Tract based spatial statistics reveals longitudinal white matter changes in normal ageing

T. R. Barrick[1], R. A. Charlton[1], C. A. Clark[2], and H. S. Markus[1]

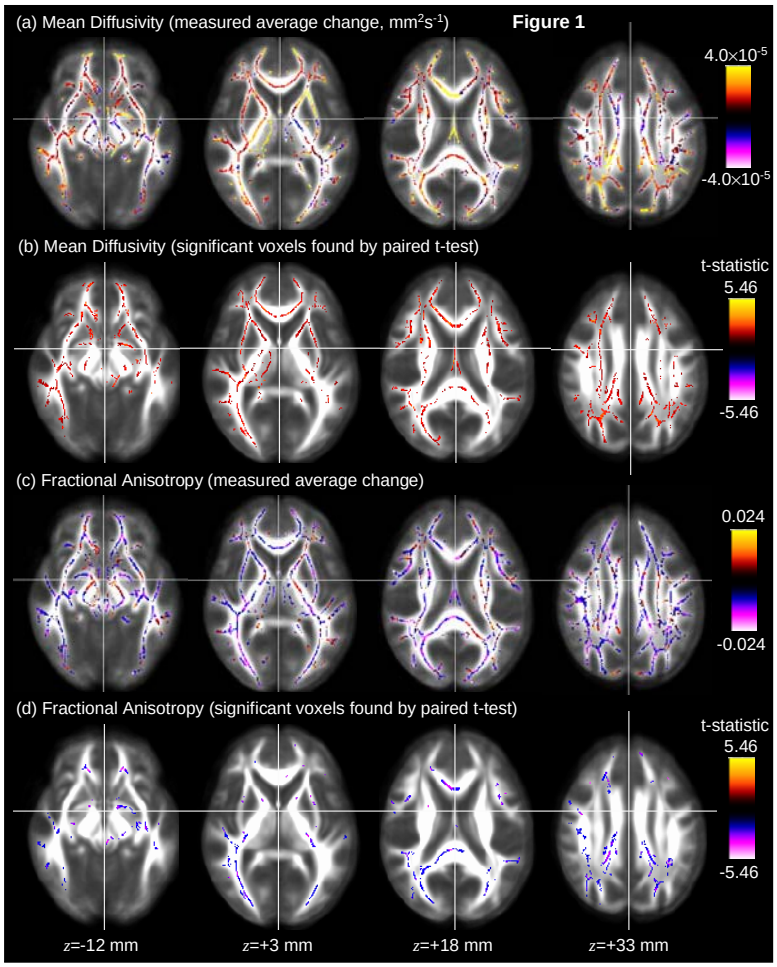
[1]Centre for Clinical Neuroscience, Saint George's, University of London, London, United Kingdom, [2]Institute of Child Health, University College London, London, United Kingdom

Introduction: During normal ageing a range of brain changes have been observed using MRI techniques [1,2]. In recent years there has been increasing interest in the role of white matter (WM) in damage in age related cognitive decline [3,4]. Diffusion tensor imaging (DTI) [5] is the only non-invasive method currently available for investigation of WM structural integrity in the human brain and offers an opportunity for quantifying age-related changes. DTI studies of normal ageing have demonstrated both an increase in mean diffusivity (MD), a measure of the overall magnitude of water diffusion [3,6,7], and a decline in fractional anisotropy (FA), a measure of WM structural organisation and coherence at each voxel, even in the absence of detectable reductions in WM volume [4]. However questions remain regarding the rate of WM change in normal ageing, whether change can be detected over short periods using DTI, whether some brain regions decline earlier or at a faster rate [8] (for example the frontal-ageing hypothesis[9]), and what factors influence individual differences in these changes. The aim of this study was to use tract based spatial statistics (TBSS) to investigate local age-related WM structural change on a voxel-by-voxel basis over a 2-year follow-up period.

Methods: *Subjects and MRI data acquisition:* 106 normal healthy middle aged and elderly adults were recruited at baseline (55 males, 51 females; age range 50 to 90 years; mean age = 69 years). Of these 84 returned for follow-up after 2 years (48 males, 36 females; age range 55 to 91 years; mean age = 71 years). Of these 74 were successfully scanned at both time points on a 1.5T GE Signa MRI system (max. field gradient strength 22mTm^{-1}). DTI was achieved using a single shot echo planar sequence with 12 diffusion sensitised directions as described previously [10]. Two interleaved acquisitions comprising 25 slices each provided whole brain coverage (resolution: in plane 2.5mm; through plane 2.8mm). MD and FA images were computed from each subject's DTI.

TBSS: Baseline and follow-up images were analysed using TBSS software (FSL4, **http://www.fmrib.ox.ac.uk/fsl/**). This involved transformation of FA images to standard space incorporating an affine transformation followed by non-linear deformation to obtain isotropic 1mm^3 voxels with skull and dura removed. Subject FA maps were group averaged and this image was then used to generate a group-wise skeleton of WM tracts. The FA images of each subject were projected onto the group-wise skeleton, a procedure designed to account for residual misalignment among individual WM tracts. The MD images were also projected onto the group-wise skeleton.

Statistical analysis was performed using randomise software (FSL4) with 5000 permutations. Multiple comparisons correction was achieved using threshold free cluster enhancement [11]. After TFCE voxel clusters were deemed significant at $p<0.05$. Longitudinal age-related differences between baseline and follow-up skeletonised images were explored using a paired t-test design.



Results: Average MD changes over 2 years are shown in Figure 1a (hot colours = increase, cold colours = decrease) and indicate that average MD increases throughout the WM (as shown by hot coloured skeleton voxels throughout the entire brain). Figure 1b illustrates clusters with significant increases in MD. There were no areas with a significant decrease in MD. Significant MD increases occurred across the entire brain, with sparing of the motor pathways (through the cerebral peduncles, internal capsules and adjacent to the motor homunculus), and the anterior cingulum. Average FA changes over 2 years are shown in Figure 1c. Although these predominately show decreases in average FA, the significance maps (Figure 1d) reveal a reduced pattern of structural integrity change (as indicated by fewer significant skeleton voxels) when compared to MD. Significant decreases in FA were located in the corpus callosum (genu, splenium and parietal fibres), temporal lobe (temporal stem, WM underlying superior and middle temporal gyri), parietal lobe (WM underlying supramarginal and angular gyri), and posterior cingulum. There were no significant increases in FA.

Discussion: We have used TBSS to investigate age-related changes in WM tracts in normal ageing. After a two-year time interval, TBSS revealed significant changes through the white matter on both MD and FA data. In particular, TBSS revealed WM integrity changes across the whole brain for MD. MD TBSS analysis found significant changes in the genu and splenium of the corpus callosum, the pericallosal white matter, the external capsule, and the posterior cingulum. Fewer areas demonstrated significant changes on FA analysis, and there was no evidence of a specific frontal effect. FA changes were noted in the genu and splenium of the corpus callosum, external capsule, and the posterior cingulum. We have found that DTI parameters are sensitive to detection of white matter change in normal middle aged and elderly adults after a relatively brief time interval of two-years. We found no evidence of a greater rate of change in the anterior frontal regions, which has been suggested previously. Future work should assess whether these changes are functionally important by investigating their associations with age-related cognitive decline.

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