Voxel based analysis of diffusion tensor imaging in early human brain development

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INTRODUCTION. Diffusion tensor imaging is a powerful tool to assess microstructural changes occurring during early brain development (1,2). The studies performed so far have used a priori ROI selection for measurement of quantitative changes in ADC and Anisotropy. This approach may be biased due to ROI selection, which makes it problematic in group comparisons. We therefore used a voxel-based-analysis (4) approach to globally detect regions of significant maturational changes in human brain development in premature infants studied shortly after birth and again at term.

METHODS. 20 preterm (gestational age 28 to 35 weeks) infants were studied longitudinally with two MR examinations. The first MR examination was performed shortly after birth at a mean age: 34.4±1.4 weeks and a second time at post menstrual ages (PMA = Gestational age + Postnatal Age) 39-40 weeks using diffusion tensor imaging (DTI). Infants studied were free of prematurity-associated cerebral pathology, such as intraventriuclar hemorrhage, ventriculomegaly or periventricular leukomalacia. Earmuffs (Natus Medical Inc. San Carlos, CA) were used to minimize noise exposure. No sedation was used for any of the studies. 1.5 T Eclipse system (Marconi Medical Systems, Cleveland, OH) was used for DTI measurements. DTI used SE-EPI with TE = 108 ms, 22 contiguous 4 mm slices, in plane resolution of 1.5 x 1.5 mm^2, 1 average. Six independent diffusion gradients with a b-factor of 700 $s/\mu m^2$ were applied to get the tensor. The diffusion gradient matrix used was 1/sqrt(2)[(1,1,0),(0,1,1),(1,0,1),(0,1,-1),(1,-1,0),(-1,0,1)]

Data Processing: After Eddy-currents correction, the ADC matrix was computed for each pixel and diagonalized. ADC and fractional anisotropy (FA) were derived (5). Spatial normalization for each case was performed using its reference image (b=0) in SPM2 software (Wellcome Department of Cognitive Neurology, London, England). A template for normalization was chosen from a reference image of a normal infant at 40 weeks gestational age. This transformation was applied to ADC and FA maps. Statistical Analysis to find brain regions with significant group difference on FA and ADC was performed using a custom software written in Matlab (Mathworks INC, Natick, MA, USA). In order to avoid partial volume effects occurring during the normalization process, the ROIs were back-transformed onto original images using a inverse transformation computed by SPM2. We have performed and compared ROI statistics on normalized and original images to assess quality of voxel-based analysis in diffusion tensor imaging on each subjects.

RESULTS. Significant changes in ADC and FA maps from first to second examination were detected in several regions. Group analysis on normalized FA images determined clusters with significant changes in the optic radiation, the internal capsule, in frontal and central-parietal white matter. Group analysis on normalized ADC images determined important clusters in temporal lobe, occipital lobe, central and frontal white matter. The detected ROIs are presented in Fig 1,2. Mean absolute values of ADC and FA in these ROIs on both normalized and original images are presented in Table 1 and Table 2.

DISCUSSION&CONCLUSION. Voxel-based analysis on diffusion tensor images reliably detected regions of significant maturational changes in a population of premature infants. Regions of significant changes in FA were found in the optic radiation and the internal capsule both white matter fiber structures that show myelination during this developmental period. Further frontal and central-parietal white matter fiber organization with axonal diameter changes occurring in the pre-myelinating state is known to occur during this period. Regional differences during brain maturation were detected in ADC maps with decreasing ADC values in occipital, temporal, frontal and central white matter similar to single ROI analysis in prior studies during human brain development (2). Absolute values of ADC and FA measured in normalized and original images were similar therefore validating the use of spatial normalization for voxel-based analysis in DTI. This study confirms the value of voxel-based-analysis to eliminate a priori ROI selection with size and selection bias and will be useful in group comparison studies.

Table 1, Mean values in original and normalized FA images
(roi id 1,2 – optical fiber right, left, 3 – internal capsula posterior,
4,5 – white matter frontal right, left, 6,7 white matter central right left)

roi_id	p orig	mean ex1 orig	mean ex2 orig	p norm	mean ex1 norm	mean ex2 norm
1	3.81E-05	0.23 +- 0.046	0.3 +- 0.043	7.90E-06	0.23 +- 0.043	0.3 +- 0.039
2	4.74E-06	0.21 +- 0.043	0.29 +- 0.049	2.94E-06	0.21 +- 0.04	0.28 +- 0.044
3	2.30E-04	0.29 +- 0.06	0.38 +- 0.074	5.26E-05	0.29 +- 0.048	0.38 +- 0.066
4	3.67E-07	0.12 +- 0.021	0.18 +- 0.034	1.64E-06	0.12 +- 0.024	0.18 +- 0.032
5	3.59E-07	0.13 +- 0.022	0.19 +- 0.033	4.05E-06	0.13 +- 0.021	0.18 +- 0.033
6	3.74E-09	0.16 +- 0.03	0.23 +- 0.022	7.66E-10	0.17 +- 0.027	0.23 +- 0.02
7	4.75E-08	0.18 +- 0.033	0.25 +- 0.028	4.50E-08	0.18 +- 0.032	0.25 +- 0.026

Table 2, Mean values in original and normalized ADC images
(roi id 1,2 – temporal lobe right, left, 3,4 – occipital region right left,
5,6 – frontal region right, left, 7,8 – central region right left)

roi_id	p orig	mean ex1 orig	mean ex2 orig	p norm	mean ex1 norm	mean ex2 norm
1	6.79E-06	1.7 +- 0.15	1.5 +- 0.12	2.08E-05	1.7 +- 0.13	1.5 +- 0.12
2	2.57E-04	1.7 +- 0.17	1.5 +- 0.18	2.34E-04	1.8 +- 0.21	1.5 +- 0.17
3	1.91E-04	1.5 +- 0.12	1.3 +- 0.19	8.45E-05	1.5 +- 0.12	1.3 +- 0.19
4	5.04E-05	1.5 +- 0.1	1.3 +- 0.21	4.13E-05	1.5 +- 0.11	1.3 +- 0.21
5	2.98E-05	1.7 +- 0.11	1.5 +- 0.15	2.50E-05	1.7 +- 0.11	1.5 +- 0.14
6	6.18E-05	1.7 +- 0.12	1.4 +- 0.16	3.62E-05	1.7 +- 0.12	1.4 +- 0.16
7	1.00E-05	1.6 +- 0.15	1.4 +- 0.14	1.50E-05	1.6 +- 0.15	1.4 +- 0.14
8	5.81E-05	1.6 +- 0.17	1.4 +- 0.16	8.38E-05	1.6 +- 0.17	1.4 +- 0.16

Fig 1. Detected regions with significant changes in normalized FA images on selected slices

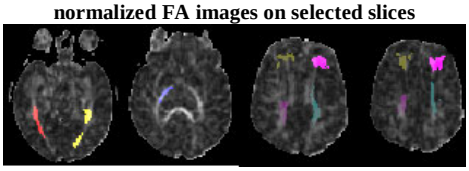
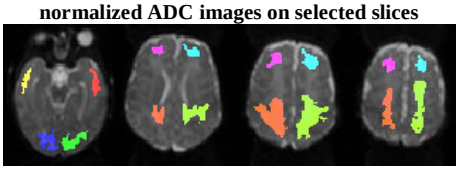


Fig 2. Detected regions with significant changes in normalized ADC images on selected slices



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