Brain connectomics and social cognition from infancy to early adolescence: effects of IUGR

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INTRODUCTION

Brain development is a complex process starting in utero. Perinatal conditions altering its normal course can have consequences in the short- and long- term brain structure and function. Prematurity and intrauterine growth restriction (IUGR) have been associated to structural reorganization of the brain as well as higher risk of sociocognitive disabilities in the long term [1]. Connectomic analysis has been used to show differences between IUGR and control preterm subjects at different ages, showing changes in brain connectivity associated to IUGR [2, 3, 4]. In this work, we analyze how the brain network reorganization at 1, 6 and 10 years of age of children with and without IUGR correlates with their performance in neuropsychological tests evaluating hyperactivity and executive function.

METHODS

Subjects. Three cohorts (denoted as C1, C6 and C10) of preterm children (gestational age (GA): 28-35 weeks), were analyzed at 1, 6 and 10 years of age respectively. Infants were classified in two groups: children with normal intrauterine growth (controls) and children with IUGR, defined as estimated fetal weight below 10th centile confirmed after birth together with abnormal umbilical artery pulsatility index and/or cerebroplacental ratio and/or mean uterine artery pulsatility index. Cohort characteristics are shown in Table 1. All studies were performed with informed parental consent and were approved by the ethical committee of each hospitals.

	C1		C6		C10	
	Control	**IUGR**	**Control**	**IUGR**	**Control**	**IUGR**
Sample	7	8	8	10	8	8
Age at scan	1.07+/- 0.16	1.01+/-0.13	6.84+/-2.3	6.90+/-0.72	10.01+/-0.98	10.25+/-0.91
Age at test	1.73+/-0.28	1.77+/-0.20	6-30+/-0.66	6.23+/-0.50	9.82+/-1.01	10.05+/-0.91

Table 1. *Sample size, age at scan and age at test of each cohort.*

MRI acquisition. Structural and diffusion MRI were performed in a 3T TIM TRIO MR Siemens scan. C1 was scanned at Barcelona Clinic Hospital, and C6 and C10 at Geneva Hospital. T1-weighted images were acquired by MPRAGE sequence (TR=2050ms, TE=2.41ms, 0.86×0.86×0.9mm³, for C1; TR=2500ms, TE=2.91ms, 1.8×1.8×2mm³, for C6 and C10). Diffusion weighted images (DWI) were acquired using a diffusion-sensitized EPI sequence of 30 diffusion directions with a b-value of 1000s/mm² and one baseline image (TR=9300ms, TE=94ms, 1.64×1.64×3 mm³, for C1; TR=10200ms, TE=107ms, 1.8×1.8×2 mm³, for C6 and C10).

Cognitive evaluation. Neurodevelopmental outcome was assessed by means of age-specific tests in the three cohorts. Since executive functions are usually described at school age, C1 was evaluated by means of a more general developmental test, the Bayley Scale for Infant and Toddler Development (BSID-III), which measures: cognitive, motor, socio-emotional behavior, language and adaptive behavior [5]. C6 and C10 were assessed for social cognition, namely, we considered the hyperactivity/inattention score of the Strengths and Difficulties Questionnaire (SDQ) [6], and the behavioral regulation index (BRI) and metacognition index (MI) of the Behavior Rating Inventory of Executive Function (BRIEF) [7]. BRIEF inhibition score was also individually considered in C10.

Connectomics. Connectivity matrices were obtained according to the methodology described in [2, 4]. White and gray matter tissue was segmented in T1-w images by the unified segmentation model [8], and parceled in 93 regions based on AAL atlas [9], using block-matching registration to adapt the template to the subject image. A specific 1-year-old AAL atlas [10] was used for C1, whereas the adult version was suitable for C6 and C10. The parcellation was transformed to the diffusion space by affine registration. Diffusion tensor image (DTI) was estimated from the DWI and tractography performed using MedInria (http://med.inria.fr/). If there was at least one streamline linking two regions, they were considered to be connected. Connection weight was defined as the average fractional anisotropy (FA) along the streamlines of the connection, obtaining FA-weighted (FA-w) connectomes. Besides, a FA-normalized (FA-n) connectivity matrix was obtained for each subject normalizing the FA-w matrix by brain network strength. Hence, FA-n networks have the same strength for every subject, and can describe changes in the weighted connectivity organization, independently of differences in average strength. Average FA-strength, global and local efficiency and clustering coefficient were computed [11].

Statistical analysis. Network metrics and cognitive scores were corrected by the age at scan and test respectively, using a general linear model (GLM). Partial correlation was computed between the corrected network metrics and cognitive scores, considering gender, GA at birth, parental education and IUGR condition as confounders. Case-control analysis was performed considering gender and parental education as cofactors and GA at birth and age at test as covariates.

		C1			C6	C10			
		Cogn.	**Motor**	**Socio emotio**	**BRIEF bri**	**SDQ Hyp**	**BRIEF BRI**	**BRIEF MI**	**BRIEF Inhib**
FA-w connectome	FA strength	–	–	0.7000	–	-0.7001	–	-0.6196	-0.6647
	Global Eff.	0.7334	–	–	–	-0.9644	–	–	–
	Local Eff.	0.6753	0.6816	–	–	-0.6769	–	–	–
	Clustering	–	–	–	–	-0.8165	–	–	–
FA-n connect	Global Eff.	–	–	-0.8834	–	–	0.5722	0.5544	0.7025
	Local Eff	–	–	-0.9355	0.6450	–	–	0.5682	0.6376
	Clustering	–	–	-0.8728	0.5920	–	–	–	–

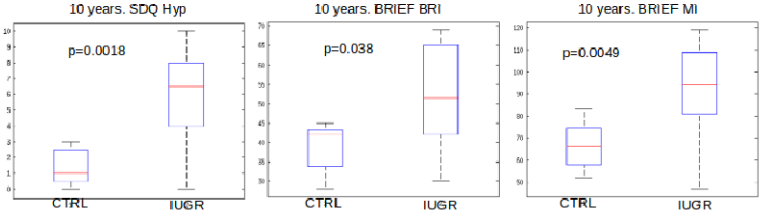
Table 2. *Correlation between network metrics and neuropsychological scores.*

RESULTS

In Table 2, the Spearman coefficient of the statistically significant correlations ($p<0.05$) are compiled. Figure shows test's scores being significantly different between IUGR and controls (higher scores corresponds to worse performance).

DISCUSSION AND CONCLUSION

This study evaluates how brain network organization correlates with altered neurodevelopment in preterm IUGR and normal growth infants. It has been previously shown that IUGR produces a reorganization of brain networks [2,3,4]. In this work, we show how this reorganization has consequences in the long-term performance of children in social cognition. Although we have observed a trend of IUGR performing worse in all the tests (lower scores in BSID-III, and higher scores in SDQ and BRIEF), the differences are only significant when considering the tests at 10 years of age, where altered behavior is more easily detectable, showing that the IUGR group has more abnormal scores. At this age there is also a strong correlation between network metrics and test scores. It deserves to be highlighted that FA-w metrics are correlated with SDQ hyperactivity/inattention score, while the FA-n connectome correlates with the BRIEF scores in both C6 and C10. This may indicate hyperactivity/inattention being more influenced by the overall FA strength in the whole brain, and the daily life executive function being more sensitive to the difference in the brain connectivity organization. FA-w metrics have been described to be decreased in IUGR [2,4] and they correlate positively with BSID scores and negatively with SDQ and BRIEF, relating less efficient brain network organization with worse cognitive outcome and higher risk of hyperactivity disorders. FA-n metrics were found to be increased in IUGR [4] and the correlation is positive with SDQ and BRIEF scores and negative with BSID, showing again the relationship between the brain network reorganization in IUGR and a higher risk of altered neurodevelopment. Note that, even in the youngest cohort, correlation between brain structure and BSID scores is observed regarding cognitive, motor and socio-emotional competences, which may well be related to sociocognitive disabilities in the future.



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