LONGITUDINAL ANALYSIS OF BRAIN NETWORK REORGANIZATION IN PRETERM IUGR CHILDREN AT 1, 6 AND 9 YEARS OF AGE

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INTRODUCTION

Intrauterine Growth Restriction (IUGR) due to placental insufficiency affects 5-10% of all pregnancies and it is associated with a wide range of short and long-term neurodevelopmental disorders [1]. Different approaches have been considered to understand IUGR effects on brain development. Recently, connectomics has been used to analyze brain reorganization in IUGR children at one [2] and six years of age [3]. Connectomics [4] estimates the brain network and describes it by different graph measures [5]. Diffusion tensor imaging (DTI) can be used to infer the connectivity between regions, since it allows in-vivo estimation of fiber tracts inside the brain. In this study, DTI based connectomics was used to describe short- and long-term brain reorganization in IUGR. The connectome of a cohort of preterm IUGR and control children at 1, 6 and 9 years of age was estimated and analyzed to evaluate differences in the architecture of neural circuitry and its evolution during development.

SUBJECTS

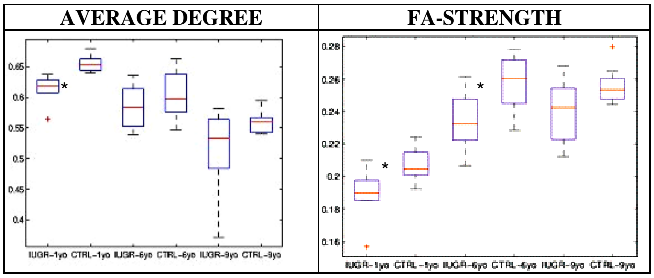
Three cohorts of preterm children (gestational age (GA): 28-35 weeks) were considered, being scanned at 1, 6 and 9 years of age respectively. The 1-year-old cohort was acquired at Barcelona Clinic Hospital, and the 6- and 9-year-old cohorts were acquired at Geneva University Hospital. Subjects were scanned in a 3T TIM TRIO MR Siemens. T1-weighted images were acquired by MPRAGE sequence (TR=2050ms, TE=2.41ms, TI=1050ms, 0.86x0.86x0.9mm³, for the 1-year-old infants; TR=2500ms, TE=2.91ms, TI=1100ms, 1.8x1.8x2mm³, for the 6- and 9-year-old children). Diffusion weighted images (DWI) were acquired using a diffusion-sensitized EPI sequence covering 30 diffusion directions with a b-value of 1000s/mm² and an additional image without diffusion weight (TR=9300ms, TE=94ms, 1.64x1.64x3 mm³, for 1-year-old; TR=10200ms, TE=107ms, 1.8x1.8x2 mm³, for 6- and 9-year-old). All studies were performed with informed parental consent and were approved by the ethical committee of both hospitals. Infants were classified in two groups: children born moderately preterm with normal growth (controls) and children with IUGR defined as estimated fetal weight below 10th centile confirmed after birth together with an abnormal umbilical artery pulsatility index and/or cerebroplacental ratio and/or mean uterine artery pulsatility index. Group distribution is shown in the Table.

	1-year-old		**6-year-old**		**9-year-old**	
	Controls	***IUGR***	***Controls***	***IUGR***	***Controls***	***IUGR***
Sample	8	6	10	11	8	8
GA	30.8 +/- 1.7	32.2 +/- 1.8	32.1 +/- 2.3	32.5 +/- 1.4	32.7 +/- 1.8	32.6+/- 1.5

METHODS

Connectivity matrices were estimated for each subject, and graph metrics describing the network were computed, following a methodology described earlier [2]. First, the brain was segmented in white matter (WM) and gray matter (GM) using the unified segmentation model [6], and parcelled in 93 regions based on AAL atlas [7]. Parcellation was performed using a block-matching algorithm to obtain the elastic transformation relating the AAL template and the subject T1 volume. Specific 1-year-old AAL atlas [8] was considered for the younger group, whereas the adult version was suitable for the 6- and 9-year-old cohorts. Affine registration between T1 volume and the baseline image was performed to translate the parcellation to the diffusion space. DTI was estimated from the DWI and connectivity between regions was inferred by tractography, using MedInria (http://med.inria.fr/). Connection between a pair of regions *i* and *j* was considered if there was at least one fiber tract going from *i* to *j*. FA-weighted (FA-w) connectivity matrices were considered, where the connection weight was defined as the average fractional anisotropy (FA) along the fiber bundles, that is related to the organization and integrity of fiber tracts, increasing during myelination. Besides, FA-normalized (FA-n) connectivity matrices were also estimated, where the FA-w matrix was normalized by the total weight of the connections in the whole brain. In such a way, all the subject's matrices have the same strength of connections, and differences between them is more related to pure brain reorganization. Average degree, FA-strength and global, local and nodal efficiency [5] were computed, and their values were compared between groups by means of a GLM analysis including GA at birth as covariate.

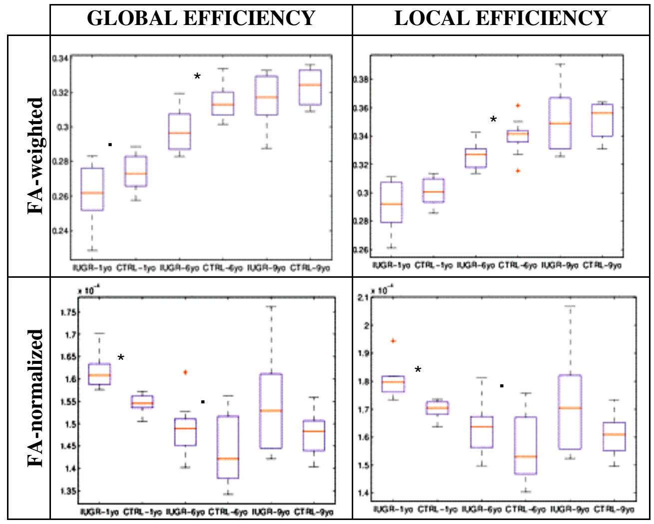
AVERAGE DEGREE | **FA-STRENGTH**



RESULTS

Results show a similar pattern of variation between IUGR and controls at every age, as can be seen in figures, where * stands for differences between cases and control with a significance level $p<0.05$; and •, significance level $p<0.1$. Average degree, FA strength and global and local efficiency of FA-w network were decreased in IUGR, while the global and local efficiency of FA-n network were increased in IUGR. Differences were more significant at younger period. At 1 year of age, differences in degree ($p=0.003$), FA-strength ($p=0.023$), global ($p=0.002$) and local ($p=0.004$) FA-n efficiency were statistically significant. At 6 years of age, the differences were significant in FA-strength ($p=0.006$), global ($p=0.004$) and local ($p=0.025$) FA-w efficiency. At 9 years of age, the differences were not significant, but they followed the same trend than in younger ages.

GLOBAL EFFICIENCY | **LOCAL EFFICIENCY**



DISCUSSION AND CONCLUSION

This study uses connectomics to analyze brain reorganization of preterm children longitudinally. Results suggest that differences in brain organization in IUGR children persist upon reaching the school age. Despite the small sample size, a similar pattern of differences between IUGR and controls was observed at each time point. Lower degree and FA strength in IUGR compared to controls suggest less numerous and weaker connections. In both IUGR and controls, nodal degree decreased with age, which could be related to axonal retraction occurring during development [9], while FA strength (which could be related to myelination) increased, as the brain connections become stronger and more organized with age [9]. Efficiency (both local and global) was decreased in IUGR in the FA-w networks, but increased in the FA-n networks. This fact could be explained as a compensatory mechanism in IUGR, where brain would be reorganized in order to compensate diminished connectivity (decreased connection amount or strength). In summary, network measures showed a pattern of brain reorganization in IUGR that is consistent in cohorts of subjects of different ages. In addition, a pattern of developmental reorganization can be identified, that seems to be preserved both in IUGR and controls regardless of structural differences between them [10].

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