Voxel Based Analysis of Diffusion Indices and Deformation Based Volumetric Alterations in Late Childhood and Adolescence

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Introduction

Studies of normal brain development using diffusion tensor imaging (DTI) may provide insights into the mechanisms of neurological and neurobehavioral disorders originating from abnormal maturation of white matter. Several groups have employed DTI to study microstructural white matter changes during early and late childhood [1-3]. These studies relied on cross-sectional analyses of subjects at different age groups. However cross-sectional studies may not be sensitive when age-related changes or pathological abnormalities are subtle and inter-subject variation is large. The purpose of this study was to perform an analysis of diffusion indices acquired in a longitudinal study to identify white matter microstructural changes in healthy brain during late childhood and adolescence. Voxel based analysis (VBA) was employed to test each voxel for age-related statistical differences using diffusion indices. A strategy based on free-form transformation was adopted to generate a template representing an average shape model of the population under study. VBA was performed for data collected at two time points with diffusion indices transformed to the coordinate system of the template. Using a similar approach, the deformation-based volumetric changes in brain over the same time period were also examined.

Methods

Fifteen healthy children aged 7.5-18.3 years were recruited (mean age 12.7±3.1 years, 6 girls, all right-handed). All the participants underwent two scans: at baseline and 15 months follow-up. The data were acquired at 1.5 T using a spin-echo single shot EPI pulse sequence with 15 non-collinear diffusion gradient directions (b=1000 s/mm^2), two b=0 s/mm^2 (b0) images, 2 averages, and 0.94 mm x 0.94 mm x 5 mm spatial resolution. FA, ADC, and eigenvalue maps were calculated from raw data using the 'DTI Studio' software. Axial diffusivity was defined as the largest eigenvalue and radial diffusivity was defined as average of the second and third largest eigenvalues. To improve the image matching process, all the images were re-sampled to 0.94 mm x 0.94 mm x 2.5 mm resolution. Using b0 images of all subjects acquired at the baseline scan, a template was generated employing an iterative process. First, the b0 image of one of the subjects was used as a reference shape. All the other b0 images were matched to this reference shape using an affine transformation. Second, a non-linear diffeomorphic (smooth and invertible transformation) algorithm [4] was used to match the selected reference shape to all other affine transformed b0 images. Deformation fields generated from these steps were averaged and used to deform the reference b0 image. This procedure was repeated several times until the reference shape converged onto the true population average b0 image as determined by the lack of change in the magnitude of the averaged displacement vectors (3 iterations were needed for convergence). Parametric maps (FA, ADC, axial and radial diffusivity) from individual subjects, computed at baseline and follow-up scans, were transformed to the coordinate of the average template utilizing affine and non-linear diffeomorphic transformations. Spatially normalized maps were smoothed using a 3D spatial Gaussain filter (FWHM of 5 mm) and compared by voxel based non-parametric permutation based paired *t*-test (10000 permutations) using SnPM software. To perform displacement-based volumetric study, b0 images of the follow-up scans were matched to the baseline using rigid body and non-linear diffeomorphic algorithms. The determinant of the Jacobian maps was computed using the deformation fields. The Jacobian maps were transformed to the coordinate of the template using the same affine and non-linear transformations estimated for the baseline images described above. The statistical significance for the age-related volumetric differences was examined for individual subjects by implementing a non-parametric linear regression test. To reduce the partial volume effect, only voxels with FA values greater than 0.2 were analyzed. Statistical significance was set to $p<0.001$.

Results

VBA demonstrated age-related FA increase in the mid-brain, external capsule, and superior regions of corona radiata (Fig. 1a). A significant age-related decrease in ADC was detected in the external capsule, genu and posterior limb of internal capsule, and corona radiata (Fig. 1b). VBA analysis of axial diffusivity demonstrated an age-related decline in superior regions of the corona radiata (Fig. 1c). Evaluation of radial diffusivity revealed a decline in multiple regions, including mid-brain, external capsule, genu and posterior limb of internal capsule, forceps minor, and corona radiata (Fig 1d). Deformation-based volumetric study of white matter did not reveal any statistically significant age-related changes. However, there were trends indicating on average up to a 6% increase in volume of white matter in the forceps minor, and the posterior region of the corona radiata ($p \sim 0.1$) (Fig. 2).

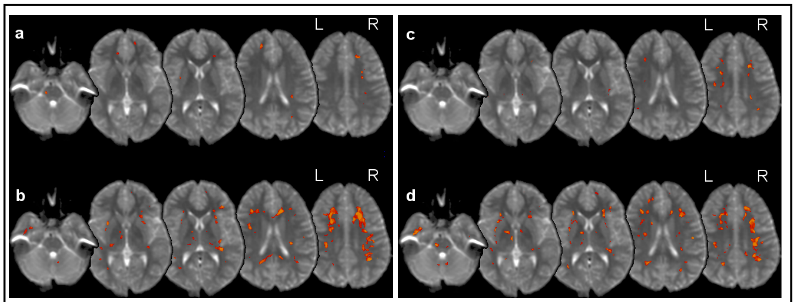

Fig.1. Voxels showing a significant age-related increase in FA (a), decline in ADC (b), decline in axial (c), and radial diffusivities (d), superimposed on the b0 template. The map was generated by computing the voxel level paired *t*-tests between the baseline and the follow up scans. The color coding represents uncorrected *p* values, with orange corresponding to voxels with the highest significance ($0.001 \le p \le 0.0001$).

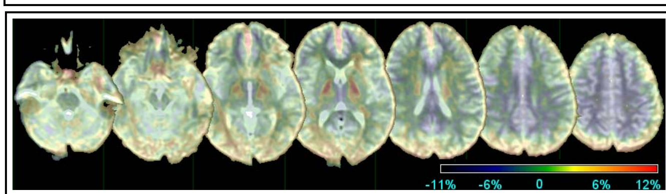

Fig.2. Percentage of average tissue volume changes within 15 months period superimposed on the template image.

Discussion and Conclusions

This is the first longitudinal study to examine changes in DTI indices (FA, ADC, axial and radial diffusivity maps) in late childhood and adolescence. A sophisticated spatial normalization technique was utilized to establish a one-to-one correspondence between the different diffusion indices. Application of this novel spatial normalization technique allowed for measurement of longitudinal changes in diffusion indices and tissue volume changes with brain maturation using VBA. The VBA results (including detection of more widespread changes in radial diffusivity) are in good agreement with earlier cross-sectional ROI and tract-based analyses of ADC and FA values [3, 5]. Our results suggest that the combination of all DTI parameters (including axial and radial diffusivities) and measures of tissue volume may help to explain white matter changes associated with brain maturation. For example, the combined observation of increased tissue volume in the forceps minor and reduced radial diffusivity may indicate an increase in compactness or density of fiber bundles. The results of our study also indicate continuation of regional brain maturation and increase in fiber density during late childhood and adolescence.

References

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