# Hippocampal and Insula volume in mild cognitive impairment with Lewy bodies

Authors

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## Abstract

Introduction: Diagnostic criteria for prodromal dementia with Lewy bodies have recently been published. These include the use of imaging biomarkers to distinguish mild cognitive impairment with Lewy bodies (MCI-LB) from MCI due to other causes. Two potential biomarkers listed, though not formally included in the diagnostic criteria, due to insufficient evidence, are relatively preserved hippocampi, and atrophy of the insula cortex on structural brain imaging.

Methods: In this report, we sought to investigate these imaging biomarkers in 105 research subjects, including well characterised groups of patients with MCI-LB (n=38), MCI with no core features of Lewy body disease (MCI-AD; n=36) and healthy controls (N=31). Hippocampal and insula volumes were determined from T1 weighted structural MRI scans, using grey matter segmentation performed with SPM software.

Results: Adjusting for age, sex and intracranial volume, there were no differences in hippocampal or insula volume between MCI-AD and MCI-LB, although in both conditions volumes were significantly reduced relative to controls.

Conclusion: Our results do not support the use of either hippocampal or insula volume to identify prodromal dementia with Lewy bodies.

# Introduction

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia, accounting for between 5 and 20% of dementia cases.[1-3] Ideally diagnosis should be made in the prodromal stage to allow for optimal planning of future care. Identification of prodromal cases is also essential to further research in the field, especially regarding putative disease modifying therapies which are likely to be most efficacious when initiated early on. Recently, diagnostic guidelines to identify one form of prodromal DLB, Mild Cognitive Impairment with Lewy bodies (MCI-LB), were published [4]. These include the core clinical features, and the use of imaging biomarkers including dopaminergic brain and noradrenergic cardiac imaging. The guidelines also suggested potential biomarkers, for which there was, as yet, insufficient evidence. These included relatively preserved medial temporal structures, and atrophy of the insula cortex as determined on structural MR imaging.

In DLB, several studies have found that hippocampal volumes, whilst reduced relative to normal, are larger than in AD [5, 6] and relatively preserved medial temporal lobe is a supportive biomarker in the most recent diagnostic guidelines for DLB.[7] Preserved hippocampal volume in MCI has been found to predict conversion to DLB rather than AD,[8, 9] and atrophy of the medial temporal lobe in amnestic MCI has also been established to have reasonable predictive power to identify those at risk of progressing to AD.[10]

A meta-analysis of voxelwise studies in grey matter in DLB found atrophy in the bilateral insula cortex[11] and some studies have also found insula atrophy in prodromal DLB.[12, 13] However, insula atrophy has also been identified in AD,[14] fronto-temporal dementia,[15] and associated with cognitive impairment in HIV infected individuals.[16]

Since there have been relatively few studies investigating the diagnostic utility of these two structural brain markers in mild cognitive impairment (MCI), the aim of this study was to investigate them in a cohort of probable MCI with Lewy bodies (MCI-LB) compared to MCI with no core features of Lewy body disease (MCI-AD).

We hypothesised that:

1) Hippocampal atrophy would be greater in MCI-AD compared to MCI-LB
2) Atrophy of the insula cortex would be more marked in MCI-LB than MCI-AD

# Methods

## Participants

This study included participants aged over 60 diagnosed with mild cognitive impairment (MCI). They were recruited from local memory services in the north east of England between April 2016 and September 2019 where they had received a health service diagnosis of MCI. In addition to MCI, to enter the study all participants reported at least one clinical symptom that was either a core LB clinical feature (cognitive fluctuations, visual hallucinations, parkinsonism, REM sleep behaviour disorder) or a feature supportive of (but not specific to) a diagnosis of LB disease (e.g. mood changes, sleep disturbance, or autonomic symptoms). Following informed consent, participants underwent an interview, clinical assessment and neurological examination by a medical doctor (RD, SL).

The Movement Disorders Society (MDS) Unified Parkinson's Disease Rating Scale – Motor Examination (UPDRS-III), Epworth Sleepiness Scale (ESS), and Geriatric Depression Scale (GDS) were administered to patients. The Instrumental Activities of Daily Living (IADL) scale, Neuropsychiatric Inventory (NPI), North-East Visual Hallucinations Inventory (NEVHI), Mayo Sleep Questionnaire (MSQ), Dementia Cognitive Fluctuation Scale (DCFS), and Clinician Assessment of Fluctuation (CAF) were administered to informants. Clinical Dementia Rating scale (CDR) and Cumulative Illness Rating Scale for Geriatrics (CIRS-G) were completed on the basis of the clinical history and other research assessments. A detailed neuropsychological evaluation was also carried out similar to that reported previously [17] which included the Addenbrooke's Cognitive Exam revised (ACE-R), a 100-point cognitive screening test from which Mini-Mental State Examination (MMSE) score was derived and the Rey Auditory Verbal Learning Test (AVLT). All participants were offered imaging with 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy to determine cardiac sympathetic denervation and 123I-N-3-fluoropropyl-2beta-carbomethoxy-3beta-4-iodophenyl tropane (FP-CIT) SPECT to determine dopamine transporter loss, both of which are biomarkers for DLB [7] and for MCI-LB.[4] FP-CIT images were rated as normal/abnormal by an experienced consensus panel blind to clinical information.[18] For MIBG, the heart to mediastinum ratio (HMR) was calculated from manually drawn regions of interest, and scans were classified as normal/abnormal using a predefined HMR cut off of 1.85 based on local control data, again blind to clinical information.[19]

Diagnosis of MCI was confirmed by a consensus panel of three experienced old-age psychiatrists according to NIA-AA criteria [20] after reviewing medical records. This was based on evidence of

minimal functional impairment and a CDR of 0 or 0.5, and a history of subjective and objective cognitive decline on assessment. We excluded those who fulfilled criteria for dementia or who only had subjective cognitive impairment not fulfilling criteria for MCI, as well as those with vascular or frontotemporal etiologies, or parkinsonism pre-dating cognitive impairment by more than one year. Those with history or evidence of stroke on neurological examination were excluded, along with those with evidence of major cerebrovascular disease on brain scans (either previous or as part of the imaging protocol). We included patients with cardiovascular risk factors, those with diabetes and those with known mild heart disease, so that our population would be a representative sample of older people. Myocardial infarction within one year of recruitment or heart failure of class II or worse were exclusion criteria.

To determine the etiology of the MCI, the presence or absence of core Lewy body (LB) symptoms were rated by the panel blind to imaging findings. Core features were determined in accordance with the recently published MCI-LB criteria.[4]

Participants all had baseline research assessments and most had annual review data available by the time of data locking. Annual review data was used for the consensus panel diagnosis where available. A diagnosis of probable MCI with Lewy bodies (MCI-LB) was given if a patient had two or more core Lewy body symptoms (with positive or negative scan results) or one core symptom in addition to a positive FP-CIT or MIBG scan. A diagnosis of MCI due to Alzheimer's disease (MCI-AD) was given to patients who had no core Lewy body symptoms and negative FP-CIT and MIBG findings and who the panel judged as having a cognitive decline consistent with Alzheimer's disease. The medical notes of the participants were used to identify and exclude those with probable vascular cognitive impairment. Results from these participants have been previously published,[21] including further details of their cognitive and clinical characteristics.

According to these criteria, (see supplementary figure S1) we performed MRI scans on 39 participants diagnosed with probable MCI-LB and 37 diagnosed with MCI-AD. Healthy controls (N=31) were recruited from friends and relatives of the patients and from a local research register and had no history of psychiatric or neurological illness, no evidence of cognitive decline and MR scans within normal limits. We also recruited 21 subjects who had only one Lewy body core feature or positive biomarker at their most recent review and who thus met the diagnostic criteria for possible but not probable MCI-LB. These participants were not included in the analysis presented here as our focus was on probable MCI-LB vs MCI-AD, consistent with previous work in dementia, where probable DLB has been compared with dementia due to AD.

Written informed consent was obtained from all participants prior to study participation and the study was approved by the National Research Ethics Service Committee North East - Newcastle & North Tyneside 2 (Research Ethics Committee Identification Number 15/NE/0420).

## Imaging

Imaging was performed on a 3T Philips Intera Achieva scanner, and included T1 weighted structural images acquired with a magnetization prepared rapid gradient echo (MPRAGE) sequence, sagittal acquisition, echo time 4.6ms, repetition time 8.3ms, inversion time 1250ms, flip angle = 8°, SENSE factor = 2, in-plane field of view 240 x 240 mm2 with slice thickness 1.0 mm, yielding a voxel size of 1.0 x 1.0 x 1.0 $mm^3$. A FLAIR (fluid attenuated inversion recovery) sequence was also obtained with repetition time 11000 ms, inversion time 2800 ms, echo time 125 ms voxel size 0.94 x 0.94 mm, 50 slices with thickness 3mm.

## Image processing

Structural T1 weighted images were segmented into grey and white matter and CSF with the SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/). FLAIR images were co-registered with the T1 weighted structural image, and areas of white matter hyperintensity (WMH) identified using in house developed code based on SPM.[22] The WMH segmentation was used to correct the structural T1 segmentations so that areas of WMH which had been misclassified as grey matter were relabelled as white matter. We used the DARTEL toolbox in SPM12 to create a group specific template to which all grey and white matter segmentation images were aligned, and thus spatially normalised to the Montreal Neurological Institute 152 space. The insula volume was determined by calculating the sum of the modulated normalised grey matter image within the insula region of interest from the marsbar toolbox in SPM12. Intracranial volume was calculated for each subject using the tissue volume tool in SPM12 to sum grey matter, white matter and CSF. The hippocampus was segmented using previously validated in-house software[23] utilising SPM segmentation output. This code is freely available on request from the corresponding author. For both insula and hippocampus volume, we calculated the average of left and right for each participant.

We also performed voxel based morphometry (VBM) to investigate any other regions of atrophy by taking the grey matter normalised and modulated images with 8mm Gaussian smoothing. These were entered into a general linear model, with covariates of group, sex, intracranial volume and age.

### Statistics

For image voxelwise comparisons, we used the general linear model in SPM, thresholded voxelwise at $p < 0.001$ uncorrected, and then clusters which were significant after family wise error correction ($p < 0.05$) were reported. R version 3.6.3 was used for all other statistical analysis. . T-tests were done without assuming equal variance. Comparisons of hippocampus and insula volume between groups were done with a type III ANCOVA, with covariates of age, sex, intracranial volume, and group factor. Post hoc group comparisons were done with the Tukey HSD test. Correlations with clinical variables were done with Spearman's rho. For WMH volumes, we calculated the log of the ratio of WMH to total brain volume in order to render the data more normally distributed. Table 1 gives the mean volume in $mm^3$ for ease of interpretation, but the t-test was done on the logged values.

## Results

Two subjects (1 MCI-AD, 1 MCI-LB) were excluded due to poor structural scan segmentation resulting from head motion. Demographic variables for the subjects included in the analysis are shown in table 1. Compared with MCI-AD subjects, those diagnosed probable MCI-LB were more likely to be male, had higher UPDRS motor scores, lower ACE-R visuospatial scores and higher Epworth sleepiness and Neuropsychiatric inventory scores. There were no significant differences between MCI-LB and MCI-AD in MMSE, total ACE score, ACE memory subscore or the Rey Auditory verbal learning test recall scores. Five MCI participants have since died and had autopsy assessments. Two with probable MCI-LB both had neocortical Lewy body disease and three with MCI-AD all met standard criteria for AD. As shown in table 1, the majority of subjects were diagnosed based on their follow-up data. Eight MCI-LB had negative FP-CIT and MIBG scans, 6 had only their FP-CIT scan positive, 5 their MIBG scan positive, and 19 had positive FP-CIT and MIBG scans. Full details on the number of diagnostic features in the MCI-LB group are given in table 2.

Controlling for age, sex and intracranial volume, the hippocampus volume was significantly different between groups ($F_{2,99}=10.6$; $p<0.001$) with the MCI-LB group ($p<0.001$) and MCI-AD ($p<0.001$) having significantly lower hippocampal volumes compared to controls but no significant difference between

MCI-LB and MCI-AD (p=0.99) - see Figure 1A and supplementary table S1. For the insula cortex, similarly (Figure 1B), volume was significantly different between groups ($F_{2,99}$=3.22; p=0.044) with lower volumes in MCI-LB (p=0.025) and MCI-AD (p=0.032) compared to controls but not between MCI-LB and MCI-AD (p=1.00). These findings remained after we repeated this analysis, controlling in addition for ACE total score.

In the VBM analysis, compared to the control group, the MCI-LB group had reductions in the right hippocampus and middle temporal gyrus, left fusiform gyrus, and anterior cingulate cortex (Figure 2). The MCI-AD group had reductions in grey matter in the bilateral hippocampus and amygdala (Figure 3). There were no significant differences between MCI-AD and MCI-LB.

In the MCI-LB group, we looked at correlations between normalised hippocampus and insula volume and clinical scores, (supplementary table S2) with hippocampus being significantly associated with ACE-R Visuospatial and Total score, and Rey AVLT recall (sum A1-A5). The insula volume correlated with Rey recall, but not with any ACE-R scores. There was no association with number of LB core clinical diagnostic features at baseline with either anatomical structure.

## Discussion

We did not find any significant difference in either hippocampal or insula cortex volume between patients with MCI-LB, and those with MCI-AD. Both MCI-LB and MCI-AD groups had significant hippocampal volume reductions compared with controls, whilst neither group had reductions in insula volume compared to controls on the VBM analysis. As such, our findings do not support the use of the presence or absence of atrophy in either of these structures in the differential diagnosis of prodromal dementia with Lewy bodies.

Few studies have been performed investigating medial temporal preservation in prodromal Lewy body disease, and the evidence is mixed. Roquet et al. [13] compared mild DLB with mild AD using VBM. They found reductions in medial temporal grey matter in the AD but not DLB group compared to controls. However, there were no significant differences between mild AD and DLB in grey matter in any region. A study in patients with the core LB feature of REM sleep behaviour disorder (RBD) found smaller hippocampi [24] compared to unaffected control subjects, and hippocampal atrophy has also consistently been found early in Parkinson's disease.[25] Yoo et al. [26] compared

Alzheimer's disease against Lewy body disease (with a mixture of MCI and dementia), and they found LB disease hippocampus volumes in-between Alzheimer and control participants. They also had a group of 'mixed LB' patients who met criteria for probable Lewy body disease, but who also had a positive amyloid PET scan. These patients had hippocampal volumes similar to the Alzheimer group, and smaller than the Lewy body amyloid negative group. However, their mixed LB group had a greater proportion of subjects with dementia than the other groups, making it difficult to conclude whether the smaller hippocampi were due to mixed pathology, or disease severity. We previously found a correlation between hippocampal atrophy and presence of amyloid in DLB [27] suggesting a contribution of Alzheimer's pathology to hippocampal changes in mixed disease.

In our study, we found, as expected, reduced hippocampus volume in the MCI-AD group. But, against our hypothesis, the hippocampus volume in the MCI-LB group was not significantly different to the MCI-AD group. Whilst we found reduced hippocampal volume in MCI-AD and MCI-LB, there was also a substantial overlap with the control group (see figure 1) reflecting perhaps the heterogeneous nature of MCI, the relatively early disease stage, and the fact that not all MCI will progress to dementia.

Regarding the insula cortex, Blanc et al. [12] found bilateral insula atrophy in prodromal DLB vs controls using VBM although they did not find a difference between DLB vs AD. In a separate study, Roquet et al. [13] also found insula grey matter reduction with VBM in prodromal LB relative to controls, but not compared to prodromal AD. Philippi et al. found associations between change in taste and insula grey matter in DLB, but did not compare insula volume against other groups.[28] We are not aware of any other studies specifically investigating the insula cortex in prodromal DLB or MCI-LB. Our findings are in part agreement with these reports – we found a modest (<10%) reduction in insula cortex grey matter in MCI-LB compared with the control group, but there were no differences between MCI-LB and MCI-AD. Furthermore, our VBM analysis, unlike the previous reports, did not find any significant differences in grey matter in the insula of MCI-LB compared to controls. Our MCI-LB group is broadly similar in age and cognitive score to the two previous VBM studies in prodromal DLB.

Since our study was cross-sectional, we cannot say whether the rate of brain tissue loss in insula or medial temporal lobe is different in MCI-LB compared to MCI-AD. However, for both these structures, the large overlap between MCI and control subjects volumes suggests that at this stage of disease, the rate of change is unlikely to be substantially different in MCI-LB.

Strengths of our study include the prospective design and consensus clinical assessment including for LB core features, along with the use of two imaging biomarkers (FP-CIT and MIBG). This leads to

strong confidence in identifying LB disease, which was the purpose of this study. Thus although we did not include specific AD biomarkers, which in other contexts is a limitation, we believe we have robustly identified MCI groups with and without LB disease, and this is validated by the pathology data available. In support of the MCI-AD diagnosis, the VBM analysis of that group is entirely as expected,[14] showing atrophy confined to the medial temporal lobe. There may have been an element of selection bias in our patients, since patients were recruited at a memory clinic, hence the MCI-LB may have had some amnestic features; also, all patients (including the MCI-AD) had to have some clinical symptoms suggestive of Lewy body disease (e.g. sleep problems). Thus it is possible that despite meeting the relevant diagnostic criteria, the MCI-LB had some Alzheimer like symptoms, and the MCI-AD group some Lewy body ones. However, these patients are precisely those who are liable to be diagnostically challenging, in whom robust biomarkers are likely to prove most useful, and hence our results are more clinically applicable.

In conclusion, we did not find evidence of marked insula atrophy, nor preservation of the hippocampus in mild cognitive impairment due to probable Lewy body disease compared to Alzheimer's disease, and so we suggest that these are unlikely to be useful biomarkers in the diagnosis of prodromal DLB.

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RD – No conflicts in relation to this work. RD has received an educational travel grant from Britannia.

JOB has acted as a consultant, been a recipient of grant support and received honoraria for talks for GE Healthcare. Outside of this work JOB has acted as a consultant for TauRx, Axon, Eisai, Roche and GE Healthcare and received grant funding from Alliance Medical and Merck

GR has received honoraria from GE Healthcare for delivering educational workshops on FP-CIT imaging.

JPT has received honoraria from GE Healthcare for delivering educational presentations on Lewy body disease. Outside of this work JPT has acted as a consultant for Kyowa Kirin, Heptares Sosei, and received grant funding from Heptares Sosei.

PCD has received grant funding form Alzheimer's Research UK and Alzheimer's Society.

AJT has received support for investigator led studies and honoraria from GE Healthcare.

MJF, LMA, SB, JC, CAH, SL, declare that they have no conflicts of interest to disclose.

## Author Roles

Michael J Firbank: Design and conceptualised study, statistical analysis design and execution. Wrote first draft.

Rory Durcan: Research project execution, revised the manuscript for intellectual content.

John T O'Brien: Design and conceptualised study, revised the manuscript for intellectual content.

Louise M Allan: Design and conceptualised study, revised the manuscript for intellectual content.

Sally Barker: Research project execution, revised the manuscript for intellectual content.

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Sarah Lawley: Research project execution, revised the manuscript for intellectual content.

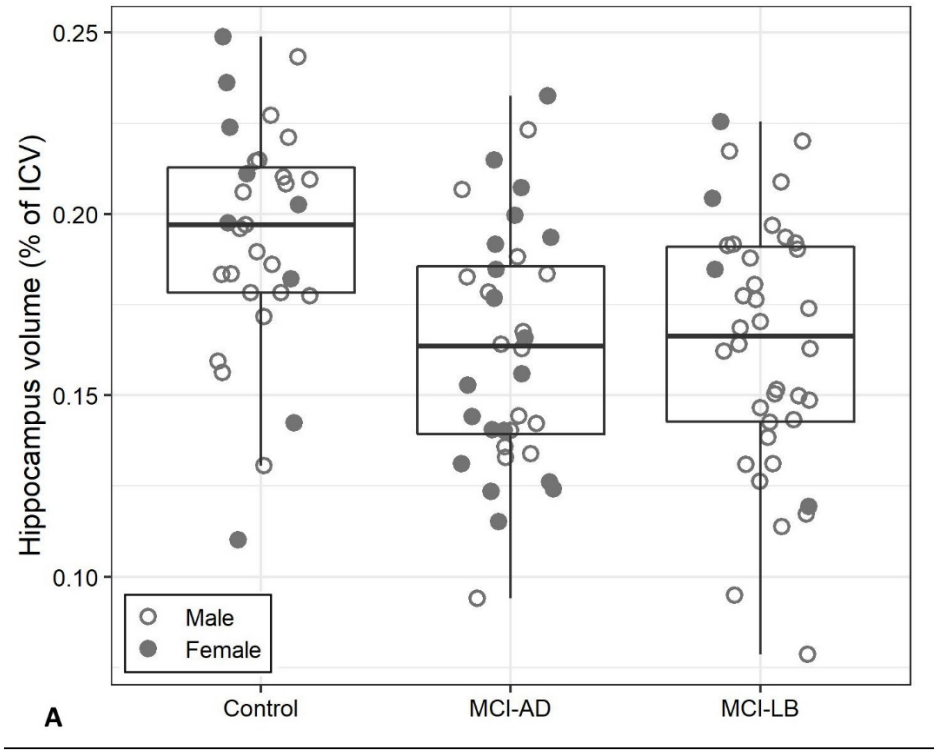
Gemma Roberts: Research project execution, revised the manuscript for intellectual content.

John-Paul Taylor: Design and conceptualised study, revised the manuscript for intellectual content.

Alan J Thomas: Design and conceptualised study, statistical analysis design, revised the manuscript for intellectual content.

# Figures

Figure 1 A) Volume of hippocampus as a percentage of intracranial volume in the 3 groups; B) Volume of insula cortex as a percentage of intracranial volume in the 3 groups.



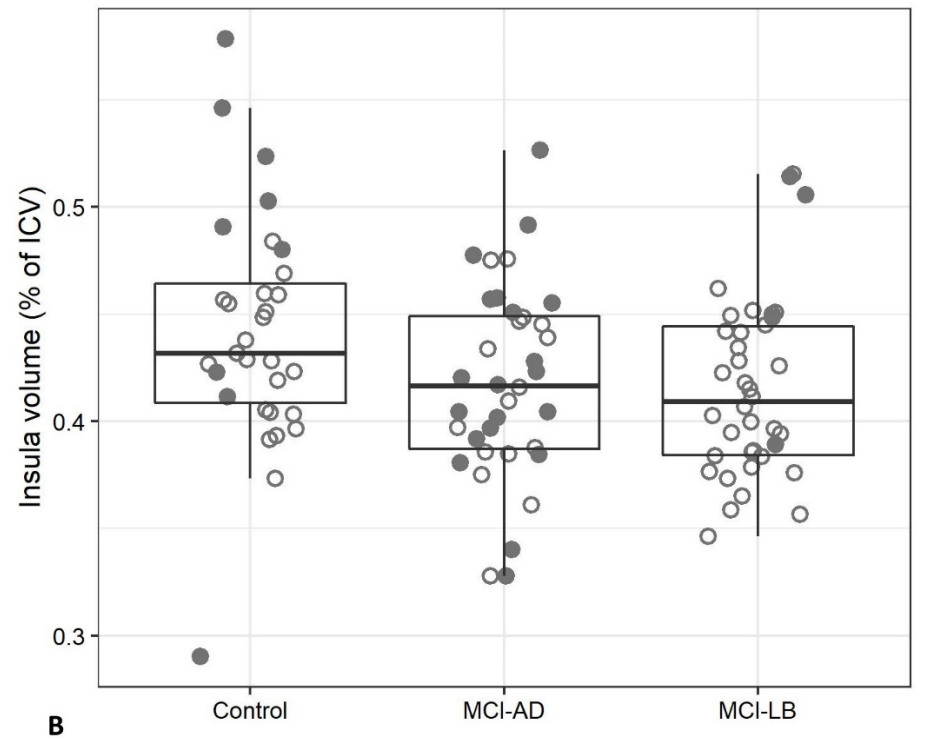



Figure 2. Pattern of reduced grey matter in MCI-LB vs controls. Significant clusters shown on average structural image in Montreal Neurological Institute (MNI) Space. Colorbar shows t statistic.

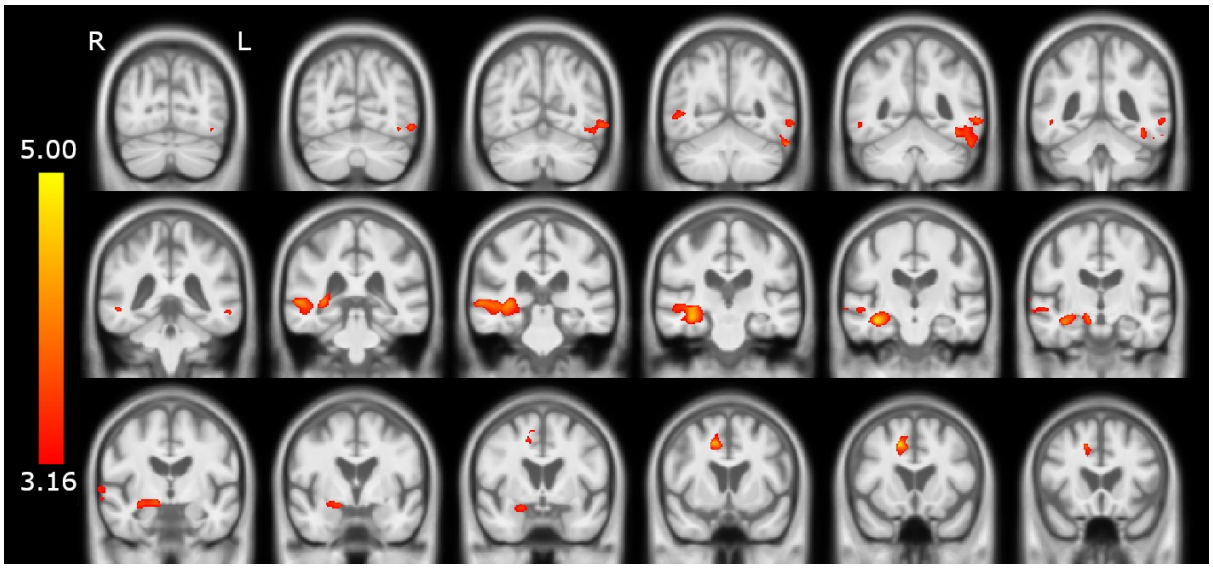
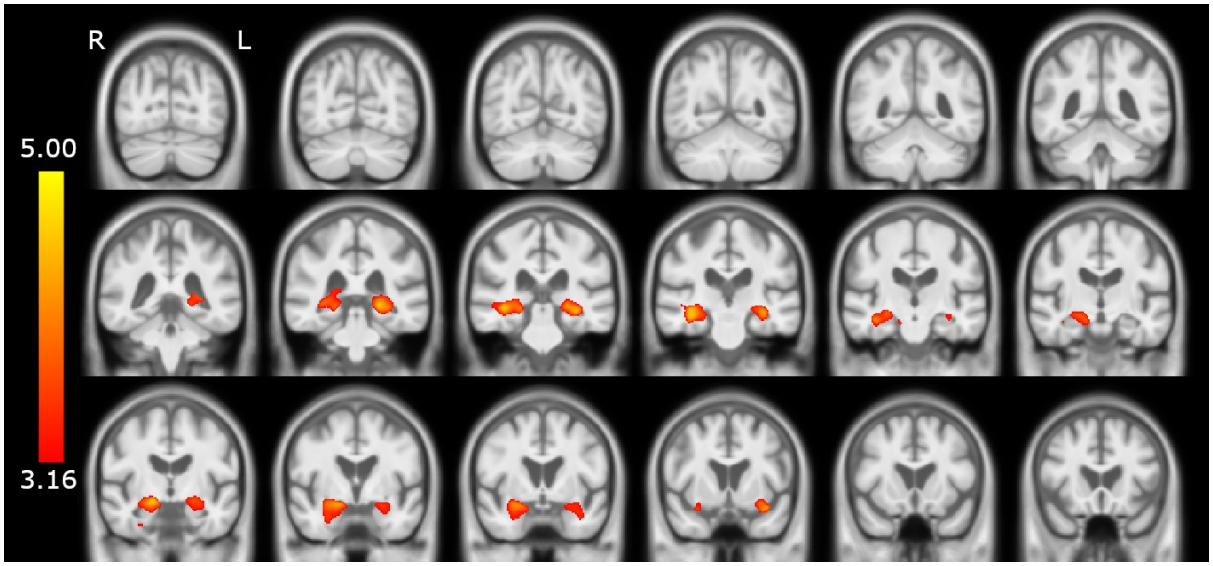



Figure 3. Pattern of reduced grey matter in MCI-AD vs controls. Significant clusters shown on average structural image in Montreal Neurological Institute (MNI) Space. Colorbar shows t statistic.



# Tables

Table 1. Subject demographics for those included in the analysis.

MMSE = mini-mental state exam. ACE-R = Addenbrooke's cognitive exam revised. UPDRS = Unified Parkinson's disease rating scale; Epworth = Epworth sleepiness scale. GDS15 = 15 point geriatric depression scale; IADL = Instrumental activities of daily living; NPI = neuropsychiatric index; CDR = Clinical dementia rating scale; RAVLT = Rey Auditory Verbal Learning Test; WMH = white matter hyperintensity. The statistics on the WMH were performed on the log values. FET = Fisher exact test. Statistical comparison between the MCI-AD and probable MCI-LB is shown in the last column. * $p < 0.05$; ** $p<0.01$

| | Control [N=31] | MCI-AD [N=36] | MCI-LB [N=38] | MCI-LB vs MCI-AD |
|---|---|---|---|---|
| Age | 73.71 (7.32) [61:89] | 76.03 (7.77) [62:89] | 74.53 (6.52) [60:87] | $t_{68.4}$=0.90 p=0.37 |
| Years in Education | 14.7 (4.0) [8.5:24.0] | 13.1 (3.4) [10.0:20.0] | 11.9 (2.8) [9.0:21.0] | $t_{66.7}$=1.57 p=0.12 |
| Female | 9/31 (29%) | 20/36 (56%) | 4/38 (11%) | FET p < 0.001 ** |
| UPDRS motor score | 5.5 (4.4) | 13.4 (11.4) | 23.5 (14.3) | $t_{69.9}$=-3.34 p=0.001 ** |
| MMSE | 28.5 (1.1) | 26.8 (2.1) | 26.4 (2.4) | $t_{71.4}$=0.73 p=0.47 |
| ACE-R Memory | 22.6 (3.0) | 17.8 (4.9) | 19.8 (4.7) | $t_{71.4}$=-1.77 p=0.082 |
| ACE-R VisuoSpatial | 15.5 (0.9) | 14.9 (1.2) | 13.9 (1.9) | $t_{63.6}$=2.81 p=0.0065 ** |
| ACE-R Total | 92.7 (4.2) | 82.9 (8.5) | 83.4 (9.2) | $t_{71.9}$=-0.25 p=0.81 |
| RAVLT recall | 44.5 (11.1) | 32.6 (10.6) | 31.9 (8.3) | $t_{66.3}$=0.30 p=0.77 |
| Epworth Total | 4.7 (2.9) | 5.3 (4.5) | 8.3 (4.5) | $t_{71.8}$=-2.82 p=0.0061 ** |
| GDS15 Total | 1.3 (1.8) | 3.3 (2.4) | 4.9 (4.0) | $t_{61.9}$=-2.09 p=0.04 * |
| IADL Total | NA | 7.2 (1.4) | 6.3 (1.4) | $t_{58.4}$=2.35 p=0.022 * |
| CDR Total | 0.0 (0.0) | 0.5 (0.0) | 0.5 (0.1) | $t_{37.0}$=1.78 p=0.083 |
| NPI Total | NA | 8.3 (9.3) | 16.0 (13.0) | $t_{60.4}$=-2.72 p=0.009 ** |
| Cholinesterase Inhibitors | 0/30 (0%) | 6/34 (18%) | 18/37 (49%) | FET p=0.12 |
| Antiparkinsonian medication | 0/30 (0%) | 0/34 (0%) | 4/37 (11%) | FET p < 0.001 ** |
| WMH volume (ml) | 4.6 (4.5) | 10.1 ( 9.6) | 10.1 ( 9.7) | $t_{68.5}$=-0.29 p=0.78 |
| One year review data availiable | 25 (81%) | 17 (47%) | 31 (82%) | FET p=0.003 ** |

Table 2. The number of MCI-LB participants with positive imaging biomarkers for different combinations of clinical features at their latest follow-up.

| Parkinsonism | RBD | Visual Hallucinations | Fluctuations | All Imaging Negative | FP-CIT Positive | MIBG Positive | FP-CIT and MIBG Positive |
|---|---|---|---|---|---|---|---|
| | | | ✓ | 0 | 0 | 1 | 1 |
| | | ✓ | | 0 | 0 | 0 | 1 |
| | ✓ | | | 0 | 0 | 1 | 3 |
| ✓ | | | | 0 | 1 | 0 | 1 |
| | ✓ | | ✓ | 6 | 0 | 0 | 2 |
| | ✓ | ✓ | | 0 | 2 | 1 | 0 |
| ✓ | | | ✓ | 0 | 1 | 0 | 1 |
| ✓ | | ✓ | | 0 | 1 | 0 | 0 |
| ✓ | ✓ | | | 1 | 1 | 0 | 2 |
| ✓ | ✓ | | ✓ | 1 | 0 | 1 | 4 |
| ✓ | ✓ | ✓ | | 0 | 0 | 0 | 1 |
| ✓ | ✓ | ✓ | ✓ | 0 | 0 | 1 | 3 |

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