Gestational age at birth influences brain white matter development

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***Introduction*:**
In vivo MRI and postmortem studies have demonstrated that there is substantial increase in myelinated cerebral white matter (WM) volume after 36 weeks of gestational age (GA) [1]. At 29 weeks there is minimal myelinated WM and the process is relatively slow until the 36th week. After the 36th week, a dramatic increase is seen in myelination of WM [1]. Therefore, this is a period when the brain development is highly vulnerable to internal and external insults caused by premature birth (e.g. changes in nutrition, infection, administration of drugs and hormones, etc). Several studies have been conducted using MRI Diffusion Tensor Imaging (DTI) to study these deficits in WM development in prematurely born children [2, 3, 4, 5, 6]. However, most of those studies were conducted on infants at term equivalent age and only a few have investigated persistent changes in the cerebral WM in preadolescent or early adolescent ages [3, 4]. Besides, in almost all of those studies extremely premature infants (GA at birth < 29 weeks) were studied in which the potential WM injuries are more prominent. Most importantly, those studies have used a categorical comparison between preterm and term children and overlooked the fact that the fetal brain development is a continuous process. It may be expected that GA at birth (GAB) will be an important factor that determines the time of the onset of the insults, hence the time point at which the cortical WM development might be disrupted. Therefore, we studied the persisting effects of GAB on the WM of children who were 8 to 10 years old. We recruited only preterm children born after 29 weeks' GA with a relatively uncomplicated neonatal course. This GA range was selected because the rates of mortality and major developmental disorders level off at 29 weeks of gestation. We have also used a much larger population compared to previous studies and utilized a higher directional and spatial resolution to achieve better spatial specificity and sensitivity.

***Methods*:**
99 subjects, who were born between 29 and 41 weeks of GA, underwent the MRI scans in a 3T Philips Achieva system. The study was approved by the Institutional Review Board of UCI and written consents were obtained from the parents. DTI was acquired using SE-EPI pulse sequence with 32 non-collinear gradient directions with b=800 and a single acquisition with b=0 for reference. The whole brain was acquired with 60 axial slices using FOV=224×224mm^2 and 1.75×1.75×2mm^3 voxel size, NEX=1. TR/TE=9290ms/55ms, SENSE=2.4. Structural MRI scans were reviewed by a radiologist and subjects with an evidence of intraventricular hemorrhage, periventricular leukomalacia, and/or low-pressure ventriculomegaly were excluded from analysis. Preprocessing of DTI data (eddy current and motion correction) was done using 12 parameter affine transformations. The Fractional Anisotropy (FA) maps were generated using FDT toolbox of FSL software (http://www.fmrib.ox.ac.uk/fsl/) [7]. The FA maps were processed and analyzed using Tract Base Spatial Statistics (TBSS) software in FSL [8]. In the first step of TBSS, a nonlinear registration tool aligned FA maps from all subjects into the subject-specific template that we generated from our data set. In the next step, a mean FA skeleton was created, which represents the centers of all tracts common to the group. In the final step, FA maps from each subject were projected onto this skeleton. The pixel-wise correlation between the GAB and FA values across subjects were investigated using a permutation test [9], which tests the statistical significance of pixel-wise differences between the two groups for correct labeling of the data against random re-labelings of the same data. Approximately 4200 permutations were tested for this study.

***Results and Conclusion*:**
Major fiber pathways that showed statistically significant correlation between FA values and GAB ($p<0.05$) were overlaid in red-yellow colors onto the group FA template (Fig.1). For example, the left uncinate had increasing FA values with increasing GAB. This pathway, which is implicated in verbal IQ and full scale IQ performance, was previously reported to have lower FA in preterm children [3]. Similarly, the body of corpus callosum, the genu and the splenium showed increased FA with increasing GAB. The fornix, which is the major connection of recognition memory and reward/reinforcement circuitry as well as the cingulum, which connects brain regions involved in emotional regulation and attention, were also strongly influenced by the GAB. Another major fiber pathway that was strongly affected by the GAB was the anterior limb of internal capsule (ALIC), which contains fibers that connect frontal cortex to the thalamus and the pons. These results show that several major WM fiber pathways that connect the limbic system and the higher order cognitive processing areas were strongly influenced by the gestational age at birth. Higher FA values are generally associated with more densely and uniformly organized fiber tracts, which, in most cases, is an indication of increased connectivity and better cognitive performance. Since the development of the brain of the fetus is a continuous process, it may be expected that the process will be disrupted during different phases depending on the GAB. In this study, we have demonstrated that late preterm and early term infants, who are considered as low risk, might still have experienced disruptions in brain development due to shorter gestational period.

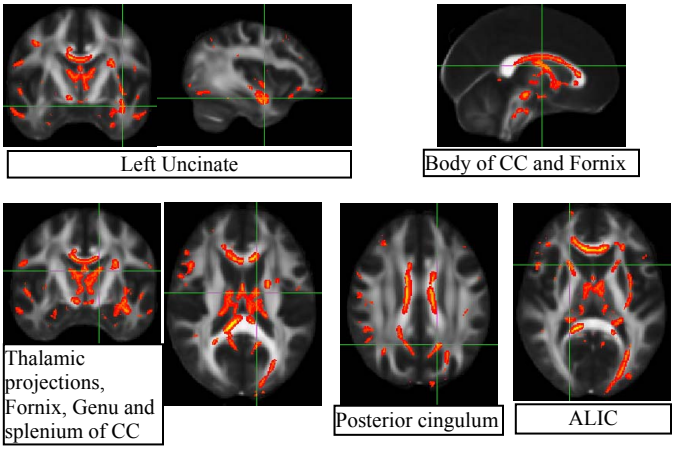

Fig.1. Major WM fiber tracts that demonstrated strong correlation between GAB and FA ($p<0.05$) overlaid in red-yellow colors onto a mean FA map that was derived from the subject population. Images are in the radiological orientation (image right is subject's left)

References: [1] *Huppi PS et al Annals of Neurology 43:224-35 (1998)*; [2] *Anjari M. et al NeuroImage 35 1021-27 (2007)*; [3] *Constable RT Pediatrics 121:306-16 (2008)*; [4] *Vangberg TR,et al NeuroImage 32:1538-48 (2006)*; [5] *Counsell SJ, et al Pediatrics 117:376-86 (2006)*; [6] *Partridge SC et al JMRI 22:467-474 (2005)*; [7] *Smith SM et al NeuroImage, 23:208-219 (2004)*; [8] *Smith SM et al NeuroImage 31:1487-1505 (2006)*; [9] *Nichols TE and Holmes AP Human Brain Mapping, 15:1-25 (2002)*.

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