

Tissue microstructural changes in dementia with Lewy bodies revealed by quantitative MRI

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Abstract

Objective: We aimed to characterize dementia with Lewy bodies (DLB) by the quantitative MRI parameters of longitudinal relaxation time (qT1) and transverse relaxation time (qT2). These parameters reflect potential pathological changes in tissue microstructures, which may be detectable noninvasively in brain areas without evident atrophy, so may have potential value in revealing the early neuropathological changes in DLB.

Methods: We conducted a cross-sectional study of subjects with DLB (N = 35) and similarly aged control participants (N = 35). All subjects underwent a detailed clinical and neuropsychological assessment and structural and quantitative 3T MRI. Quantitative MRI maps were obtained using relaxation time mapping methods. Statistical analysis was performed on gray matter qT1 and qT2 values.

Results: We found significant alterations of quantitative parameters in DLB compared to controls. In particular, qT1 decreases in bilateral temporal lobes, right parietal lobes, basal ganglia including left putamen, left caudate nucleus and left amygdala, and left hippocampus / parahippocampus; qT2 decreases in left putamen and increases in left precuneus. These regions showed only partial overlap with areas where grey matter loss was found, making atrophy an unlikely explanation for our results.

Conclusions: Our findings support that DLB is predominantly associated with changes in posterior regions, such as visual association areas, and

subcortical structures, and that qT1 and qT2 measurement can detect subtle changes not seen on structural volumetric imaging. Hence, quantitative MRI may compliment other imaging techniques in detecting early changes in DLB and in understanding neurobiological changes associated with the disorder.

(248 words)

Keywords

dementia, Lewy body disease, quantitative MRI, neuroimaging, VBQ

Introduction

Dementia with Lewy bodies (DLB) is the second commonest subtype of degenerative dementia in older people after Alzheimer disease (AD) [1]. It shares common clinical and neuropsychological features with other subtypes of dementia such as AD and Parkinson's disease dementia (PDD), but has a distinctive pattern of pathological changes [2,3]. In comparison to AD, DLB has been shown to have less severe atrophy than AD, but with a more diffuse and less focal pattern [4,5], with relatively preserved medial temporal lobes [2,6,7,8]. One of the most notable characteristics of DLB is visuo-spatial deficit, and imaging studies using mostly PET/SPECT in DLB have highlighted the involvement of occipital [9,10,11], temporoparietal [1,3,12] and subcortical areas [13,14,15]. These characteristics of functional rather than structural changes make conventional volumetric MR technique insufficient to fully describe DLB.

There is evidence that other MR parameters, for example, longitudinal relaxation time ($qT1$) and transverse relaxation time ($qT2$), may be more sensitive to changes in tissue microstructure, biochemical environment and integrity than macrostructural volume reductions [16]. For example, significant variations in these parameters were found during aging [17] and underlying physiological processes at the cellular and molecular level demonstrated by postmortem histological investigations in transgenic 5xFAD mouse animal model of AD [18]. We therefore hypothesize that quantitative $qT1$ and $qT2$ mapping is able to differentiate DLB from healthy controls and indirectly reveal neurobiological abnormalities of DLB at subvoxel scale.

In this study, we evaluated maps of quantitative modulation of $qT1$ and $qT2$ in grey matter, and compared MRI parameters between the DLB and the similarly aged control groups using the voxel-based quantification (VBQ) approach [17]. The main aims of this study were to characterize the neuropathology in DLB based on high-resolution quantitative MR parameter images, and explore their clinical relevance.

Material and methods

Subject recruitment and assessment

Thirty-five individuals with probable DLB were recruited from a community-dwelling population of patients referred to local old age psychiatry, geriatric medicine, or neurology services as previously described [2]. Thirty-five controls were recruited from among spouses and friends of the subjects with dementia or from advertisements in local community newsletters. All participants underwent clinical and neuropsychological evaluations with diagnostic procedures previously employed by our group [3]. The research was approved by the local ethics committee. All participants (or, where appropriate, their nearest relative) provided written informed consent.

Assessment of global cognitive measures in all participants involved use of the Cambridge Cognitive Examination (CAMCOG), which incorporates the Mini-Mental State Examination (MMSE) [19]. Motor Parkinsonism was assessed with the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) [20]. For patients with dementia, neuropsychiatric features were assessed

with the Neuropsychiatric Inventory (NPI) [21], and function was assessed with the Bristol Activities of Daily Living (Bristol ADL) [22].

MRI data acquisition

Participants underwent MRI scanning on a 3T Philips Achieva MRI system with an 8-channel receiver head coil. Structural images were acquired using a T1 weighted volumetric sequence (3D MPRAGE, sagittal acquisition aligned with the AC-PC line, 1mm isotropic resolution, matrix 240×240×180, TR=9.6ms, TE=4.6ms, flip angle=8°, SENSE factor 2). Quantitative images were acquired using a fast quantitative T1 measurement based on a custom inversion recovery prepared EPI sequence [23] (axial slices, 2mm isotropic resolution, matrix 128×128×72, TR=15s, TE=24ms, inversion time TIR=0.25 to 2.5s in 12 uniform steps); and a fast quantitative multi-echo T2 measurement based on a Gradient and Spin Echo Imaging sequence (2mm isotropic resolution, matrix 128×128×72, TR=4.7s, 8 spin echoes at 20ms spacing, EPI factor 5). Please see Supplementary Information E1 for a validation of quantitative imaging methodology. In addition, a B0 field-map using a dual echo 3D GRE (2mm isotropic resolution, matrix 128×128×72, TR=27ms, TE=2.6/6.1ms) was acquired.

Statistical Tests of Demographic, clinical, and cognitive measures.

Group characteristics were evaluated with Statistical Toolbox of Matlab (www.mathworks.co.uk/products/statistics). Differences in demographic and clinical data were assessed with use of either t-tests for continuous variables or χ^2 tests for categorical measures. For each test statistic, a probability value

of $p < 0.05$ was regarded as significant.

Voxel-based quantification

MRI data processing was performed in a combined FSL (fsl.fmrib.ox.ac.uk/fsl/fslwiki) and SPM (www.fil.ion.ucl.ac.uk/spm) based on the previously validated voxel-based quantification (VBQ) procedure [17]. Grey matter volume changes but not other data on this cohort has been previously published [2] and we undertook a similar analysis here to determine whether qT1 and qT2 changes were associated with grey matter atrophy (see Supplementary Information E2). Volumetric structural T1 weighted images were firstly segmented using Gaussian mixture model implemented in the VBM toolbox [24], and brain tissues were classified into grey matter (GM), white matter (WM) and Cerebrospinal fluid (CSF). GM probability maps were non-linearly normalized to standard MNI space (www.mni.mcgill.ca) using the diffeomorphic registration algorithm (DARTEL) [24] in SPM. Raw qT1 and qT2 imaging datasets were corrected for field inhomogeneities using B0 maps and the PRELUDE/FUGUE algorithm in FSL [25]. Then, the bias corrected qT1 and qT2 maps were calculated on voxel-by-voxel basis using non-linear least squares fitting to standard single exponential models [16] before further analysis.

In order to minimize the influence of partial volume effect, we used a multimodal approach during the preprocessing stages [17]. The qT1 and qT2 maps were firstly co-registered with the GM probability maps derived from structural T1 images, and then masked using the thresholded GM probability

maps (at $p > 0.5$) in each participant's native space. We then transformed the GM maps of qT1 and qT2 MRI parameters into standard MNI space using the participant-specific diffeomorphic parameters estimated from the previous DARTEL procedure. However, we did not apply modulation to these quantitative MRI parameters in order to avoid confound of age and disease related GM volume changes. Finally, all normalized quantitative qT1 and qT2 maps were smoothed with an isotropic Gaussian kernel of 6mm full width at half maximum. For the qT1 analysis only, images of three participants in the DLB group were excluded due to the excessive amount of artifact and distortions.

For statistical analysis investigating disease induced regional microstructural alterations between the DLB and control groups, we used the General Linear Model (GLM) with age and gender as covariates. Then, two-tailed t-tests were performed at each voxel to detect regional difference between the DLB and control groups. The false positive rate was controlled using family-wise error (FWE) correction for multiple comparisons, and thresholded at $p < 0.05$ at the cluster level.

Post-hoc region-of-interest analysis

To quantify the magnitude of changes in qT1 and qT2, we extracted the averaged quantitative MRI values from significant clusters and from two regions, which did not show significant changes (bilateral middle occipital lobes and bilateral middle prefrontal lobes defined using AAL atlas [26]). Here, we used the unsmoothed maps in order to preserve the original values of the

MR parameters. These plots are not for statistical inference but illustrating the underlying $qT1$ and $qT2$ values.

To explore the clinical relevance of $qT1$ and $qT2$, in a post-hoc region-of-interest (ROI) analysis, we have correlated the averaged quantitative MRI values extracted from the significant clusters obtained from the previous group comparison with cognitive and clinical measures. These measurements included the CAMCOG total score (CAM total), also divided into executive function, remote memory (which reflects semantic knowledge), and recent memory (which reflects episodic information) sub scores [19], UPDRS, MMSE, Bristol ADL, NPI and Geriatric Depression Scale (GDS). Multiple comparisons were controlled using Bonferroni correction for the number of cognitive and clinical measures.

Results

Demographic clinical and cognitive measures

As shown in Table 1, there were no significant differences between DLB and control groups for age, sex and educational level. As expected, on all cognitive and clinical measures (shown in Table 1) DLB patients scored less well than the controls.

Insert Table 1 here

Group difference in longitudinal relaxation time ($qT1$)

As shown in Figure 1A and Table 2A, we found a significant decrease

($p < 0.0001$, FWE) in qT1 for the DLB group compared to controls in bilateral superior and middle temporal lobes, and right angular gyrus. In addition, there was a significant decrease of qT1 in several key subcortical / striatal nuclei such as the left amygdala (extending to hippocampus and parahippocampus) ($p = 0.001$, FWE), left putamen ($p < 0.0001$, FWE) and left caudate ($p = 0.004$, FWE). There was also a marginally significant reduction in qT1 in the right hippocampus, right putamen and right caudate (not shown). The actual averaged qT1 values from the significant clusters are shown as bar graphs in Figure 1 illustrating the group differences although qT1 in the two control regions in frontal and occipital lobes were not different between groups; see Figure 1B.

Insert Table 2 here

Insert Figure 1 here

Group difference in transverse relaxation time (qT2)

For the transverse relaxation time (qT2), the DLB group showed a significant reduction in left putamen ($p = 0.002$, FWE); see Figure 2A and Table 2B.

Moreover, there was also a marginally significant reduction in qT2 in the right putamen (not shown). We also found a significant increase in qT2 for the DLB subjects compared with controls in the left precuneus ($p = 0.021$, FWE); see Figure 2B and Table 2C. Similar to qT1, qT2 in both clusters except for the two control regions were different between groups (see bar graphs in Figure 2).

Insert Figure 2 here

Correlation between cognitive / clinical measures and quantitative MRI

A significant correlation was found between the CAMCOG executive function score and the qT1 values in left middle temporal lobe ($r=0.39$, $p=0.027$) and left putamen ($r=0.36$, $p=0.044$). In addition, a significant correlation was also found between CAMCOG recent memory score and the left hippocampus extending to amygdala and parahippocampus ($r=0.53$, $p=0.0018$). Finally, a significant inverse correlation was found between Geriatric Depression Scale and the left middle temporal ($r=-0.45$, $p=0.011$) and left putamen ($r=-0.42$, $p=0.016$). No other significant correlation between cognitive / clinical measures and quantitative MRI values was found.

Among the above results, only the correlation between recent memory (but not the remote memory) performance and qT1 in left hippocampus survives the correction for the multiple comparisons (see Figure 3). This relationship was still significant after controlling for age, gender and illness duration as covariates. In addition, DLB patients scored significantly lower than controls in recent ($t(68)=-6.45$, $p<0.00000001$) and to a lesser degree but still significantly in remote ($t(68)=-4.27$, $p<0.00001$) COMCOG memory tests.

Insert Figure 3 here

Discussion

The main findings of this study were tissue water environment changes in

posterior areas of the cortex and subcortical regions of the brain for DLB. This is consistent with previous MRI [2], SPECT [13,27], PET [28,29,30] and DTI [3,31] studies implicating these regions as most affected by the disease. In particular, we have found alterations in qT1 and qT2 measures in posterior parts of the temporoparietal lobes, and in several subcortical regions such as amygdala, putamen and caudate nucleus. And most strikingly, the majority of these regions do not overlap with where grey matter atrophy was found in DLB (see Supplementary Information E3 and E4). This not only makes atrophy an unlikely explanation for our findings, but suggests that quantitative MRI mapping may compliment other imaging techniques in detecting early changes in DLB when none are demonstrable on conventional structural imaging.

The significant decrease in T1 relaxation time in the bilateral superior/middle temporal lobes and right parietal regions, e.g. angular gyrus, was associated with a GM volume reduction. This may be related to the memory and attention impairments in DLB. For example, the qT1 value in left hippocampus region (composing of amygdala and parahippocampus) was significantly positively correlated with episodic memory impairment (i.e. CAMCOG recent memory score) but not semantic memory impairment (i.e. CAMCOG remote memory score) in DLB. The absence of a significant correlation between semantic memory and abnormality in temporal cortex is perhaps due to the weaker remote memory deficit in DLB and the relatively more distributed representations of semantic knowledge in the brain. The decrease in qT1 at left middle temporal and putamen was negatively correlated with the severity

of depression symptoms (at uncorrected level). This implies that the reduction of qT1 in these brain areas may have specific clinical implications. We have also found quantitative MRI parameter (qT2) differences between DLB and controls in precuneus, an area that plays important role in visuospatial processing. Such abnormality in visual and visual association areas may also underpin the clinical and cognitive impairments in patients with DLB, such as recurrent visual hallucinations and visuo-perceptual dysfunction. Consistent with our finding, decreased qT1 is also associated with the layer specific increase in β -amyloid deposition in 5xFAD mice [18].

Despite the significant clinical manifestations of parkinsonism for DLB, most previous morphometric studies of DLB using structural MRI did not find consistent volume reduction in anatomical areas related to the dopaminergic system. On the one hand, FP-CIT SPECT studies using specific imaging ligands have reported a substantial 40-50% loss in dopaminergic activity in the striatum [27]. On the other hand, Cousins et al [15] have only reported an approximately 13% volume reduction in bilateral putamen in DLB compared to controls. With the minimal reduction in subcortical volume, previous MRI studies on GM volume changes did not fully reflect the notable dopamine transporter deficiencies found in DLB.

However, we have identified several subcortical regions in the brain that are potentially associated with dopamine functions. In comparison to control subjects, the averaged qT1 and qT2 values in putamen were decreased by 45% and 52% respectively with DLB suggesting that these local tissue

alterations may be due to Lewy body related pathology and agreeing with findings from FP-CIT SPECT studies [27]. In addition, we have shown that qT1 value in left putamen was correlated with executive function deficit in DLB (at the uncorrected level). During healthy aging, qT2* (a quantitative MRI parameter related to qT2) has also been found to be negatively correlated with age in a wide range of brain areas, in particular in bilateral putamen, reflecting an increased level of iron [32]. In parkinson's disease, lower qT2* in putamen is also associated with more severe motor symptoms [33]. In addition, we have shown that qT1 parameters were decreased in the left caudate nucleus by 68% with DLB. This finding is consistent with the volume reduction in this area and with the known degeneration of the nigrostriatal dopamine pathway associated with DLB.

In terms of determining the possible underlying biophysical interpretation of these quantitative MRI parameters, qT1 is predominantly influenced by water content but also relates to the degree of myelination [34,35,36]. Both qT1 and qT2 are also sensitive to the level of iron (or other paramagnetic ions in the tissue) [37,38]. It is difficult to say precisely what causes qT1 or qT2 to change since they are affected by a range of processes, e.g. demyelination, inflammation, iron, ischemia, edema, and so on. It remains to be seen whether changes in quantitative MRI values reflect abnormalities in the local tissue environment associated with neurodegenerative diseases in general, or whether they may indicate a more specific degenerative process.

Nonetheless, the potential ability of quantitative MRI in detecting early changes of tissue property caused by neurodegenerative disease without

evident atrophy is clinically promising. Compared to nuclear imaging and structural MRI, quantitative MRI is a new and versatile diagnostic tool in investigating neurobiological changes in DLB, with potential for the early detection of DLB since it is not only a noninvasive method, but can also provide more subtle information on local pathology than morphometric measures.

A potential weakness of this approach is the relatively low 2mm isotropic resolution compared to the cortical thickness. Other studies have achieved finer resolution in healthy controls but at the expense of substantially longer times, which are challenging for this patient group [36]. Our scans were acquired with scan times of less than 4 minutes each making them acceptable in ageing populations. At 2mm resolution there is a potential for partial volume effects, particularly with CSF, which can substantially skew quantitative values [39]. Such partial volume effects would cause significant increases in qT1 and qT2 and would be most evident in regions of cortical atrophy. As our data show reduced values and do not coalign with the previously described pattern of atrophy in this patient cohort [2] we are confident that these changes reveal true disease related, parametric changes in the underlying gray matter (see Supplementary Information E5).

Conclusions

In conclusion, we have shown that quantitative MRI is applicable in both understanding the neurobiology of the disease and has the potential in clinical diagnosis. Further research should investigate at what stages in the disease

qT1 and qT2 changes start to occur, and how they alter with disease progression.

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Author contributions

L.S. designed the study, carried out the statistical analysis and wrote the manuscript. A.M.B. codesigned the study, assisted with data interpretation, assisted with writing of the manuscript, and obtained funding for the project. R.W. codesigned the study, recruited and assessed study participants and reviewed the manuscript. J.H. and B.A. were involved with design of the imaging protocol and reviewed the manuscript. J.T.O. codesigned the study, provided subject diagnostic rating, assisted with the development of the research question and with writing of the manuscript, and obtained funding for

the project.

Disclosure

L. Su, A. Blamire, R. Watson, J. He and B. Aribisala report no disclosures. J.

O'Brien has been a consultant for GE Healthcare, Servier, and Bayer

Healthcare and has received honoraria for talks from Pfizer, GE Healthcare,

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