Longitudinal age-related changes in radial and axial diffusion using tract-based spatial statistics

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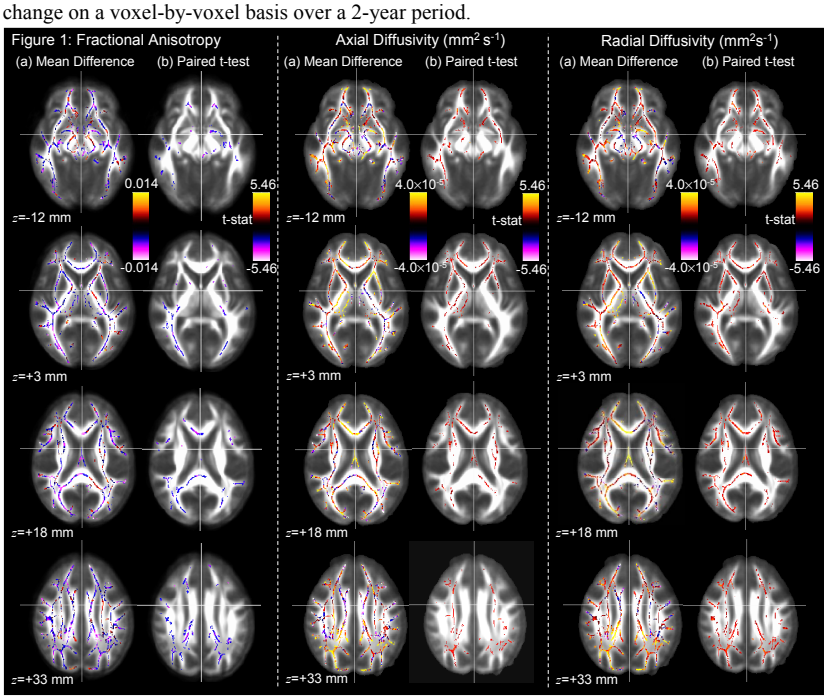
Introduction: A range of neuropathological changes occur in normal ageing and an important aim of neuroimaging research is to detect these changes *in vivo*. Diffusion tensor imaging (DTI) measures water diffusion in tissue and is used to infer white matter structural integrity. Recent animal studies suggest that neuropathological change can be further elucidated, beyond simple tissue integrity, with evidence suggesting that increases in radial diffusion are associated with demyelination and increases in axial diffusion with axonal damage [1,2,3]. Histological studies in humans have further supported the association between radial diffusion and myelin, and several studies have identified increases in radial diffusion with older age [4,5,6]. Patterns of axial diffusion with increasing age are more complex with both increases and decreases observed in different brain regions, and radial diffusion has shown greater differences than axial diffusion when comparing older and young adults [4,5,6]. To date, no studies have investigated longitudinal changes in axial and radial diffusion. The aim of this study is to use tract based spatial statistics (TBSS) to investigate local age-related white matter structural change on a voxel-by-voxel basis over a 2-year period.

Methods: *Subjects and MRI data acquisition:* 106 normal healthy ageing 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 spin-echo planar sequence with 12 diffusion sensitised directions as described previously [7].

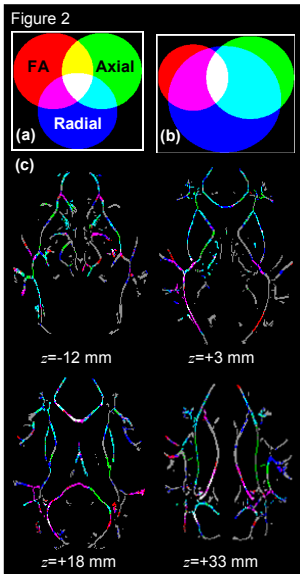
Tract-based spatial statistics: Baseline and follow-up images were analysed using TBSS software (FSL4,http://www.fmrib.ox.ac.uk/fsl/). Fractional anisotropy (FA), axial and radial diffusivity images were projected onto the group-wise skeleton. Statistical analysis was performed using randomise software (FSL4) with 5000 permutations. Multiple comparisons correction was achieved using threshold free cluster enhancement at $p<0.05$ [8]. Longitudinal age-related differences were explored using a paired t-test design. The relationship between risk factors and difference in diffusion parameters between baseline and follow-up was investigated for (i) blood pressure (dystolic and systolic), (ii) cholesterol levels, (iii) body mass index, (iv) volume of hyperintense lesions on FLAIR MRIs, (v) amount of smoking.



Results: Mean FA, axial and radial diffusivity changes over 2 years are shown in Fig-1a with significance maps for the paired t-tests shown in Fig-1b (hot colours represent parameter increases with cold colours representing decreases). In general, Fig-1a shows increases in average radial diffusivity and decreases in FA throughout the white matter. This is in contrast to axial diffusivity that shows more variability in change between time-points.

Paired t-test maps show significant between time-point increases for axial and radial diffusion and decreases for FA. No significant decreases in axial or radial diffusivity, or increases in FA were observed. Fig-2 and Table 1 show the location and amount of overlap between voxels exhibiting significant longitudinal change. In particular, these results are shown as percentages of the white matter skeleton (in Table 1) and in the form of a Venn diagram in Fig-2b (for colour key see Fig-2a). Voxel locations representing the areas in Fig-2b are shown on the white matter skeleton in Fig-2c. In particular, the radial diffusivity analysis identifies the largest region of age-related change and includes 79% of significant voxels. Of further note is a bilateral region superior to the internal capsule that shows axial but not FA or radial diffusion changes over the observed period.

Table 1 Voxel Sets	Percentage Of Skeleton
FA	13.20%
Axial	20.54%
Radial	33. 96%
FA ∩ Axial	0.01%
FA ∩ Radial	6.94%
Axial ∩ Radial	12.10%
FA ∩ Axial ∩ Radial	2.78%
Insignificant Voxels	56.90%



No significant results were found by statistical analysis of the relationship between risk factors and difference in diffusion parameters between baseline and follow-up.

Discussion: After a two-year delay, TBSS revealed significant changes throughout the white matter in both axial and radial diffusion, although radial diffusion showed more widespread changes. Overlap of significant paired t-test voxels was observed between either two or all three measures in 51% of significant voxels (with almost all overlapping voxels including the radial measure). This is to be expected as all DTI invariant parameters are calculated from the principal diffusivities, and axonal damage and demyelination are highly correlated [1,9]. The bilateral increase in axial diffusion superior to the internal capsule is of note. It has been suggested that extended periods of demyelination without remyelination may increase the incidence of axonal degeneration [1], although further work is required to assess this fully. We have found that DTI parameters are sensitive to detection of white matter change in normal older adults after a relatively brief delay of two-years. However, we also observe that no significant relationships were observed between differences in diffusion characteristics and risk factors. Future work will assess whether these changes are functionally important by investigating their associations with age-related cognitive decline.

References

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