Partial volume effect as a hidden covariate in tractography based analyses of fractional anisotropy: Does size matter?

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INTRODUCTION

In recent years, diffusion tensor imaging[1] (DTI) has been used extensively to investigate the aging brain, in both young and aging adults. Using fiber tractography (e.g. Basser et al.[2]), it has been shown that fractional anisotropy (FA) of white matter fiber tracts increases during maturation and subsequently decreases with age above the age of approximately 30-40 years[3-5]. This relation between FA and age has been linked to changes in microstructural organisation[3]: neuronal demyelination, for instance, is thought to result in a lower FA along tracts in elderly people compared to young adults[6]. A well-known influence on accuracy of fiber tractography is the presence of partial volume effects (PVE) in voxels with different tissue organisations[7-9]. PVE may well have an influence when calculating the FA along a tract, an effect not addressed in the results finding a relationship between age and tract FA. As total brain volume changes with age, and therefore the volume of fiber tract bundles, the relative contribution of PVE will be different between fiber bundles that have a different volume. We hypothesize that there is a correlation between tract volume and FA, through PVE, that could, at least in part, explain the observed age-related FA changes. Preliminary support for our hypothesis can be found in a left-sided co-lateralization of FA with tract volume[10]. In this work, we confirmed our hypothesis using simulations and experiments.

METHODS

Acquisition: DTI images were acquired from 27 subjects (16 male; median age 32.5 years; range 18.9-44.0 years), on a GE 3T HDx system using an SS-SE EPI sequence with b-value=1200 s/mm^2 along 60 directions; 6 B0-images; FOV = 23cm; acquisition matrix 96×96; reconstruction matrix 128×128; 2.4 mm slice thickness; 60 axial slices; ASSET factor=2, effective TR=15 R-R intervals; total acquisition time=25 min.

Tract simulations: Neural fiber bundles of varying thickness (3-15 voxels) were constructed using a maximal FA of 0.9 according to Leemans[11] (Figure 2).

Tractography: Whole brain deterministic tractography was performed using ExploreDTI[12]. A segment of each cingulum bundle was selected by placing 3 'AND' regions of interest (ROI) at selected anatomical landmarks[13] and placing two additional 'AND' ROIs roughly 11mm anterior and posterior of the central ROI (Figure 1). Tract characteristics were investigated only within the segments. ROIs were defined by a single blinded rater.

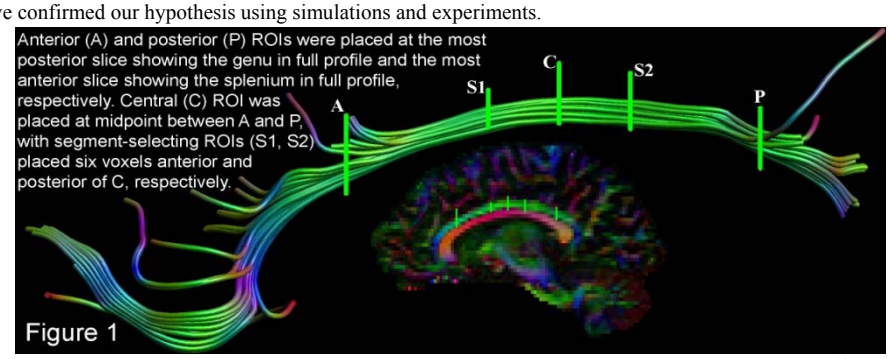

Figure 1

Statistical analysis: Spearman's rank correlation coefficient was calculated for simulated tract volume and FA. Paired t-test analysis was performed to investigate differences between left and right segments in FA and tract volume, as an initial indication of co-lateralization. Unpaired t-test analysis was used to investigate the relation between FA and volume, and gender. Spearman's rank correlation coefficient was used to test for an effect between tract volume and FA.

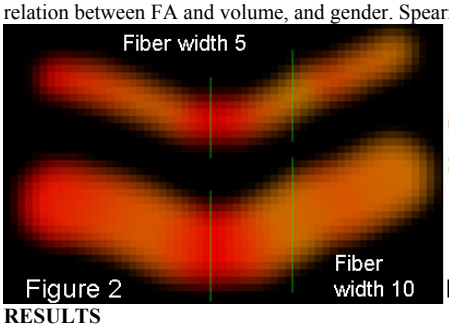

Figure 2

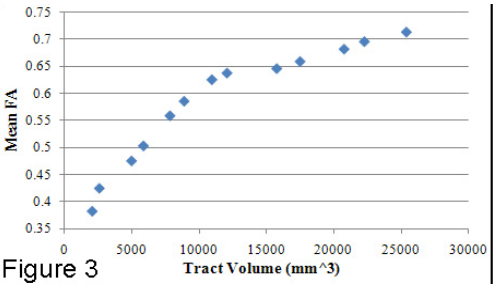

Figure 3

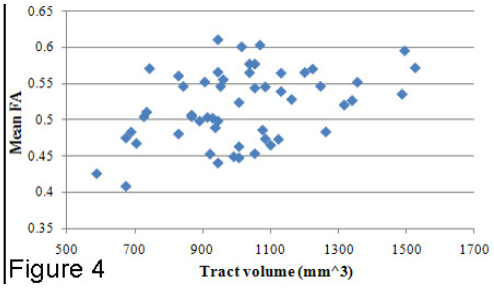

Figure 4

RESULTS

Simulated fibers showed a strong correlation (P<0.001) between FA and volume (Figure 3). Intrasubject analysis of left vs. right cingulum segments reveals a significantly higher FA left than right (P<0.001); where only a trend is visible when comparing tract volumes (mean volume left 1045 mm^3 vs. right 979 mm^3, P>0.1). Age had no effect on any of the tract properties investigated, with P-values 0.73/0.67/0.95 for age-FA; and 0.31/0.31/0.12 for age-volume (right segment/left segment/segments pooled). This is likely the result of the age range within our subjects, chosen to be at the top of the quadratic relation between age and FA as described in literature[5]. A significantly higher mean tract volume was observed in male (1084mm^3; range 674-1527 mm^3) vs. female (909mm^3; range 588-1100 mm^3) subjects (P=0.0011) and, although not significant (P=0.42), mean FA was higher in male then in female subjects (0.524 vs. 0.512, respectively). Figure 4 shows a significant correlation between tract volume and FA in the cingulum bundles (P<0.01).

DISCUSSION & CONCLUSION

The method of cingulum segment selection has been chosen to reduce influence of tract length on volume calculations. Positioning of the ROIs for segment selection ensures this is reproducible, as can be seen from the low deviation in mean segment length over all subjects: 23.97 ± 0.44 mm. Group analysis over all subjects shows a correlation between tract volume and FA, indicating that the PVE affects fiber tract analysis. This is also supported by a strong correlation between volume and FA in simulated neural fibers. Although FA and volume correlations are different between genders, we argue it acceptable to pool the subjects. Previous work in a larger population showed a significantly greater FA and volume in men than women[10], not only indicating that the lack of significance of FA between genders in our study is possibly due to a small population, but once more indicating that volume and FA are correlated. In conclusion, our work shows that PVE is indeed a covariate in tractography based analyses of FA. So far, analyses that correlate FA with other covariates, such as age, do not take into account tract size and resultant PVE on FA calculations. Reduced tract size, due to whole brain atrophy in the aging brain, may therefore be the cause for the observed FA reduction. However, it is still unclear whether the observed PVE is fully, or only in part, accountable for the effect of the age-FA relationship seen in other studies. Analogously, age-related changes of diffusivity measures may be explained by a tract size dependent PVE of CSF.

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