Voxel-Based Investigation Of White Matter Changes In Normal Ageing Using Diffusion Tensor Imaging

T. R. Barrick[1], R. A. Charlton[1], M. O'Sullivan[1], H. S. Markus[1], C. A. Clark[1]

[1]Clinical Neuroscience, Saint George's, University of London, London, United Kingdom

Introduction

In recent years the importance of changes in white matter integrity in normal ageing has been reported (1). Diffusion tensor imaging has enabled us to investigate white matter structural integrity *in vivo*, and region of interest approaches have lead to debate about the regional specificity of white matter decline in ageing, in particular that the frontal lobes are preferentially affected (2, 3, 4). Voxel-based statistical analyses allow us to investigate anatomical distribution of white matter damage across the ageing brain. Here we present data from a large sample of normal older adults using voxel-based statistical analysis. We analyse 3D mean diffusivity (MD) and fractional anisotropy (FA) maps, and investigate MD and FA perpendicular to the mid-sagittal plane (using 2D column maps, 5) and through coronal slices (1D coronal slice profiles, 5) in standard space. Post-hoc streamline tractography was performed through significant clusters, in order to investigate the extent of white matter pathways affected in the ageing process.

Methods

MRI data acquisition and preliminary analysis: 99 healthy adults between 50 and 90 years were scanned on a 1.5T GE Signa MRI system (max. field gradient strength 22 mTm^{-1}). Diffusion tensor imaging (DTI) was achieved using a single shot echo planar sequence with 12 diffusion sensitised directions as described previously (6). Two interleaved acquisitions comprising 25 slices each provided whole brain coverage (resolution: in plane 2.5mm; through plane 2.8mm). Each subject's DTI was normalised to standard space by affine transformation (7) and resampled to contain 1.0 mm^3 voxels. MD and FA images were generated for each subject DTI and voxels corresponding to CSF were removed prior to further analysis.

Generation of MD and FA (2D) column and (1D) coronal slice profile maps: For each subject mean MD and FA values were computed perpendicular to the mid-sagittal plane through white matter of both cerebral hemispheres in standard space. This generated pixelated 2D column maps (5) of MD and FA through the entire brain of each subject. In addition, coronal slice profile maps (5) were generated by computing the mean values of MD and FA through white matter of both cerebral hemispheres for each coronal slice in standard space.

Statistical analysis: 3D and 2D data were smoothed (3D 3mm FWHM; 2D 2mm FWHM) and statistical analysis was performed in SPM2 using a linear correlation model. MD and FA 3D, 2D column and 1D coronal slice profile maps were correlated with age. In all analyses, multiple comparisons correction was applied using a family wise error at $p < 0.05$ corrected for peak height. Significant positive and negative correlations are represented using hot and cold colours, respectively, in the significance maps.

Post-hoc tractography: Subvoxel streamline tractography was performed as described previously (6). Streamlines (vector step length 1.0mm, termination criteria FA < 0.08) were initiated from the centre of every voxel in each individual normalised DTI dataset. Only streamlines passing through significant 3D clusters determined from the 3D MD and FA statistical analyses were retained. Pathway variability maps were generated for each significant cluster and represent the percentage of subjects for which white matter pathways passed through voxels in standard space.

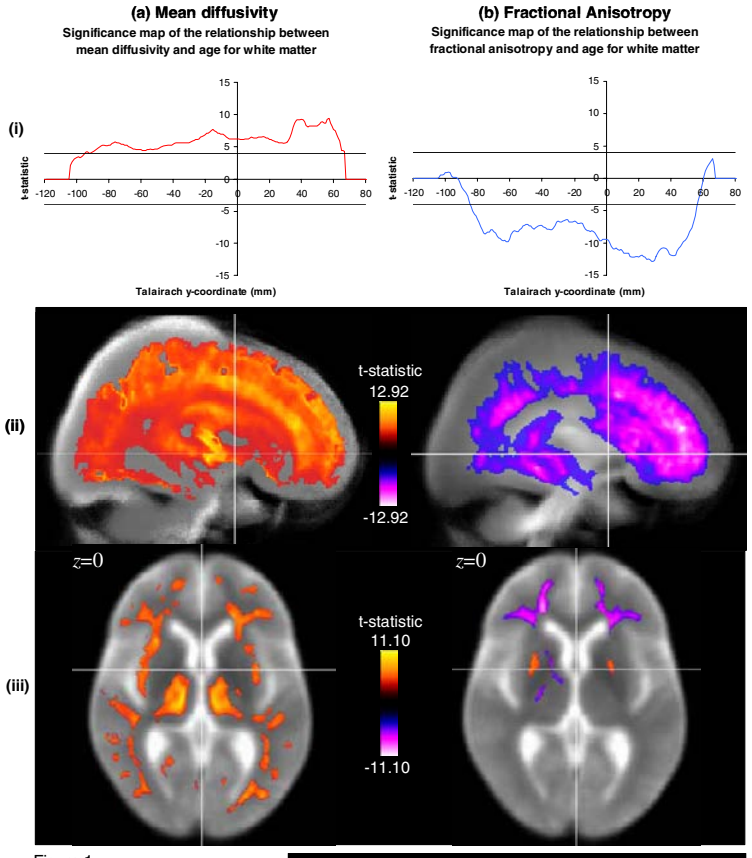

Figure 1

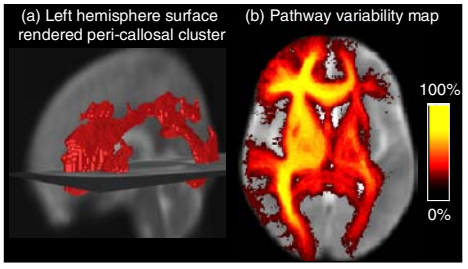

Figure 2

Results

White matter coronal slice profile significance maps (Figure 1i) show MD to have a significant positive correlation with age, such that MD increases with age across the entire brain (Figure 1ai). FA was shown to have a significant negative correlation across the entire brain (Figure 1bi). However, age related FA reduction was more significant in the anterior frontal lobes than across the rest of the brain. White matter MD and FA column maps were also significantly correlated with age (Figure 1ii). Investigation of MD revealed positive correlations for pixels across the entire brain (Figure 1aii) whereas FA was negatively correlated, particularly in the anterior frontal lobes (Figure 1bii). Although other brain regions were identified as significant by the column map FA analysis these were not as significant as the frontal lobe effect. Voxel-based 3D statistical analysis of the MD maps again revealed extensive, significant voxel clusters representing positive correlations with age across the white matter and in the thalamus (Figure 1aiii), while the FA maps revealed extensive negatively correlated peri-callosal clusters in both hemispheres (Figure 1biii). The significant peri-callosal FA clusters included white matter of the frontal, parietal, occipital and temporal lobes (see left hemisphere surface rendered FA cluster, Figure 2a). Although the significant FA clusters were small in comparison to the significant MD clusters post-hoc tractography revealed white matter pathways through the FA clusters to connect all cerebral lobes (see pathway variability map for left peri-callosal FA cluster, Figure 2b).

Discussion

These results suggest decline of white matter integrity across the whole brain, but with the anterior frontal lobes being particularly affected. This is in keeping with results from other authors (8). In addition, tractography results suggest that localised peri-callosal white matter degeneration may affect pathway connectivity throughout the whole brain. Consequently, white matter pathway degeneration may explain the pattern of impaired and spared cognitive functions that are apparent in normal ageing. In particular, abilities that activate diffuse networks could be more affected, compared to abilities relying upon localised networks which remain relatively stable (9). It remains to be investigated as to whether voxel-based analyses of cognitive function will support this inference.

References [1] Morrison, JH & Hof PR, 1997. *Science*, 278: 412-419.
[2] Pfefferbaum A et al., 2000. *Mag Res Med*, 44: 259-268.
[3] Sullivan EV et al., 2001. *NeuroReport*, 12: 99-104.
[4] Charlton RA et al., (in press). *Neurology*.
[5] Barrick TR et al., 2005. *NeuroImage*, 24(3): 678-691.
[6] Barrick TR & Clark CA, 2004. *NeuroImage*, 22(2): 481-491.
[7] Alexander DC et al., 2001. *IEEE Trans Med Imaging*, 20(11): 1131-1139.
[8] Head D et al., 2004. *Cerebral Cortex*, 14: 410-423.
[9] Mega MS & Cummings JL, 1994. *J of Neuropsychiatry & Clin Neuro*, 6: 358-370.