Novel atlas-based technique for longitudinal investigation of diffusion tensor tractography data: Application to healthy ageing

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Introduction: Diffusion tensor (DT) tractography methods have been previously applied in cross-sectional studies on ageing, epilepsy and brain tumours [1,2,3] to assess structural integrity differences in white matter pathways. Here we extend tractography techniques to enable investigation of longitudinal changes in white matter pathway integrity. In a pilot study of age-related change we apply these techniques to quantify structural changes determined from DT images in middle-aged and elderly individuals between baseline and follow-up after 2 years. Using a labelled white matter tract atlas [4], we consistently extract similar tracts over time. The pathways of interest in this study are those shown to be involved in working memory (WM) [5] and include fronto-temporal, fronto-parietal and temporo-parietal white matter pathways. Here we present the first longitudinal tractography study on healthy ageing subjects.

Methods: *Subjects and MRI acquisition:* 74 normal, healthy middle-aged and elderly adults were scanned at baseline and again two years later as part of the GENIE study [6]. For our pilot study the 10 youngest and 10 eldest participants were selected (middle-aged group - 6 male, mean age 53.9 ± 1.04; elderly group - 7 male, mean age 82.7 ± 3.05). A diffusion-weighted single shot spin-echo planar acquisition was performed on a GE 1.5 T Signa system as described in [6].

Image Analysis: A labelled white matter anatomical atlas [4] was coregistered to each subject's image space using TBSS software [7] (as described in Fig-1A). Cortical areas associated with working memory were defined on the atlas and separated into 3 tractography seed regions of interest (ROIs) in the left hemisphere only. These regions were located in the anterior frontal, middle and superior temporal gyri and inferior parietal lobule (Fig-1B, for full anatomical description see [4]), as identified from Charlton et al [5]. Wild bootstrap [8] DT probabilistic tractography was performed between fronto-temporal (FT), fronto-parietal (FP) and temporo-parietal (TP) ROIs. Tracking was initialised 200 times from each seed voxel in the ROIs and only tracts passing between ROI-pairs were retained (step length = 0.5mm, fractional anisotropy (FA) threshold ≤ 0.1). Median DT measures of FA, radial and axial diffusivity were computed from voxels visited by greater than 90% of the retained tracts. The above procedure was performed on both age groups and time points.

Statistical Analysis: Median values of each diffusion parameter were investigated using a repeated measures MANOVA design with between subject factor Age-Group, within-subject factors are Time (baseline, follow-up) and Tract (FT, FP, TP).

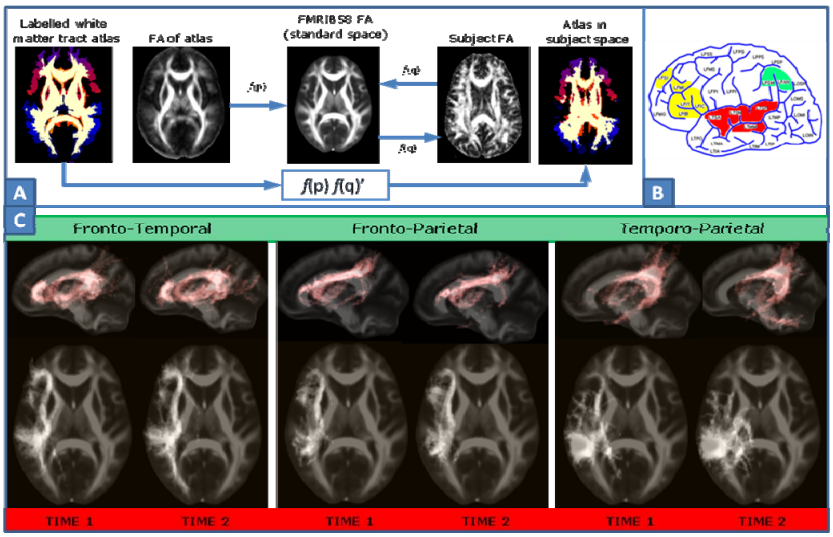

Figure 1: (A) Using TBSS for coregistration, the transformation of the atlas FA map and inverse transform of the subject FA map into standard space were combined in order to map the labelled white matter atlas into subject space, (B) regions associated with working memory identified on the atlas in the frontal (yellow), temporal (red) and parietal (green) lobes, (C) sagittal and axial projections of retained FT, FP and TP tracts for the 10 subjects in the middle-aged group overlaid onto an average FA map in standard space.

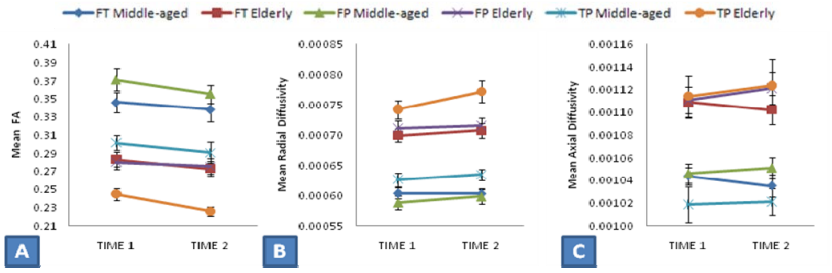

Figure 2: Age-related changes in average median of (A) FA, (B) radial and (C) axial diffusivity between time points. All three tracts are presented for both age groups. Standard errors are marked on the graphs.

Results: Fig-1C shows that similar tracts are consistently extracted using our method for both time points in the middle-aged cohort, these are also consistently extracted for the elderly group. Extracted FT pathways include the direct segment of the arcuate fasciculus and the medial pathway, and for the FP and TP pathways the anterior and posterior segments of the arcuate fasciculus are extracted, respectively (all also found by [5]). Fig-2A shows a significant decrease in FA across time points for both groups and all tracts ($p = 0.001$), with greater FA values in the middle-aged cohort than in the elderly ($p < 0.001$). Radial diffusivity (Fig-2B) significantly increases across time points for both groups and all tracts ($p = 0.047$), with lower values for the middle-aged than the elderly cohort for all regions ($p < 0.001$). The FP and TP pathways show a trend towards axial diffusivity increasing across time points for both subject groups (Fig-2C). Axial diffusivity within tracts is significantly greater for elderly than middle aged individuals ($p < 0.001$). Furthermore, as shown in Fig-2 all tracts possess different structural integrities as measured by FA and radial diffusivity ($p < 0.001$) whereas for axial diffusivity there is no significant difference between tracts ($p = 0.249$). No other significant interactions were observed between Age-Group, Time and Tract variables.

Discussion: We have demonstrated a technique for longitudinal measurement of diffusion characteristics of white matter tracts. Decreases in FA found between time points in specific white matter tracts showed a similar trend to those reported for global white matter integrity measured using whole brain histograms [6]. Cross-sectional age-related decrease in FA and increase in radial diffusivity have been reported for the superior longitudinal fasciculus [9] and are consistent with the results obtained here for the fronto-temporal pathways. We have previously shown WM performance to decline with increasing age [6]. The associated WM white matter pathways presented in our pilot study suggest a decrease in white matter structural integrity with age that could potentially be related to decline in WM. Processing the remaining 54 GENIE subjects and increasing the number of bootstraps for tractography will provide greater statistical power to extend the analysis of our current pilot study. By combining diffusion information of tracts between carefully selected cortical ROIs with neuropsychological test results, we aim to define the neuronal networks associated with various cognitive processes and track their changes with normal ageing. Our method enables similar cortical regions to be chosen from which to seed tractography, and shows reliable tract reconstruction across time and between subjects. We have shown that our technique quantifies white matter pathway specific changes in structural integrity over 2 years and that these changes are not significantly different between the middle-aged and elderly cohorts.

References

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