cornu ammonis 1 (CA1), fimbria, and fissure. In contrast, all the hippocampal subfields except the fissure were significantly atrophied in AD compared with both DLB and HC groups. Among DLB subjects, CA1 was correlated with the Recent Memory score of the CAMCOG and Delayed Recall subscores of the HVLT.* **Conclusions:** *DLB is characterized by milder hippocampal atrophy that was accompanied by preservation of the CA1. The CA1 was also associated with memory function in DLB. Our findings highlight the promising role of hippocampal subfield volumetry, particularly that of the CA1, as a biomarker for the distinction between AD and DLB.* (Am J Geriatr Psychiatry 2015; ■:■−■)

Key Words: Lewy bodies, Alzheimer disease, neuroimaging, MRI, hippocampus

Dementia with Lewy bodies (DLB) is the second leading cause of degenerative dementia in older people after Alzheimer disease (AD), accounting for up to 15% of cases at autopsy.[1] DLB shares common clinical, neuropsychological, and pathological features with other dementia subtypes such as AD and

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Parkinson 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, with many DLB subjects misdiagnosed. In light of this uncertainty, and with important implications for subsequent patient management, there is need for reliable imaging markers to help distinguish DLB from other subtypes of dementia, most especially AD.

Structural neuroimaging studies have found reduced global atrophy in DLB compared with AD.[2] The relative preservation of the hippocampus in DLB compared with AD is recognized as one of the most consistent structural magnetic resonance imaging (MRI) findings,[2,3] and has been incorporated as a supportive feature in the revised criteria for the diagnosis of DLB.[1]

Most previous studies, however, have compared total hippocampal volumes using a region of interest approach. Considering the functional specialization of the histologically distinct subfields of the hippocampus, local analyses of the hippocampus are increasingly recognized as a viable method to characterize the involvement of cytoarchitectonic regions in the pathology of neurodegenerative diseases, most commonly in AD, mild cognitive impairment,[4] and Parkinson disease.[5]

Using a manual tracing technique on 4T MR images, Mueller and colleagues[6] have demonstrated atrophy of the cornu ammonis (CA)1 and the subiculum in AD. Interestingly, a similar pattern of hippocampal changes in healthy comparisons (HCs) has also been associated with development of amnestic mild cognitive impairment.[4] There is also histopathological evidence that the CA1 region is preferentially vulnerable to the neuropathology of AD.[7]

There have been few direct comparisons of the hippocampal subfields in DLB and AD. Two previous studies have reported a milder degree of atrophy in the subiculum and CA1 regions of the hippocampus in DLB compared with AD,[8,9] although another study did not find any significant difference in hippocampal volumes.[10] As such, the clinical utility of hippocampal subfield volumetry to aid in the differential diagnosis of DLB from AD remains unclear.

The discrepancy of findings in the literature could be attributed to the variability of methods that are currently used to examine the hippocampal subfields. To date, manual tracing is widely acknowledged as the gold standard of hippocampal subfield delineation. It is labor intensive, however, and its reproducibility might be limited by inter-/intra-rater variability. There is also the possibility of asymmetric bias in manual segmentations because of laterality of visual perception.[11] To overcome these limitations, we used a validated and automated technique[12] to compare the volumetric differences of the hippocampal subfields in DLB and AD and investigate their associations with memory performance.

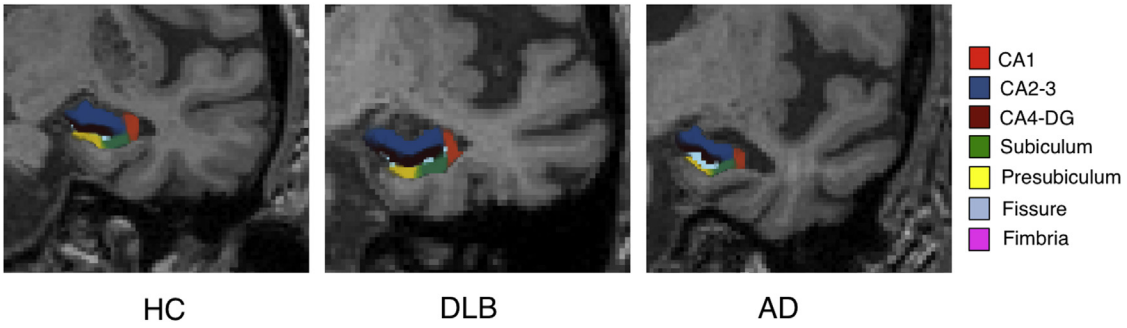
METHODS

Subjects, Assessment, and Diagnosis

Seventy-one individuals over the age of 60 years (36 subjects with probable AD[13] and 35 with probable DLB[1]) were recruited from a community-dwelling population of patients referred to local Old Age Psychiatry, Geriatric Medicine, or Neurology Services. Thirty-five similarly aged HC subjects were recruited from relatives and friends of subjects with dementia or volunteered via advertisements in local community newsletters. The research was approved by the local ethics committee. All subjects or, where appropriate, their nearest relative, provided written informed consent.

Subjects underwent clinical and neuropsychological evaluation. Neuropsychological assessments of global cognitive measures included the Cambridge Cognitive Examination (CAMCOG),[14] which incorporates the Mini-Mental State Examination (MMSE)[15] in addition to a number of subscales assessing domains including orientation, language, memory, attention, praxis, calculation, abstract thinking, and perception. Verbal and visuospatial memory was assessed with the Hopkins Verbal Learning Test (HVLT)[16] and the Brief Visuospatial Memory Test (BVMT),[17] respectively. Motor parkinsonism was evaluated with the Unified Parkinson's Disease Rating Scale Part III (UPDRS)[18] (2003). For subjects with dementia, neuropsychiatric features were examined with the Neuropsychiatric Inventory (NPI),[19] and cognitive fluctuations were assessed with the cognitive fluctuation scale,[20] a test to obtain

FIGURE 1. Segmented hippocampal subfields from each representative subject in all three diagnostic groups.



information about the historical pattern of cognitive fluctuation over time in a patient.

MRI Acquisition

Subjects underwent T1-weighted MR scanning on the same 3T MRI system using an eight-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] × 240 [superior-inferior] × 180 [right-left]; repetition time [TR] = 9.6 ms; echo time [TE] = 4.6 ms; flip angle = 8°; SENSE factor = 2).

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 have been described previously.[21,22] In summary, the initial processing of T1 MRI images includes the following steps: removal of non-brain tissue,[23] automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures,[24] intensity normalization,[25] tessellation of the gray matter/white matter boundary, automated topology correction,[26] and surface deformation to optimally place the gray matter/white matter and gray matter/cerebrospinal fluid boundaries.[21] All surface models in our study were visually inspected for accuracy and manual corrections while blinded to diagnostic information. Two subjects (both AD subjects) with extensive pial/white matter surface errors failed the hippocampal segmentations and were excluded from the analyses. The data set for all subsequent analyses comprised 35 HC, 34 AD, and 35 DLB subjects.

Total hippocampal volumes were obtained from the automated pipeline for volumetric segmentation of subcortical structures implemented in Freesurfer. Subsequently, the hippocampal subfields were segmented using a Bayesian inference approach, and a probabilistic atlas of the hippocampal formations based on manual delineations of subfields from several training subjects. The left and right hippocampi were segmented into seven subfields: CA1, CA2−3, CA4−DG, subiculum, presubiculum, fimbria, and hippocampal fissure (Fig. 1). The detailed procedures for subfield delineations have been described elsewhere.[12]

Statistical Analyses

Statistical analyses were performed with 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. Demographic differences across the three diagnostic groups were assessed with analysis of variance (ANOVA) or the Kruskal-Wallis test, and clinical and cognitive scores were compared between DLB and AD using t tests or Mann-Whitney tests depending on the normality of distributions. The χ^2 test was used to examine sex distributions between groups. Comparisons of hippocampal subfield

TABLE 1. Demographics and Clinical and Neuropsychological Measures

	HC	DLB	AD	p Value
N	35	35	34	
Sex (M:F)	20:15	27:8	19:15	$\chi^2 = 4.27$, 0.118[a]
Age (years)	76.7 ± 5.2	78.4 ± 6.9	78.1 ± 5.8	$F_{(2,101)} = 0.74$, $p = 0.479$[b]
Education (years)	11.7 ± 2.6	10.8 ± 2.6	11.1 ± 3.5	$p = 0.060$[c,*]
UPDRS	2.0 ± 1.9	26.0 ± 10.7	5.6 ± 4.4	$p < 0.001$[d,*]
NPI		21.5 ± 17.1	17.0 ± 12.2	$p = 0.461$[d]
CogFluct		6.1 ± 3.8	2.3 ± 3.7	$p < 0.001$[d,*]
MMSE	29.1 ± 1.0	20.3 ± 5.3	19.6 ± 4.5	$p = 0.556$[e]
CAMCOG	97.3 ± 3.8	67.7 ± 15.2	65.4 ± 12.2	$p = 0.491$[e]
HVLT-Total Recall	25.9 ± 4.6	10.8 ± 4.8	10.7 ± 5.0	$p = 0.932$[e]
HVLT-Delay Recall	8.5 ± 2.9	1.7 ± 2.3	0.3 ± 0.8	$p = 0.001$[d,*]
HVLT-Retention	80.6 ± 22.7	30.2 ± 38.0	4.1 ± 12.2	$p = 0.001$[d,*]
BVMT-Total	18.8 ± 6.5	6.9 ± 6.7	4.0 ± 2.5	$p = 0.119$[d]

Notes: Values expressed as Mean ± 1 SD. AD: Alzheimer's disease; BVMT: Brief Visuospatial Memory Test; UDLB: dementia with Lewy bodies; HC: Healthy comparison subjects; CAMCOG: Cambridge Cognitive Examination; CogFluct: Cognitive Fluctuation Scale; HVLT: Hopkins Verbal Learning Test; MMSE: Mini-Mental State examination; NPI: Neuropsychiatry Inventory; PDRS: Unified Parkinson's Disease Rating Scale, Part III.

*signifcant at $p < 0.05$.

[a]χ^2 (df = 2).

[b]ANOVA.

[c]Kruskal-Wallis test (df = 2).

[d]Mann-Whitney test: AD and DLB.

[e]Student's t test (df = 67): AD and DLB.

volumes between groups were examined with analysis of covariance (ANCOVA), controlling for age, sex, education, and intracranial volume (ICV), followed by post hoc pairwise Bonferroni tests. Subsequently, we also performed Bonferroni correction for the number of subfields, with an adjusted significance threshold of p equal to 0.007. Within each group, we further investigated associations of hippocampal subfields that were differentially affected with memory functions scores using partial correlations to account for the effects of age, sex, education, and ICV.

RESULTS

Subject Characteristics

The demographic and clinical data for patients and HC subjects are summarized in Table 1. Subject groups were well matched for age ($F_{(2,101)} = 0.74$; $p = 0.479$), sex ($\chi^2_{(2)} = 4.27$; $p = 0.118$), and years of education ($\chi^2_{(2)} = 5.62$; $p = 0.060$). As expected, the DLB group had significantly higher UPDRS scores than the AD group ($Z = -6.817$, $p < 0.001$) DLB subjects also scored significantly higher on the Cognitive Fluctuations Scale ($Z = -3.915$, $p < 0.001$), although there were no significant differences between dementia groups in scores of NPI ($Z = -0.738$, $p = 0.461$), MMSE ($t_{(67)} = -0.5921$, $p = 0.556$), CAMCOG ($t_{(67)} = -0.692$, $p = 0.491$), and HVLT-Total Recall ($t_{(66)} = -0.086$, $p = 0.932$). Compared with the DLB group, the AD group performed significantly poorer on the HVLT-Delayed Recall ($Z = -3.20$, $p = 0.001$) and HVLT-Retention ($Z = -3.27$, $p = 0.001$).

Hippocampal Subfields

The volumetric comparisons of the hippocampal subfields between groups are shown in Figure 2 and Table 2. Overall, ANCOVA analyses revealed a main effect of diagnosis on total hippocampal volumes. The AD group showed the most atrophy of the hippocampus, with the DLB group being intermediate between AD and HC (AD < DLB < HC). The relative extent of hippocampal subfield atrophy in DLB and AD compared with the healthy comparison group is shown in Table 3. After controlling for age, sex, education, and ICV, we found significant atrophy affecting all the hippocampal subfields, with the exception of the fissure, in AD compared with both HC and DLB groups. In contrast, the CA1, fimbria, and the fissure were preserved in DLB relative to HC.

Correlations with Memory Functions

Hippocampal subfield analyses revealed that the CA1 volumes in DLB were also significantly correlated with the Recent Memory scores of the CAMCOG ($r = 0.40$; $p = 0.029$) and Delayed Recall scores from the HVLT ($r = 0.37$; $p = 0.043$). The AD group did not show any significant associations of total hippocampus and the CA1 with any cognitive test.

DISCUSSION

The main findings of the study were a) DLB was associated with significantly milder hippocampal

FIGURE 2. **Volumetric comparisons of hippocampal subfields in AD (N = 34), DLB (N = 35), and HC (N = 35) subjects, in mean (SD). The bars in the figure represent standard error bars. AD: Alzheimer disease; CA: cornu ammonis; DG: Dentate gyrus; DLB: dementia with Lewy bodies; HC: healthy comparison subjects.**

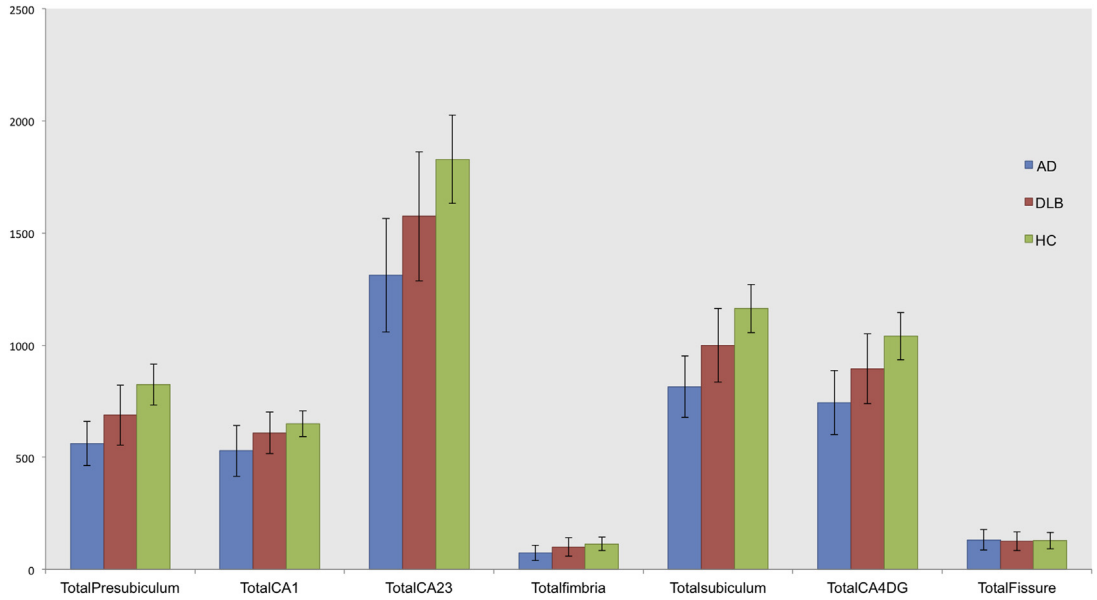


TABLE 2. **Volumetric Comparisons of Hippocampal Subfields**

	HC (N = 35)		DLB (N = 35)		AD (N = 34)		
Hippocampal Subfields (mm^3)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Group Comparisons (df = 2)**
Total	5,456	702	4,894	775	3,848	716	$p < 0.001^{a,b,c,d,*}$
Presubiculum	823	92	688	136	562	101	$p < 0.001^{a,b,c,d,*}$
CA1	650	58	608	94	528	116	$p < 0.001^{a,b,*}$ $p = 0.002^{c,*}$ $p = 0.082^{d}$
CA2–3	1,828	200	1,574	293	1,312	257	$p < 0.001^{a,b,c,d,*}$
Fimbria	113	30	100	42	74	35	$p < 0.001^{a,b,*}$ $p = 0.005^{c,*}$ $p = 0.615^{d}$
Subiculum	1,163	109	999	166	815	140	$p < 0.001^{a,b,c,d,*}$
CA4–DG	1,040	106	895	158	743	144	$p < 0.001^{a,b,c,d,*}$
Fissure	128	37	125	42	132	46	$p = 0.867^{a}$

Notes: After Bonferroni correction for the number of subfields, the significance threshold is set at p = 0.007. AD: Alzheimer disease; CA: cornu ammonis; DG: dentate gyrus; DLB: dementia with Lewy bodies; HC: healthy comparison subjects.

[a]ANCOVA (df = 2) controlling for age, sex, education, and intracranial volumes with post-hoc Bonferroni pairwise tests.

[b]AD < HC.

[c]AD < DLB.

[d]DLB < HC.

atrophy than AD; b) AD showed a global pattern of hippocampal atrophy affecting all the subfields with the exception of the fissure; c) the CA1 region was relatively preserved in DLB compared with HC and AD groups; and d) the CA1 region is associated with memory functions in DLB.

Neuropathological studies have shown that the hippocampus is one of the earliest sites of pathology in the disease course of AD, which progresses in a systematic fashion: Neurofibrillary tangle originates in entorhinal areas before spreading to the CA1 and subiculum, and subsequently to the CA2 and CA3

TABLE 3. Relative Extent (in Percent) of Total and Regional Hippocampal Atrophy in AD and DLB Compared with Healthy Comparison Subjects

	AD	DLB
Total hippocampus	−29.5	−10.3
Presubiculum	−31.7	−16.3
CA1	−18.6	−6.3
CA2−3	−28.3	−13.9
Fimbria	−34.5	−11.6
Subiculum	−29.9	−14.1
CA4−DG	−28.5	−13.9
Fissure	2.6	−2.6

Notes: DG: dentate gyrus.

areas before affecting the neocortex.[27] Despite growing evidence suggesting that the neurodegenerative pathology is not uniformly distributed throughout the hippocampus, the majority of volumetric studies in DLB and AD have considered the hippocampus as a unitary structure. Therefore, to appreciate the complex anatomical structure of the hippocampus, we used an automated technique to compare local volumetric differences in the hippocampus in DLB subjects with those of AD and age-matched HC subjects.

In accordance with previous estimates of hippocampal atrophy ranging from 23%[8,9] to 28%,[28] we demonstrated that AD subjects had 29.5% smaller hippocampal volumes relative to HC subjects. At the subregional level, we found that the AD group had significant atrophy in all hippocampal subfields compared with both DLB and HC groups, with the exception of the fissure. Our finding is corroborated by previous imaging studies,[29] including postmortem evidence indicating greater CA1, CA2, CA3, and subiculum atrophy in AD relative to HC.[30,31] Taken together, the global pattern of hippocampal atrophy observed in our AD group is congruent with a previous finding that subfield measurements may not confer additional sensitivity over total hippocampus volumes in the detection of AD.[32]

The relative preservation of the hippocampus in DLB compared with AD is in agreement with the literature[2] and fits with the different neuropsychological profiles of each group, where memory deficits are more prominent in AD. Previous studies have also suggested that DLB is associated with lesser pathology affecting the perforant pathways.[33]

To date, only a few studies have compared atrophy patterns of the hippocampal subfields between DLB and AD with considerable heterogeneity in methodologies and findings. The CA1, fimbria, and fissure were the most preserved regions in our DLB subjects. Notably, the present results are in partial agreement with previous work from our group.[8] In that study, we used a manual drawing approach and reported a lower degree of atrophy affecting the CA1 and subiculum regions in DLB compared with AD. It is noteworthy that our findings, despite different methodologies (automatic segmentation versus manual tracing), are also consistent with histopathological evidence in DLB, indicating that neuronal loss and Lewy neurites are largely confined to the presubiculum and the CA2-3, with sparing of the CA1 and subiculum regions.[31] Nevertheless, two previous studies, using the hippocampal radial distance technique, have reported increased atrophy (rather than preservation) of the CA1 in DLB relative to HC.[9,10] Methodological differences in the anatomical delineations of the subfields might account for the conflicting findings. The CA1 as well as other hippocampal structures are parallel to each other and are organized along the anterior-medial to posterior-lateral axis of the hippocampus. The hippocampal radiance distance technique, which measures in perpendicular directions to this axis, might be limited in its capacity to reveal differential volume changes in CA1 and other subfields, and, in fact, overestimate the volume reduction of CA1 due to atrophy of other parallel structures.

The hippocampus is a complex structure, with interconnected subfields having different projections. The CA1 has extensive reciprocal projections with the entorhinal cortex,[34] and emerging evidence from high-resolution 4T imaging[35] and lesion[36] studies have pointed toward a critical involvement of CA1 neurons in episodic memory functions. The preservation of the CA1 region in DLB subjects also parallels with significantly better memory function compared with AD subjects in our study. Furthermore, consistent with our previous work,[8] the CA1 volumes in our DLB group were also significantly associated with memory functions. We are not aware of other studies that have examined correlations of hippocampal subfields with cognitive measures in DLB.

Although a previous study using the same Freesurfer technique has reported a correlation between hippocampal volumes and delayed recall scores in AD,[37] we did not find any significant association in

the AD group with memory function, most likely due to a floor effect of memory performance. In future, the domain-specific contribution of hippocampal subfields will be better understood as this automated technique receives more recognition.

The major strengths of the study include the comprehensive neuropsychological assessment and a well-characterized group of probable DLB and AD subjects. Furthermore, in light of significant disparities in age,[10] sex, and education[9] across comparison groups in previous studies, we extend the literature by investigating a cohort that was matched for age, sex, and educational level. We also used a publicly available technique that is capable of segmenting the hippocampal subfields in a reproducible and automatic fashion. Thus, we are able to address limitations associated with manual delineations of the hippocampus and the practical challenges of processing large data sets. Lastly, this technique has also been validated against manual volume estimations.[12] Nevertheless, the operational definition of the medial boundaries of CA1 varies between segmentation protocols, resulting in a smaller volume of CA1 for the Freesurfer technique compared with other studies.[8,38] Also, whereas this method reports a combined volume of CA2 + CA3, others have reported CA2 separately, and combined CA3 with CA4 and dentate gyrus. In addition, Van Leemput et al. originally assessed hippocampal subfields with ultra-high resolution MPRAGE (slice thickness = 0.8 mm) and enhanced signal-to-noise ratio.[12] Consistent with other studies, we used a standard 3T MPRAGE acquisition sequence (slice thickness = 1 mm isotropic). However, this automated technique has been used to segment hippocampal subfields from 1.5T scans with a much lower resolution and a longer acquisition time of 35 minutes.[5] Finally, although this technique has been widely applied in neurodegenerative diseases, the probabilistic atlas from Van Leemput et al. was built upon healthy subjects, but this is an inherent limitation in many imaging studies where a common template is necessary for the investigation of group differences. Hence, some caution must be exercised in comparing findings between studies.

Additional 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 antemortem imaging studies. Furthermore, we have previously demonstrated good agreement between clinical and pathological diagnosis using the consensus clinical diagnostic method adopted here.[39]

CONCLUSIONS

To date, very few studies have compared atrophy patterns of the hippocampal subfields in DLB and AD. The main findings of CA1 preservation and milder global hippocampal atrophy in clinically diagnosed DLB subjects are largely consistent with the topography of neuronal loss described in histopathological studies as well as with previous imaging studies. The distinct involvement of the CA1 in DLB and AD suggests that hippocampal subfield volumetry could be a promising biomarker to aid in the differential diagnosis of DLB.

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References

1. McKeith IG, Dickson DW, Lowe J, et al: Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005; 65:1863–1872
2. Mak E, Su L, Williams G, O'Brien J: Neuroimaging characteristics of dementia with Lewy bodies. Alzheimers Res Ther 2014; 6:18
3. Watson R, O'Brien JT, Barber R, et al: Patterns of gray matter atrophy in dementia with Lewy bodies: a voxel-based morphometry study. Int Psychogeriatr 2012; 24:532–540
4. Apostolova LG, Mosconi L, Thompson PM, et al: Subregional hippocampal atrophy predicts Alzheimer's dementia in the cognitively normal. Neurobiol Aging 2010; 31:1077–1088

5. Pereira JB, Junqué C, Bartrés-Faz D, et al: Regional vulnerability of hippocampal subfields and memory deficits in Parkinson's disease. Hippocampus 2013; 23:720–728
6. Mueller SG, Weiner MW: Selective effect of age, Apo e4, and Alzheimer's disease on hippocampal subfields. Hippocampus 2009; 19:558–564
7. Bobinski M, de Leon MJ, Tarnawski M, et al: Neuronal and volume loss in CA1 of the hippocampal formation uniquely predicts duration and severity of Alzheimer disease. Brain Res 1998; 805: 267–269
8. Firbank MJ, Blamire AM, Teodorczuk A, et al: High resolution imaging of the medial temporal lobe in Alzheimer's disease and dementia with Lewy bodies. J Alzheimers Dis 2010; 21: 1129–1140
9. Sabattoli F, Boccardi M, Galluzzi S, et al: Hippocampal shape differences in dementia with Lewy bodies. Neuroimage 2008; 41: 699–705
10. Chow N, Aarsland D, Honarpisheh H, et al: Comparing hippocampal atrophy in Alzheimer's dementia and dementia with Lewy bodies. Dement Geriatr Cogn Disord 2012; 34:44–50
11. Maltbie E, Bhatt K, Paniagua B, et al: Asymmetric bias in user guided segmentations of brain structures. Neuroimage 2012; 59: 1315–1323
12. Van Leemput K, Bakkour A, Benner T, et al: Automated segmentation of hippocampal subfields from ultra-high resolution in vivo MRI. Hippocampus 2009; 19:549–557
13. McKhann G, Drachman D, Folstein M, et al: 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. Neurology 1984; 34:939
14. Huppert FA, Brayne C, Gill C, et al: CAMCOG—a concise neuropsychological test to assist dementia diagnosis: socio-demographic determinants in an elderly population sample. Br J Clin Psychol 1995; 34:529–541
15. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–198
16. Brandt J: The Hopkins verbal learning test: development of a new memory test with six equivalent forms. Clin Neuropsychol 1991; 5:125–142
17. Benedict RHB, Schretlen D, Groninger L, et al: Revision of the Brief Visuospatial Memory Test: studies of normal performance, reliability, and validity. Psychol Assess 1996; 8:145–153
18. Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease: The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Mov Disorde 2003; 18:738–750
19. Cummings JL, Mega M, Gray K, et al: The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994; 44:2308–2314
20. Walker MP, Ayre GA, Cummings JL, et al: The clinician assessment of fluctuation and the one day fluctuation assessment scale. Two methods to assess fluctuating confusion in dementia. Br J Psychiatry 2000; 177:252–256
21. Fischl B, Dale AM: Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 2000; 97:11050–11055
22. Fischl B, Sereno MI, Dale AM: Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 1999; 9:195–207
23. Ségonne F, Dale AM, Busa E, et al: A hybrid approach to the skull stripping problem in MRI. Neuroimage 2004; 22: 1060–1075
24. Fischl B, Salat DH, van der Kouwe AJW, et al: Sequence-independent segmentation of magnetic resonance images. Neuroimage 2004; 23(suppl 1):S69–S84
25. Sled JG, Zijdenbos AP, Evans AC: A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging 1998; 17:87–97
26. Ségonne F, Pacheco J, Fischl B: Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. IEEE Trans Med Imaging 2007; 26:518–529
27. Schönheit B, Zarski R, Ohm TG: Spatial and temporal relationships between plaques and tangles in Alzheimer-pathology. Neurobiol Aging 2004; 25:697–711
28. Callen DJ, Black SE, Gao F, et al: Beyond the hippocampus: MRI volumetry confirms widespread limbic atrophy in AD. Neurology 2001; 57:1669–1674
29. Apostolova LG, Dinov ID, Dutton RA, et al: 3D comparison of hippocampal atrophy in amnestic mild cognitive impairment and Alzheimer's disease. Brain 2006; 129:2867–2873
30. Bobinski M, Wegiel J, Wisniewski HM, et al: Atrophy of hippocampal formation subdivisions correlates with stage and duration of Alzheimer disease. Dementia 1995; 6:205–210
31. Harding AJ, Lakay B, Halliday GM: Selective hippocampal neuron loss in dementia with Lewy bodies. Ann Neurol 2002; 51: 125–128
32. Mueller SG, Schuff N, Yaffe K, et al: Hippocampal atrophy patterns in mild cognitive impairment and Alzheimer's disease. Hum Brain Mapp 2010; 31:1339–1347
33. Lippa CF, Pulaski-Salo D, Dickson DW, et al: Alzheimer's disease, Lewy body disease and aging: a comparative study of the perforant pathway. J Neurol Sci 1997; 147:161–166
34. Duvernoy H: The Human Hippocampus. Functional Anatomy, Vascularization and Serial Sections with MRI. Berlin, Springer, 1998
35. Mueller SG, Chao LL, Berman B, et al: Evidence for functional specialization of hippocampal subfields detected by MR subfield volumetry on high resolution images at 4 T. Neuroimage 2011; 56:851–857
36. Rempel-Clower NL, Zola SM, Squire LR, et al: Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J Neurosci 1996; 16: 5233–5255
37. Lim HK, Hong SC, Jung WS, et al: Automated segmentation of hippocampal subfields in drug-naïve patients with Alzheimer disease 2013. AJNR Am J Neuroradiol 2013;34: 747–751
38. Mueller SG, Stables L, Du AT, et al: Measurement of hippocampal subfields and age-related changes with high resolution MRI at 4T. Neurobiol Aging 2007; 28:719–726
39. McKeith IG, Ballard CG, Perry RH, et al: Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology 2000; 54:1050–1058