DTI study of Effects of Glucocorticoids on White Matter Development

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Introduction: The goal of this study was to investigate changes cerebral white matter morphology in children with prenatal exposure to glucocorticoids (GCs). Pregnant woman at risk for premature delivery are routinely administered GCs to promote lung development and survival among premature infants, but major concerns have risen about the lasting impact of GC treatment on development [*Matthews SG, Semin Neonatol, 6(4), 309-317, 2001*]. Findings from human and animal studies show that exposure to GCs has life long influence on emotion and stress regulation, cognitive functioning and brain morphology [*Welberg & Seckl, Journal of Neuroendocrinology, 13, 113-128, 2001*]. It has been shown that cerebral cortical gray matter brain volume was reduced in premature infants treated with antenatal GCs as compared to untreated infants [*Murphy et al., Pediatrics, 107(2), 217-221, 2001*]. Additionally, among ten near term infants exposed to multiple courses of antenatal GCs, it was found that complexity of cortical folding and brain surface area were reduced compared to controls [*Modi et al., Pediatric Research, 50, 581-585, 2001*]. This poses an important problem because synthetic GCs such as betamethasone are frequently given to women at risk for premature delivery.

Methods: Ten children between ages 8-9 were scanned in a 3T Philips Achieva system. Five of the subjects were born preterm and exposed to GCs, while the other five were born at term and never exposed to GCs. The study was approved by the IRB at UCI and written consents were obtained from the parents. To minimize head motion, padding was placed around the head. The imaging protocol included a high resolution T1 anatomical scan acquired by MPRAGE pulse sequence and a Diffusion Tensor Imaging (DTI) sequence. The parameters for MPRAGE were: FOV=240*240mm^2, 1mm^3 isotropic voxel dimensions, 150 slices, TR=11ms, TE=3.3ms, flip angle=18, NEX=1. DTI was acquired with SE-EPI pulse sequence using an 8-channel SENSE head coil. 32 non-collinear gradient directions with b=800 and a single acquisition with b=0 for reference were acquired. 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=11667ms and TE=55ms were used with a SENSE=2.4. Total scan duration was 8 minutes including high order shimming, de-ghosting and RF calibrations. Prior to DTI processing, eddy current and motion correction was done using 12 parameter affine transformations. Each image was also visually inspected to exclude scans with artifacts due to motion and other factors. The data were processed and FA maps were generated using DTI studio software (Jiang & Mori, Rad. Dept. Johns Hopkins U. Baltimore, MD). Quality of the data was tested by generating well-known fiber tracks from LGN to V1, as well as from the motor cortex to spinal cord although those fiber tracks were not used in the analysis. If fibers terminated early or unusual deviations were observed, the raw DTI images were investigated again to exclude additional slices with minor artifacts. Overall, only a few slices from 2-3 scans had to be discarded from two subjects, so no severe impact in the DTI quality was anticipated. Once the FA maps were generated for each subject, non-brain tissues were removed from the images using BET software available in FSL software package (http://www.fmrib.ox.ac.uk/fsl). Then each FA map was spatially normalized to a standard adult FA map available in FSL package. We observed that 12-parameter affine normalization was insufficient to obtain a good match between the images and template, therefore spatial normalization tool in the SPM5 software was used, which allows non-linear deformations in addition to affine transformations, (http://www.fil.ion.ucl.ac.uk/spm/). Low degrees of freedom due to the small number of subjects would not yield reliable statistics based on parametric testing, therefore, we have used Statistical non-Parametric Testing (SnPM5b) tool separately available from the SPM5 web page (by Holmes & Nichols). This approach tests the statistical significance of pixel-wise differences between the two groups for correct labeling of the data (images from children exposed to GCs and from those who are not) 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. Therefore, unlike the parametric approaches, assumptions about the statistical distribution of the data are weak. 252 permutations of re-labeling were tested in this application.

Results: The SnPM maps obtained from the analysis were thresholded at p=0.001 and presented in Fig.1. Both positive effects ($FA_{GC\_child} > FA_{control}$) and negative effects ($FA_{GC\_child} < FA_{control}$) were tested. It was observed that the FA values in children exposed to GCs (FA_{GC_child}) were significantly higher in the white matter in ventral basal ganglia. The area involved includes a region where AC fibers intermix with striato-pallido and internal pallido subcortical projection fibers, including some from the ventral striato-pallidal complex. Although the difference was seen bilaterally, the effect was stronger and spatially more extended in the right hemisphere. Test of negative effects, where $FA_{control}$ was larger than FA_{GC_child} did not reveal any statistically significant clusters in the cerebral white matter.

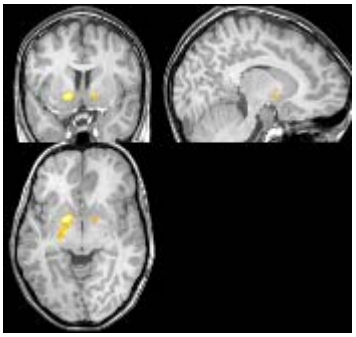

Fig1. SnPM maps overlaid in yellow to red colors onto a normalized T1 anatomic image. Changes in FA values in ventral basal ganglia were observed in the white matter of children exposed to GCs compared to those of controls.

Discussion: In this preliminary study, we have demonstrated that there are statistically significant differences in white matter morphology in children who were born preterm and exposed to GCs. Since we do not expect degradation in myelination in any of the two groups, increase in FA values can be interpreted as decreased complexity of fiber distribution in those areas, for example fewer crossing fibers in the region. Further studies have to be conducted on a larger cohort of subjects and fiber structures from each individual subject have to be analyzed to understand the underlying physiological changes that lead to these findings. The areas that showed differences include part of a cortico-striato-thalamo-cortical loop. The axons that cross in that region contain the fiber projections between various structures in the basal ganglia as well as axon projections from the basal ganglia to prefrontal cortex. Therefore, these initial findings are in line with the literature and provide evidence that the white matter morphology is altered in children who were born pre-term and exposed to GCs during pregnancy. In this study, the effects of preterm birth might have amplified the effects of GC exposure and potentially confounded the effects of GC exposure alone. We are currently recruiting children who were born at term and exposed to GCs as well as children who were born preterm and were not exposed to GCs so that confounding effects can be assessed better.

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