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Diffusion tensor imaging in Alzheimer's disease and dementia with Lewy bodies

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ABSTRACT

White matter changes have been investigated in Alzheimer's disease (AD) in a number of studies using diffusion imaging. Fewer studies have investigated dementia with Lewy bodies (DLB). We used diffusion-weighted magnetic resonance imaging (MRI) and high-resolution (0.3 mm in-plane) coronal 3T MRI of the medial temporal lobe in 16 subjects with AD, 16 with DLB and 16 similarly aged healthy subjects. We found increased mean diffusivity in the temporal lobe of AD, and reduced fractional anisotropy (FA) in a small cluster in the right postcentral gyrus region in the DLB group. Mean FA in this cluster correlated with UPDRS (Unified Parkinson's Disease Rating Scale) motor score. We had previously reported reduced visibility in the AD group of a dark appearing layer of the hippocampus in the high-resolution images. In an SPM analysis on all subjects, there were significant clusters of reduced FA in the corpus callosum, fornix and stria terminalis that correlated with the visual rating of the hippocampus. These results suggest that changes to the hippocampus are associated with structural changes to the white matter fibres of the hippocampus output, and that changes in motor function are associated with changes in white matter underlying somatosensory cortex.

1. Introduction

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia following Alzheimer's disease (AD), accounting for approximately 15% of cases at autopsy (McKeith et al., 2004). DLB shares clinical and pathological features with AD, making it potentially difficult to distinguish in clinical practice. Early and accurate diagnosis of DLB is important for optimum management, including provision of appropriate information to patients and carers, initiation of effective treatments and avoidance of potentially life-threatening antipsychotic drugs.

Diffusion imaging with magnetic resonance has been widely used to investigate the integrity of the white matter microstructure. Mean diffusivity (MD) of water is typically higher where there are fewer barriers to diffusion such as cell walls. Fractional anisotropy (FA) indicates the degree of angular variation in the magnitude of water motion (diffusion), and is highest in directionally coherent fibre bundles such as those found in corpus callosum. Change in MD and FA of the frontal, temporal and parietal lobes has been observed in AD (Kantarci et al., 2001; Bozzali et al., 2002; Head et al., 2004; Naggara et al., 2006; Firbank et al., 2007; Kiuchi et al., 2009) though some studies have found few differences between AD and comparable healthy subjects (Bozzao et al., 2001). Studies vary as to which regions are found to be altered, with, for instance, findings of only limited changes in FA of temporal lobe (Damoiseaux et al., 2009), change in temporal lobe MD (Stahl et al., 2007), and changes in frontal lobe and corpus callosum of MD and FA (Chen et al., 2008). However, diffusion changes in the temporal lobe have been consistently reported, with suggestions that the connectivity of the hippocampus is reduced in AD (Kalus et al., 2006; Ringman et al., 2007; Zhou et al., 2008). A recent study (Kiuchi et al., 2011), using tractography, found decreased FA in the uncinate fasciculus of both AD and DLB, with DLB additionally showing more posterior change. The few other studies in DLB also suggest more posterior changes (Firbank et al., 2007; Ota et al., 2009; Kantarci et al., 2010), with the temporal lobe relatively unaffected, in keeping with structural preservation in DLB compared to AD (Whitwell et al., 2007). We hypothesised that in this study we would find decreases in FA and increases in MD principally in the temporal lobe of AD, and more parietal changes in DLB.

In an analysis of high resolution coronal magnetic resonance images (MRI) of the hippocampus, we found that a structure probably representing the stratum moleculare, stratum lacunosum and stratum radiatum was less visible in AD subjects than in DLB (Firbank et al., 2010). Neuropathological studies have found that this layer is one of the earliest affected by Alzheimer type pathology (Lace et al., 2009) and that pathology spreads through the hippocampus in stages defined broadly by the internal connectivity — i.e. from input to

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output layers. We hypothesised that these hippocampal changes would be associated with changes to the white matter (WM) connecting the hippocampus to other brain areas, in particular, the fornix, which is the main output from the hippocampus, and the cingulum bundle, which is the main input (Duvernoy, 1998; Mori et al., 2005). Although medial temporal lobe atrophy is less common in DLB, it is still present (Tam et al., 2005), and we hypothesised that any alterations in connecting WM would be present regardless of the origin of the hippocampal changes.

In this study, we used diffusion-weighted imaging to investigate differences in WM integrity between AD, DLB and healthy subjects. We also investigated the relationship between the changes seen on the high-resolution hippocampus imaging and FA changes in WM.

2. Methods

2.1. Participants

We recruited 16 people with Alzheimer's disease and 16 with dementia with Lewy bodies, from clinical Old Age Psychiatry, Geriatric Medicine and Neurology Services. Sixteen healthy subjects of similar age were also recruited from spouses and friends of participants with dementia, as well as from a register of subjects who have previously indicated willingness to participate in research. Subjects are the same as those in our previous article (Firbank et al., 2010).

All subjects were aged over 60 and did not have contra-indications for MRI. Subjects with dementia had mild to moderate severity (MMSE>10). All Alzheimer's disease subjects fulfilled criteria for probable AD according to NINCDS/ADRDA (McKhann et al., 1984). Cases of dementia with Lewy bodies all met criteria for probable DLB according to the consensus criteria (McKeith et al., 2005). All diagnoses were made by consensus between two experienced clinicians, a method we have previously validated against autopsy diagnosis (McKeith et al., 2000). Routine clinical workup for dementia included detailed physical, neurological and neuropsychiatric examinations, including screening blood tests and CT scan. Additional assessments performed were of cognition (Cambridge Cognitive Examination (CAMCOG)) (Roth et al., 1986), mood (Cornell Depression Scale) (Alexopoulos et al., 1988), neuropsychiatric features (Neuropsychiatric Inventory (NPI)) (Cummings et al., 1994), clinical fluctuation (Clinical Assessment of Fluctuation Scale) (Walker et al., 2000), memory (Rey Auditory Verbal Learning Test (Rey, 1964)) and motor features of parkinsonism (UPDRS (Unified Parkinson's Disease Rating Scale) subsection III, recorded for each side of the body) (Fahn et al., 1987). Nine of the DLB subjects were taking anti-parkinsonian medications. The UPDRS assessment was not timed relative to subjects taking parkinsonian medication. Duration of dementia was determined from a review of the patient's medical case notes.

Exclusion criteria included severe concurrent illness (apart from dementia for patients), space-occupying lesions on imaging, history of stroke and contraindications to MRI. In addition, controls had no history of psychiatric illnesses. The study was approved by the local ethics committee, and all subjects gave signed informed consent for participation.

2.2. MRI acquisition

Subjects were scanned on a 3T MRI system (Intera Achieva scanner; Philips, Eindhoven, the Netherlands). Images acquired included a T1 weighted volumetric sequence covering the whole brain (MPRAGE, Sagittal acquisition, slice thickness 1.2 mm, voxel size 1.15×1.15 mm; TR = 9.6 ms; TE 4.6 ms; flip angle = 8°; SENSE factor = 2).

Diffusion images were acquired with FLAIR weighting to reduce the influence of CSF. Acquisition parameters were TR 7000 ms, TE 68 ms, TI 2200 ms. SENSE factor = 2, slice thickness = 2.5 mm, field of view 260×260 mm, acquisition matrix 120×93. Two b values were used: 4 acquisitions with b = 0 s/mm^2, and images with diffusion weighting in 30 directions (1 acquisition each) with b = 1000 s/mm^2, with the gradient directions uniformly spaced around a sphere.

High resolution coronal imaging was also performed, based on previous work (Mueller et al., 2007) with a sequence optimised locally to provide good hippocampal contrast (turbo spin echo — turbo factor 15; 24 slices; slice thickness 2 mm, field of view 210×167; pixel resolution 0.41×0.52 mm; TR 2568 ms; TE 19 ms; centric-ordered, flip angle 90°; 2 acquisitions — acquisition time = 2×2:50).

After the first 13 subjects (5 Control, 7 AD, 1 DLB) one of the acquisitions was replaced by three acquisitions of a higher resolution sequence for the remaining subjects to improve visualisation of the hippocampus structure (Firbank et al., 2010) with the following parameters altered: 12 slices; pixel resolution 0.27×0.35 mm; TR 3852 ms; 3 acquisitions — acquisition time = 3×2:07. The number of acquisitions was increased to maintain signal-to-noise ratio (SNR) in the face of smaller voxels. Data were acquired using multiple acquisitions to allow correction of patient motion prior to averaging to increase SNR. This approach was found to maintain highest resolution in pilot studies compared with direct averaging by the scanner.

The coronal images were positioned for each subject so that they were at an angle of 25° to the line from genu to splenium of the corpus callosum. We have found previously that this is a reliable method of angling the slices approximately perpendicular to the main axis of the hippocampus (Firbank et al., 2010).

2.3. Volumetric image analysis

The T1 weighted anatomical images were segmented into grey and white matter, and spatially normalised using the segmentation algorithm in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). The ratio of total brain volume/intracranial volume was derived from the ratio of grey+white/grey+white+CSF volume.

2.4. High resolution image analysis

The analysis of the high resolution coronal images is described elsewhere (Firbank et al., 2010). Briefly, we used the FLIRT image registration tool (Jenkinson and Smith, 2001)(part of FSL http://www.fmrib.ox.ac.uk/fsl/) to register all the high resolution images from each subject together, and interpolate to 0.27×0.27 mm resolution. A high SNR image was then created by summing together all the registered high resolution images for that subject. Images were reviewed to check for subject motion, and one subject (DLB) was excluded due to excessive motion, and for one other subject, one of the high resolution images was unacceptable. The other subjects did not have excessive motion artefacts on the images. Images were viewed with the freely available itk-snap package (Yushkevich et al., 2006) (http://www.itksnap.org/pmwiki/pmwiki.php). We examined three coronal slices, starting on the slice on which the head of the hippocampus was no longer visible, and the two slices posterior to that. A hypointense line could be seen in the hippocampus which is likely to represent fibres in the hippocampal layers of stratum moleculare, stratum lacunosum and stratum radiatum (Wieshmann et al., 1999; Thomas et al., 2008) (see Fig. 1). We observed considerable variability in how clearly this line could be visualised between subjects, and a single rater (blind to diagnosis) assigned each hippocampus a score (1 to 5) according to how clearly the hippocampus internal structure was depicted throughout the three slices examined. On this scale, 5 = line clearly visualised throughout, 4 = most of the line clearly visualised with good contrast for most of its length, 3 = line semi clearly defined, either with some sections of good contrast and some poor, or partly blurred along all its length, 2 = line mostly not clearly defined, but recognisable, typically with