Original Research Article

An SBM and TBSS Analysis in Early-stage Patients With Alzheimer's Disease, Lewy Body Dementias, and Corticobasal Syndrome

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Abstract

Objective: To compare gray matter (GM) and white matter (WM) changes in patients with Alzheimer's disease (AD), Lewy body dementias (LBD), corticobasal syndrome (CBS), and healthy controls (HC). **Methods:** Surface-based morphometry (SBM) was assessed on 3D T1-weighted images using FreeSurfer image analysis and WM microstructure was studied using Tract-Based Spatial Statistics (TBSS) in 12 AD, 15 LBD, 10 CBS patients, and 10 HC. **Results:** Patients with AD, compared with HC, exhibited reduced cortical surface area and volume in the superior frontal, middle frontal, and medial orbitofrontal cortex. In TBSS, AD patients, compared with HC and LBD, displayed decreased fractional anisotropy, axial diffusivity, and increased radial diffusivity in all major WM tracts. Other comparisons between the groups yielded no differences, either in the SBM or the TBSS analysis. **Conclusions:** The results indicate significant early structural changes in the GM of the frontal lobe, along with WM alterations early in AD patients.

Keywords

Alzheimer's disease, dementia with Lewy bodies, Parkinson's disease dementia, corticobasal syndrome, surface-based morphometry, tract-based spatial statistics

Introduction

Neurodegenerative diseases comprise an heterogenous cluster of neurological disorders. Despite significant progress in understanding their nature and cause, their diagnosis remains challenging, even for the most experienced clinician. Indeed, their overlapping clinical features among different neurodegenerative diseases make accurate diagnosis a difficult task.

Alzheimer's disease (AD) is the most common neurodegenerative cause of dementia, followed by Lewy body dementias (LBD).[1] LBD is an umbrella term, encompassing both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD).[1] DLB and PDD are considered two ends of the Lewy body disease spectrum, as they share both clinical and pathological features.[2] Corticobasal syndrome (CBS) is a relatively rare clinical syndrome, often not the result of corticobasal degeneration (CBD), but of other pathological entities, including AD and Lewy bodies.[3]

Furthermore, CBS shares many clinical features with atypical variants of AD, including visuospatial, language, and executive deficits. Attention, executive and

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visuospatial skills are also frequently impaired in DLB.[4] Emerging novel treatments that could hasten or even modify the disease course for some neurodegenerative diseases require a proper diagnosis.[5]

Magnetic Resonance Imaging (MRI) of the brain is an invaluable tool for evaluating neurodegenerative diseases. However, visual assessment of MRI seems to fail in yielding distinct patterns of atrophy or other significant changes.[4,6] Automated analysis of MRI sequences at voxel or region of interest (ROI) level may reveal changes that escape the most experienced naked radiological eye. Voxel-Based Morphometry (VBM) has been largely used for the evaluation of cortical volume at a voxel level, but surface-based morphometry (SBM) which analyses cortical thickness, cortical surface area, and gyrification seems to detect cortical atrophy more efficiently than VBM.[7] Tract-Based Spatial Statistics (TBSS) is a voxel-wise analysis of diffusion tensor imaging (DTI) data, and it is widely used, because of its advanced registration capabilities, as wells as its robust non-parametric assessment of local differences in WM integrity between groups.[8]

While SBM has already shown changes at the mesial temporal lobe structures in AD patients,[9] previous studies have shown widespread atrophy of the neocortex,[10] without any specific pattern that could possibly discriminate AD from other neurodegenerative diseases and improve our insight in the pathogenetic course of the disease. Moreover, studies that compare between AD, DLB, and CBS patients, either with SBM or with TBSS are lacking. Disparities of the structural changes in the GM and WM between AD, DLB, and CBS could shed more light on their pathogenesis, especially in the early stages, when the diagnosis is more challenging, and a more accurate discrimination for future research is needed, hoping for early and effective therapeutic interventions to emerge. The aim of the study was to assess potential disparities in structural alterations in the neocortex within both grey and WM among individuals with clinically established AD, LBD, and CBS, in comparison to healthy controls (HC), utilizing both SBM and TBSS. Noted, this is the first study, which compares early-stage patients with all the aforementioned clinical syndromes, either with SBM or with TBSS.

Methods

Participants

All patients were recruited from the Neurology Department of the University Hospital of Ioannina. The study received approval by the hospital's Scientific Advisory Board. Informed consent forms were signed by all patients and HC participating in the study. Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki were followed. Inclusion criteria were age 50-80 years. Exclusion criteria included a history of major psychiatric or neurodevelopmental disorder, substance abuse, ischemic or hemorrhagic stroke, severe head trauma, intracranial surgery, tumor, arteriovenous malformation, or other intracranial mass, as well as a significant burden of WM hyperintensities (Fazekas 2 or higher) on T2 and FLAIR sequences, or motion artefacts.

All patients were thoroughly evaluated by two Neurologists (blinded). Patients were diagnosed with probable AD dementia, according to the National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic guidelines.[11] Those with probable PDD were diagnosed based on clinical diagnostic criteria for dementia associated with Parkinson's disease.[2] The diagnosis of probable DLB was made according to the criteria of the DLB Consortium.[4] Lastly, all patients with CBS met the criteria for probable CBS phenotype, associated with CBD pathology.[3] Patients with either PDD or DLB were studied together, as an LBD group.

The study recruited 12 patients with AD, 15 patients with LBD (8 with DLB and 7 with PDD), 10 patients with CBS, and 11 HC. For all subjects, relevant demographic data including age (in years), sex (female sex), education level (years of education) and disease duration (in months) were recorded for structural brain evaluation. Years of age, female sex, years of education, and disease duration in months were used as covariates in the group comparisons conducted, as it has been shown before that all of them are associated with significant structural brain changes.[12-14]

Neuropsychological Assessment

All patients and HC underwent an extensive neuropsychological assessment by a specialized speech therapist (blinded). However, the cognitive assessments were administered solely to evaluate the cognitive status of the patients and healthy controls. The results of these assessments were not included in the current study analysis. The following neuropsychological batteries were administered: Addenbrooke's Cognitive Examination-Revised, Frontal Assessment Battery, Verbal Fluency Task, Trail Making Test A and B, Neuropsychiatric Inventory, and Geriatric Depression Scale.

Statistical Analysis

Continuous demographic and clinical variables were assessed for normality using the Shapiro-Wilk test and subsequently analyzed with one-way ANOVA, followed by post-hoc comparisons to assess group differences between study groups. For nominal variables, the Pearson Chi-Square test and Fisher's Exact test were employed to determine significance. Data analysis was conducted using the SPSS statistical package, (IBM SPSS Statistics for

Windows, Version 26.0, IBM Corp, Armonk, NY), with statistical significance set at a threshold of P = 0.05.

MRI Acquisition

All MRI examinations were conducted using the same 3T MRI unit (Ingenia CX; Philips Medical Systems, Best, The Netherlans). The imaging protocol for both patients and HC included the following sequences: (i) T2W turbo spin echo (TR/TE: 2.945/80, matrix: 576 × 576, field of view (FOV): 230 × 230 mm, slice thickness: 4 mm, gap: 1 mm); (ii) FLAIR sequence (TR/TE: 4800/261, inversion recovery time: 1650 ms, FOV: 251 × 251 mm, matrix: 248 × 248, slice thickness: 1 mm, gap: −0.6 mm); (iii) T1W high resolution (1 × 1 × 1 mm^3) three-dimensional spoiled gradient-echo sequence (TR/TE: 7.9/3.5, matrix: 560 × 560, FOV: 240 × 240 mm), used for structural imaging; and (iv) a single-shot spin-echo echo-planar sequence (TR/TE: 2812/80 ms, FOV: 204/204 mm, matrix: 128 × 128, section thickness: 2.5 mm, maximum b-value: 1000 s/mm^2, 16 noncollinear diffusion directions, intersection gap: 0 mm), used for DTI.

Image Analysis

Regarding SBM, gray matter (GM) segmentation and cortical reconstruction of the high-resolution T1-weighted structural images were conducted using the FreeSurfer image analysis suite (version 7.4.0, Martinos Center for Biomedical Imaging, MA, USA). The processing workflow involved motion correction, elimination of non-brain tissue, intensity normalization, tessellation of the cortical GM and WM boundary, automated topology correction, surface deformation to precisely define cortical surface borders, registration to a spherical atlas (Desikan-Killiany)[15] and, finally, creation of grey matter thickness, volume, and surface area maps, at each point on the cortical surface. The maps were smoothed with a 10 mm full-width half maximum filter and used in a general linear model to assess GM thickness, volume, and surface area differences between study groups controlling for demographic and clinical factors. A standard false discovery rate (FDR) correction of 5% (q = 0.05) was applied.

A TBSS analysis, part of the FMRIB Software Library (FSL), was employed to investigate WM microstructural differences among study groups. Diffusion-weighted magnetic resonance imaging data underwent preprocessing using FSL, which included eddy current correction, brain extraction, and fitting of diffusion tensors. Subsequently, fractional anisotropy (FA), axial diffusivity (AxD), mean diffusivity (MD), and radial diffusivity (RD) maps were generated and aligned to a common space using FSL's nonlinear registration tool. A mean FA skeleton, representing the centers of major WM tracts with FA >0.2, was created. Individual subject FA, AxD, MD, and RD maps were then projected onto this skeleton for further statistical analysis. A non-parametric permutation-based approach, employing 10 000 permutations and implemented in FSL's Randomise tool, was used to assess group differences, while controlling demographic and clinical factors. Threshold-free cluster enhancement was applied for cluster-wise inference across the various diffusion metrics, with a significance threshold set at P = 0.05.

To assess group differences in diffusion metrics, we used a non-parametric permutation-based approach, implemented in FSL's randomize tool. This method is advantageous, because it does not rely on assumptions of normality and can handle the complex distribution of neuroimaging data.[8] Specifically, we performed 10 000 permutations for each comparison to obtain a robust statistical inference. To control for multiple comparisons, we applied Threshold-Free Cluster Enhancement (TFCE), which enhances the sensitivity of detecting cluster-wise differences, while maintaining a strict control over the family-wise error (FWE) rate at a significance threshold of $p < 0.05$. While the FWE correction ensures that the risk of type I errors is controlled at the voxel level within each contrast, it is important to note that this correction was applied independently for each contrast. Consequently, the potential for type I errors increases when considering multiple contrasts collectively. The consistency of our findings across all major WM tracts underscores the robustness of our approach, despite the inherent statistical challenges.

Results

Demographics and Clinical Data

Descriptive statistics of the demographic and clinical data are presented in Table 1. No differences were found between groups for sex, disease duration or years of education. However, the AD group was younger ($P < 0.05$), compared to the LBD and CBS groups.

In addition, mean GDS scores yielded no differences between groups. Specifically, mean GDS score were 4.33 (2.49 - 6.18 95% CI) for the AD group, 3.93 (1.86 - 6.01 95% CI) for the LBD group, 3.50 (1.09 - 5.91 95% CI) for the CBS group, and 1.36 (−0.12 - 2.84 95% CI) for HC (p = 0.127).

Surface-Based Morphometry

Table 2 summarizes the identified differences in cortical surface area, cortical volume, and cortical thickness among the study groups, illustrated in Figure 1. All patient groups exhibited atrophy compared to HC. AD showed cortical surface area reduction in the frontal lobe, especially in both

Table 1. Demographic Disease Group Values, Presented in Means.

Group	Age (y)	Female Sex (%)	Education (y)	Disease Duration (m)
AD (n = 12)	61.83 (56.21-67.46 95% CI)	66.67	12.42 (9.57-15.26 95% CI)	20.42 (10.50-30.33 95% CI)
LBD (n = 15)	69.33 (65.80-72.87 95% CI)	33.33	9.47 (7.05-11.88 95% CI)	21.67 (14.89-28.45 95% CI)
CBS (n = 10)	68.60 (64.68-72.52 95% CI)	50.00	8.80 (5.77-11.83 95% CI)	25.80 (17.45-34.15 95% CI)
HC (n = 11)	62.91 (58.36-67.36 95% CI)	54.55	13.09 (9.78-16.40 95% CI)	Not applicable

AD = Alzheimer's disease, LBD = lewy body dementia, CBS = corticobasal syndrome, n = number, y = years, m = months.

Table 2. Clusters of Cortical Surface Metrics Differences Among Groups, Characterized by Cluster Size, Coordinates, and Locations of the Most Significant Point.

Comparison (Cortical Metric)	Size (mm^2)	X	Y	Z	*P*-value	Brain Area (Laterality-Desikan Label-lobe)
HC>AD (Area)	450.97	11	55.2	9.5	<0.001	R-superior-frontal
	183.02	34.1	29	38	0.011	R-rostralmiddle-frontal
	165.65	7	58	−9.7	0.016	R-medialorbito-frontal
	427.92	−11.6	63.2	4.1	<0.001	L-superior-frontal
HC>AD (volume)	245.14	8.4	61.6	−5.6	<0.001	R-medialorbito-frontal
	218.46	8.4	58.7	24.9	<0.001	R-superior-frontal
	102.93	40.1	19.8	40.1	0.015	R-caudalmiddle-frontal
HC > LBD (area)	122.31	−63.8	−41.1	10.8	0.037	L-superior-temporal
HC > CBS (area)	192.01	−62	−40	7.5	0.013	L-bankssts
LBD > AD (thickness)	99.46	36.5	−45.6	35.2	0.016	R-inferior-parietal

AD = Alzheimer's disease, LBD = Lewy body dementias, CBS = Corticobasal syndrome, HC = healthy controls, L = left, R = right, X, Y, Z = coordinates of the most significant point in the cluster at the Montreal Neurological Institute brain atlas, bankssts = banks of superior temporal sulcus.

left and right superior frontal cortices, as shown in Figure 1A and B. ($P = 0.0002$), along with reduction in the right orbitofrontal cortex, and right middle frontal cortex ($P < 0.05$), as shown in Figure 1A. Cortical volume reduction was also observed in the right superior frontal cortex ($P = 0.0002$), right orbitofrontal cortex ($P = 0.0002$), and right middle frontal cortex, ($P < 0.05$), as shown in Figure 1C.

Additionally, LBD showed atrophy of the left superior temporal cortex, as shown in Figure 1D, while atrophy in another area of the superior temporal cortex was also shown in the CBS group (Figure 1E). No differences were detected between patient groups, except in the case where LBD demonstrated larger cortical thickness than AD in a region of the inferior parietal lobe (Figure 1F).

Diffusion Metrics

Widespread differences in diffusion metrics were detected in all major WM tracts between individuals with AD and HC, as well as between AD and those with LBD (Table 3, Figures 2 and 3). In both cases, individuals with Alzheimer's disease exhibited lower FA and AxD, along with higher RD, indicating significant alterations suggestive of reduced structural integrity and increased water diffusivity within the WM microstructure. Finally, patients with CBS presented larger RD than patients with LBD in a small region of the left cingulate gyrus (Table 3).

Discussion

The main findings of the study were cortical atrophy in the superior frontal cortex, middle frontal cortex, and medial orbitofrontal cortex, alongside microstructural abnormalities in all major WM tracts in AD patients, compared to HC. Additionally, decreased cortical thickness was observed in the right inferior parietal cortex, when compared to LBD. On the other hand, patients with LBD and CBS demonstrated only a decrease in cortical surface area in two restricted regions of the superior temporal cortex, compared to HC, respectively. Furthermore, AD patients exhibited decreased FA and AxD, as well as increased RD in all major WM tracts compared to HC and LBD patients, with decreased AxD, when compared with CBS.

While the frontal lobe is frequently implicated in other forms of neurodegenerative dementia,[16] both microstructural and macrostructural changes have been previously described in AD patients. Previous studies in AD patients have demonstrated alterations in the frontal lobe structure, revealing reduced surface area and/or thickness of the frontal cortex, often in conjunction with other cortical regions, including temporal, parietal, occipital, and insular areas.[10]

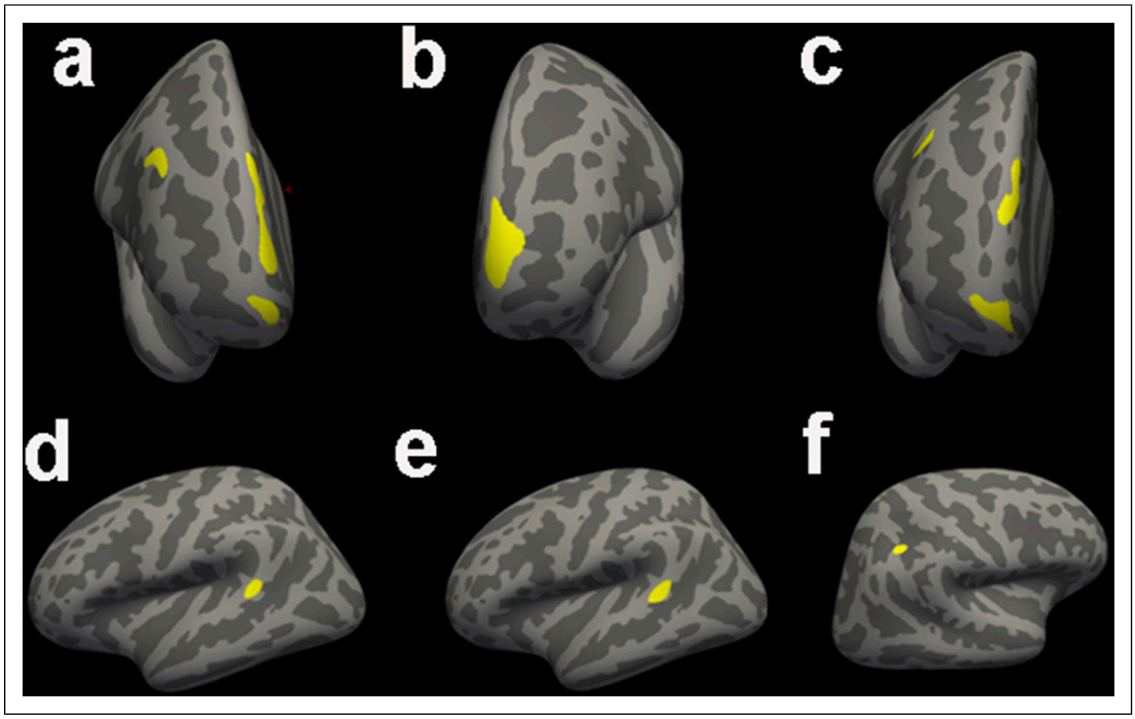

Figure 1. Brain areas highlighted in yellow are overlaid on hemispheres of a brain template, indicating differences in cortical surface metrics among groups. Specifically, these areas indicate where patients with Alzheimer's disease show smaller cortical surface area (a, b) and volume (c) compared to healthy controls. Additionally, they reveal areas where patients with Lewy body dementias (d) or corticobasal syndrome (e) have less cortical surface area than healthy controls, and aras where patients with Alzheimer's disease have less cortical thickness than patients with Lewy body dementias (f).

Table 3. Clusters of Diffusion Metrics Differences Among Groups, Characterized by Cluster Size, Coordinates of the Most Significant Voxel and the WM Tracts Involved.

Comparison (Diffusion Metric)	Number of Voxels	X	Y	Z	*P*-value	White Matter Tract
HC>AD (FA)	60619	21	43	3	0.009	ATR, CST, Cg (cingulate gyrus, hippocampus), FM, Fm, IFOF, ILF, SLF, UNC, SLF (temporal part)
HC>AD (AxD)	3874	−23	−29	41	0.015	ATR L, CST L, Cg (cingulate gyrus, hippocampus) L, FM, IFOF L, ILF L, SLF L, UNC L, SLF (temporal part) L
	25	−34	2	−31	0.049	ILF L
AD > HC (RD)	54162	−16	36	−11	0.012	ATR, CST, Cg (cingulate gyrus), Cg (hippocampus), FM, Fm, IFOF, ILF, SLF, UNC, SLF (temporal part)
LBD > AD (FA)	71639	−42	−28	−14	0.007	ATR, CST, Cg (cingulate gyrus), Cg (hippocampus), FM, Fm, IFOF, ILF, SLF, UNC, SLF (temporal part)
LBD > AD (AxD)	647	29	−49	−30	0.034	ATR R, CST R
AD > LBD (RD)	5416	−16	36	−11	0.012	ATR, CST, Cg (cingulate gyrus), Cg (hippocampus), FM, Fm, IFOF, ILF, SLF, UNC, SLF (temporal part)
CBS>AD (AxD)	762	−19	−14	41	0.029	ATR L, CST L, Cg (cingulate gyrus) L, SLF L
	39	−26	−26	22	0.049	ATR L, CST L, SLF L

AD = Alzheimer's disease, LBD = Lewy body dementias, CBS = Corticobasal syndrome, HC = healthy controls, FA = fractional anisotropy, AxD = axial diffusivity, RD = radial diffusivity, L = left, R = right, X, Y, Z = coordinates of the most significant voxel in the cluster at the Montreal Neurological Institute brain atlas, SLF = Superior longitudinal fasciculus, ILF = Inferior longitudinal fasciculus UNC = Uncinate fasciculus, Cg = Cingulate, CST = Corticospinal tract, IFOF = Inferior frontal occipital fasciculus, ATR = Anterior thalamic radiation, FM = Forceps Major, Fm = Forceps minor.

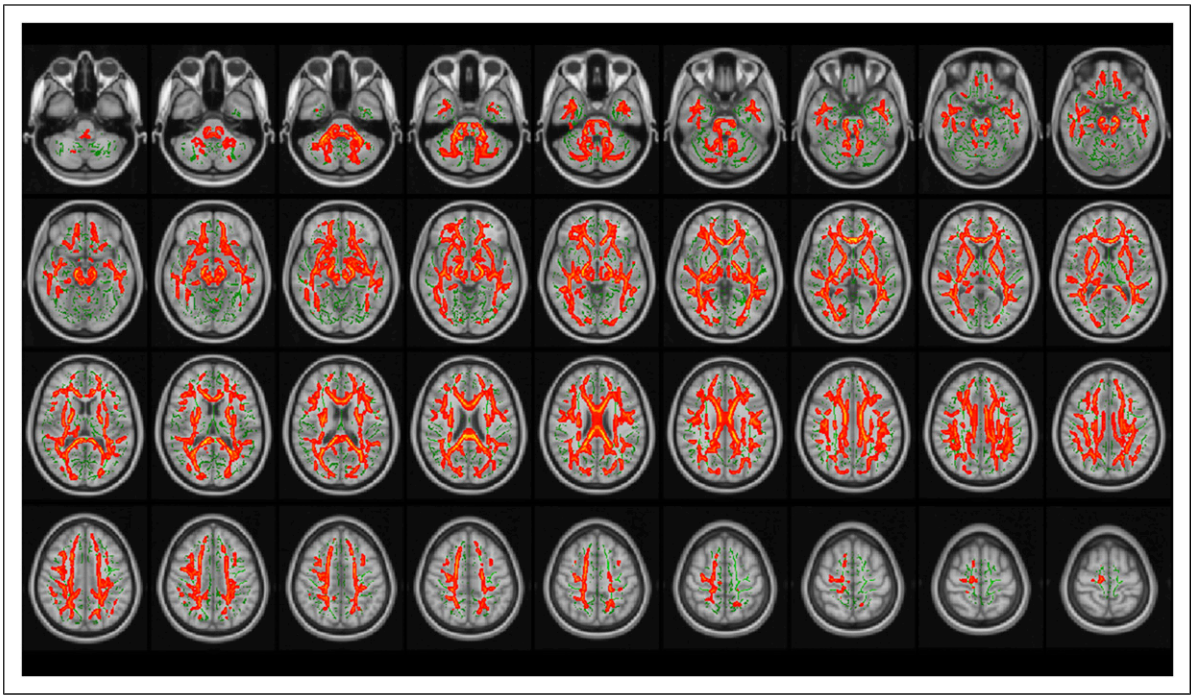

Figure 2. Track-based spatial statistics results are depicted in yellow-red areas, indicating reduced fractional anisotropy in patients with Alzheimer's disease compared to healthy controls. These areas are projected onto the mean FA skeleton (green) and an axial, grayscale T1W template image.

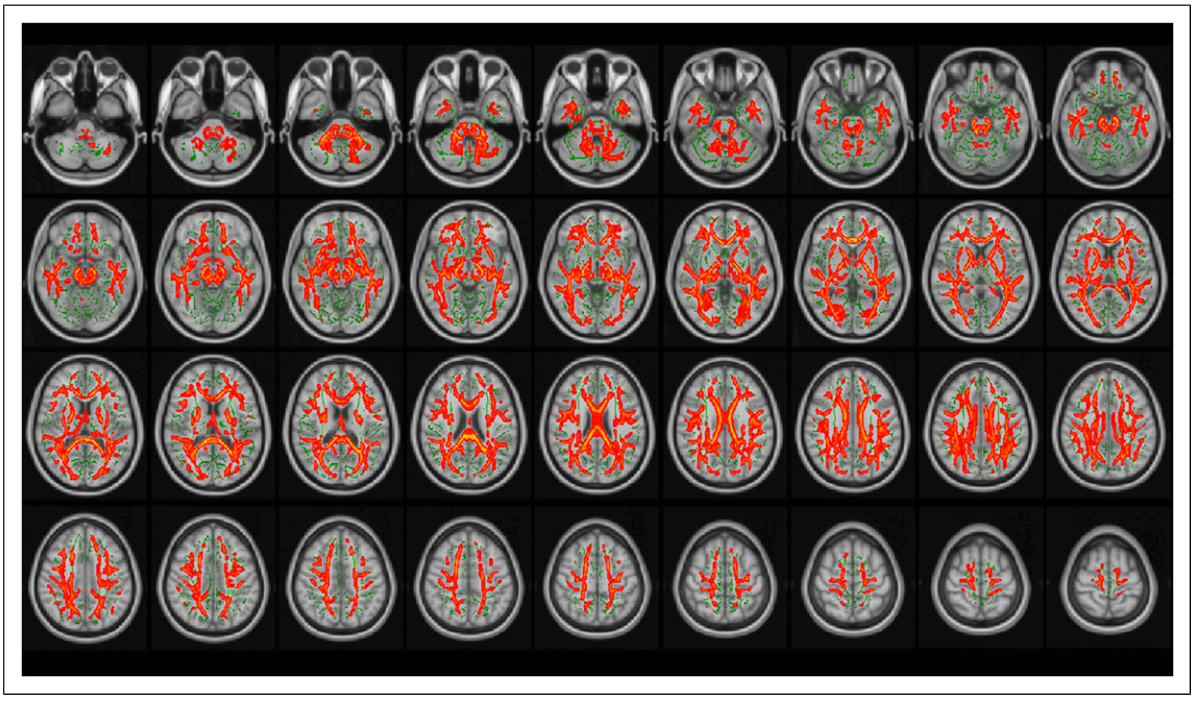

Figure 3. Track-based spatial statistics results are depicted in yellow-red areas, indicating higher fractional anisotropy in patients with Lewy body dementia compared to patients with Alzheimer's disease. These areas are projected onto the mean FA skeleton (green) and an axial, grayscale T1W template image.

Notably, the cortical surface area of the superior frontal cortex was reduced in young- and middle-aged individuals with the Apolipoprotein E homozygous ε4 allele (APOE4).[17] However, other regions of the frontal, temporal, and occipital cortex appeared to be affected as well.[17] Moreover, methylation of the neighboring TOMM40 gene has been associated with amyloid-β deposition in the superior frontal cortex in AD patients.[18] Interestingly, certain TOMM40′523-APOE haplotypes have been associated with reduced cortical thickness of the precuneus, temporal, and limbic cortices in both AD and Mild Cognitive Impairment (MCI) patients.[19] Reduced FA and increased RD of the superior frontal WM have been identified, indicating alterations of the periventricular frontal WM.[20] Additionally, cortical thickness of the frontal cortices has been associated with changes in diffusivity of the frontal WM in AD patients.[21] This pattern of decreased FA in the superior frontal WM has also been observed in the amnestic MCI subtype,[22] suggesting microstructural changes of this region, even in the earliest stages of AD. Decreased FA of the superior frontal WM is also found in elderly patients at risk of AD.[23] Connectivity analysis has showed the involvement of the superior frontal cortex in several stages of AD,[24] especially in those with working memory issues.[25] Another study yielded more pronounced changes for the medial frontal cortices.[26]

The orbitofrontal cortex is one of the most complex areas of the neocortex, where multiple sensory stimuli converge. Furthermore, it plays a fundamental role in behavior, emotion, and cognition, being a part of temporo-amygdala-orbitofrontal network, which is known to be affected in AD.[27] Indeed, the accumulation of neurofibrillary tangles in multiple cortical layers of the orbitofrontal cortex is well established.[28] In addition, medial orbitofrontal cortex atrophy has been positively correlated with impaired self-awareness in AD patients before.[29]

The association of these findings with the course of AD remains undefined. Moreover, dysregulation of molecular signaling, which is fundamental for higher cognition, is known to cause Tau accumulation in areas of the frontal cortex in primates, implying a possible pathogenetic role in the early stages of AD.[30] Interestingly, a marked down-regulation of the olfactory and taste receptors in the orbitofrontal cortex has also been associated with the appearance of AD pathology in the earlier stages of the disease,[31] which could account for the reduced surface area and volume in our AD group. In addition, a recent study suggests that amyloid-β and tau may represent two independent processes, with differing initial topographical distributions, affecting the medial temporal lobe and the neocortex, respectively.[32]

Another possible explanation is the so-called disconnection hypothesis, suggesting that AD symptomatology is not solely the result of the topographical distribution of accumulated amyloid plaques and neurofibrillary tangles, but rather a disorganized interaction between neuronal networks, leading to disturbed connectivity within the brain.[33] Early dysfunction of the hippocampal connectivity has been associated with memory decline,[34] and FA reduction in WM tracts and perfusion deficits in the parietal lobe have been linked to atrophy of the medial temporal lobe in prodromal AD.[35] WM hyperintensities of the superior longitudinal fasciculus have also been associated with executive performance decrements, even in healthy individuals.[36] Furthermore, individuals with amnestic MCI seem to utilize brain networks differently than HC, reflected in increased beta/delta activity of the superior frontal cortex in the electroencephalogram.[37] Thus, it might be suggested that the atrophy of the frontal cortex areas is an indirect result of disturbed network connectivity in our AD group, already present at an early stage.

Our hypothesis is also supported by the results of the TBSS analysis, since AD was the only group with significant alterations in all diffusion metrics, FA, AxD, and RD. AxD reflects changes along the axons of WM fibers, as it measures diffusion coefficient along the direction of maximum diffusivity.[8] Meanwhile, RD reflects myelin sheath and axonal membrane alterations, as it measures the diffusion coefficient perpendicular to the direction of maximum diffusivity.[8] Lastly, FA reflects the anisotropic diffusion in the WM fractions. Thus, FA reduction can be the result of reduced AxD and/or increased RD.[38]

In addition, FA may be reduced either primary, due to direct insult of the WM tracts, or secondary, due to Wallerian degeneration. One of the main pathological features of AD are the neurofibrillary tangles.[39] These are formatted by aggregations of hyperphosphorylated protein Tau, a necessary component for stabilization of axonal microtubules in normal brains.[39] Neurofibrillary tangles result to axonal instability and, consequently, degeneration. Alternatively, WM changes can be the result of Wallerian degeneration. Amyloid accumulations in the GM lead to neuronal cell death and, eventually, axonal disruption.[39] Axonal damage may lead to reduced AxD and FA. Thus, it is reasonable to assume that the WM structural disintegration in the AD group is a result of a primary pathological process, such as Tau aggregation. Death of the oligodendrocytes and reactive gliosis are also part of AD pathology, which could result in increased RD and reduced FA.[39] This agrees with the retrogenesis model, according to which the late-myelinated projection fibers of the neocortex are the first to be affected in AD pathology.[40] On the other hand, α-synuclein, the pathological hallmark of LBD, may spread through anatomically connected brain regions, but it mainly accumulates presynaptically in the axons, which could account for the less prominent changes in the WM tracts.[41] Lastly, astrocytic plaques and thread-like pathology in CBD can affect both grey and WM.[42]

These have been associated with asymmetrically reduced AxD of the WM.[42] However, AxD was smaller for the AD group than the CBS group, implying a more widespread and more severe disruption of the WM structural integrity in AD, in comparison with both CBS and LBD.

Regarding, LBD, our SBM analysis showed that a decrease has been identified in the cortical surface area of the superior temporal cortex. Limited studies have explored SBM in PDD and DLB. PDD is associated with cortical thinning of the left superior temporal gyrus, left fusiform gyrus, right fusiform gyrus, and right insula, with some regions correlating with the Mini Mental State Examination (MMSE) score.[43] Microstructural changes have been observed in the medial superior frontal, orbitofrontal, anterior cingulate cortices, and the right dorsolateral primary motor cortex in patients with idiopathic rapid eye movement sleep behavior disorder, a significant risk factor for both PD and DLB.[44] PD is also linked to microstructural changes in frontal, parietal, temporal, and striatal regions.[45] Decreases in cortical thickness in prefrontal and temporal areas are commonly associated with depression in both AD and DLB.[46] Cortical thickness variations appear to be more severe in mid-anterior temporal, occipital, and subgenual cingulate cortex for AD patients and dorsal cingulate, posterior temporal, and lateral orbitofrontal cortex for PD patients.[47] Another study, using VBM, demonstrated significant atrophy of the frontal, temporal, and parietal cortices for both PDD and DLB, compared to AD.[48] On the other hand, while widespread FA reduction in AD patients, even in the earlier stages of the disease has been shown before,[49] it is more commonly encountered in parietooccipital regions in DLB patients.[50] Greater FA reduction in the amygdala and inferior longitudinal fasciculus has also been found for DLB.[51]

The decrease in the cortical surface area of the left superior temporal cortex for CBS patients aligns with the characteristic asymmetry of the syndrome.[3] Another study found a decrease in cortical thickness in bilateral frontal, parietal, and temporal regions, though not greater than in DLB patients.[52] The regions where cortical surface area reduction seems more prominent include the prefrontal cortex, precentral gyrus, supplementary motor area, insula, and temporal pole.[53] Lastly, CBS is linked to diffusivity alterations in the supplementary motor area, premotor area, prefrontal cortex, precentral gyrus, postcentral gyrus, cingulum, corpus callosum, motor thalamus, and corticospinal tract, typically showing asymmetry.[54]

To sum up, it seems that in AD patients the neocortex is implicated early in the course of the disease. In fact, the majority of GM alterations involved the frontal cortex. On the contrary, the findings of the SBM analysis are much less remarkable for LBD and CBS patients and involve more restricted areas of the temporal neocortex. WM changes are even more widespread in the AD group, in comparison with HC, as well as the LBD group. On the other hand, LBD and CBS patients failed to show significant structural changes in WM tracts, in comparison with HC. A possible explanation is that the AD pathology is distributed in both GM and WM of the cortical hemispheres early in the course of the disease, while LBD and CBS affect mainly subcortical structures, at least initially.

Clearly, our study has several limitations. Firstly, the sample size is small. Hence, it's important to note that our findings may not be fully representative of the broader population, potentially limiting the strength of the inferences we can draw. Nevertheless, both the cortical surface area and cortical volume reduction in the superior frontal cortex of AD patients achieve high statistical significance ($p = 0.0002$). Secondly, while we applied family-wise error correction at the voxel level using FSL's randomize, this was done independently for each contrast. As a result, the risk of type I errors may be elevated, when considering the multiple contrasts collectively. Additionally, TBSS assumes that white matter tracts are well-aligned across all subjects after non-linear registration to a common space, which can be challenging in populations with significant anatomical variability, such as those with neurodegenerative diseases.[8] This could potentially lead to inaccuracies in detecting true group differences. Moreover, TBSS focuses on the core of white matter tracts by projecting diffusion data onto a mean FA skeleton, enhancing statistical power but possibly overlooking subtle changes in peripheral regions or areas with crossing fibers.[8] However, the consistency of our diffusion findings across all major white matter tracts in AD patients, along with the observed widespread WM aberrations, suggests that the primary results are robust. These findings reflect significant early structural disruptions in AD, supporting the extended involvement of white matter integrity beyond typical regions.

Furthermore, our patient's diagnoses were not pathologically confirmed, nor did we use any biomarker to support our patient's assignation to the study groups. However, while neuropathologically diagnosed cases of AD, DLB, and CBS often exhibit overlapping pathological features,[3,4] our study aimed to exclusively assess MRI structural alterations from a clinical perspective. By focusing on individuals with clinically established AD, LBD, and CBS, we sought to evaluate the structural changes associated with specific clinical syndromes using MRI, a tool commonly employed in the initial evaluation of neurodegenerative diseases.[11] We acknowledge that clinical diagnosis can be challenging, especially in the early stages of these diseases. However, our approach provides valuable insights into the relationship between MRI findings and the clinical manifestations of AD, DLB, and CBS.

In addition, the study focused on structural changes in the neocortex. Therefore, we may have missed potential

subcortical alterations in LBD and CBS patients, which often appear early in the disease course.[2,3]

Moreover, the AD group had a younger mean age. However, considering that structural brain alterations are expected to increase with age,[55] one might anticipate the younger AD group to exhibit milder changes than the LBD and CBS groups. Contrarily, it was the only one with significant alterations in the superior frontal cortex and significant changes for FA, AxD, and RD, making these findings even more noteworthy.

Finally, we combined our PDD and DLB patients in one group. While some investigators suggest a common neuropathological basis, others argue that there are some differences between the pathology of DLB and PDD.[56] Both may present with and dementia and parkinsonism, although the latter may be absent in the early stages of DLB.[2] On the other hand, parkinsonism is a necessary component of PDD.[2] Thus, the clinical distinction is primarily based on the timing of motor and cognitive symptoms. According to the 1-year rule, the diagnosis of PDD is appropriate in the context of an established PD, whereas the diagnosis of DLB should be made when parkinsonism is preceded by dementia or coincides within 1 year of onset.[2] Nevertheless, the definition of this time interval for the distinction of DLB and PDD was made on no solid basis, neither clinical nor pathological.[2] Despite ongoing research, the exact relationship between DLB and PDD remains unclear. Thus, due to their many common clinicopathological features,[57] we chose to present them as a continuum of LBD. However, combining DLB and PDD patients into a single LBD group may limit our ability to determine the specific contributions of each condition to the observed results. Moreover, the results may not be applicable to either DLB or PDD patients individually.

Conclusions

In conclusion, our study yielded significant, early GM structural changes in AD patients compared to those with LBD and CBS, especially in the frontal cortex, which is not classically associated with the disease. Moreover, AD patients exhibited a widespread pattern of hemispherical WM alterations, in contrast to the unremarkable WM changes of the LBD and CBS groups. These findings might be the result of alterations in the underlying connectivity networks and could contribute to a better understanding of the pathogenetic mechanisms of AD. Future studies focusing on network analysis of human brain connectivity are needed to test this hypothesis.

Declaration of Conflicting Interests

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Ethical Statement

Ethical Considerations

Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki were followed.

Consent to Participate

Every patient and healthy control that was included in the study signed an informed consent.

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Data Availability Statement

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at University Hospital of Ioannina.

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