

# Voxel Based versus Region of Interest Analysis in Diffusion Tensor Imaging of Neurodevelopment

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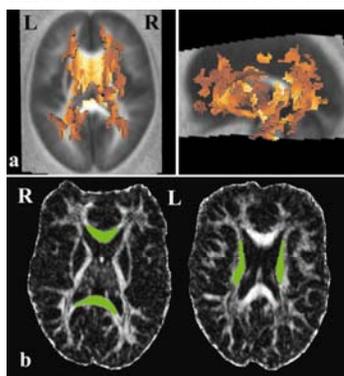
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**Introduction:** Diffusion tensor imaging (DTI) studies of neurodevelopment<sup>1,2</sup> demonstrate more widespread changes in the white matter than standard T1-weighted MRI<sup>3</sup>. However, the degree of reported changes depends also on the analysis method since region of interest analysis may sample limited brain regions due to time constraints and the ability to identify the structure of interest on a 2D image<sup>2</sup>, whereas whole brain, voxel based analysis depends greatly on accurate spatial normalization<sup>4</sup>. The purpose of this study is to determine whether these two analysis methods lead to different conclusions of neurodevelopment on the same DTI data set.

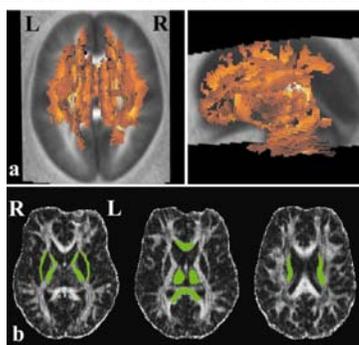
**Methods:** 32 children aged 8 – 12 years (mean 11.1 ± 1.3 years) and 28 young adults aged 21 – 27 years (mean 24.4 ± 1.8) were scanned with a 1.5T Siemens Sonata scanner, as previously published<sup>2</sup>. Subjects had no history of psychiatric disorder or neurological injury. DTI used single shot EPI with 40 - 3 mm slices, no gap, TR = 6400 ms, TE = 88 ms, FOV = 220 x 220 mm<sup>2</sup>, 6 diffusion gradient directions, b = 1000 s/mm<sup>2</sup>, 8 averages, matrix of 96 x 128 and a 6:06 minute acquisition. Three tests were performed on both apparent diffusion coefficient (Trace/3 ADC) and fractional anisotropy (FA) maps using either manual ROI analysis or voxel based analysis with SPM2. **Test 1:** linear correlation with age within 21 – 27 years. **Test 2:** linear correlation with age within 8 – 12 years. **Test 3:** two sample t-tests to compare the two age groups. 30 ROIs were placed manually in 13 different brain structures, however only the 8 structures with FA greater than 0.2 are considered for comparison to SPM data: genu of the corpus callosum, splenium of the corpus callosum, anterior limb of the internal capsule, posterior limb of the internal capsule, external capsule, corona radiata, centrum semiovale, and thalamus. For SPM method, images were normalized to the MNI EPI template for a resulting voxel size of 2x2x2mm<sup>3</sup>, and smoothed with a 4x4x4mm<sup>3</sup> smoothing kernel<sup>5</sup>. An absolute threshold of FA>0.2 was used to eliminate correlations in the gray matter by not considering a voxel if any one subject has an FA value lower than 0.2. Clusters in illogical anatomical locations were discarded. Significance was placed at p<0.05 for both SPM and ROI methods.

**Results:** Trace/3 ADC had very similar results with both ROI and SPM analysis, showing widespread decreases with age. Conclusions on regional FA variations with age, however, differed between analysis methods. **Test 1:** Correlative analysis within 21 – 27 years showed very little change in FA for both ROI and SPM analysis. Both analyses identified changes in the centrum semiovale; however SPM analysis did find a few more regions than were identified by ROI analysis. These include left anterior limb of the internal capsule, right frontal white matter, corona radiata and the right thalamus. **Test 2:** Within 8 – 12 years, correlative ROI analysis only showed increases of FA with age in 3 (of a possible 8) white matter regions: the genu of the corpus callosum, splenium of the corpus callosum and the corona radiata. However, SPM found that the majority of the white matter had increases in FA with age, including a cluster of 6422 voxels (p<0.0001, r=0.65 at the voxel of highest significance) which encompasses the cerebellar peduncles, brain stem, inferior fronto-occipital fasciculus, uncinate, inferior longitudinal fasciculus, frontal white matter, internal and external capsules (with the exception of the right external capsule), thalamus, hippocampus, genu of the corpus callosum, the body of the corpus callosum, cingulum, and the corona radiata up to the top of the brain (**Fig 1**). SPM analysis failed to identify the splenium of the corpus callosum. **Test 3:** SPM and ROI analyses agreed quite well in the group statistics. Of the regions measured, only the centrum semiovale was identified as not changing with ROI analysis. SPM analysis showed a cluster of 13988 voxels (p=10<sup>-13</sup>, difference of 35% at voxel of highest significance) encompassing almost all of the white matter, with the exception of the centrum semiovale (**Fig 2**). However, the clusters it identified in the genu and splenium of the corpus callosum as well as the corona radiata didn't encompass the entire structures, likely due to imperfect spatial normalization and biological variability, and had much lower statistical significance than with ROI analysis (with SPM p-values of 0.02, 0.05 and 0.05 respectively, with ROI all were p<0.0001).

**Discussion:** It appears that ROI analysis under-estimates the extent of the changes occurring with neurodevelopment due to its sampling limitations of the brain (i.e. time constraints and difficulties in identifying certain structures). It is also possible that significance is lost by averaging over all the voxels within an ROI of a structure, rather than focusing on the individual voxels as in SPM. SPM analysis, on the other hand, is highly dependent on spatial normalization. In conclusion, SPM and ROI analyses tend to agree with one another, but neither method gives the complete story of neurodevelopment.



**Figure 1:** a) SPM significant clusters (orange) and b) significant ROIs (green) for linear correlation within 8 – 12 years. ROI analysis under-estimates the extent of the changes occurring over this age range.



**Figure 2:** a) SPM and b) ROI results for group analysis (8 – 12 years versus 21 – 27 years). Although both methods demonstrate widespread increases in FA with age, SPM analysis misses the largest portion of the genu and splenium of the corpus callosum likely due to imperfect spatial normalization

## References:

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