DTI study of cerebral white matter development in preterm children at preadolescent ages to examine persisting changes

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Introduction:

In this study, we used DTI to investigate prematurely born children at preadolescent ages to examine persisting changes in their cerebral white matter development. Preterm children were previously studied by others to investigate possible deficits in brain development. Special attention was given to white matter injuries that this population might have suffered because it is known that synaptic proliferation, pruning and ongoing myelination strongly influence cognitive development. However, a majority of those studies were conducted with infants at term equivalent age and there are only a few studies done with adolescents to study persisting effects of preterm birth on brain connectivity [1,2,3]. The reported results varied significantly, possibly because of the variations in the cohorts chosen. For example, only extremely premature children with very low birth weight were studied in [2, 3], and only those with attention deficits were selected in [3]. Spatial and directional resolution of DTI scans might have also played a role, since only 6 diffusion directions were used in [1, 2] and 20 directions were used in [3]. The acquisition slices were also relatively thick (3-5mm). Moreover, conventional voxel based morphometry were used in the analyses, which is reported to be sensitive to partial volume effects and variations in terminal and peripheral branches across subjects. Here, we attempted to minimize the heterogeneity of the study cohort and used relatively high directional and spatial resolutions for better sensitivity. DTI parameters of this cohort and term-born controls were compared.

Methods:

The subjects were scanned in a 3T Philips Achieva system. The study was approved by the IRB of the university and written consents were obtained from the parents. DTI was acquired using SE-EPI with 32 non-collinear gradient directions with b=800 and a single acquisition with b=0. 60 axial slices were collected to cover the whole brain with FOV=224*224mm^2 and 1.75*1.75*2mm^3 voxel size, NEX=1. TR=9290ms and TE=55ms were used with SENSE=2.4. Total scan time was 6 min and 40 sec including high order shimming, de-ghosting and RF calibrations. 22 preterm and 23 term-born children between ages 8-10 were scanned. Only preterm children born between 29 to 34 weeks' gestational age (GA) with a relatively uncomplicated neonatal course were studied. This GA range was selected because the rates of mortality and major developmental disorders level off at 29 weeks of gestation. The mean GA for preterms and terms were 32.27(±2.28) and 39.34 (±1.27), respectively. Structural MRI scans were reviewed to ensure that subjects with an evidence of intraventricular hemorrhage, periventricular leukomalacia, and/or low-pressure ventriculomegaly were excluded from analysis. To avoid heterogeneity due to handedness, only right-handed subjects were scanned. Data processing and tensor model fitting were done using FSL 4.1 software (http://www.fmrib.ox.ac.uk/fsl/) [4]. FA maps were processed using Tract Base Spatial Statistics (TBSS) software in FSL 4.1. All FA maps were spatially normalized to a template, which was created from our cohort for more precise registration. Next, the mean FA map was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. In the final step, normalized FA maps from each subject were projected onto this skeleton. This approach avoids partial volume effects and variations of terminal and collateral branches across subjects. Group differences were investigated using a permutation test. This method tests the statistical significance of pixel-wise differences between the two groups for correct labeling of the data against random re-labeling (permutations) of the same data. If there is no significant group difference, then each random re-labeling should result in equally plausible statistical distribution.

Results and Discussion:

The statistical maps were thresholded at p=0.05 and presented in Fig.1 (overlaid onto the mean FA map). Higher FA values were found in the term group in several major white matter pathways: tracts that connect to amygdala (emotional learning and memory), fornix-fimbria system (connections of the hippocampus with the mammillary bodies and septal nuclei, among others: Memory processing, reward and reinforcement, control of emotional responses), Brodmann area (BA) 35 (the transentorhinal area, transitional area linking inferotemporal cortices involved, with adjacent parahippocampal cortices, in visual processing and emotional memory processing, e.g., of faces), retrosplenial cortex, posterior cingulate cortex (BA23; visual and episodic memory, navigation), splenium of Corpus Callosum, anterior cingulate (BA 24) interconnections with dorsolateral prefrontal cortex (DLPFC – BA9/46: executive function, planning) and occipitotemporal fasciculus (naming of objects: BA38) and amygdaloid cortices (emotional memory modulating processes). Some of these findings are similar to the results published in related studies [1-3]. However, fornix, right and left fronto-occipital fasciculi and the tracts that connect to amygdala and DLPFC (BA9/45) were not reported before. We believe that higher directional and spatial resolution that we have used, more homogenous subject population and utilization of more robust TBSS technique afforded better sensitivity and allowed detection of differences in such smaller fiber tracts. These findings are important to assess how premature birth might have affected normal brain development, hence cognitive and behavioral abilities.

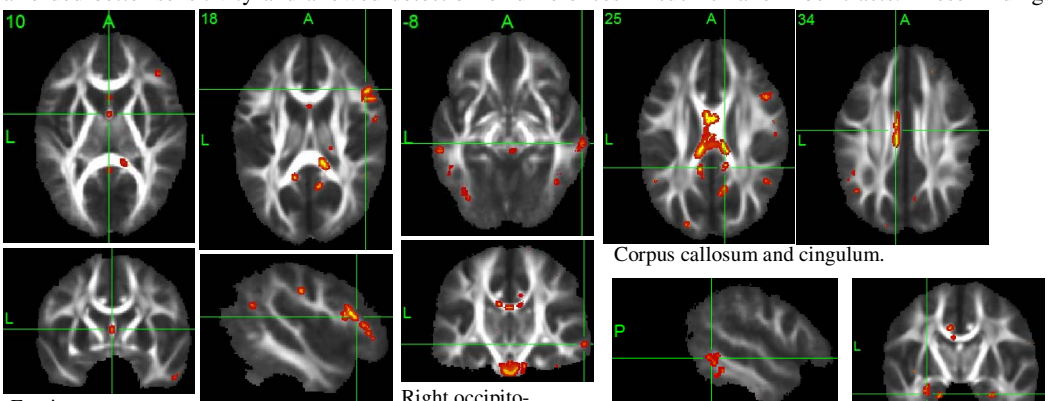

Fig.1. White matter tracts that showed higher mean FA values in term born children compared to preterms.

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Acknowledgement: This research is supported in part by NIH R01-HD050662