Prewmaturity 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 6 years old, recruited from the Child Development 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=2500/0.9,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 weeks of gestation age and were classified as Extreme Premature (EP). The control group comprised children moderately preterm with normal birth weight (see table for group count).

METHOD
As motion correction in fMRI data, to minimize the distortion by the affine transformation due to the gradient coils, for each subject, the T1 acquisition was registered to the non-diffusion-weighting (b=0) image by the FLIRT transformation package implemented in FSL (http://www.fmrib.ox.ac.uk/fsl). This transformation applies a full affine alignment of each structural image with its corresponding b0. Diffusion tensor elements were then computed by 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 calculation 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. After alignment, FA images were affine-transformed to the MN152 space (1x1x1 mm). The selection of the MN152 standard space was due to the fact that our subjects were young children, so it wasn't appropriate to align them to the adult-derived MRRBI58-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 the control 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, \(\lambda_2,\lambda_3,\lambda_4\), 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 involvement of this zone. This region is linked to the prefrontal 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 perhippocampal 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 presented a central 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 diffusivity (i.e. increased \(\lambda_2\) and \(\lambda_3\)) that implies a reduction in axial diffusivity (i.e. \(\lambda_1\)).

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 statsitc, 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.

BIBLIOGRAPHY