Prematurity and Prenatal Growth Restriction Differently Affects Brain Connectivity

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ABSTRACT
Survival of children born prematurely or with very low birth weight has increased dramatically in the last decades, but the long term developmental outcome remains a concern. The most common cerebral neuro-pathology observed in case of premature birth is a diffuse white matter abnormality. However, many of the children born prematurely present indeed deficits in their cognitive capacities, in particular involving executive domains. The origins of these disabilities are largely unknown but are likely to involve an overriding central nervous system deficit. To understand the neurostructural origin of these disabilities and to investigate the effect of prematurity and intra uterine growth restriction in pre-school children aged 6 years old, we have combined imaging with DWI, that allows us to study white matter maturation in vivo, and Tract Based Spatial Statistics (TBSS).

SUBJECTS and MRI ACQUISITION
We studied 60 prematurely born children aged six years old, recruited from the Child Developmental Unit at the University Hospitals of Geneva and Lausanne *(HUG* and *CHUV)*. Children underwent MRI examinations on a 3T Siemens TrioTim system (Siemens Medical Solutions, Erlangen, Germany). T1-weighted MPRAGE images (TR/TE=2500/2.91,TI=1100,res.=1x1x1mm,256x154) were acquired. Diffusion weighted images were acquired using a diffusion-sensitized EPI sequence. 64 slices 2mm thick were acquired with a 112x112 matrix providing whole brain coverage. Following an acquisition without diffusion sensitization, images were acquired with gradients (max. b-value= 1000 s/mm^2) applied in 30 directions (TR/TE=10200/107, res=1.8x1.8x2 mm). Perinatal data (birth weight (BW), gestation age (GA)), and infant growth parameters were collected. All studies were performed with informed parental consent and were approved by the medical ethical board of the two hospitals. After preprocessing, 7 data sets where discarded due to bad quality of the images. 53 subjects were finally considered. The infants were classified in 3 different groups : 21 were born moderately preterm with *Intra Uterine Growth Restriction (IUGR)* and placental insufficiency, 23 were born < 28 weeka of gestation age and were classified as *Extreme Premature (EP)*. The *control group* comprised chidren moderately preterm with normal birth weight (*see table for group count*).

Groups	Control	EP	IUGR
Count MRI	9	23	21
Gender repartition	3M / 6F	11M / 12F	12M / 9F
GA at birth	32.02 ± 2.47	26.34 ± 1.29	30.05 ± 3.07
Birth weight	1652.50 ± 402.45	943.26± 198.17	919.54 ± 328.28

METHOD
As motion correction in fMRI data, to minimize the distortion due to eddy currents produced by the gradient coils, for each subject, the T1 acquisition was registered to the non-diffusion-weighting (b=0) image by an affine transformation using the FLIRT package implemented in FSL (*http://www.fmrib.ox.ac.uk/fsl*) [1,2]. This transformation applies a full affine alignment of each structural image with its corresponding *b0*. Diffusion tensor elements were then computed by a least square fit of the tensor model of the diffusion data. After the fitting, tensor eigenvalues were calculated in the three main directions describing the diffusion strength. Once having the tensors, the computation of the fractional anisotropy (FA) is then straightforward [3,4]. The statistical analysis of the FA data of the subjects was performed by using TBSS implemented in FSL (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html). TBSS needs all images to be aligned in a common space to allow for valid conclusion to be drawn from the subsequent analysis. Following Smith's work [5], our target was chosen as one real FA image of one control subject (instead of an averaged FA image), considered as the most typical subject. It was selected as the image that minimized the amount of transformations required for all other subjects to align to it. After alignement, FA images were affine-transformed to the MNI152 space (1x1x1 mm). The election of the MNI152 standard space was due to the fact that our subjects were young children, so it was not appropriate to align them to the adult-derived FMRBI58-FA standard-space image. A mean FA skeleton was then computed, representing the centers of all tracts common to the group. A threshold of value 0.2 was applied to avoid peripheral and noisy tracts to give significant inter-subject variability. With this threshold we also excluded some partial volume effects that can give false positives when comparing two groups. Each's subject aligned FA was then projected to this skeleton and t-tests were performed between groups. The statistical cross-subjects tests where then corrected by Bonferroni correction for multiple comparisons to avoid false positives. λ_1,λ_2,λ_3 where also computed to explore the differences found in FA values.

RESULTS
For EP infants, we found that the main white matter regions presenting lower FA when compared to control subjects were located in within the fronto-parietal junction of corpus callosum giving a bilateral involvation of this zone. This region is linked to the precuneus cortex, post central and precentral gyrus and superior parietal lobe. On the other hand, for IUGR subjects the most significant reduction in FA compared to controls were found in perihippocampal white matter, in internal capsule and in superior longitudinal fasciculus. Those infants born preterm with an added placental insufficiency displayed additional FA reductions, as EP subjects, in postcentral gyrus and superior parietal lobe as well as within middle and superior temporal areas , leading to a more extensive reduction in FA. In both cases, that reduction in FA can be due to a higher radial diffusitivity (i.e. increased λ_2 and λ_3) that implies a reduction in axial diffusitivity (i.e. λ_1).

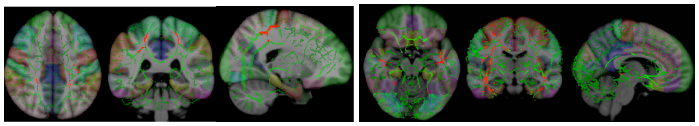

Figure 1: Mean FA skeleton overlaid on the mean FA map for comparison between EP and control subjects (left) and between IUGR and controls subjects (right). Regions of the mean FA skeleton in green represent areas where there were no significant differences in FA values in the EP/IUGR infants compared to the controls whereas areas in red are regions where the FA was significantly lower in the EP/IUGR group (p-value<0.05). The results have been corrected for multiple comparisons by Bonferroni correction and are presented overlaid on the Harvard-Oxford Cortical Structural Atlas.

DISCUSSION
The goal of our study was to determine the effect of prematurity and intra uterine growth restriction on neurostructural development at age 6 years old. For this purpose, we used DTI and automated tract-based statistic, as it allows us to study white matter maturation in vivo and to detect white matter differences in groups of subjects. When compared to control subjects, both EP and IUGR subjects displayed a reduction in FA due to a decrease in axonal diffusivity. This decreased value can be due to a reduction on axonal thickness, density and myelination, characterized by various proceses including axonal widening and packing. In our work, we found that extreme prematurity and prenatal growth restriction differently affect brain connectivity as suggested in previous studies [7,8,9]. Indeed we presented a new insight into neurostructural changes in children born prematurely (with or without placental insufficiency) that can be probably link to cognitive and behavioral problems presented at school age.

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