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Sex differences in brain atrophy in dementia with Lewy bodies

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Consent Statement

All patients or appropriate surrogates gave written informed consent to their participation in the study.

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Abstract

Introduction.—Sex influences neurodegeneration but it has been poorly investigated in dementia with Lewy bodies (DLB). We investigated sex differences in brain atrophy in DLB using MRI.

Methods.—We included 436 patients from the European-DLB consortium and the Mayo Clinic. Sex differences and sex-by-age interactions were assessed through visual atrophy rating scales (n=327; 73±8 years, 62% males) and automated estimations of regional gray matter volume and cortical thickness (n=165; 69±9 years, 72% males).

Results.—We found a higher likelihood for frontal atrophy and smaller volumes in 6 cortical regions in males and thinner olfactory cortices in females. There were significant sex-by-age interactions in volume (6 regions) and cortical thickness (7 regions) across the entire cortex.

Discussion.—We demonstrate that males have more widespread cortical atrophy at younger ages, but differences tend to disappear with increasing age, with males and females converging around the age of 75.

Keywords

Atrophy; MRI; dementia with Lewy bodies; sex differences

Background

Recently, the influence of sex and gender on neurodegenerative diseases, especially Alzheimer's disease (AD) and Parkinson's disease (PD), has been spotlighted[1,2]. Sex differences are central to current precision medicine approaches. They are expected to play a role in the prevention, diagnosis, and treatment of neurodegenerative diseases in the coming years[3,4]. However, fewer studies have investigated sex differences in dementia with Lewy bodies (DLB), another common form of neurodegenerative disease. Particularly, neuroimaging studies on sex differences in DLB are scarce.

Although DLB is considered a predominantly male disease, the sex ratio in DLB varies across cohorts. For example, the female-to-male ratio ranges from 0.59:1 in the Swedish Dementia Registry to 0.81:1 and 0.88:1 in cohorts from the UK and China, and 1.20:1 in the French National Alzheimer database, with a more balanced ratio above the age of 75[5–8]. Sex influences core clinical features. While parkinsonism and rapid eye movement sleep behavior disorder (RBD)[9,10], visual hallucinations are more frequent in female DLB patients[11,12], with some opposite reports[10].

Regarding pathological changes, a recent neuropathological study of over 1,500 donors demonstrated that DLB males more frequently have “pure” Lewy body pathology[13]. Another report of 205 donors showed that DLB males tended to have Lewy body pathology confined to the brainstem and limbic system at an earlier age[14]. In contrast, DLB females tended to accumulate Lewy body pathology at older ages with more pronounced spreading across neocortical areas, perhaps reflecting a more aggressive disease course[14]. This finding may partially explain the delay in meeting DLB diagnostic criteria in female patients[15]. Furthermore, female DLB donors are more likely to have brain co-pathologies such as AD and cerebrovascular disease[13]. The higher frequency of AD co-pathology observed in DLB females in postmortem studies has also been supported in vivo with the use of β-amyloid and tau cerebrospinal fluid (CSF) biomarkers[12,16]. Alzheimer’s disease and cerebrovascular co-pathologies influence the clinical presentation of DLB by reducing the likelihood of core clinical features[17–19], particularly in older male DLB patients[20].

Two recent neuroimaging studies revealed lower dopaminergic activity in female DLB patients compared with male DLB patients, and a greater vulnerability of the cholinergic system in male DLB patients[21,22]. Unfortunately, the data on sex differences in magnetic resonance imaging (MRI) measures of neurodegeneration in DLB is limited to only two previous studies. A study from 2004 investigated sex differences in regional cortical gray matter (GM) volume in 8 male and 8 female DLB patients[23]. Male DLB patients had smaller GM volumes than females in the right dorsal frontal and bilateral parietal cortices. In a recent multicenter study on 86 DLB patients (49 males and 37 females) from the European DLB (E-DLB) consortium[24], we found that frontal atrophy as assessed on visual ratings was associated with the male sex and older age in DLB[25].

Magnetic resonance imaging studies in DLB are usually conducted in relatively small cohorts, which makes it difficult to reach sufficient statistical power, especially for the female patient group which is often even smaller in sample size. This likely explains the lack of MRI studies on sex differences in DLB, despite the interest in the topic. We overcame this limitation by leveraging a large multicenter MRI cohort of 442 probable DLB patients, the largest cohort of this type in the field. The cohort included 280 male and 162 female DLB patients. Our main aim was to investigate sex differences in measures of neurodegeneration using MRI, through two different methods: visual ratings of brain atrophy and automated methods for volumetric and cortical thickness measures. The main reason for using two methods was to generate knowledge directly applicable to clinical settings (visual ratings from radiologists), at the same time that we replicated and expanded radiological findings using more sensitive automated techniques for regional brain atrophy. This approach also served to validate the findings and generalize across common MRI techniques. We

hypothesized that male DLB patients would have more frontoparietal atrophy than female DLB patients, based on the two previous studies[23,25]. Further, we anticipated that female DLB patients would have more GM atrophy in the medial temporal lobe, based on previous reports indicating more frequent AD co-pathology in female DLB patients compared to male DLB patients[13,16]. We also had a strong interest in investigating the interaction between sex and age with MRI measures because our previous study informed us of the combined effect of both sex and age on frontal lobe atrophy in DLB[25]. Hence, we hypothesized that DLB patients would show a sex-by-age interaction in frontal regions. Elucidating sex differences and sex-by-age interactions will be relevant to reveal their contribution to the clinical heterogeneity of DLB, in particular when interpreting MRI in clinical practice.

Methods

Participants

This study includes patients from multiple centers from the European DLB consortium (https://www.e-dlb.com/)[24] and the Mayo Clinic in the U.S.[26]. To address our study aim, we divided the cohort into two partially independent samples. First, we assessed sex differences using visual rating scales on clinical T1-weighted MRIs from 327 DLB patients from 14 E-DLB centers (204 males and 123 females). Second, we assessed sex differences using research-oriented automated methods, volumetric and cortical thickness measures, on high-resolution 3D T1-weighted MRIs from 165 DLB patients (119 males and 46 females; 56 of them shared with the 327 sample) from three E-DLB centers (n = 97) and the Mayo Clinic cohort from Rochester, MN, U.S. (n = 68). See Supplementary Table 1 for more details about the cohorts. For the research-oriented automated methods, we also included a group of cognitively unimpaired (CU) participants matched in sex and age with the DLB patients (Supplementary Table 2).

Dementia with Lewy bodies diagnosis was established following the 2005 international consensus criteria for probable DLB[27]. The presence of core clinical features was collected, including parkinsonism, visual hallucinations, cognitive fluctuations, and clinical history of probable RBD. Exclusion criteria were: (i) presence of acute delirium; (ii) terminal illness; (iii) previous stroke; (iv) psychotic or bipolar disorder; (v) craniocerebral trauma; and (vi) recent diagnosis of significant systemic disease. Age and years of education were collected for statistical analysis, and the Mini-Mental State Examination (MMSE) was used as a measure of global cognitive performance.

Alzheimer's disease co-pathology was assessed through positivity in β-amyloid and tau biomarkers: E-DLB centers used CSF β-amyloid 1–42 and phosphorylated tau biomarkers, while the Mayo Clinic used positron emission tomography (PET) Pittsburgh compound B (PiB) and Flortaucipir (18F-AV-1451). Cerebrospinal fluid and PET biomarkers were combined as done before[16], and biomarker levels were classified as normal or abnormal based on center-specific established cut-points, as explained in prior publications[16,26]. Moreover, the *APOE* genotype was recorded and carriership was considered as one or more copies of the ε4-allele.

For white matter hyperintensity (WMH) burden as a common biomarker of cerebrovascular disease, we used both the Fazekas scale[28] and a semi-automated method for WMH volume estimation, which is fully described elsewhere[18,29].

The ethics committee of each center approved the data collection. All patients or appropriate surrogates gave written informed consent to their participation in the study.

MRI acquisition

The MRI scans were acquired using 1.5 and 3 T scanners, including a high-resolution 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence and a fluid-attenuated inversion recovery (FLAIR) sequence, as described in more detail in previous publications[18,30].

MRI visual assessment and automated preprocessing

Magnetic resonance imaging scans of the clinical cohort were rated centrally at Karolinska Institutet by a single experienced neuroradiologist, who had previously demonstrated excellent intra-rater and inter-rater reliability[31]. Ratings were performed fully blinded to sex, demographic, and clinical information, within the period of one year. Lobar atrophy was assessed with three visual rating scales based on T1-weighted images[32]. Frontal lobe atrophy was assessed with the global cortical atrophy-frontal subscale (GCA-F)[33], medial temporal lobe atrophy with the medial temporal atrophy (MTA) scale[34]; and posterior cortex atrophy with the posterior atrophy (PA) scale[35]. We classified the visual ratings into normal/abnormal using established cutoffs based on normative data from 345 healthy individuals, as explained elsewhere[32]. In the case of the MTA scale, both age-adjusted and unadjusted scores were used, depending on the statistical analysis as explained below. Since age corrections for GCA-F and PA do not improve their diagnostic performance, unadjusted scores were used[32]. Procedures and methods are described in detail in previous publications[28,32].

Regarding the research-oriented method for automated estimation of regional volume and cortical thickness, preprocessing was performed centrally at the Mayo Clinic as detailed previously[36]. Briefly, the unified segmentation algorithm in SPM12 (Wellcome Centre for Human Neuroimaging, London, UK) was used for volume estimation with the Mayo Clinic Adult Lifespan Template (MCALT, https://www.nitrc.org/projects/mcalt/) tissue priors and settings[37]. Regions of interest were propagated using Advanced Normalization Tools (ANTs)[38]. Altogether, 82 cortical, 12 subcortical, and 2 brainstem regions of interest (ROIs) were estimated (see ROIs in Supplementary Table 3). Next, ANTs DiReCT was used for the cortical thickness estimation of the cortical ROIs from the tissue probabilities[39]. Moreover, the estimated total intracranial volume was calculated from the tissue probabilities.

Statistical analyses

All the analyses were performed using R (The R Foundation for Statistical Computing; version 4.1.0).

Differences in demographic and clinical variables and biomarkers were assessed by t-test for continuous variables, Mann–Whitney U test for ordinal variables, and Pearson's chi-squared test or Fisher's exact test for categorical variables.

Regarding the clinical cohort, visual rating scales were analyzed using two types of binary logistic regression models for dichotomized variables as the outcome (0, normal visual rating score; 1, abnormal visual rating score). The first model tested for the effect of sex while controlling for the age effect. The second model tested for the interaction between sex and age. For the MTA scale, age-adjusted scores were used to test for the effect of sex, and the unadjusted scores were used to test for the interaction between sex and age.

Regarding the research-oriented automated method, two series of analyses were performed separately on volume and cortical thickness estimations after controlling for the effect of confounding variables. Control for confounding variables was done as follows. For analyses on the effect of sex, for each ROI we obtained residuals from a multiple linear regression model with age and center as predictors (*model 1*), separately for volume and cortical thickness as the outcome measures. Note that modeling the effect of center also corrected for the effect of field strength (3 T versus 1.5 T). For analyses investigating the interaction between sex and age, the residuals were obtained from a model with center as the only predictor (*model 2*), separately for volume and cortical thickness as the outcome measures. Total intracranial volume was included as an additional predictor in models 1 and 2 when volume was the outcome measure (but not when cortical thickness was the outcome measure). Supplementary models 1 and 2 including MMSE as an extra predictor were fitted for sensitivity analyses. Once confounding variables were controlled for by obtaining residuals as explained above, we conducted main analyses consisting of a first series of one-way ANOVA models with sex as the independent variable and volume or cortical thickness measures as dependent variables, with Cohen's *d* for effect sizes; followed by a second series of multiple linear regression models with sex, age, and the interaction between sex and age as independent variables and volume or cortical thickness measures as dependent variables. For ROI analyses on volume and cortical thickness, we report uncorrected *P*-values followed by false discovery rate (FDR)[40] adjusted *P*-values within the type of measure (volume or cortical thickness) and model (one-way ANOVA or multiple linear regression), to account for multiple testing.

Additionally, we followed main analyses with three further one-way ANOVAs to test whether our sex findings were independent of AD co-pathology, *APOE* genotype, and WMH burden as a common biomarker of cerebrovascular disease. These analyses were limited to the ROIs showing significant sex differences in the main analyses. For WMH burden and *APOE* genotype, we compared DLB males and DLB females on new residuals calculated using WMH burden or *APOE* genotype (separately) as extra predictors for model 1 explained above. This approach was not feasible for AD co-pathology due to the limited group size of females with a positive AD biomarker. Hence, we replicated the main one-way ANOVA in the subsample of DLB patients with AD biomarkers available (n = 122), and then we further replicated the analyses for the significant findings in the subsample of male and female DLB patients with a negative AD biomarker (n = 109). For these last one-way ANOVAs, we used the residuals from model 1 explained above.

We next investigated whether the findings from the models explained above were DLB-specific or merely reflect sex differences captured in a group of CU participants. To do that, we replicated all the analyses from the research-oriented cohort showing statistically significant sex differences or sex-by-age interactions using an external sex- and age-matched sample of CU participants, across the same regional MRI data as for the DLB patients.

Finally, we investigated whether the ROIs that resulted statistically significant in the between sex comparisons and sex-by-age interaction analyses described above were associated with clinical measures, using Pearson and point biserial correlations. For clinical measures, we initially considered the MMSE score as a continuous variable (Pearson correlation) and the four core clinical features as dichotomous variables (point biserial correlations). For ROI measures, we used residuals from model 1.

The significance level was set at P-value ≤ 0.05 in all statistical models.

Results

Sociodemographic and clinical characteristics

Table 1 shows that there were no statistically significant differences between probable DLB males and females in most of the demographic and clinical variables. Nonetheless, in the clinical cohort, DLB females were older than DLB males. In the research-oriented cohort, DLB males had a lower MMSE score than DLB females, and DLB males had a higher frequency of parkinsonism than DLB females. There were also statistically significant differences in the estimated total intracranial volume, with DLB females showing a smaller intracranial volume as expected. Therefore, further volumetric analyses were controlled for the estimated total intracranial volume, as explained in the Methods section.

Visual rating scales of lobar atrophy (clinical cohort)

We found a significant sex effect on frontal atrophy: based on normative data from healthy individuals[32] the odds for an abnormal score in GCA-F were statistically significantly higher for DLB males (40% had an abnormal GCA-F score) as compared to DLB females (28% had an abnormal GCA-F score, P-value = 0.004) (Table 2). Specifically, the odds for a male DLB patient to have an abnormal score in GCA-F was 2 times higher than for a female DLB patient (95% CI [1.28, 3.57]). For the MTA (36% abnormal in males, 41% in females) and PA (63% abnormal in males, 55% in females), there were no statistically significant sex differences. We did not find a significant interaction between sex and age in any of the three scales (Table 2).

Automated estimations of regional atrophy (research-oriented cohort)

We found statistically significant smaller GM volumes in DLB males than in DLB females in the orbital part of the middle frontal cortex, as well as in the middle frontal, fusiform, middle occipital, middle temporal, and supramarginal cortices (Figure 1, P-value ≤ 0.05 in all measures; Supplementary Table 4). In contrast, DLB females had a smaller GM volume than DLB males in the right entorhinal cortex, as well as thinner olfactory cortices (Figure 1, P-value ≤ 0.05; Supplementary Table 3).

We found statistically significant sex-by-age interactions in GM volume in the anterior cingulum, middle frontal, fusiform, supramarginal, and superior temporal cortices (Figure 2, Panel A; *P*-value ≤ 0.05; Table 3). There were also statistically significant sex-by-age interactions in cortical thickness in the angular, insular, superior occipital, and superior parietal cortices as well as in the precuneus (Figure 2, Panel A; *P*-value ≤ 0.05; Table 3). All these interactions showed that DLB males had significantly smaller GM volumes or thinner cortex than DLB females at younger ages, but sex differences were no longer significant at older ages (Figure 2, Panel B).

The sensitivity analyses with MMSE score as an extra predictor showed that male DLB patients had smaller left middle occipital and right supramarginal volumes than female DLB patients (*P*-value ≤ 0.05). Further, female DLB patients had smaller right entorhinal cortex volume and thinner olfactory cortices than male DLB patients (*P*-value ≤ 0.05). All sex-by-age interactions remained significant after controlling for MMSE (*P*-value ≤ 0.05).

Concerning the follow-up models accounting for AD co-pathology, *APOE* genotype, and WMH burden, all the models for sex differences remained statistically significant except for the right middle frontal cortex when accounting for *APOE* genotype, and the left fusiform cortex when accounting for WMH burden. The sub-analysis for AD status reduced the sample from 165 to 122 participants due to missing data on biomarkers of AD. Hence, we first had to replicate our main analyses in the reduced cohort. These new analyses showed sex differences in 4 out of the 9 ROIs with statistically significant sex differences in the 165 cohort, including volume of left middle temporal, right supramarginal, and right entorhinal cortices, as well as thickness of left olfactory cortex (*P*-value ≤ 0.05). Starting the sub-analyses from those 4 ROIs, when we restricted the sample to male and female DLB patients with negative AD status (n = 109), the sex differences remained statistically significant for the 4 ROIs (*P*-value ≤ 0.05).

All significant ROIs reported in this section for sex differences and sex-by-age interactions were analysed in the CU group to clarify whether the findings are DLB-specific or merely reflect sex differences captured in the normal population. We found that CU females had a smaller GM volume than CU males only in the right entorhinal cortex (DLB males, mean = −0.083, SD = 0.270; DLB females, mean = 0.031, SD = 0.262; $F = 6.112$; *P*-value = 0.014). Otherwise, all findings reported above failed to be replicated in the CU group, suggesting that our findings are DLB-specific.

Correlations between regional atrophy and clinical measures

To ensure a proper fitting of the models, we excluded clinical measures that had less than 12 cases per sex group. Because of the high frequency of parkinsonism, cognitive fluctuations, and probable DLB in our research-oriented cohort, we did not have enough variability to model these variables, and our correlation analyses were thus limited to the MMSE and visual hallucinations. The results showed different correlations in male and female DLB patients. In male DLB patients, we observed that a smaller volume in the left middle temporal gyrus, left anterior cingulum, and right fusiform gyrus, as well as thinner bilateral olfactory cortices significantly correlated with lower MMSE scores (*P*-value ≤ 0.05, Supplementary Table 5). Further, a smaller volume in the orbital part of the left middle

frontal gyrus and a thinner left olfactory cortex significantly correlated with the presence of visual hallucinations (*P*-value ≤ 0.05, Supplementary Table 5). In contrast, we found no statistically significant correlations between regional atrophy and clinical measures in female DLB patients.

Discussion

We investigated sex differences in brain atrophy in DLB. Using visual ratings and normative data from 345 healthy individuals[32] we demonstrated frontal atrophy in 40% of male and 28% of female DLB patients, medial temporal atrophy in 36% of male and 41% of female DLB patients, and posterior atrophy in 63% of male and 55% of female DLB patients. These sex differences resulted statistically significant for frontal atrophy. We replicated this finding in a largely independent cohort using a research-oriented method for regional atrophy and demonstrated that the sex differences tend to disappear with increasing age, with atrophy levels converging in male and female DLB patients after the age of 75. Overall, our findings suggest more severe neurodegeneration in young DLB males, with no significant sex differences at older ages. This regional atrophy correlated with global cognitive impairment and visual hallucinations only in male DLB patients.

The greater frequency of abnormal scores in frontal atrophy visual ratings in DLB males replicates the finding from our previous study with a smaller sample[25]. Despite using data from the E-DLB, the statistical approach and focus differed between both studies. When explicitly testing for sex differences in our current study, DLB males showed greater frontal atrophy than DLB females. Visual ratings were interpreted clinically based on normative data from healthy individuals[32]. Hence, abnormal scores can be interpreted as atrophy. The clinician could expect that almost 40% of DLB males would display frontal atrophy, while DLB females would rarely show any frontal atrophy below the age of 70. This finding suggests that currently available cut-offs for frontal atrophy may need to be revisited for DLB and redefined by adjusting for sex and age, similar to previous studies in AD[32]. Furthermore, sex may interact with other factors such as education and disease duration, in driving frontal atrophy[25]. These data jointly encourage following up on sex differences in visual ratings of frontal atrophy. Advancing our current understanding of sex differences could optimize interpretations in clinical workups and enhance the current role of structural MRI in the diagnostic criteria of DLB[41].

We replicated the clinical results in a largely independent cohort using automated estimations of volume and cortical thickness. We found a smaller GM volume in male than female DLB patients in several frontal, temporal, parietal, and occipital regions. In contrast, DLB females showed a smaller volume than DLB males in the right entorhinal cortex and thinner olfactory cortices. None of these sex differences resulted significant in the CU group, except for the right entorhinal cortex, indicating that our findings likely reflect sex differences that are disease-related. Only one previous publication explored sex differences in regional atrophy, in 16 DLB patients[23]. The authors found a smaller GM volume in male compared with female DLB patients in frontal and parietal regions. By increasing the sample size to 165 DLB patients, our study showed smaller GM volumes in male compared to female DLB patients not only in frontal and parietal regions but also in temporal and

occipital cortices. These findings support a cortical vulnerability in DLB males, not only restricted to anterior brain areas. While effect sizes were comparable across areas, it seems that visual ratings only capture sex differences in frontal lobes, while automated methods may be more sensitive to detect differences across the cortical mantle. Nonetheless, frontal regions were more represented in the findings from the automated method, which may explain the sensitivity of the GCA-F scale.

We observed thinner olfactory cortex in DLB females. Olfactory function impairment has been described as a potential hallmark to discriminate between AD and DLB[42–44]. Notwithstanding, previous studies reported no sex differences in odor identification in DLB[42,44]. A promising prospect would be to investigate sex differences in DLB in olfactory identification and their structural correlates. This avenue is of interest to advance our current knowledge about the less investigated “olfactory bulb only” pathologic DLB subtype[45]. We recently showed that the olfactory cortex is one of the main discriminative regions between subtypes with widespread predominant cortical and predominant fronto-occipital atrophy[46]. The interplay between sex, age, and heterogeneity in regional atrophy and clinical phenotype in DLB deserves future investigation.

We also found that DLB females had a smaller volume in the right entorhinal cortex. Atrophy in medial temporal regions in DLB females could be explained by their higher frequency of AD co-pathology[13]. However, this explanation is unlikely in our cohort since we did not observe any statistically significant sex difference in AD biomarkers. Instead, our replication analyses using an age- and sex-matched group of CU participants revealed a smaller volume in the right entorhinal cortex in CU females compared with CU males. Previous studies reported the same result in CU participants[47,48]. Hence, one could interpret that the sex differences for the right entorhinal cortex in our cohort are likely not specific to DLB but rather reflect a common finding in the normal population.

For all findings on sex differences, we explored the potential contribution of co-pathologies. In this regard, we replicated analyses restricting the sample to patients with negative AD biomarkers. We also adjusted our statistical analyses for *APOE* genotype due to its association with AD pathology and temporal atrophy. Since WMH burden also correlates with GM neurodegeneration in DLB[18,19], we also adjusted our models for WMH. Many of the brain regions with significant sex differences survived these sensitivity analyses, suggesting that the reported sex differences are independent of these co-pathologies and *APOE* genotype.

An important contribution of this study is the sex-by-age interaction, particularly in the right middle frontal gyrus. In this region, DLB males had similar GM volume across ages, while DLB females showed a steeper slope with a smaller GM volume at older ages, converging with male DLB patients around the age of 75. This finding expands our previous report, which showed the combined contribution of male sex and older age to frontal atrophy in 86 DLB patients[25]. In the current study, we demonstrated a statistical interaction and circumscribed the influence of sex and age on a specific frontal region using a more sensitive method in a largely independent cohort of 165 DLB patients. This finding reinforces the contribution of the male sex to frontal atrophy in DLB and includes

the consideration of sex differences minimizing with increasing age. The shallow slope for male patients in the interaction plots could reflect a plateau level of high atrophy across all sampled ages since around 40% of male DLB patients demonstrated frontal atrophy[32].

We found other similar sex-by-age interactions including volume in frontal (bilateral anterior cingulate gyri), temporal (right fusiform gyrus and left superior temporal pole), and parietal (left supramarginal gyrus) regions. In addition, the mean cortical thickness analyses showed significant interactions in occipital (left superior occipital gyrus), left insular, and parietal (left angular gyrus, superior parietal lobules, and bilateral precuneus) regions. These interactions may reflect cortical neurodegeneration initiated at early stages in DLB males, beyond frontal areas. A study on individuals with isolated RBD, a prodromal phase of alpha-synucleinopathy, showed cortical GM loss at that early phase[49]. This finding is coherent with an earlier onset and flatter disease course in DLB males, opposite to a more aggressive disease course upon dementia diagnosis in DLB females[12]. Future longitudinal studies should confirm if male patients display more brain atrophy earlier than female patients.

One could speculate that the steeper slope of brain atrophy in DLB females could be explained by neuroprotective factors. Perhaps, hormonal levels may delay atrophy in females[50]. The reduction of estrogen levels after menopause and with aging may increase the vulnerability to pathology and neurodegeneration in females. In a study about the effects of menopausal hormone therapy, we found superior and middle frontal gyri volume preservation after seven years in the treatment group (17β-estradiol) compared with placebo[51]. The maintenance of the dorsolateral prefrontal cortex correlated significantly with lower β-amyloid deposition. That finding highlights the sensitivity of frontal areas to estradiol neuroprotection. However, we acknowledge that the exact biological mechanisms underlying sex differences in DLB are largely unknown. Therefore, the interpretation of neuroprotective factors remains speculative, but it may encourage future studies on hormones and neurodegeneration in DLB and other diseases.

We also performed sensitivity analyses adjusting for MMSE scores. Several sex differences remained significant except mainly for frontal regions, which may suggest that the worse global cognitive performance in male DLB patients could primarily be associated with frontal atrophy. In contrast, all sex-by-age interactions remained significant.

Finally, correlation analyses showed that in male DLB patients greater GM atrophy in the middle temporal gyrus, olfactory cortex, anterior cingulum, and fusiform gyrus was associated with lower MMSE scores,and atrophy in the middle frontal gyrus and olfactory cortex was associated with the presence of visual hallucinations. A previous study demonstrated an association between atrophy in the middle frontal cortex and the presence of visual hallucinations in DLB[52] Our study expands this previous finding by showing that this association is more prominent in male DLB patients.

A strength of this study is the dual analysis and validation of sex differences in clinical and research-oriented brain atrophy measures in two largely independent multi-center DLB cohorts. Besides, this is the first report on sex-by-age interactions in brain atrophy, providing

findings that may have implications for clinical workup and treatment monitoring in DLB. Moreover, our automated analyses replicated the findings from visual ratings, which were assessed against normative data from 345 healthy individuals[32]. Our findings do not seem to reflect the sex differences reported in normal aging[53,54] and were not replicated in a group of CU participants except for the right entorhinal cortex, which indicates that our findings are likely disease-specific. Future studies should investigate sex-specific neurodegenerative trajectories in DLB from early stages, including prodromal DLB. Longitudinal atrophy patterns could improve our understanding of the role of sex along the disease course in DLB. For instance, previous studies in PD showed variation in sex differences throughout the disease course[55–59]. Another limitation is that we estimated cognitive impairment with the MMSE score, which is a rough measure of global cognitive performance. Moreover, data on ethnicity and race was missing in our cohort, although we acknowledge that racial-ethnic diversity should be considered in future research on sex differences in DLB[60].

In conclusion, male DLB patients have a more widespread cortical atrophy pattern than female DLB patients, mainly in frontal regions, which correlates with global cognitive impairment and the presence of visual hallucinations. However, these sex differences are minimized with increasing age, especially after the age of 70. These findings may have implications for the interpretation of MRI markers in clinical workup and as an endpoint in clinical trials. The characterization of sex differences from early disease stages emerges as a relevant prospect for precision medicine approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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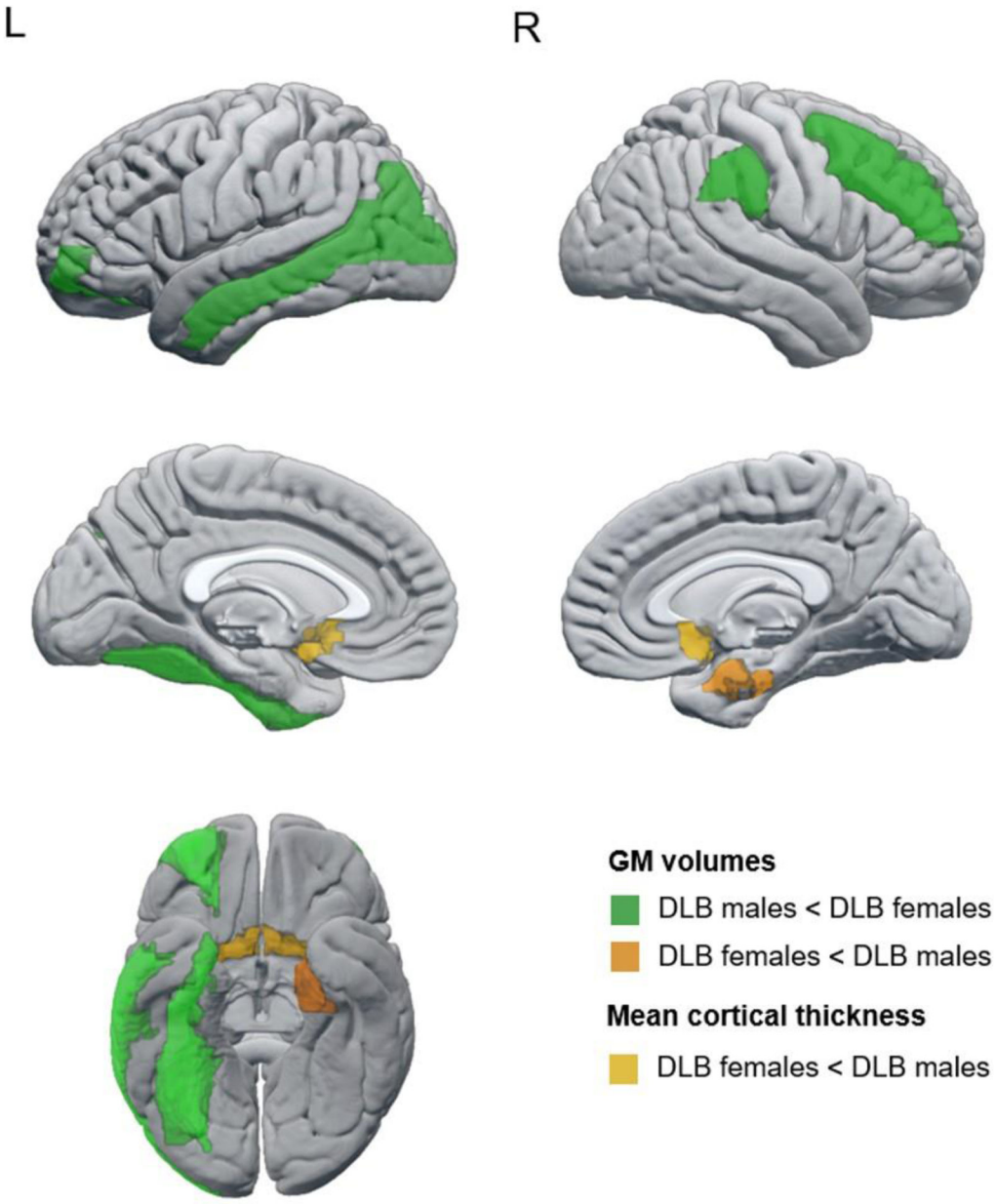

Figure 1.

Regions showing statistically significant sex differences in automated estimations of regional atrophy in probable DLB. Regions colored in green showed a smaller GM volume in DLB males than in DLB females; regions colored in orange showed smaller/thinner estimations in DLB females than DLB males, the darker one for GM volumes and the lighter for mean cortical thickness.

Abbreviations: DLB, dementia with Lewy bodies; GM, gray matter; L, left; R, right.

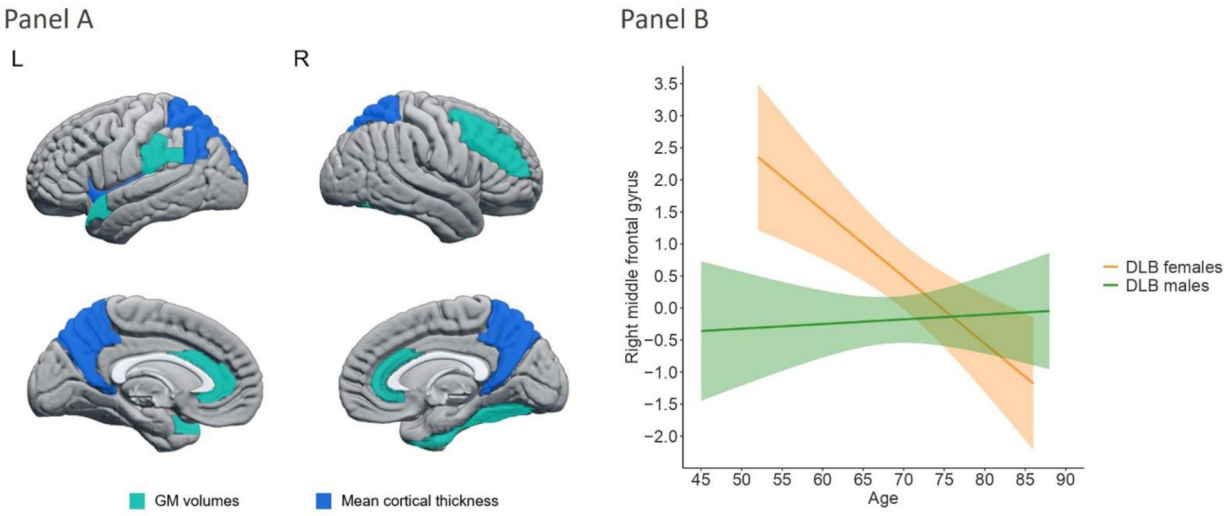

Figure 2.

Panel A. Regions showing statistically significant sex-by-age interactions in automated estimations of regional atrophy in probable DLB. Regions colored in lighter blue correspond to GM volume estimations, and regions colored in darker blue correspond to mean cortical thickness estimations. **Panel B.** Significant sex-by-age interaction in the right middle frontal cortex (the region with the highest effect size, see Table 3). For all regions showing significant sex-by-age interaction, sex differences were statistically significant at younger ages and tended to be non-significant at older ages.

Abbreviations: GM, gray matter; L, left; R, right.

Table 1

Demographic and clinical characteristics of probable DLB males and females

	Clinical cohort (N = 327)				*Research-oriented cohort (N = 165)*			
	Males	**Females**	***n*, M/F**	**t-stat/χ2 (*P*-value)**	**Males**	**Females**	***n*, M/F**	**t-stat/χ2 (*P*-value)**
Age, mean (SD)	72.07 (8.21)	74.81 (8.13)	204/123	**2.940 (0.004)**	68.73 (8.40)	70.02 (9.03)	119/46	0.867 (0.387)
Years of education, mean (SD, minimum - maximum)	10.91 (4.00, 2 – 22)	10.04 (3.75. 3 – 18)	170/102	1.771 (0.078)	13.71 (4.63, 5 – 22)	13.41 (3.20, 6 – 22)	119/46	0.446 (0.656)
Disease duration (years), mean (SD)	3.23 (2.01)	3.26 (2.58)	90/27	0.070 (0.944)	5.83 (4.63)	5.02 (3.20)	97/26	0.839 (0.403)
MMSE, mean (SD)	22.58 (3.93)	21.90 (4.33)	201/121	1.451 (0.148)	22.33 (5.47)	24.44 (4.18)	119/45	**2.350 (0.020)**
Visual hallucinations (presence)	55.2%	64.4%	174/101	2.221 (0.136)	53.4%	58.7%	116/46	0.366 (0.545)
Cognitive fluctuations (presence)	82.7%	87.5%	110/80	0.816 (0.366)	83.9%	82.2%	112/45	0.068 (0.795)
Parkinsonism (presence)	75.3%	80.7%	166/88	0.945 (0.331)	90.6%	78.3%	117/46	**4.478 (0.034)**
Probable RBD (presence)	78%	50.0%	41/14	0.085 (0.052)	80.2%	71.8%	111/39	1.183 (0.277)
Fazekas scale, *n* 0/1/2/3	10/70/30/35	7/38/28/20	145/93	6530.0 (0.662)	4/25/10/5	1/6/4/1	44/12	249.5 (0.748)
WMH volume (cm^3), mean (SD)	*N/A*				16.01 (13.65)	16.39 (12.26)	119/46	0.166 (0.868)
TIV (mm^3), mean (SD)	*N/A*				1632.00 (134.99)	1441.99 (117.27)	119/46	**8.397 (<0.001)**
AD co-pathology (presence)	14.0%	15.4%	43/13	1.000 (0.603)	10.6%	10.8%	85/37	1.000 (0.598)
APOE ε4 carriers (presence)	67.5%	46.2%	40/13	0.200 (0.147)	45.2%	38.6%	115/44	0.561 (0.454)

Statistically significant differences are shown in bold (*P*-value ≤ 0.05).

Abbreviations: F, females; M, males; MMSE, Mini-Mental State Examination; N/A, not applicable; RBD, rapid eye movement sleep behavior disorder; TIV, total intracranial volume; WMH, white matter hyperintensities; AD, Alzheimer's disease; APOE, apolipoprotein E.

Table 2

Logistic regression models of visual rating scales

Model 1: Sex effects	**Effect**	***OR***	***SE***	**95% CI**	***P*-value**	**Abnormal score, *n* (%)**	
						Males	**Females**
GCA-F	Sex	**2.121**	**0.260**	**[1.284, 3.566]**	**0.004**	81 (39.71%)	34 (27.64%)
MTA	Sex	0.804	0.234	[0.508, 1.273]	0.350	74 (36.27%)	51 (41.46%)
PA	Sex	1.459	0.237	[0.917, 2.325]	0.111	128 (62.75%)	68 (55.28%)
Model 2: Sex-by-age interaction	**Effect**	**OR**	**SE**	**95% CI**	***P*-value**	**Age of abnormal score, mean (SD)**	
						Males	**Females**
GCA-F	Sex*age	1.018	0.034	[0.951, 1.087]	0.590	74.68 (6.66)	77.06 (7.05)
MTA	Sex*age	1.028	0.036	[0.956, 1.103]	0.451	73.43 (6.20)	77.11 (6.72)
PA	Sex*age	0.977	0.029	[0.922, 1.034]	0.417	72.45 (8.48)	75.93 (8.24)

Model 1 is a binary logistic regression model with visual rating scale scores as the dependent variable (normal versus abnormal) and both sex (variable of interest) and age (control variable) as the independent variables. For the MTA scale, the model included age-adjusted score as the dependent variable (normal versus abnormal) and sex (variable of interest). Model 2 is a binary logistic regression model with visual rating scale scores as the dependent variable (normal versus abnormal) and the interaction between sex and age (variable of interest), together with sex and age as the independent variables. For visual rating scales, values “0” and “1” correspond to “normal” and “abnormal” scores according to established cutoffs. For sex, values “0” and “1” correspond to male and female sex, respectively. Statistically significant effects are shown in bold (*P*-value ≤ 0.05).

Abbreviations: GCA-F, global cortical atrophy frontal-subscale; MTA, medial temporal atrophy scale; PA, posterior atrophy scale.

Table 3

Significant sex and age interactions in automated estimations of regional atrophy in probable DLB

	B	*SE*	95% CI	*P*-value
Volumes				
Left anterior cingulum	0.023	0.011	[0.001, 0.046]	0.035
Right anterior cingulum	0.032	0.015	[0.002, 0.062]	0.037
Right middle frontal gyrus	0.111	0.038	[0.036, 0.186]	0.004
Right fusiform gyrus	0.046	0.019	[0.007, 0.084]	0.020
Left supramarginal gyrus	0.033	0.016	[0.002, 0.064]	0.039
Left superior temporal pole	0.017	0.009	[0.001, 0.035]	0.046
Mean cortical thickness				
Left angular gyrus	0.016	0.006	[0.004, 0.028]	0.008
Left insular cortex	0.012	0.006	[0.001, 0.024]	0.040
Left superior occipital gyrus	0.015	0.005	[0.005, 0.025]	0.004
Left superior parietal lobule	0.014	0.006	[0.003, 0.026]	0.015
Right superior parietal lobule	0.012	0.006	[0.001, 0.024]	0.042
Left precuneus	0.016	0.007	[0.003, 0.029]	0.017
Right precuneus	0.014	0.006	[0.001, 0.028]	0.036

Multiple lineal regression analysis was used with each region of interest (ROI) as the dependent variable and sex, age, and the sex-by-age interaction as independent variables.

Abbreviations: CI, confidence interval.