Free Water Modulation of White Matter Integrity Measures - with Application to Schizophrenia

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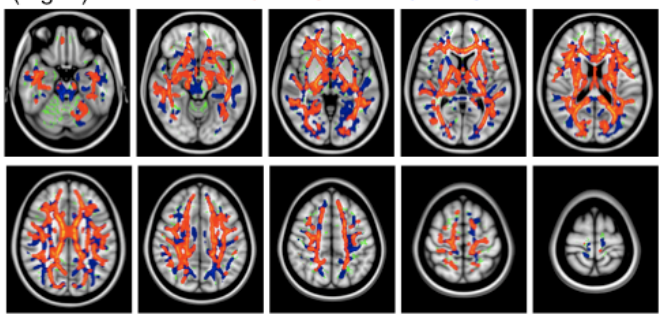
Fractional anisotropy (FA) is an important parameter derived from diffusion tensor MRI (DTI) [1], and abnormalities in the FA value were found in various brain disorders [2]. A common interpretation for decreases in FA in white matter is change in the myelin, rendering FA a measure of white matter integrity; yet, it is known that FA is not a specific biomarker for myelin, since other possible microstructural abnormalities might cause reductions in FA [3]. For example, it was demonstrated that an isotropic increase change (simultaneous equal change to all eigenvalues) of an initially anisotropic sample not only increases the mean diffusivity (MD), but also decreases FA [4]. Schizophrenia (SZ) is an example of a disorder where abnormal decreases in FA are found in various white matter bundles [5], and these findings - associated also with genetics and post-mortem studies demonstrating myelin abnormalities in SZ patients - have led to the hypothesis that SZ is a neurological disorder that involves anomalies in the formation or function of myelin sheaths and consequently, white matter functionality [6]. In order to better understand the microstructural origin of the observed decreases in FA in SZ, we have applied the free water elimination framework [4] to separate isotropic and anisotropic components of group-wise abnormalities. The framework fits the diffusion images to a bi-tensor model; one compartment estimates the volume of free water, and the other provides a free water eliminated estimation of tensor quantities such as corrected FA. We tested the effects of these parameters by comparing a group of SZ patients in their first psychotic episode (n=18) with matching controls (n=20), with the goal of improving our understanding of the etiology of the disorder as it is expressed at onset of illness.

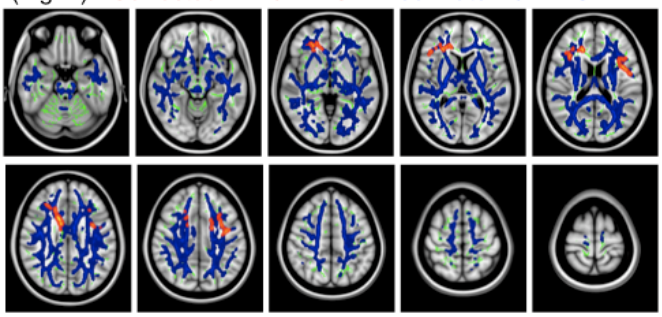
Methods: Diffusion images were acquired for 18 SZ patients (age 21.6±4.3), and 20 sex and age-matched (age 24.0±4.0) healthy controls (HC) on a 3T GE Signa magnet. The patients were diagnosed with a first episode of SZ, and were either medication-naïve or not medicated for a long time period. The diffusion sequence was a double-refocused EPI-DTI that had 51 gradient directions with b=900 s/mm^2 and 8 additional b=0 images. We collected 85 axial slices with isotropic voxels (1.7mm)^3 to cover the entire brain. All diffusion images were corrected for motion and eddy current artifacts (FSL), and FA and MD maps were obtained. The groups were statistically compared using the tract-based spatial statistics (TBSS) method [7], which created a white matter skeleton representing all the subjects, and then projected each individual map onto the skeleton. The FA and MD values on the skeleton were compared between the groups using non-parametric two-sample t-test (Randomise) controlled for age, weight and motion, reporting significant differences for $p<0.05$ corrected for multiple-comparisons (TFCE), and visualized using the TBSSfill and FSLview softwares, over the T1 MNI-space template brain. Free water maps and free water eliminated FA maps (corrected FA) were produced for the motion corrected diffusion images using the methods described in [4]. The maps were then projected onto the skeleton and used to compare the DTI parameters, and the statistical test was run for each parameter separately.

Results: Widespread significant changes in MD and FA were found when comparing the DTI results of the SZ patients to their matching controls (Fig. 1, FA drawn over MD). The MD of the patients was increased in most of the white matter skeleton on both hemispheres, whereas FA decreased for the patients compared to the control group. The extent of significant FA changes is smaller than that of the MD changes; still, FA abnormalities extend throughout most anatomical areas of the skeleton. When applying the free water correction, significant FA decreases were limited to the frontal lobe alone (Fig. 2), in areas that consist of parts of the superior longitudinal fasciculus on both hemispheres, the right inferior frontal occipital fasciculus, and the intersection of the callosal fibers with the right superior corona radiata. Significant, widespread free-water increases were found, largely overlapping with the MD changes.

(Fig. 1) •FA: SZ<HC •MD: SZ>HC



(Fig. 2) •Corrected FA: SZ<HC •Free Water: SZ>HC



Discussion: The results suggest that most of the FA and MD changes can be captured by the free water volume measure. Free water is water molecules that do not experience hindrance or restriction; it is therefore likely that the free water measured at white matter structures originates from the extra-cellular space around white matter. An increase in the free water volume observed across the brain for the SZ population could therefore indicate either reduced neuronal density or deterioration of extra-neuronal components, such as the glial cells or the extracellular matrix. Importantly, the extent of the findings - along with the typical isotropic change - makes it unlikely to be originating from demyelination, which is known to cause shape changes [8]. The fact that there was no significant difference observed for the corrected FA value in most brain areas suggests that the tissue component in these areas maintained its shape, and therefore it is likely that the neuronal density has been maintained as well. The limited areas where the corrected FA decreased in SZ subjects could be focal points where myelin changes do play a role; interestingly, we find these focal areas to be on white matter tracts that were previously found to have abnormalities in chronic SZ patients [5].

Conclusion: We demonstrated how free water analysis extends information provided by diffusion tensor imaging data to provide better tissue specificity of FA changes. Free water volume accounts for any isotropic (volume) changes, and remaining anisotropy (shape) changes are captured by the free water corrected FA measure. Applying this method on SZ subjects further illuminates the etiology of the disease, suggesting that at its first stages, a whole-brain process causes mainly volume abnormalities, while shape abnormalities are limited to focal areas in the frontal lobes. We speculate that the volume changes precede the myelin-related shape changes, encouraging future studies to better understand the cause for the free water changes observed, which might better explain the source of the disease.

References: [1] Pierpaoli et al., Radiology 201(3), 1996. [2] Assaf and Pasternak, J Mol Neurosci 34(1), 2008. [3] Peled, IEEE-TMI 26(11), 2007. [4] Pasternak et al., MRM 62(3), 2009. [5] Kubicki et al., J Psychiatr Res 41(1), 2007. [6] Konrad and Winterer, Schizophr Bull 34(1), 2008. [7] Smith et al., Neuroimage 31(4), 2006. [6] [8] Song et al., Neuroimage 20(3), 2003.