# Extreme prematurity and intrauterine growth restriction effects in brain network topology at school age

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## *INTRODUCTION*

Higher risk for long-term behavioral and emotional sequelae are now becoming one of the hallmarks of premature birth and birth after pregancy conditions leading to intrauterine growth restriction (IUGR) [1,2]. The normal development of cerebral cortex and cortical axonal pathways happens in a series of sequential events that are specific for each of the developmental phases [3]. For example, the preterm phase (24-36 post conecptional weeks PCW) is known to be crucial for growth of the thalamocortical fiber bundles as well as for the development of long projectional, commissural and projectional fibers [4]. Thus, is it logical to expect that changes in the intrauterine or extra-uterine environment due to the IUGR and/or preterm birth consequently influence the intensities of these events that, in turn, leads to changes in neuronal architecture and its reorganisation [5] even during the childhood [6]. The novel MRI techniques are just starting to define the quantitative and qualitative MRI biomarkers that are related with the cognitive outcome [6] seen as a result of underlying changes in prental histogenesis. To test the hypothesis that the extreme premature birth (EP) and moderate premature birth with IUGR (mIUGR) represent two different conditions affecting different regions of the brain connectivity, we have used diffusion MRI (dMRI) tractography and dMRI-derived brain graphs [7,8,9]. This relatively simple way of modeling the brain connectivity enabled us to use graph theory in order to study the effect of EP and IUGR on brain connectivity and brain networks' topological properties at school age.

## *METHOD*

| 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 |

We studied 60 children aged six years old, recruited from the Child Developmental Unit at the University Hospitals of Geneva and Lausanne. For each subject, we acquired T1-weighted MPRAGE images (TR/TE=2500/2.91, TI=1100, res.=1x1x1mm, 256x154) and diffusion weighted images using a diffusion-sensitized EPI sequence (30 directions, max bvalue=1000 s/mm$^2$, TR/TE=10200/107, res=1.8x1.8x2 mm) on a 3T Tim Trio system [10]. After quality check of the images, 53 subjects were finally included in the study. All analyses were performed with informed parental consent and were approved by the medical ethical board of both hospitals. Subjects were classified in three groups: 21 subjects were born moderatelly preterm with *intra uterine growth restriction (mIUGR)*, 23 were born at <28 weeks of gestational age (GA) and classified as e*xtreme premature (EP).* The rest (9) were born moderate preterm with normal birth weight (BW) and considered as controls (*see table).* For each subject, we extracted a connectivity matrix using a freely available software [11] that follows the procedure described in [12,13]. As in [14], the individual connectome was defined as being composed of two terms: the connection density (CD) and connection efficacy (CE). For computing the CD term, we averaged together all subjects' connectomes of each group (as we assumed that the density of connections maintained the same pattern inside a group). The CE was considered as being subject-dependent and computed as a matrix storing the mean fractional anisotropy (FA) value of the bundle connecting each pair of cortical regions. Thus, each individual participant contribution was considered to be the product of the average connection density (so that structural connection matrices within a group maintained an equal number of pathways) and the individual connection efficacy. From these weighted matrices, we derived brains graphs and perform statistical comparisons in terms of node degree and betweenness centrality. We used a novel two-steps methodology that exploits the information of positive dependence of the data to increase the power of testing [15]. In short, we grouped the graph's nodes in subsets where tests were supposed to be positively dependent. These node's subsets defined brain subnetworks and were selected in two different ways: as (i) 13 subnetworks within the 4 main cerebral lobes (*lobe decomposition*) and as (ii) 13 subnetworks defined based on a recent study [16], where authors exploit the inherent hierarchical, modular (and predominantly symmetric among hemispheres) genetic structure of the cortical area to define a new cortical parcellation (*Chen decomposition*).

## *RESULTS*

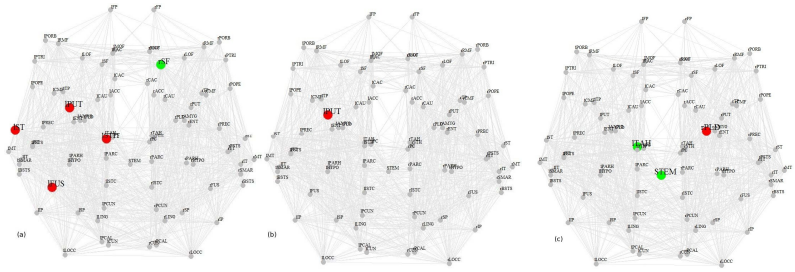

*Figure1: Brain graph nodes with statistically significant differences in degree for comparison between EP and control (a) and IUGR and controls (b) and in betwenness centrality for comparison between EP and control (c).*

When using the lobe decomposition, in terms of node degree (the most fundamental network measure considered as the sum of node's incoming (afferent) and outgoing (efferent) connections), both EP and IUGR subject displayed a significant reduction in the left putamen. In this case, no other alteration was found for IUGR subjects. Contrarily, when compared with control subjects, EP subjects showed smaller node degree mainly in the left hemisphere, in the fusiform and the superior temporal gyrus, the left subthalamus, and the putamen (figure 1(a), red dots). Alterations in the right hemisphere were only found in the superior frontal pole. This alteration was found when using the 2 different decompositions tested (*lobes* and *Chen decomposition*) (figure 1(a), green dot). For the betweenness centrality, we found significant differences only in the EP group. For the Chen decomposition, these alterations were found in the left thalamus, the brain stem and the right pallidum (figure 1(c) green dots). The right pallidum also appeared significantly altered when using the lobe decomposition. Therefore, this region is marked with a red dot in figure 1(c).

## *CONCLUSION and DISCUSSION*

Our results corroborate our previously stated hypothesis. We found regional differences on the nodal degree for EP and mIUGR subjects and differences in the betweenness centrality in the case of EP. Thus, our results suggest that both EP and mIUGR affect the reorganization of axonal circuitry during the childhood. The extreme preterm birth has as an effect of the axonal reorganization mainly in the cortical areas of the left hemisphere. Furthermore, the EP as well as the mIUGR affects the axonal connectivity of the left basal ganglia (putamen, subthalamus). Taken all together we propose that the extreme premature birth might be associated with the reorganization of connectivity (afferent and efferent) in the areas linked with the early exposure to the sensory information (eg. fusiform gyrus that is known to have major role in face recognition [17] and the superior temporal gyrus is known to interact with fusiform in the recognition of faces and emotions [18]). Contrarily, the reorganization of the connectivity during the childhood, following the extreme and moderate premature birth with or without IUGR, strongly affects the connectivity of the left putamen (known to play a major role in the process of learning as well as in the processes of the motor skill control [18,19]). In conclusion we suggest that this analysis might be a valuable parameter in defining the structural correlates of the cognitive outcome following the premature birth with or without IUGR.

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