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Atrophy of hippocampal subfields and adjacent extrahippocampal structures in dementia with Lewy bodies and Alzheimer's disease

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ABSTRACT

The hippocampus and adjacent extrahippocampal structures are organized in distinct and specialized regions which process heterogeneous functions, including memory, and visuospatial functions. Specific alterations of the different hippocampal subfields and adjacent extrahippocampal structures could differently contribute to the pathophysiology of Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). Based on visual symptoms which characterize DLB patients, the hippocampal subfields and the adjacent extrahippocampal structures which are mainly involved in the visual functions could be impaired in DLB and preserved in AD. To test this hypothesis, we performed structural magnetic resonance imaging on 19 DLB, 15 AD, and 19 age-matched healthy controls. FreeSurfer's pipelines were used to perform parcellation of hippocampus and adjacent extrahippocampal structures and to assess the structural changes within each region. The cornu ammonis and subiculum were bilaterally damaged in AD and preserved in DLB. The perirhinal cortex and parahippocampus were damaged in DLB but not in AD. Our findings demonstrate that the hippocampal subfields and adjacent extrahippocampal structures were differently altered in AD and DLB. Particularly, DLB patients showed a more focused alteration of the extrahippocampal structures linked to visual functions.

1. Introduction

Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) represent the 2 most common forms of neurodegenerative dementia in elderly (Vann Jones and O'Brien, 2014). Although AD and DLB are characterized by a clinical overlap especially in the early stage, DLB patients show greater attentional and visuoperceptual impairment (Calderon et al., 2001; Collerton et al., 2003) and a less prominent memory loss (Calderon et al., 2001; Ferman et al., 2006) as compared with AD patients. Particularly, visual hallucinations, together with fluctuating cognition and extrapyramidal signs, represent the core clinical feature of DLB (McKeith et al., 2005).

The hippocampus is an heterogeneous brain structure consisting of distinct and specialized regions which process different functions including information consolidation from the episodic memory to the long-term memory, spatial navigation, local spatial representation, and visual perception and/or identification (Bird and Burgess, 2008; Strange et al., 2014).

Although the hippocampal atrophy has been consistently reported in AD and DLB (Barber et al., 2000; Chow et al., 2012; Firbank et al., 2010; Hashimoto et al., 1998; Mak et al., 2015; Sabattoli et al., 2008), the adjacent extrahippocampal structures including entorhinal, perirhinal, and parahippocampal structures have been poorly investigated.

In the present study, we hypothesize that specific alterations of the hippocampal subfields and adjacent extrahippocampal structures could differently contribute to the pathophysiology of AD and DLB. Specifically, based on visual symptoms present in DLB patients, we expect that the extrahippocampal structures which are mainly involved in the visual functions could be impaired in DLB and preserved in AD. To verify this hypothesis, we studied the possible alterations of the hippocampal and extrahippocampal structures in DLB and AD patients by using automated data-analysis approaches (Fischl and Dale, 2000; Van Leemput et al., 2009), which allow to: (1) parcellate the hippocampal subfields and the extrahippocampal structures in different regions and (2) determine their physical measures.

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2. Material and methods

2.1. Study sample

This research was approved by the local Ethics Committee and was performed according to the Declaration of Helsinki (1997) and subsequent revisions. All subjects (or their caregivers, where appropriate) provided written informed consent. Nineteen DLB and 15 AD patients were recruited from our Memory Clinic and Movement Disorder Clinic. Nineteen age-matched volunteers were recruited from our nondemented case register cohorts. All subjects were right-handed. Probable AD diagnosis was made in agreement with the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria (Dubois et al., 2007; McKhann, 2011). Probable DLB diagnosis was carried out in agreement with the consensus guidelines (McKeith et al., 2005). As part of their clinical work up, all patients underwent Computerized Tomography or magnetic resonance imaging (MRI) and dopaminergic presynaptic ligand ioflupane SPECT (DAT scan) within 6 months before the inclusion in the project. Furthermore, all patients were assessed with electroencephalography (EEG) recordings as abnormalities characterized by parietooccipital dominant frequency alterations have previously been observed to reliably differentiate probable DLB from AD (Bonanni et al., 2008).

2.2. Clinical investigation

All participants underwent clinical and neuropsychological assessment. Mini Mental State Examination (MMSE; Folstein et al., 1975), Clinical Dementia Rating (CDR; Morris, 1993), and Dementia Rating Scale-2 (DRS-2; Jurica et al., 2001) were used to assess the cognitive deterioration. Neuropsychiatric Inventory (NPI) was used to determine the frequency and severity of any neuropsychiatric features (Cummings et al., 1994). Particularly, the NPI item-2 hallucinations investigated the occurrence as well as severity × frequency of visual hallucinations. Frontal Assessment Battery (FAB; Dubois et al., 2000) and Clinician Assessment of Fluctuations (Walker et al., 2000) were included to investigate respectively the severity of frontal dysfunction and the presence and severity of cognitive fluctuations. Unified Parkinson's Disease Rating Scale—motor section III (Fahn and Elton, 1987) assessed the presence and severity of extrapyramidal signs. The presence and/or absence of rapid eye movement sleep behavior disorder (RBD) was determined according to minimal International Classification of Sleep Disorders criteria (1992) and confirmed by polysomnography.

2.3. Neuropsychological evaluation of the healthy elderly

Age-matched healthy subjects were further evaluated to ascertain the brain normal functioning. Specifically, Activities of Daily Living Scale (Katz, 1963) and Instrumental Activities of Daily Life Scale (Lawton and Brody, 1970) were used for daily functions assessment. Attention skills, sustained attention, divided attention, task coordination, and set shifting were evaluated using the Trail Making Test A and B (Robertson et al., 1996; Rossini and Karl, 1994). Attentional matrices were used to evaluate speed and attention (Abbate et al., 2007). Short-term and long-term verbal memory (Babcock Story Recall Test; Horner et al., 2002) were assessed as well as auditory working memory (Baddeley and Wilson, 2002). Visuospatial memory and ability were also investigated (Shin et al., 2006). Finally, the forward and backward Digit Span test was used to evaluate auditory working memory (Wechsler, 1939).

2.4. MR data acquisition

MR measurements were performed with a Philips Achieva 3T scanner (Philips Medical System, Best, the Netherlands) equipped with 8-channel receiver coil. Three-dimensional T_1-Weighted Turbo Field-Echo (repetition time/echo time = 11/5 ms, slice thickness = 0.8 mm, field of view = 256 × 192 × 170 mm) sequence was performed on all participants.

2.5. MRI morphometry

Structural T_1-weighted images were processed by using FreeSurfer processing stream (http://ftp.nmr.mgh.harvard.edu; version 5.3; Fischl and Dale, 2000). By using recon-all command line, we performed the automated reconstruction and labeling of cortical and subcortical regions (classified by using the Desikan-Killiany Atlas) on the high-resolution anatomical T_1-weighted images of each subject. The "recon-all" command line followed by "hippocampal-subfields" option was used to subdivide the hippocampi in fimbria, fissure, cornus ammonis (CA), presubiculum, and subiculum. CA was further divided in CA1, CA2-3, and CA4-dentate gyrus (DG). The total hippocampal volumes and the estimated total intracranial volume (eTIV) were calculated by using "asegstats2table" command line. The mean thickness of the entorhinal and parahippocampal structures was extracted by using "aparcstats2table" command line. The "mri_label2label" command line was used to compute the perirhinal thickness. Representative images of the hippocampal subfields and extrahippocampal structures were shown in the Fig. 1.

2.6. Statistical analysis

One-way ANOVA and Bonferroni post hoc test was performed on demographic and clinical data. The χ^2 test was carried out for sex. For MRI data, differences among groups were tested using analysis of covariance, controlling for age, education, and eTIV and adjusting for multiple comparisons by Bonferroni correction. In case of significant mean interactions among groups, pairwise Bonferroni post hoc was applied. Because the volumes of the total hippocampi and hippocampal subfields and the thickness of the extrahippocampal structures were obtained from different processing pipelines and measures, separate statistical analyses were performed. Within each patient group, linear regression was performed to assess the relationship between MRI outcomes and the demographic and primary clinical outcomes (independent variables: age, scores of the FAB, MMSE, NPI hallucination item, Unified Parkinson's Disease Rating Scale).

3. Results

3.1. Demographic and clinical features

Demographic features and neuropsychological test scores were summarized in Table 1.

No differences in terms of age, sex, and educational level were observed among groups.

No differences on global test of cognition (DRS-2, MMSE, CDR) and on the severity of frontal dysfunction (FAB score) were found between AD and DLB patients. Seventeen DLB patients had RBD. All DLB patients had visual hallucinations and cognitive fluctuations. None of the AD patients had visual hallucinations or cognitive fluctuations. All DLB patients showed an abnormal quantitative EEG pattern profile consistent with a DLB diagnosis (Bonanni et al., 2008). It was represented by slow dominant frequency (in the

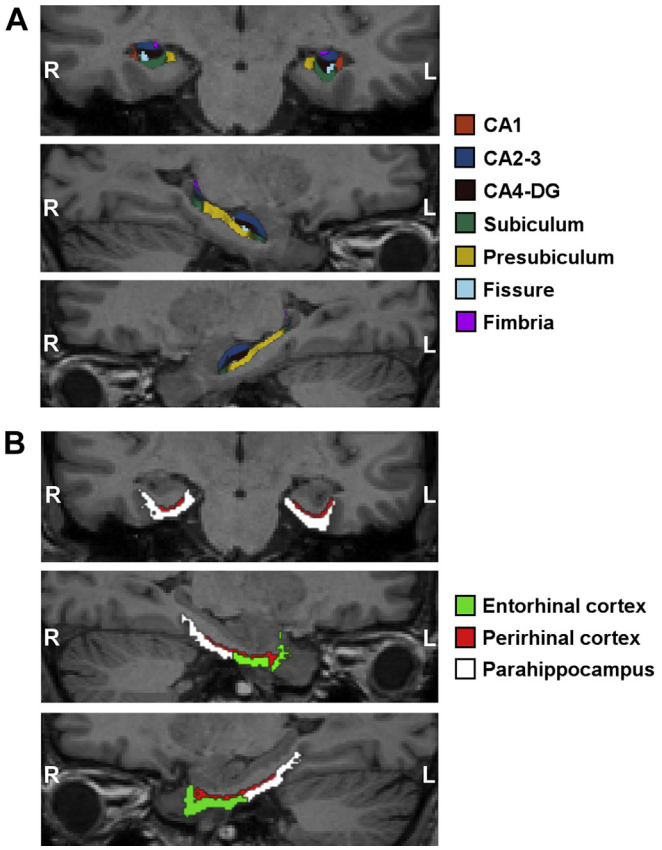

Fig. 1. Representative subdivision of (A) the hippocampal subfields and (B) adjacent extrahippocampal structures. The mask of each region was overlapped on T_1 structural image. Color classification: CA1 = dark red; CA2-3 = dark blue; CA4-DG = black brown; subiculum = dark green; presubiculum = yellow; fimbria = fuchsia; fissure = blue sky; entorhinal cortex = green, perirhinal cortex = red; parahippocampus = white. Abbreviations: R, right; L, left. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

theta and prealpha band) in posterior leads and a dominant frequency variability >1.5 Hz. None of the AD patients or controls showed DLB-specific EEG characteristics (Bonanni et al., 2008). All DLB patients had dopamine-transporter hypocaptation in the caudate nuclei (bilateral in 12 patients) at SPECT-DAT scan. None of the AD patients or control subjects showed SPECT-DAT scan abnormalities.

Patients were treated with L-Dopa (all DLB patients), rivastigmine, or donepezil (all AD and DLB patients with same daily dosages), quetiapine (8 DLB and 6 AD), clozapine (4 DLB), risperidone (4 AD), and clonazepam (17 DLB patients, who presented with RBD).

3.2. Total hippocampal volumetry

Table 2 summarizes the statistical results for the right and left hippocampi. No differences were found among groups for eTIV. As compared to controls, the total hippocampal volumes were reduced bilaterally in AD patients, and in the right hemisphere in DLB patients. Comparing the 2 forms of dementia, the left total hippocampal volume was significantly reduced in AD patients.

3.3. Hippocampal subfields volumetry

Table 3 summarizes the statistical results for each hippocampal subfield. The volumetric analysis showed specific sites of atrophy in the 2 forms of dementia. The volumes of CA1 (bilaterally) and of left CA2-3, CA4-DG, and subiculum were significantly reduced in AD as compared to DLB patients and controls. The right CA2-3, CA4-DG, subiculum, and presubiculum were altered in both forms of dementia as compared to controls.

Table 1
Demographic and clinical features

Characteristics	DLB	AD	Controls
Number of subjects/ patients	19	15	19
Age[a,b]	76.37 ± 4.35	76.47 ± 7.17	76.21 ± 4.49
Male gender (in percentage)[c]	47%	40%	47%
Disease duration (y)[d]	2.95 ± 0.91	3.00 ± 0.93	—
Education level (y)[a,e]	7.26 ± 3.97	6.40 ± 3.85	7.53 ± 3.80
CDR[a,f]	1.42 ± 0.48	1.50 ± 0.56	—
MMSE[a,g]	18.00 ± 4.83	16.73 ± 6.31	27.58 ± 0.69
DRS[a,h]	91.68 ± 17.33	84.13 ± 18.69	136.94 ± 0.85
FAB[a,i]	5.95 ± 2.88	5.67 ± 1.76	16.26 ± 1.41
CAF	4.0 ± 3.03	0.0 ± 0.0	0.0 ± 0.0
UPDRS III	23.1 ± 9.4	0.0 ± 0.0	0.0 ± 0.0
NPI item-2 hallucinations	6.5 ± 2.3	0.0 ± 0.0	0.0 ± 0.0

Values are expressed as mean ± standard deviation (SD).
Key: AD, Alzheimer's disease; ANOVA, analysis of variance; CAF, Clinician Assessment of Fluctuations; CDR, Clinical, Dementia Rating; DLB, dementia with Lewy bodies; DRS, Dementia Rating Scale; FAB, Frontal Assessment Battery; MMSE, Mini Mental State Examination; NPI, Neuropsychiatric Inventory; UPDRS III, Unified Parkinson's Disease Rating Scale—motor section III.
[a] The *p*-values were calculated using the one-way ANOVA; Bonferroni post hoc test was also performed when *F*-test was significant.
[b] Main interaction among groups: $F_{2,52} = 0.010$, $p = 0.990$.
[c] The *p*-values were calculated using χ^2 test: $\chi^2_1 = 0.472$, $p = 0.492$.
[d] The *p*-values were calculated using the independent-samples *t* test: $t_{32} = -0.166$, $p = 0.869$.
[e] Main interaction among groups: $F_{2,52} = 0.376$, $p = 0.689$.
[f] The *p*-values were calculated using the independent-samples *t* test: $t_{32} = -1.607$; $p = 0.100$.
[g] Main interaction among groups: $F_{2,52} = 32{,}117$, $p < 0.001$; post hoc: controls versus AD, $p < 0.001$; controls versus DLB, $p < 0.001$; and AD versus DLB, $p = 1.000$.
[h] Main interaction among groups: $F_{2,52} = 138{,}552$, $p < 0.001$; post hoc: controls versus AD, $p < 0.001$; controls versus DLB, $p < 0.001$; and AD versus DLB, $p = 1.000$.
[i] Main interaction among groups: $F_{2,52} = 70{,}960$, $p < 0.001$; post hoc: controls versus AD, $p < 0.001$; controls versus DLB, $p < 0.001$; and AD versus DLB, $p = 0.403$.

3.4. Extrahippocampal structures thickness

Table 4 summarizes the statistical results for each extrahippocampal structure. When compared to controls, specific sites of atrophy in the right extrahippocampal structures were found in the 2 forms of dementia. Specifically, the thickness of the right entorhinal cortex was reduced in both AD and DLB patients. The thickness of the perirhinal cortex and the parahippocampus was reduced in the right hemisphere in DLB patients but not in the AD patients in the comparison with controls. No significant difference was found between AD patients and DLB patients.

3.5. Correlation analysis

Although no significant correlations were found between imaging and clinical outcomes, a trend toward a correlation was found between cortical thinning in perirhinal and parahippocampal regions and NPI visual hallucinations item ($\beta = -0.46$, $t = -1.902$, $\beta = 0.081$).

4. Discussion

In this study, we found different patterns of atrophy within the hippocampal subfields and the adjacent extrahippocampal structures in DLB and AD patients (Fig. 2).

Table 2
Volume (mm^3) for right and left total hippocampi

Region	DLB	AD	Controls	ANCOVA	Bonferroni pairwise post hoc		
					DLB vs. controls	AD vs. controls	DLB vs. AD
R-tHIP	3089 ± 582	2887 ± 559	3559 ± 416	**$F_{2,52} = 7.190$, $p = 0.002$**[a]	**$p = 0.023$**	**$p = 0.001$**	$p = 0.081$
L-tHIP	3310 ± 701	2773 ± 546	3619 ± 526	**$F_{2,52} = 8.500$, $p = 0.001$**[a]	$p = 0.355$	**$p = 0.001$**	**$p = 0.038$**
eITV	1,481,036 ± 160,165	1,476,228 ± 181,912	1,453,035 ± 167,198	$F_{2,52} = 0.137$, $p = 0.872$	NA	NA	NA

Values are expressed as mean ± standard deviation (SD).
Bold characters indicate significant results.
Key: AD, Alzheimer's disease; ANCOVA, analysis of covariance; CA, cormu ammonis; DG, dentate gysus; DLB, dementia with Lewy bodies; eITV, estimated total intracranial volume; L, left; tHIP, total hippocampus; NA, not applicable; R, right.
[a] ANCOVA followed by Bonferroni correction was carried out to test the differences among groups (adjusted significance threshold: $p = 0.05/2$ structures/3 groups $= 0.008$). When the ANCOVA was significant, pairwise Bonferroni post hoc was applied.

Specifically, the CA, DG, and subiculum were overall more atrophic in AD patients. Neuropathological studies have reported that AD and its prodromal stages are associated with neuronal loss in the CA1 and the subiculum regions (Corder et al., 2000; Kerchner et al., 2012; Thompson et al., 2003). Furthermore, it was observed that the alteration of hippocampal structures begins anteriorly in the CA1 and subiculum regions and subsequently propagate to the CA2 and CA3 subfields (Apostolova et al., 2006; Devanand et al., 2012; Wang et al., 2006, 2009). These pathological findings have been confirmed by structural imaging studies reporting bilateral atrophy in CA1, CA2-3, and subiculum in AD as compared to healthy controls (Chow et al., 2012; Firbank et al., 2010; Mak et al., 2015; Mueller et al., 2011; Sabattoli et al., 2008). The DG plays a crucial role in associative memory and its damage could be linked to disturbances in memory and learning observed in the early stages of AD (Ohm, 2007). We observed CA and subiculum preservation in DLB patients. Although the CA1 alteration in DLB is debated (Chow et al., 2012; Sabattoli et al., 2008), 2 recent studies have reported CA1 preservation in DLB in agreement with our findings (Firbank et al., 2010; Mak et al., 2015). Neuropathological studies did not find significant differences between controls and DLB in the hippocampal formation (Harding et al., 2002). Furthermore, as compared to AD patients, DLB patients showed preservation of the cell viability in the CA1 and subiculum and a selective loss of lower presubiculum pyramidal neurons (Harding et al., 2002).

As compared to controls, in our study the perirhinal cortex was reduced in DLB but not in AD patients. Anatomically, the perirhinal cortex is located between the ventral-medial surface of the temporal lobe surrounding the amygdala and anterior hippocampus and the ventral visual pathway (Suzuki and Naya, 2014). Consistently with its prominent interconnections with unimodal and polymodal cortical association areas, the perirhinal cortex contributes to a wide range of functions including visual functions (Suzuki and Naya, 2014). The perirhinal cortex ablation has been shown to impair visual object identification (Buckley and Gaffan, 1998). Furthermore, recent studies suggested that the perirhinal cortex contributes to perceptual processing (Devlin and Price, 2007) and that it is necessary for the disambiguation of perceptually and semantically confusable objects (Kivisaari et al., 2012).

The parahippocampus was damaged in DLB patients but not in AD patients. The parahippocampal gyrus is posterior to perirhinal cortex and has been associated with many cognitive processes, including visuospatial processing (Burgess et al., 2002). Recent studies have demonstrated that the parahippocampal cortex is a site for integration and processing of contextual associations (Aminoff et al., 2013) and that the direct electrical stimulation of the parahippocampal place area causes topographic visual hallucinations (Mégevand et al., 2014).

The perirhinal and parahippocampal cortices are reciprocally connected (Suzuki and Naya, 2014). Furthermore, both regions show functional and structural connections with dorsal visual and default-mode networks (Andrews-Hanna et al., 2010; Baldassano et al., 2013; Chadick and Gazzaley, 2011; Suzuki and Naya, 2014), which are strongly involved in the pathophysiology of visual hallucinations in DLB patients (Delli Pizzi et al., 2014a; Franciotti et al., 2013, 2015; Shine et al., 2014; Taylor et al., 2012). Different models

Table 3
Volume (mm^3) for right and left hippocampal subfields

Regions	DLB	AD	Controls	ANCOVA[a]	Bonferroni pairwise post hoc		
					DLB vs. Controls	AD vs. Controls	DLB vs. AD
R-CA1	309 ± 40	265 ± 39	318 ± 40	**$F_{2,52} = 9.331$, $p < 0.001$**	$p = 1.000$	**$p = 0.001$**	**$p = 0.007$**
R-CA2-3	768 ± 162	703 ± 98	899 ± 119	**$F_{2,52} = 9.398$, $p < 0.001$**	**$p = 0.011$**	**$p < 0.001$**	$p = 0.476$
R-CA4-DG	437 ± 88	397 ± 56	500 ± 64	**$F_{2,52} = 8.234$, $p = 0.001$**	**$p = 0.028$**	**$p < 0.001$**	$p = 0.359$
R-fimbria	35 ± 20	34 ± 24	51 ± 20	$F_{2,52} = 4.171$, $p = 0.022$	NA	NA	NA
R-fissure	62 ± 25	56 ± 35	54 ± 21	$F_{2,52} = 0.533$, $p = 0.590$	NA	NA	NA
R-PSUB	334 ± 51	321 ± 66	403 ± 59	**$F_{2,52} = 9.922$, $p < 0.001$**	**$p = 0.002$**	**$p = 0.001$**	$p = 1.000$
R-SUB	500 ± 69	466 ± 89	567 ± 66	**$F_{2,52} = 8.862$, $p = 0.001$**	**$p = 0.022$**	**$p = 0.001$**	$p = 0.572$
L-CA1	313 ± 45	262 ± 36	314 ± 44	**$F_{2,52} = 12.279$, $p < 0.001$**	$p = 1.000$	**$p = 0.003$**	**$p = 0.003$**
L-CA2-3	837 ± 189	684 ± 97	870 ± 116	**$F_{2,52} = 8.821$, $p = 0.001$**	$p = 1.000$	**$p = 0.001$**	**$p = 0.010$**
L-CA4-DG	467 ± 107	382 ± 65	504 ± 64	**$F_{2,52} = 10.382$, $p < 0.001$**	$p = 0.517$	**$p < 0.001$**	**$p = 0.012$**
L-fimbria	33 ± 19	33 ± 22	58 ± 27	**$F_{2,52} = 8.141$, $p = 0.001$**	**$p = 0.003$**	**$p = 0.008$**	$p = 1.000$
L-fissure	67 ± 28	56 ± 19	49 ± 20	$F_{2,52} = 2.791$, $p = 0.072$	NA	NA	NA
L-PSUB	347 ± 63	305 ± 70	410 ± 64	**$F_{2,52} = 11.763$, $p < 0.001$**	**$p = 0.014$**	**$p < 0.001$**	$p = 0.202$
L-SUB	511 ± 93	432 ± 77	573 ± 85	**$F_{2,52} = 13.462$, $p < 0.001$**	$p = 0.093$	**$p < 0.001$**	**$p = 0.030$**

Values are expressed as mean ± standard deviation (SD).
Bold characters indicate significant results.
Key: AD, Alzheimer's disease; ANCOVA, analysis of covariance; CA, cormu ammonis; DG, dentate gysus; DLB, dementia with Lewy bodies; L, left; NA, not applicable; PSUB, presubiculum; SUB, subiculum; R, right.
[a] ANCOVA followed by Bonferroni correction was carried out to test the differences among groups (adjusted significance threshold: $p = 0.05/14$ structures/3 groups $= 0.001$). When the ANCOVA was significant, pairwise Bonferroni post hoc was applied.

Table 4
Thickness (mm) for left and right extrahippocampal structures

Regions	DLB	AD	Controls	ANCOVA[a]	Bonferroni pairwise post hoc		
					DLB vs. controls	AD vs. controls	DLB vs. AD
R-EC	2.62 ± 0.63	2.61 ± 0.63	3.26 ± 0.32	**$F_{2,52}$ = 8.654, p = 0.001**	**p = 0.002**	**p = 0.003**	p = 1.000
R-PER	2.48 ± 0.58	2.60 ± 0.60	3.04 ± 0.30	**$F_{2,52}$ = 6.528, p = 0.003**	**p = 0.003**	p = 0.055	p = 1.000
R-PAR	2.10 ± 0.44	2.23 ± 0.43	2.52 ± 0.25	**$F_{2,52}$ = 6.701, p = 0.003**	**p = 0.003**	p = 0.093	p = 0.868
L-EC	2.81 ± 0.63	2.75 ± 0.59	3.30 ± 0.40	$F_{2,52}$ =5.340, p = 0.008	NA	NA	NA
L-PER	2.66 ± 0.56	2.63 ± 0.56	3.10 ± 0.34	$F_{2,52}$ = 5.397, p = 0.008	NA	NA	NA
L-PAR	2.20 ± 0.42	2.23 ± 0.40	2.60 ± 0.30	$F_{2,52}$ = 6.074, p = 0.005	NA	NA	NA

Values are expressed as mean ± standard deviation (SD).
Bold characters indicate significant results.
Key: AD, Alzheimer's disease; ANCOVA, analysis of covariance; EC, entorhinal cortex; DLB, dementia with Lewy bodies; L, left; NA, not applicable; PAR, parahippocampus; PER, perirhinal cortex; R, right.
[a] ANCOVA followed by Bonferroni correction was carried out to test the differences among groups (adjusted significance threshold: p = 0.05/6 structures/3 groups = 0.003). When the ANCOVA was significant, pairwise Bonferroni post hoc was applied.

have recently proposed that complex visual hallucinations could involve also subcortical regions outside the primary visual areas, including thalamus, amygdala, and hippocampus (Amad et al., 2014; Delli Pizzi et al., 2014b, 2015a; Ford et al., 2015, Heitz et al., 2015; Selimbeyoglu and Parvizi, 2010; Shine et al., 2014). In the present study, we did not observe a significant relationship between the frequency and the severity of visual hallucinations and the extrahippocampal atrophy. However, we are aware that the current assessment is limited by lacking of specific battery for investigating the visuoperceptual and attentional functions. Thus, further studies, by combining neuroimaging outcomes and specific neuropsychometric tests on visual functions, are request to better clarify the role of the extrahippocampal regions in the pathophysiology of the visual dysfuntion in DLB.

As compared to controls, the entorhinal cortex was affected in both AD and DLB patients. The entorhinal cortex is located between subiculum and perirhinal cortex. It plays a critical role in the episodic memory, particularly in the storage and retrieval of new declarative memories (Di Paola et al., 2007; Sasaki et al., 2015; Squire et al., 2004). Entorhinal atrophy has been linked to mild memory loss and it has been described as primary site of dysfunction in AD (Mueller et al., 2011; Whitwell et al., 2007; deToledo-Morrell et al., 2004). Less clear is the contribution of the entorhinal cortex to DLB. As compared to AD, entorhinal preservation has been found by Firbank et al. (2010), whereas comparable atrophy has been found by Kenny et al. (2008). Interestingly, the entorhinal cortex plays a central role in the visual recognition memory (Meunier et al., 1993). Hence, the damage of the entorhinal cortex could be linked to impaired visual recognition memory which has been found in DLB patients as compared to controls and PD patients (Mondon et al., 2007).

Of note, we observed that extrahippocampal thinning in DLB patients was predominant in the right hemisphere. This finding is in accordance with previous studies from our group, showing prominent structural and functional alterations in the right hemisphere of DLB patients (Delli Pizzi et al., 2014b, 2015a, 2015b, 2014a; Franciotti et al., 2013) and with the dominant role of right hemisphere in visuospatial attention (Thiebaut de Schotten et al., 2011).

In conclusion, our findings demonstrate that the hippocampal subfields and the extrahippocampal structures are differently impaired in DLB and in AD. Particularly, DLB patients showed a more focused alteration of the structures linked to visuoperceptual and attentional functions. We retain that these findings could be an important starting point to confirm the extrahippocampal involvement in the etiology of visual dysfunction in DLB.

As a limitation of the study, we must recognize that the small sample size across the groups would require the replication of the study on larger cohorts from different centers.

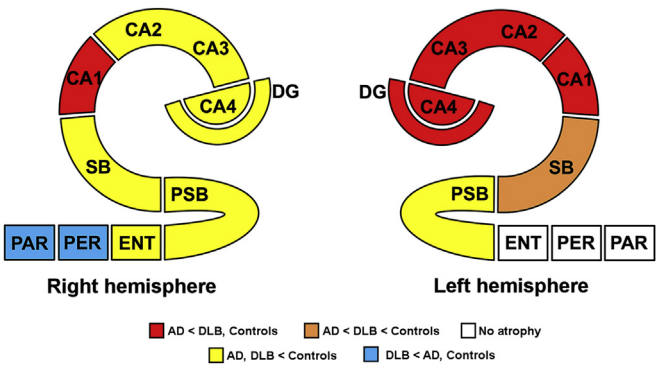

Fig. 2. Schematic representation of the gray matter (GM) atrophy in the hippocampal subfields and adjacent extrahippocampal structures. Color classification: blue = GM atrophy was found in DLB but not in the AD in the comparison with controls; yellow = GM atrophy was found in both forms of dementia as compared to controls; orange = the GM atrophy was found in both forms of dementia but the GM reduction is greater in AD as compared to DLB; red = GM atrophy was found in AD as compared to DLB and controls. The symbol "<" indicates GM reduction. Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy bodies; PAR, parahippocampus; PER, perirhinal cortex; DG, dentate gysus. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Disclosure statement

The authors have no conflicts of interest to disclose.

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