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SHORT REPORT

Occipital atrophy signature in prodromal Lewy bodies disease

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Abstract

INTRODUCTION: Dementia with Lewy bodies (DLB) is typically characterized by parietal, temporal, and occipital atrophy, but less is known about the newly defined prodromal phases. The objective of this study was to evaluate structural brain alterations in prodromal DLB (p-DLB) as compared to healthy controls (HC) and full-blown dementia (DLB-DEM).

METHODS: The study included 42 DLB patients ($n = 20$ p-DLB; $n = 22$ DLB-DEM) and 27 HC with a standardized neurological assessment and 3-tesla magnetic resonance imaging. Voxel-wise analyses on gray-matter and cortical thickness were implemented to evaluate differences between p-DLB, DLB-DEM, and HC.

RESULTS: p-DLB and DLB-DEM exhibited reduced occipital and posterior parieto-temporal volume and thickness, extending from prodromal to dementia stages. Occipital atrophy was more sensitive than insular atrophy in differentiating p-DLB and HC. Occipital atrophy correlated to frontotemporal structural damage increasing from p-DLB to DLB-DEM.

DISCUSSION: Occipital and posterior-temporal structural alterations are an early signature of the DLB continuum and correlate with a long-distance pattern of atrophy.

KEYWORDS
cortical thickness, MRI, occipital atrophy, prodromal DLB, voxel-based morphometry

1 | BACKGROUND

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative disorder characterized by cognitive deficits and the core features of parkinsonism, REM sleep behavior disorder (RBD), visual hallucinations, and cognitive fluctuations.[1] Recently, the DLB continuum has been extended to prodromal stages (p-DLB), defined by the presence of core clinical features with minimal impairment in activities of daily living.[1] The criteria include reduced occipital metabolism and perfusion as a potential prodromal DLB marker.[2] Conversely, occipital atrophy is still debated in prodromal phases, whereas it has been consistently associated with clinical progression.[3]

In this study, we hypothesize that occipital structural damage extending to posterior-temporal areas might represent an early signature of Lewy pathology, already detectable in prodromal stages. To this end, we evaluated cortical volume and thickness in p-DLB in comparison with controls and patients with dementia. Finally, we explored the relationship between occipital structures and other long-distance structural changes to evaluate possible pathways of disease progression in Lewy bodies disorders.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using conventional (eg, PubMed) sources and meeting abstracts and presentations. While patterns of structural damage in DLB in the prodromal stages remain unclear, growing evidence in autopsy-confirmed patients suggests that occipital alterations are associated with clinical progression.
2. **Interpretation**: Our findings demonstrate that occipital structural damage is present in DLB since the early stages and correlates with a long-distance pattern of atrophy.
3. **Future Directions**: This study proposes a framework for the generation of new hypotheses and the performance of additional studies. Further, longitudinal studies are warranted to extend these findings, evaluating the impact of occipital damage on clinical progression and course.

2 | METHODS

2.1 | Participants

Consecutive patients with a DLB clinical diagnosis were recruited from the Neurology Unit at the University of Brescia, Italy. Each participant underwent a 3.0-Tesla magnetic resonance imaging (MRI) acquisition session, including a T1-weighted sequence. All patients underwent a standardized neurological assessment, a neuropsychological assessment, the Neuropsychiatric Inventory (NPI), and the Clinical Dementia Rating (CDR) scale.

All patients were asked for the presence of core symptoms,[1] and only patients with at least two core symptoms fulfilling the probable DLB definition were included.[1,4] To increase sensitivity, each DLB patient showed abnormal dopaminergic DaTSCAN imaging. Patients were classified according to CDR score: prodromal DLB was defined as CDR = 0.5, whereas full-blown dementia was defined by CDR ≥ 1. The sample included only patients with mild cognitive impairment (MCI) due to Lewy bodies, as no delirium or psychiatric onset was evaluated. Participants' inclusion criteria, MRI protocol preprocessing, and additional analyses are described in Supplementary Materials.

2.2 | Statistical analyses

Differences in demographical and clinical variables between groups were assessed by ANOVA test for continuous variables and chi-squared for dichotomous variables using IBM SPSS 28.0.

2.2.1 | Structural brain differences

Preprocessed T1-MRI entered an ANOVA model on SPM12 to test differences in grey matter (GM) volume between patients with dementia (DLB-DEM), p-DLB, and healthy controls (HC), adjusting for age, sex, education, and TIV. The significant threshold was set at $p < .05$ false discovery rate (FDR) corrected for multiple comparisons with clusters larger than 100 voxels deemed significant. Possible between-group differences in GM volume are further assessed by means of a region of interest (ROI)-based analysis. Mean scores of GM volume in the insula (published criteria) and occipital lobe (region obtained from voxel-wise comparisons) were extracted from Neuromorphometrics atlas on CAT12. Then individual z-scores were calculated using HC as the reference population, with higher z-scores reflecting larger GM volumes. The obtained z-scores were entered into an ANOVA model on SPSS. Results were deemed significant at $p < .05$, after Bonferroni correction for multiple comparisons.[5] To test potential differences in cortical thickness (CTh) between patients and HC, we applied the ANOVA test on SPM12, adjusting for age, sex, and education. For contrasts not surviving at FDR correction, the threshold was set at $p < .001$, uncorrected for multiple comparisons, for exploratory purposes.

2.2.2 | Structural covariance analysis

This analysis was performed to evaluate the covariance of GM volume/CTh in a ROI, or "seed," with other brain regions. This approach relies on the assumption that interconnected brain areas exhibit a greater coherence in GM volume because of shared mechanisms of atrophy in connected regions.[6,7] Thus, we extracted individual mean scores of GM volume and CTh from the seed belonging to the largest

TABLE 1 Demographic and clinical characteristics of the studied groups.

	HC	p-DLB	DLB-DEM	*p* value
N	27	20	22	–
Age at evaluation (years)	64.7 ± 5.65	76.4 ± 5.90	78.6 ± 4.60	<.001[a]
Sex, F/M	15/12	5/15	11/11	.097
Age at onset	–	72.1 ± 5.38	73.6 ± 4.90	.591
Disease duration (years)	–	3.5 ± 1.63	3.9 ± 1.74	.558
Education	13.4 ± 3.80	7.8 ± 3.4	6.9 ± 3.5	<.001[a]
MDS-UPDRS-III, total score	–	22.4 ± 17.4	24.0 ± 15.7	.644
MMSE, total score	29.2 ± 1.2	24.2 ± 3.3	19.2 ± 3.66	<.001[b]
NPI, total score	–	20.1 ± 13.8	20.9 ± 11.7	.791
CDR, total score	0.0 ± 0.0	0.5 ± 0.1	1.3 ± 0.6	<.001[b]
TIV	1443.6 ± 121.5	1438.2 ± 121.5	1418.6 ± 120.72	.762
Core DLB criteria, % (n)				
Parkinsonism	0	10 (50%)	14 (64%)	.755
Fluctuating cognition	0	7 (35%)	11 (50%)	.283
Visual hallucinations	0	11 (55%)	13 (59%)	.286
REM sleep behavior disorder	0	8 (40%)	12 (55%)	.768

Abbreviations: p-DLB, prodromal dementia with Lewy Bodies; DLB-DEM, dementia with Lewy bodies; MDS-UPDRS-III, Movement Disorder Society-Unified Parkinson Disease Rating Scale part III; MMSE, Mini Mental-State Examination; NPI, Neuropsychiatric Inventory; CDR, Clinical Dementia Rating scale; TIV, total intracranial volume.
[a]HC ≠ P-DLB, DLB-DEM.
[b]HC > P-DLB > DLB-DEM.

significant cluster obtained in previous analyses (i.e., p-DLB < HC; DLB-DEM < HC). Specifically, individual seed mean scores were extracted from the Neuromorphometrics atlas.

First, we were interested in describing the structural covariance pattern characterizing the whole DLB sample and HC. Thus, we performed a regression analysis considering each subject's seed mean score as a covariate of interest, with age, sex, education, and TIV as confounding covariates. Second, we assessed whether the structural covariance pattern depended on the presence of DLB core symptoms by evaluating the interaction between seed mean scores and the presence/absence of each core symptom. Then we tested the structural covariance pattern specifically characterizing each DLB group, by applying the same regression analysis separately for p-DLB and DLB-DEM, to assess whole-brain volumetric changes related to occipital atrophy at different disease stages. Clusters were significant at FDR $p < .05$, with more than 100 voxels.

3 | RESULTS

Forty-two LB patients, including 22 DLB-DEM and 20 p-DLB, and 27 HC enrolled in the study. As expected, DLB-DEM exhibited higher severity in global cognitive measures ($p < .001$) and higher burden on functional activities ($p < .001$) compared to p-DLB and HC (Table 1, see Table S1 for detailed neuropsychological and behavioral data).

3.1 | Structural brain analyses

Compared to HC, p-DLB showed atrophy in the medial occipital lobe, extending to posterior-temporal cortices. DLB-DEM exhibited atrophy in occipital-temporal and parietal regions (Figure 1A, Table S2). ROI-based analysis confirmed lower occipital volume in p-DLB ($z = -1.09 \pm 1.07$, $p = .003$) and DLB-DEM ($z = -1.32 \pm 1.01$, $p < .001$) compared to HC. Conversely, ROI-based analysis on insula, currently listed in the p-DLB criteria,[1] revealed significant atrophy in DLB-DEM ($z = -1.01 \pm 1.03$, $p = .004$) but only a slight reduction in p-DLB ($z = -0.57 \pm 1.07$, $p = .200$) versus HC (Table S3).

CTh reductions were found in similar brain regions in both p-DLB and DLB-DEM groups but at $p < .001$ uncorrected threshold (Figure 1B, Table S4). The p-DLB group exhibited CTh reductions mainly involving medial occipital and posterior-temporal surfaces. The DLB-DEM group exhibited a more extended cortical thinning in occipital-temporal regions, with an additional involvement parietal cortex.

3.2 | Structural covariance analysis

Lower volume of the occipital seed (i.e., lingual gyrus) was associated with a lower volume of occipital, temporal, parietal, and frontal regions in DLB. Conversely, it was associated with a lower volume limited to occipital cortices in HC (Table S5).

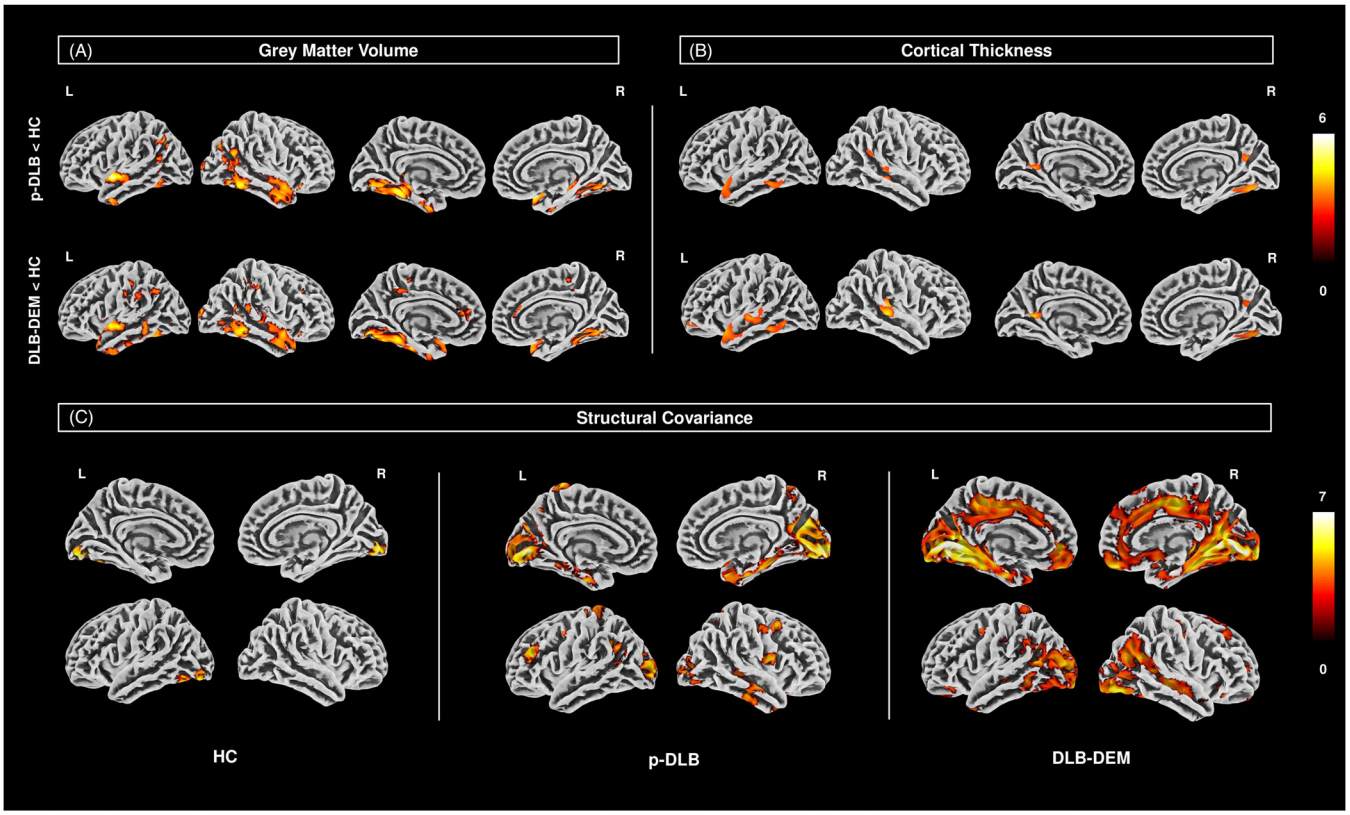

FIGURE 1 (A) Grey matter atrophy in patients with p-DLB and DLB compared to HC. Results are $p < .05$ FDR-corrected. (B) Patterns of cortical thickness in patients with p-DLB and DLB compared to HC. Images are $p < .001$ uncorrected for multiple comparisons. (C) Patterns of gray matter structural covariance between bilateral lingual gyrus and other brain regions in HC (left), p-DLB (middle), and DLB-DEM (right). Results are $p < .05$ FDR-corrected. Color bar represents *t* values. HC, healthy controls; p-DLB, prodromal dementia with Lewy bodies; DLB-DEM, dementia with Lewy bodies.

Parkinsonism, RBD, and cognitive fluctuations were not associated with different patterns of structural covariance, whereas in patients with visual hallucinations, a lower occipital volume was associated with a larger pattern of occipital-temporal atrophy.

Structural covariance analysis conducted separately in p-DLB and DLB-DEM groups revealed a pattern of covariance involving larger clusters of occipital lobes, with an additional involvement of parietal, temporal, and frontal lobes in the p-DLB group. DLB-DEM showed a more extended involvement of occipital-temporal areas spreading to frontal cortices (Figure 1C, Table S6).

Structural covariance analysis of occipital cortical thinning revealed a small occipital cluster in HC, whereas in DLB a larger occipital cluster with additional involvement of frontal and temporo-parietal areas was detected, increasing from prodromal to dementia phases (Table S7).

4 | DISCUSSION

The primary finding of this study was that structural alterations of occipital and posterior-temporal areas are present starting at the prodromal stages of DLB, independently from the presence of core criteria, namely parkinsonism, RBD, and cognitive fluctuations. This pattern of occipital damage correlates with volume and CTh reductions in temporo-occipital lobes but also in long-distance parieto-temporo-frontal structures, with an increasing impairment from prodromal to dementia stages. Occipital atrophy observed in the prodromal phases was further confirmed by cortical thinning found in occipital-temporal regions in both p-DLB and DLB-DEM. These results confirmed and extended important works evaluating volume and CTh in selected cohorts of prodromal DLB.[8,9] Moreover, the ROI-based analysis in p-DLB revealed a higher sensitivity of occipital atrophy in prodromal phases, whereas insular volume changes appeared to be significant only in dementia phases. This finding suggests that insular volumetric changes could be less sensitive compared to occipital atrophy in prodromal phases.[10] The covariance pattern analyses using occipital seed further supported these observations, showing a pattern of atrophy related to the seed involving temporo-parietal and frontal areas. These findings suggest a possible shared mechanism of neurodegeneration linked to early dysfunction of fronto-occipital tracts[11]; alternatively, it might reflect widespread extensive denervation from cholinergic fibers coming from the nucleus basalis of Meynert, an early impaired structure in DLB.[9,12]

Brain areas related to occipital seed were similar in patients presenting with parkinsonism, RBD, and cognitive fluctuations. Only patients with visual hallucinations showed a larger pattern of temporal atrophy, consistent with the literature.[13] Findings thus support the

claim that occipital damage may be an early signature of the whole DLB spectrum.[14]

We acknowledge that this study has some limitations, mainly related to its cross-sectional single-center design and limited sample size. One limitation of the study relies on the age difference between patients and controls; all the analyses were conducted adjusting for age effect, but the sample was limited in size for a proper matching without constraining the statistical model. Another possible limitation is the lack of data for evaluating the possible role of AD co-pathology in modulating volumetric changes within the medial temporal lobe structures.[15] Furthermore, the present study focused on the MCI-LB subtype, and future studies involving delirium and psychiatric onset are warranted to extend these findings. These limitations notwithstanding, this is one of the first studies providing evidence on early occipital structural alterations supported by cortical volume and thickness changes, with a possibly higher sensitivity compared to insular atrophy listed in the current criteria. Moreover, the pattern of covariance spreading from prodromal to dementia phases, involving long-distance regions, might be considered a common progression pattern in a different DLB spectrum.[14]

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CONFLICT OF INTEREST STATEMENT

All authors declare no financial or non-financial competing interests. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The Ethics Committee approved the Brescia Hospital research protocol (NP 3710). Written informed consent was obtained from all participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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