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Structural Brain Connectivity in School-Age Preterm Infants Provides Evidence for Impaired Networks Relevant for Higher Order Cognitive Skills and Social Cognition

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Extreme prematurity and pregnancy conditions leading to intrauterine growth restriction (IUGR) affect thousands of newborns every year and increase their risk for poor higher order cognitive and social skills at school age. However, little is known about the brain structural basis of these disabilities. To compare the structural integrity of neural circuits between prematurely born controls and children born extreme preterm (EP) or with IUGR at school age, long-ranging and short-ranging connections were noninvasively mapped across cortical hemispheres by connection matrices derived from diffusion tensor tractography. Brain connectivity was modeled along fiber bundles connecting 83 brain regions by a weighted characterization of structural connectivity (SC). EP and IUGR subjects, when compared with controls, had decreased fractional anisotropy-weighted SC (FAw-SC) of cortico-basal ganglia-thalamo-cortical loop connections while cortico-cortical association connections showed both decreased and increased FAw-SC. FAw-SC strength of these connections was associated with poorer socio-cognitive performance in both EP and IUGR children.

Keywords: brain connectivity, connectomics, extreme prematurity, human brain development, intrauterine growth restriction, social cognition

Introduction

Every year, both in the United States of America and in Europe, ~60 000 children are born extremely preterm (EP) or with intrauterine growth restriction (IUGR). Survival of these infants has increased steadily due to improvement in perinatal care (World Health Organisation 2012). Nevertheless, the long-term neurodevelopmental impairments seen in these survivors have been recognized as a global burden to society (World Health Organisation 2012). Despite improved survival, the literature reports an increasing number of children with impaired physical health, impaired cognitive capacities, and more recently, emotional and behavioral deficits (Bhutta 2002; Anderson 2004; Clark et al. 2008). Higher rates in externalizing and internalizing behaviors often lead to lower social competence (Ross et al. 1990). Emotional regulation problems with emotional outbursts lead to school and peer relation problems. Preterm infants also have a 3 times odds of meeting criteria for psychiatric diagnoses (Treyvaud et al. 2013). Quality-of-life assessments in ex-preterm adolescents reveal rates of poor socialization skills due to difficulties in learning and nonverbal communication. As shown in a recent twin study, lower birth weight (BW) with poor intrauterine growth adds an additional risk for these impairments (Edmonds et al. 2010). Therefore, the identification of neuroimaging biomarkers in these children at school age is crucial for understanding their cognitive and behavioral impairments (Ment et al. 2009).

In the absence of focal brain lesions, most neuroimaging studies of prematurely born children (with or without IUGR) have primarily focused on the assessment of cerebral cortex maturation in terms of thickness (de Bie et al. 2010), total cortical volume (Tolsa et al. 2004), and cortical surface complexity (Dubois, Benders, Borradori-Tolsa, et al. 2008; Dubois, Benders, Cachia et al. 2008); on volumes of deep gray matter structures (Ball et al. 2012), hippocampus (Lodygensky et al. 2008), on the cerebellum (Limperopoulos et al. 2005), and on white matter (WM) volume (for review see Ment et al. (2009)). Early diffusion magnetic resonance imaging (dMRI) studies have further associated premature birth with changes in WM at term equivalent age (Huppi et al. 1998; Partridge et al. 2004; Counsell et al. 2008).

Recent advances in dMRI and operator-independent tractography enable the noninvasive mapping of WM cortico-cortical and cortico-subcortical connections at high spatial resolution (Hagmann, Cammoun, Gigandet, Gerhard, et al. 2010). This technique has been successfully applied to the study of brain development (Hagmann, Sporns, et al. 2010; Gao et al. 2011; Yap et al. 2011; Dennis et al. 2013). Nevertheless, the effects of prematurity and low BW on the maturation of structural neural networks remain still unexplored.

This study presents a whole-brain connectomic analysis of the effects of extremely premature birth and IUGR on children's brain connectivity at 6 years of age that might underlie their poorer social and higher order cognitive functioning.

Materials and Methods

Subjects

Sixty prematurely born infants at 6 years (mean age at scan 6.7 ± 0.66 years) were recruited from the Child Development Units of the Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, and the Hôpitaux Universitaires de Genève (HUG), Switzerland. All studies were performed with informed parental and child consent after approval by the medical ethical board. After preprocessing and quality evaluation of the MRI images, 52 subjects were finally included in the analysis (Supplementary Table 1). Infant growth parameters (i.e., weight and head circumference measures) and perinatal data, including BW, gestational age (GA), gender, APGAR score, and the presence of perinatal morbidities were also collected (Supplementary Table 1). None of the children had any sign of prematurity-associated brain lesions on MRI at term equivalent age, as assessed by preterm brain injury scores (Woodward et al. 2006). Furthermore, at 6 years, their MRI scans were read as normal by experienced neuroradiologists. All of the recruited children were free from medication and from psychiatric or neurological disease (Supplementary Table 1).

Children were classified as 1) moderately premature controls, 2) extreme premature (EP), or 3) moderately premature with IUGR (see Supplementary Table 1). Extreme prematurity was defined by GA at birth of <28 weeks. IUGR was defined as BW below 10th percentile (adjusted for GA and gender) and on criteria of placental insufficiency according to intrauterine growth assessment, prenatal ultrasound, and Doppler measurement within the umbilical artery. Infants considered as controls were born with BW appropriate for GA without extreme prematurity, as moderately premature infants with normal growth generally compare with children born full term in their structural brain development (Zacharia et al. 2006).

Cognitive assessment at time of MRI scan was carried out in all subjects using the French version of Kaufmann Assessment Battery for Children (Kaufman AS and Kaufman NL 1993). Furthermore, the adaptive and problematic behavior was assessed by administering the French version (d'Acremont and Linden 2008) of the Strengths and Difficulties Questionnaire (SDQ) (Goodman 1997) in 45 subjects (8 controls, 20 EP, and 17 IUGR subjects). Four types of problematic behavior: conduct problems, hyperactivity/inattention, peer relationship problems, emotional symptoms, and prosocial behavior were assessed using 5 SDQ scales. Social reasoning abilities were assessed administering the Social Resolution Task (SRT) designed to assess the ability to judge, identify, and reason about moral and conventional rules (Barisnikov and Hippolyte 2011). Only Judgment scores (SRT Q1) and Identification scores (SRT Q2) from SRT were used in analysis, since they were considered appropriate for this age group (Barisnikov and Hippolyte 2011).

Socio-economic status (SES) was assessed for each group using the Largo scale (Largo et al. 1989).

Exploratory regression analysis (linear regression models) was used to estimate the effect of the GA and IUGR on achieved cognitive scores when adjusting for SES and sex.

Data Acquisition

Children underwent MRI examinations on a 3T Siemens TrioTim system (Siemens Medical Solutions, Erlangen, Germany). For each subject, a high-resolution T_1-weighted image was acquired using a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (TR/TE = 2500/2.91 [ms/ms]; TI = 1100 ms; resolution = $1 \times 1 \times 1$ mm; FOV = $160 \times 256 \times 208$ mm^3). Following a nondiffusion-weighted image (DWI) acquisition ($b = 0$), DWIs were acquired with a single-shot, spin-echo planar imaging (SE-EPI) sequence covering 30 diffusion directions with a maximum b-value of 1000 s/mm^2, providing whole-brain coverage (TR/TE = 10200/107 [ms/ms]; in-plane resolution = 1.8×1.8 mm^2; slice thickness = 2 mm; FOV = $230 \times 230 \times 256$ mm^3). None of the subjects were sedated during the acquisition.

Data Processing

Connectome Construction and Analysis

The extraction of the whole-brain structural connectomes was performed using the Connectome Mapping Toolkit (CMTK), a python-based open-source software that implements a full diffusion MRI processing pipeline, from raw diffusion/T_1/T_2 data to multiresolution connection matrices (www.cmtk.org (Daducci et al. 2012)). The main steps and the methods used to construct the connection matrix are 1) WM-GM surface extraction and cortical and subcortical parcellation (performed using Freesurfer software (http://surfer.nmr.mgh.harvard.edu/)), 2) streamline tractography (done using an in-house built method fully implemented in the CMTK pipeline), 3) estimation of connection density; the ratio between the sum of all virtual streamlines connecting each pair of regions of interest (ROI) and their individual length (see Supplementary Material for more detailed information about the procedure used).

Following (Hagmann, Sporns, et al. 2010), the structural connectivity (SC) between cortical regions was defined as the product of 2 components (see Supplementary Material). The first component was the group connection density (gCD), computed as the following. The individual CD matrices were normalized 1) by the size of the cortical regions and 2) by the length of the fiber bundle connecting 2 regions. The groups CD matrices were computed as the mean of all normalized connection matrices in a given group. Since the mean is non-null if at least one of the elements is non-null, these group average connectivity matrices consist a support of the connectivity in each group and represents the maximum grid for each group. Comparing these support gCD matrices, no statistically significant differences in average strength and network density were observed, which was expected due to the absence of gross brain pathology. The second component was the connection efficacy, considered to be subject-dependent. It was computed as the mean fractional anisotropy (FA) value of the bundle connecting 2 regions (in the FA-weighted analysis) and as the mean of the inverse apparent diffusion coefficient (ADC) in the ADC-weighted analysis.

As we do not consider connections for which the connectivity is 0 for one group and >0 for the other group in the second-level connection-wise analysis, we can say that, in this situation, we are using the minimum grid as support for this specific analysis.

The resulting connectomes were compared globally and locally using a Mann–Whitney (a nonparametric test) test, and the resulting P-values were corrected for multiple comparisons. This later step was performed using a two-step methodology specially designed for connectomes (Meskaldji et al. 2011; Meskaldji 2013). This new statistical correction exploits the information data structure and positive dependence of the data to increase the power of testing and is based on grouping tests into subsets in which tests are supposed to be positively dependent. In our analysis, tests were grouped in meaningful disjoint anatomical groups of ROIs (Supplementary Table 12) based on a recent study (Chen et al. 2012). In their work, Chen et al. grouped the cortical areas that share similar genetic patterns. This parcellation system reflects shared genetic influence in regional differentiation in humans, demonstrating a biologically sensible organization of the structure of the human cortex. We define subsets of connections by either the intraconnectivity or the interconnectivity between the groups of ROIs defined by the Chen decomposition.

In each of the subsets, a screening of the data using a summary statistic (in our analysis, the averaged SC) at a predefined threshold $\alpha = 0.05$. This first step was followed by a local investigation of the statistically significant subsets in such a way that the global family-wise error rate (FWER) was controlled at a significance level α (Meskaldji et al. 2011; Meskaldji, Fischi-Gomez, et al. 2013) (see Supplementary Material).

FA-weighted (FAw) and ADC-weighted (ADCw) global mean connectivity was calculated for 1) whole brain (mean FA-weighted SC [FAw-SC] and mean ADC-weighted SC [ADCw-SC] of all edges in all subjects in each group), 2) intrahemispheric left and right (mean FAw-SC and mean ADCw-SC of all intrahemispheric edges in all subjects in each group), and 3) interhemispheric connections (mean FAw-SC and mean ADCw-SC of all interhemispheric edges in all subjects in each group) and compared between groups using Mann–Whitney test and Bonferroni correction.

Finally, in order to relate the differences found in brain's biological substrate with the complex changes in cognition and behavior, connections that show significantly altered FAw-SC were correlated with the socio-cognitive scores (KABC, SDQ an SRT) using Pearson's correlations with P-values corrected using a false discovery rate (FDR) control procedure.

Graph Network Construction and Analysis

The structural connectomes can be seen as adjacency matrices that define global brain networks. This graphical representation can help to understand the large-scale structural topology of brain connectivity (Bullmore and Sporns 2009). Thus, in order to complement the information obtained from a pairwise connection study, we computed several global network measures (small-world index, normalized by the random equivalent network with same degree distribution of each subject; average node degree; average strength; average efficiency;

average betweenness centrality; and averaged shortest path) based only on the FAw-SC connection matrices. These measures were computed using the brain connectivity toolbox (http://www.brain-connectivity-toolbox.net (Rubinov and Sporns 2010)), and were compared statistically using the Mann–Whitney test. The final goal was to characterize network structure and function by measuring changes related to the refinement in specific metrics of networks topology (see (Rubinov and Sporns 2010) for definitions and detailed information of the network measures).

Results

Global Connectivity

When compared with control subjects, both EP and IUGR subjects showed alterations in FAw-SC in terms of mean connectivity in the whole brain, left, and right intrahemispheric connections and interhemispheric connections (Supplementary Tables 3 and 4).

The global ADCw-SC analysis showed significant differences between EPs and controls in the interhemispheric mean connectivity (Supplementary Table 3) while IUGR subjects, when compared with controls, showed differences in whole-brain mean connectivity as well as intrahemispheric mean connectivity (both right and left) (see Supplementary Table 4).

Global Network Analysis

When compared with controls, both groups under study (EP and IUGR) showed significantly reduced average node degree, average node strength, and global efficiency. In addition, the average shortest path was significantly increased in EP and IUGR (Table 1).

The clustering index, a measure of the degree to which nodes in a network form local communities, was globally significantly decreased only in the IUGR subjects, while it was similar between controls and EP subjects (see Table 1). EP and IUGR maintained their small-world characteristics that are defined as the ratio of "clustering coefficient versus path length."

Local Connectivity Changes in FA-Weighted Structural Connectivity

Changes in FAw-SC After extreme prematurity (EP vs. Controls)

The local analysis revealed pairwise FAw-SC alterations in both interhemispheric and intrahemispheric connections in EP children (see Fig. 1*A*–*C*). Majority of these altered connections showed weaker FAw-SC (Fig. 1*A*–*C*; red-, yellow-, and orange-colored connections).

Table 1

Global network metrics comparison for each group under study

Global network measures		Control	EP	IUGR
Similarity	Deg	15.9804	14.8743 (4.887×10^{-5}*)	15.7292 (1.28×10^{-4}*)
	Str	213.0259	193.2092 (0.0048*)	174.8194 (0.0001*)
Clustering	ci	5.9477	5.9050 (0.9820)	5.1150 (0.0233*)
Paths/distances	Lam	0.2024	0.2465 (3.65×10^{-5}*)	0.2554 (6.08×10^{-5}*)
	eff	6.9464	6.0749 (4.39×10^{-5}*)	5.7536 (6.98×10^{-5}*)
Centrality	bet	418.4307	396.6862 (0.2316)	393.5479 (0.1960)
Core structure	swi	2.9	2.39 (0.4295)	2.36 (0.2941)

Mean value and *P*-value (in parenthesis) for the Mann–Whitney comparison at level $\alpha = 0.05$ between control and EP and between controls and IUGR. *P*-values <0.05 are marked with *. Metrics: deg (average node degree), str (average node strength), ci (average cluster index), lam (average characteristic path length), eff (global efficiency), bet (average node betweenness centrality, and swi (mean small-world index).

Weaker FAw-SC was found within interhemispheric connections, in particular the callosal connections belonging to precuneus and isthmus of cingulate gyrus (Fig. 1*A*–*C*; yellow-colored connections), Supplementary Table 5*E*. Intrahemispherically, the results revealed weaker FAw-SC of cortico-basal ganglia-thalamo-cortical loop connections (CBTCL Fig. 1*A*–*C*; red-colored connections), Supplementary Table 5*B*. These connections were mostly fronto-subcortical connections between superior frontal gyrus and subcortical gray matter (thalamus, globus pallidus, putamen, and caudate nucleus) (Fig. 1*A*–*C*; red-colored connections). Connections of orbital and medial networks (between lateral and medial orbital cortex, basal ganglia, prefrontal cortex, and gyrus cinguli) were significantly weaker in EP children (Supplementary Table 5*A*). Alterations of the subthalamic and brainstem connections were also found (Fig. 1*A*–*C*); yellow-colored connections, Supplementary Table 5*D*.

Furthermore, short connections between neighboring cortical regions were also found weaker in EP (Fig. 1*A*–*C*; orange-colored connections, Supplementary Table 5*C*). These connections were short cortico-cortical connections of prefrontal cortex (middle frontal gyrus and inferior frontal gyrus), cingulate gyrus (posterior part and isthmus), precuneus, and between neighboring parietal and temporal cortex (supramarginal gyrus, superior temporal gyrus, transverse temporal gyrus, inferior parietal lobule).

While all of the altered connections showing increased FAw-SC were short cortico-cortical connections (Fig. 1*A*–*C*; blue-colored connections, Supplementary Table 6*A*), the majority of them were connections between neighboring regions of temporal cortex (fusiform, superior, middle and inferior temporal and lingual gyrus).

Changes in FAw-SC After IUGR (IUGR vs. Controls)

Comparing IUGR children to control subjects also revealed altered interhemispheric and intrahemispheric connections (Fig. 2 and Supplementary Table 7). Similar to EP, the majority of altered connections in IUGR showed weaker FAw-SC (Fig. 2*A*–*C*; yellow-, orange-, and red-colored connections).

Interhemispheric callosal connections belonging to superior frontal gyrus, precuneus, and cingulate gyrus were found significantly weaker in IUGR children (Fig. 2*A*–*C*; yellow-colored connections, Supplementary Table 7*E*). Intrahemispherically IUGR subjects also showed altered fronto-subcortical connections, mostly between middle frontal gyrus and subcortical gray structures (putamen, globus pallidus, thalamus) (Fig. 2*A*–*C*; red-colored connections, Supplementary Table 7*B*). In addition, many of the altered connections belonging to the CBTCL were short connections between subcortical gray matter structures (globus pallidus, thalamus, nucleus caudatus, and nucleus accumbens, Fig. 2*A*–*C*; red-colored connections, Supplementary Table 7*B*). Connections of the orbital and medial networks were significantly weaker in IUGR children (Supplementary Table 7*A*) as well as some of the subthalamic and brainstem connections (Fig. 2*A*–*C*; yellow-colored connections, Supplementary Table 7*D*).

Although short cortico-cortical connections between neighboring cortical regions were also weaker in IUGR children,

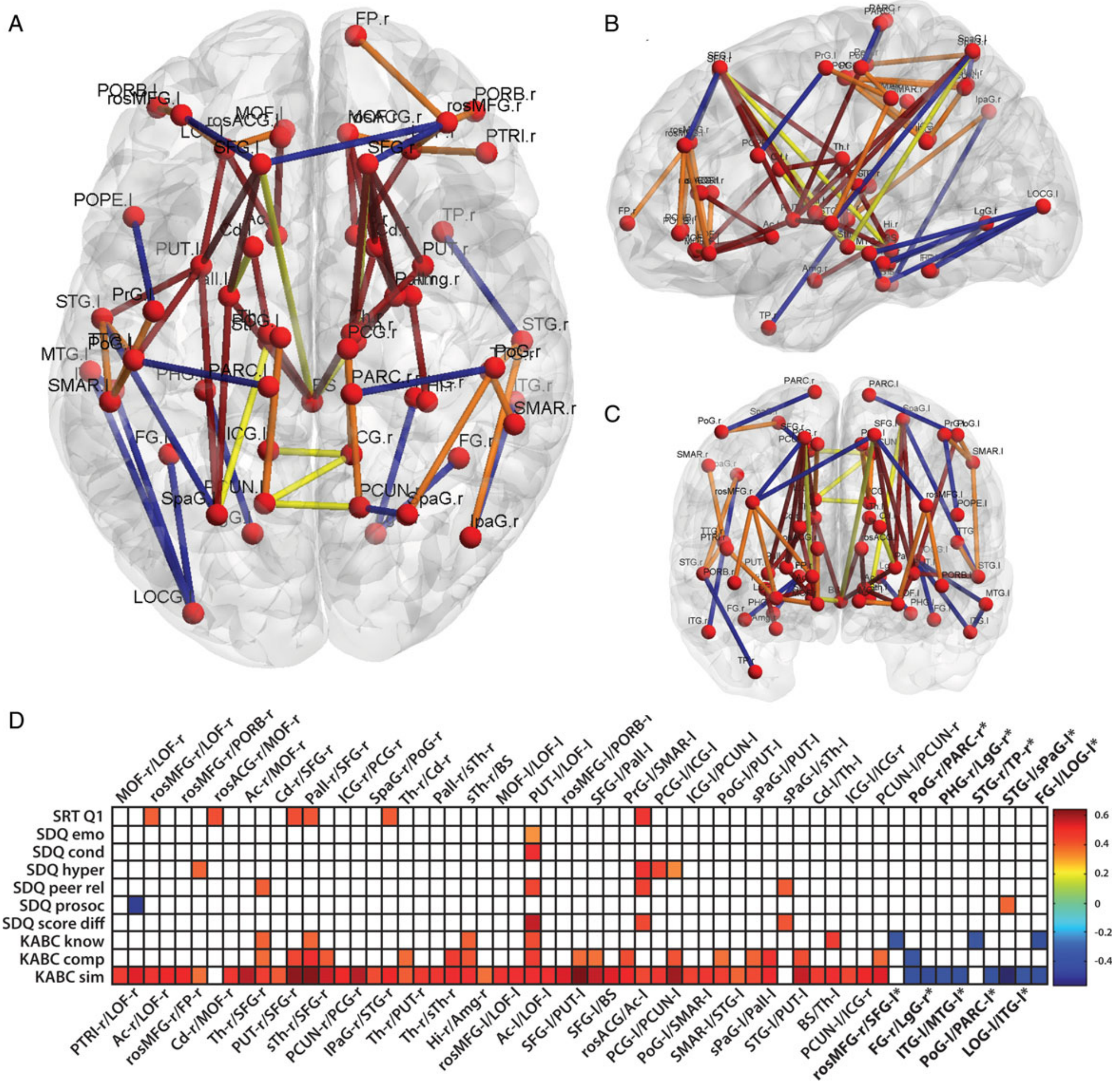

Figure 1. Connections altered in EP children at school age (*A*–*C*) and correlation matrix of their FAw-SC with the socio-cognitive outcome (*D*). Projection to axial (*A*), sagittal (*B*), and coronal plane (*C*) of connections showing statistically significant FAw-SC decrease (EP < controls; in red—the cortico-basal ganglia-thalamo-cortical loop connections; in orange—intrahemispheric cortico-cortical connections; in yellow—brainstem, subthalamic, and callosal connections) or increase (EP > controls; in blue—intrahemispheric cortico-cortical connections) when compared with controls under FWER control. (*D*) Pearson's correlation strength, *r* (color bar in the right) between FAw-SC of altered connections (*A*) and socio-cognitive outcome ($P < 0.05$, FDR corrected). Correlations that did not show statistical significance ($p < 0.05$) were not inserted. Asterisk indicate connections with significantly increased FAw-SC strength in EP. For assessment of social skills, SRT (SRT Q1 = Judgment score, SRT Q2 = Identification score) SDQ prosocial and SDQ peer relation questionnaire were administered. For assessment of higher cognitive skills, KABC and SDQ were administered. Higher KABC scores indicate higher cognitive performance. SDQ emotion, conduct, hyperactivity, difficulties, and peer relation scores use an inverse scale relative to performance (higher performance, lower score). Therefore, for illustration purposes, they were inverted in the figure. *A*–*C* were reconstructed using the BrainNet Viewer software (Xia et al. 2013).

these connections were widespread through the telencephalon (Fig. 2*A*–*C*; orange-colored connections, Supplementary Table 7*C*).

Increased FAw-SC was found only in short cortico-cortical connections of temporal (middle temporal gyrus) and inferior frontal gyrus (pars opercularis) (see Fig. 2*A*–*C*; blue-colored connections and Supplementary Table 8).

Differences in FAw-SC Between EP and IUGR

As summarized in Figure 3 and Supplementary Tables 9 and 10, comparing IUGR children to EP subjects directly revealed only intrahemispheric FAw-SC alterations. When compared with the EP group, reduced connectivity in the IUGR group was found again in the CBTCL (Fig. 3*A*–*C*); red-colored connections, Supplementary Table 9*A*. However, these alterations

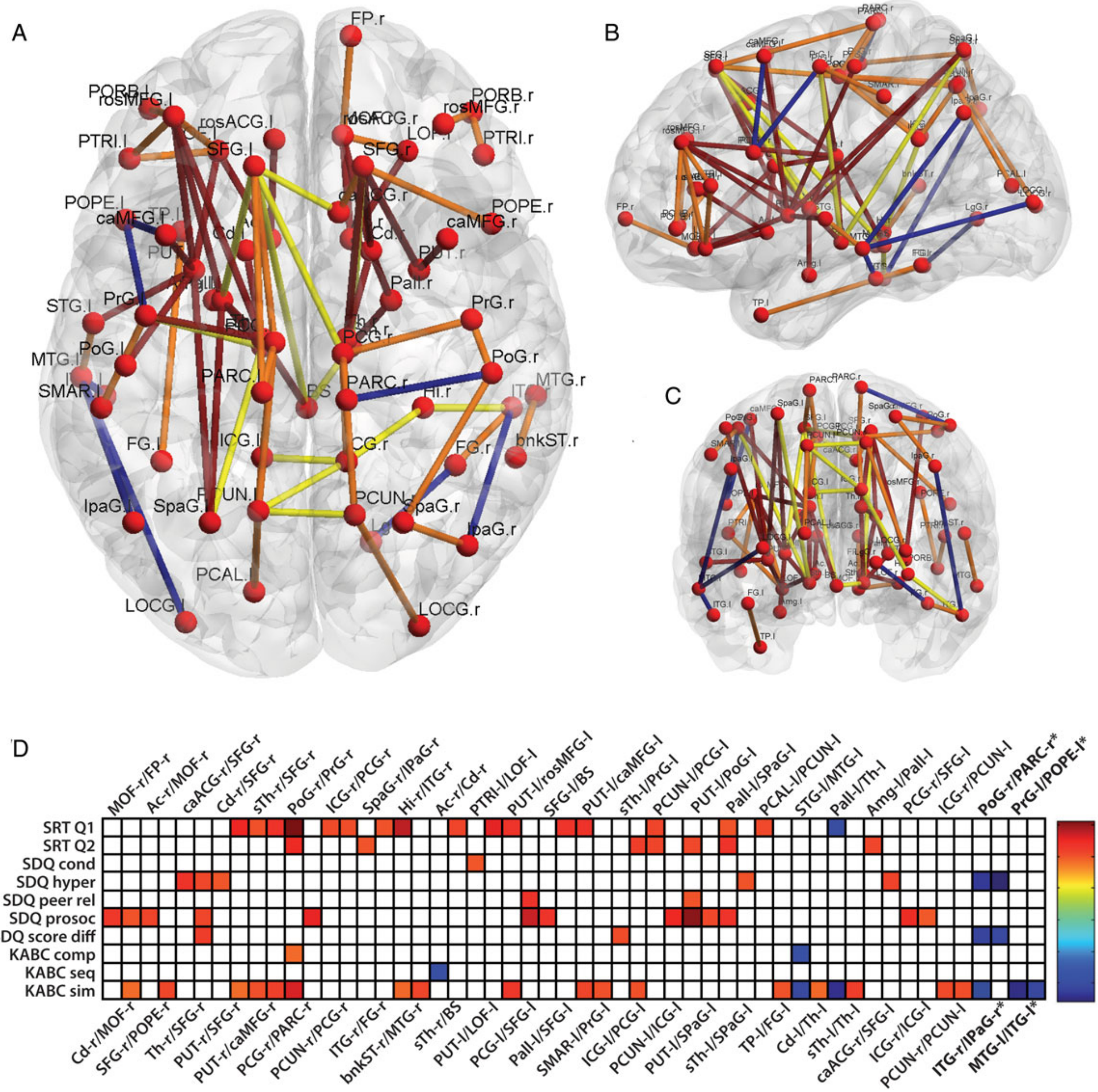

Figure 2. Connections altered in IUGR children at school age (*A*–*C*) and correlation matrix of their FAw-SC with the socio-cognitive outcome (*D*). Projection to axial (*A*), sagittal (*B*), and coronal plane (*C*) of connections showing statistically significant FAw-SC decrease (IUGR < controls; in red—the cortico-basal ganglia-thalamo-cortical loop connections; in orange—intrahemispheric cortico-cortical connections; in yellow—brainstem, subthalamic, and callosal connections) or increase (IUGR > controls; in blue—intrahemispheric cortico-cortical connections) when compared with controls under FWER control. (*D*) Pearson's correlation strength, *r* (color bar in the right) between FAw-SC of altered connections (*D*) and socio-cognitive outcome ($P < 0.05$, FDR corrected). Correlations that did not show statistical significance ($p < 0.05$) were not inserted. Asterisk indicates connections with increased FAw-SC in IUGR. For assessment of social skills, SRT (SRT Q1 = Judgment score, SRT Q2 = Identification score) SDQ prosocial and SDQ peer relation questionnaire were administered. For assessment of higher cognitive skills, KABC and SDQ were administered. Higher KABC scores indicate higher cognitive performance. SDQ emotion, conduct, hyperactivity, difficulties, and peer relation scores use an inverse scale relative to performance (higher performance, lower score). Therefore, for illustration purposes, they were inverted in the figure. *A*–*C* were reconstructed using the BrainNet Viewer software (Xia et al. 2013).

appeared only in the right hemisphere, in connections between parietal cortex (supramarginal gyrus and inferior parietal lobule) and subcortical gray matter (putamen, globus pallidus, amygdala, and thalamus) (see Fig. 3*A*–*C*; red-colored connections and Supplementary Table 9*A*). EP showed decreased connectivity, compared with IUGR, only in cortico-cortical connections of the left hemisphere; long cortico-cortical connections (between temporal (superior temporal) and prefrontal cortex (middle and inferior frontal gyrus)) and short cortico-cortical connections (between inferior and middle frontal gyrus) (Supplementary Table 10, Fig. 3*A*–*C*; blue-colored connections).

Social and Higher Order Cognitive Evaluation

Exploratory regression analysis revealed a significant association between lower GA and poorer achievement on KABC simultaneous processing subscales (Supplementary Table 2,

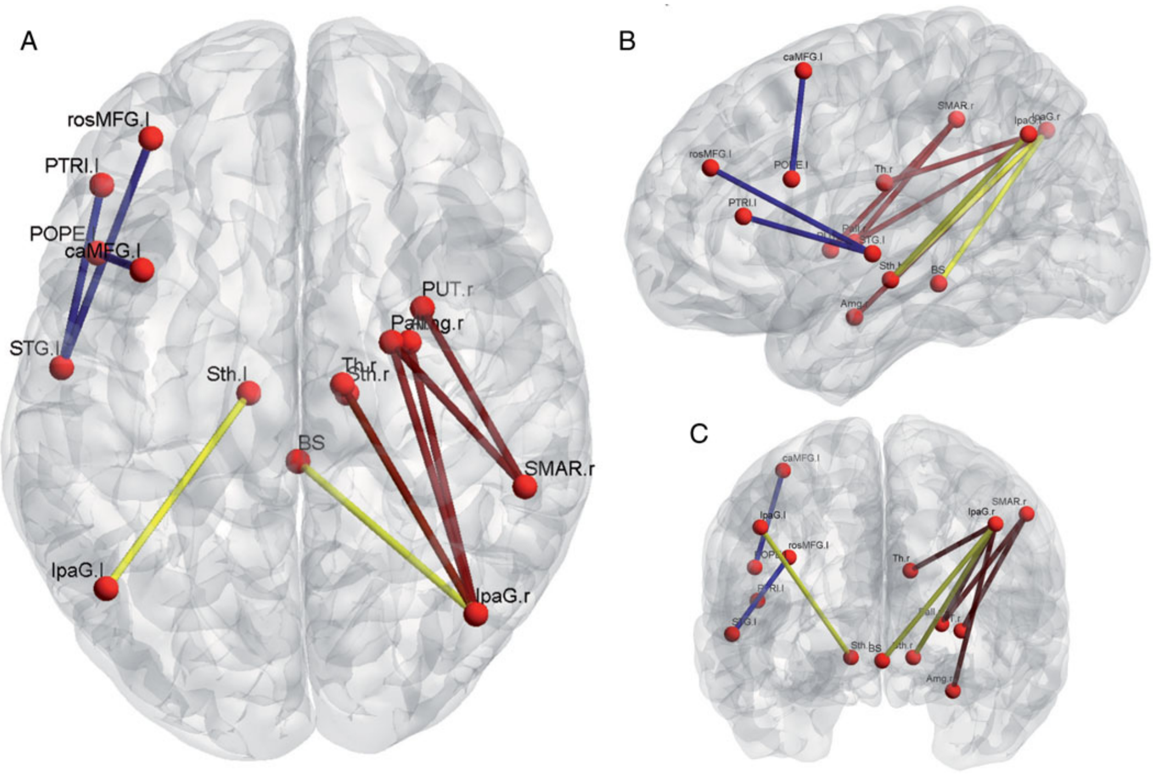

Figure 3. Altered connections between IUGR and EP children at school age. Projection to axial (*A*), sagittal (*B*), and coronal plane (*C*) of connections showing statistically significant FAw-SC decrease in IUGR (IUGR < EP; in red—the cortico-basal ganglia-thalamo-cortical loop connections; in yellow—brainstem, subthalamic, and callosal connections) or decrease in EP (EP < IUGR; in blue—intrahemispheric cortico-cortical connections) when comparing 2 groups. (*A*–*C*) were reconstructed using the BrainNet Viewer software (Xia et al. 2013).

$P < 0.05$, uncorrected, after adjustment for sex, SES, and IUGR). IUGR also showed significant association with lower KABC simultaneous processing scores (Supplementary Table 2, $P < 0.05$, uncorrected, adjusted for GA, sex, and SES). Furthermore, IUGR when tested for social skills and adjusted for GA, sex, and SES showed significant association with lower scores, poorer social skills (on average 1.3 points with a standard error 0.56), on the SDQ prosocial behavior questionnaire and SRT (SRT Q1 (Judgment score) (Supplementary Table 2, $P < 0.05$, uncorrected, adjusted for GA, sex, and SES).

Correlation of Altered FAw-SC with Socio-Cognitive Scores

The FAw-SC of the majority of connections identified as weaker in EP correlated positively (i.e., decreased connectivity led to decreased score) with the KABC simultaneous score (see Fig. 1*D*). FAw-SC of certain connections (connections of the superior frontal gyrus and lateral orbitofrontal cortex) also identified as weaker in EP, positively correlated with the SRT judgment score (Fig. 1*D*). Additionally, in EP, SDQ hyperactivity scores were negatively correlated with FAw-SC of anterior cingulate CBTCL connections (connections between anterior cingulate gyrus and nucleus accumbens) and short cortico-cortical connections (connections between posterior cingulate gyrus, isthmus gyri cinguli precuneus middle frontal gyrus and frontal pole) of the left hemisphere. As SDQ hyperactivity use inverse scale relative to performance (lower scores, better performance) lower FAw-SC of these connections was associated with higher hyperactivity (poorer outcome).

Inversely, FAw-SC of cortico-cortical connections, identified as stronger in EP, still correlated negatively with the KABC simultaneous score (higher strength of connectivity indicated lower KABC score, see connections marked with (*) in Fig. 1*D*).

For the IUGR subjects, the correlations between FAw-SC and socio-cognitive scores appeared less homogenous than in the EP group. FAw-SC of connections identified as weaker in IUGR correlated positively with SRT Q1 in most cases. These connections were mainly the ones belonging to fronto-subcortical or parieto-subcortical circuits. Some of the connections altered in IUGR subjects correlated positively with SRT Q2, SDQ prosocial (connections between medial orbitofrontal, prefrontal, parietal cortex, and the basal ganglia) SDQ hyperactivity (fronto-subcortical and parieto-subcortical connections) and KABC simultaneous score (fronto-subcortical, callosal, and short cortico-cortical connections of temporal lobe, Fig. 2*D*). FAw-SC of short cortico-cortical connections, identified as stronger in IUGR, correlated negatively with the behavior and KABC simultaneous scores (Fig. 2*D*; connections marked with (*)).

Our findings are further summarized in 2 schematic drawings (Figs 4 and 5) for better anatomical illustration. Both figures show only the altered connections in EP (Fig. 4) or IUGR (Fig. 5), whose FAw-SC significantly correlates with socio-cognitive performance (bold lines and dotted lines represent positive and negative correlations, respectively). Note that the majority of altered connections whose strength is associated with socio-cognitive performance belong to prefronto-subcortical circuits.

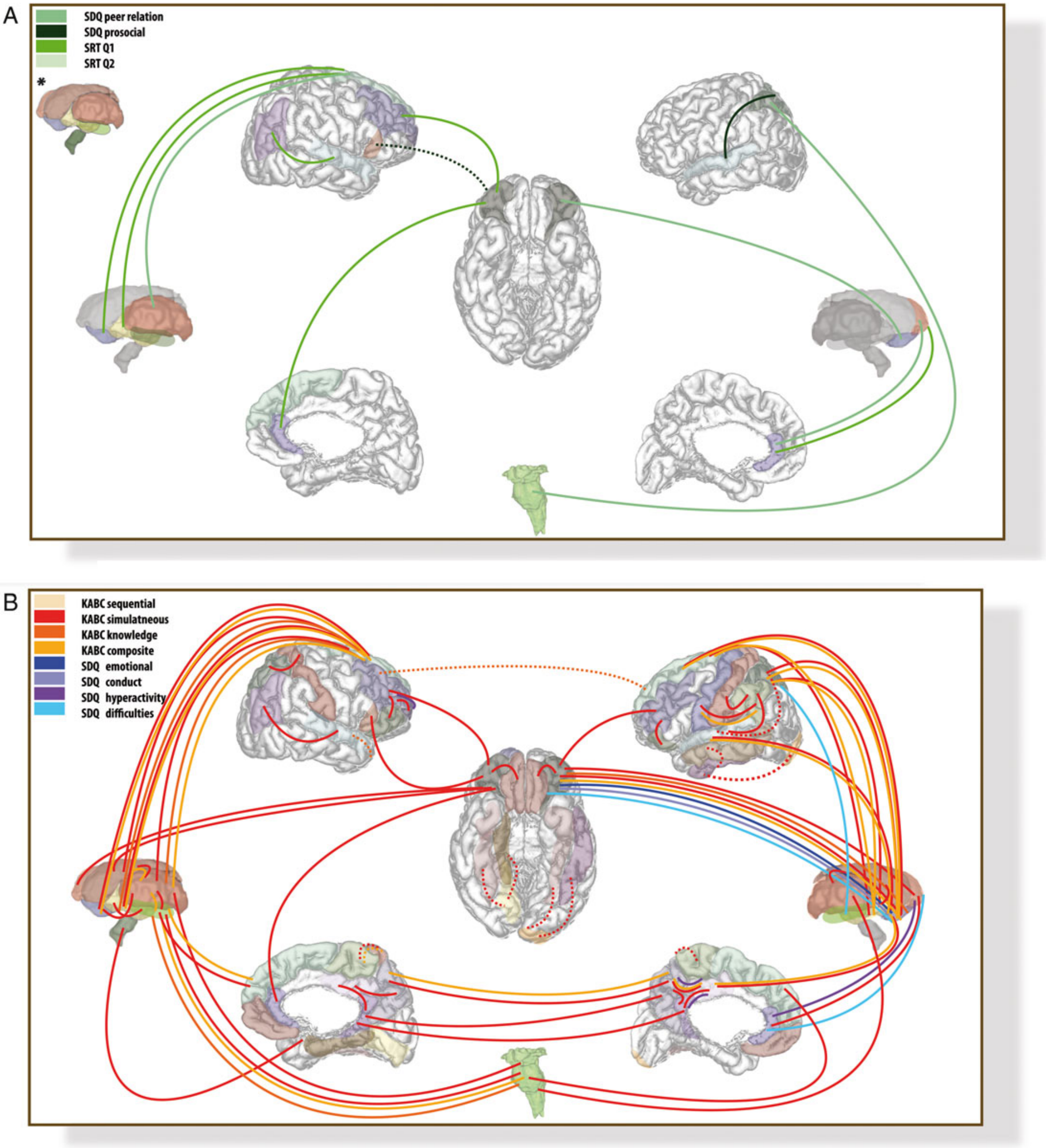

Figure 4. Schematic drawing of altered connections in EP subjects whose FAw-SC strength correlates with the socio-cognitive outcome. Drawn altered connections are connections from Figure 1*D*. Social reasoning skills, peer problems and prosocial behavior are shown in (*A*) Higher cognitive skills are shown in (*B*) Dotted lines: negative correlation. Continuous lines: positive correlation. For assessment of social skills SRT (SRT Q1 = Judgment score, SRT Q2 = Identification score) SDQ prosocial and SDQ peer relation questionnaire were administered. For assessment of higher cognitive skills, KABC and SDQ were administered. Higher KABC scores indicate higher cognitive performance. SDQ emotion, conduct, hyperactivity, difficulties, and peer relation scores use an inverse scale relative to performance (higher performance, lower score). Therefore, for illustration purposes, they were inverted in the figure. *3D basal ganglia reconstruction; nucleus accumbens (light red), nucleus caudatus (brown), thalamus (red), putamen (purple), globus pallidus (yellow), subthalamus (light green), and amygdala (dark green). 3D cortical surfaces were reconstructed using the CIVET software developed by ACE lab (http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET (Collins et al. 1995; MacDonald et al. 2000; Kim et al. 2005; Lee et al. 2006; Lyttelton et al. 2007)).

Discussion

Extremely premature birth and/or poor intrauterine growth affect social and higher order cognitive functions in school-age children (Wiles et al. 2006; Larroque et al. 2008). This study delineates global and regional brain alterations of SC with a whole-brain connectome approach and relates the brain connectivity and network changes with social and higher order cognitive functions in EP and IUGR school-age children.

Global Connectivity Analysis

The mean ADCw-SC (considered as an indicator of WM maturation and myelination) was reduced in interhemispheric WM pathways in EP, whereas, in IUGR children, it was reduced in intrahemispheric WM pathways (Supplementary Tables 3 and 4). It is known that forebrain commissures are unmyelinated at birth and that the process of myelination of axonal fibers, especially in the corpus callosum, continues into adolescence

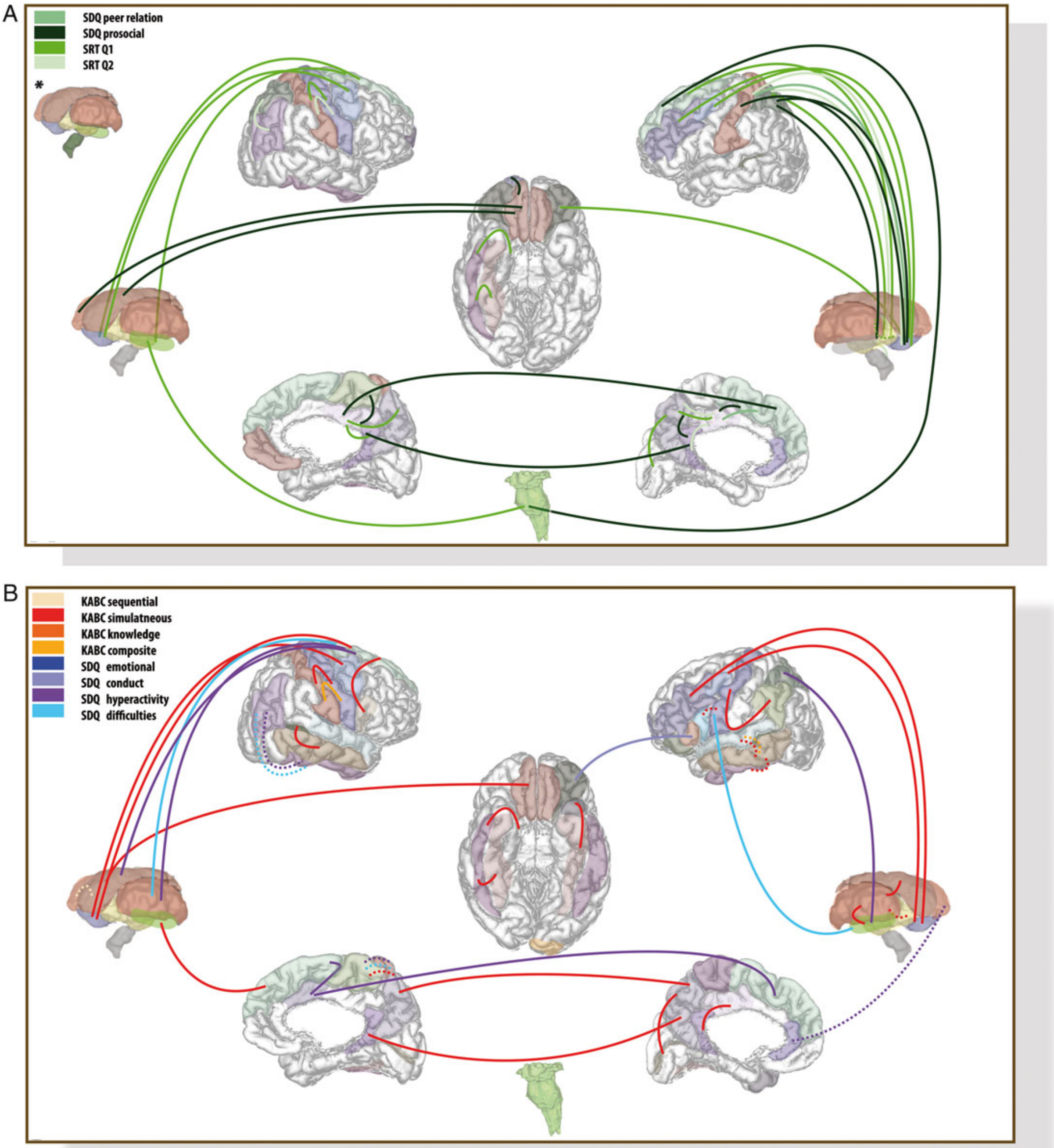

Figure 5. Schematic drawing of altered connections in IUGR subjects whose FAw-SC strength correlates with the socio-cognitive outcome. Drawn altered connections are connections from Figure 2D. Social reasoning skills, peer problems, and prosocial behavior are shown in (*A*) Higher cognitive skills are shown in (*B*) Dotted lines: negative correlation. Continuous line: positive correlation. For assessment of social skills, SRT (SRT Q1 = Judgment score, SRT Q2 = Identification score) SDQ prosocial and SDQ peer relation questionnaire were administered. For assessment of higher cognitive skills, KABC and SDQ were administered. Higher KABC scores indicate higher cognitive performance. SDQ emotion, conduct, hyperactivity, difficulties, and peer relation scores use an inverse scale relative to performance (higher performance, lower score). Therefore, for illustration purposes, they were inverted in the figure. *3D basal ganglia reconstruction; nucleus accumbens (light red), nucleus caudatus (brown), thalamus (red), putamen (purple), globus pallidus (yellow), subthalamus (light green) and amygdala (dark green). 3D cortical surfaces were reconstructed using the CIVET software developed by ACE lab (http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET (Collins et al. 1995; MacDonald et al. 2000; Kim et al. 2005; Lee et al. 2006; Lyttelton et al. 2007)).

(Keshavan 2002). Thus, our results suggest that reduced mean ADCw-SC of interhemispheric connections in EP reflect changes in the maturation of callosal fibers. These results are in agreement with previously reported DTI studies showing microstructural WM changes of major WM fiber tracts associated with premature birth (for review see Ment et al. 2009).

Global mean FA was significantly altered for interhemispheric as well as for intrahemispheric SC in both groups (EP and IUGR, Supplementary Tables 3 and 4). This provides new evidence that alterations of WM maturation associated with premature birth are present not only, as previously demonstrated, at term equivalent age (Huppi et al. 1998; Hüppi and

Dubois 2006), but also persist upon reaching school age. Furthermore, our results show that poor fetal conditions leading to IUGR provoke structural abnormalities similar to ones seen in EP, with high impact on their socio-cognitive potential.

Global Network Properties

Complex systems such as the brain show remarkably similar macroscopic behavior, despite profound differences at the microscopic level (Alexander-Bloch et al. 2013). Nevertheless, altered maturation of axonal pathways could lead to changes in global brain network properties. Indeed, even if the graph analysis demonstrated that both EP and IUGR maintained the network small-world characteristic, they showed distinct differences in networks properties. Significantly lower average node metrics (average node degree and average node strength (Table 1)) suggest that anatomical regions in EP and IUGR subjects generally have less well-organized global networks leading to lower efficiency (Table 1). Additionally, the longer shortest path lengths in EP and IUGR (Table 1) subjects confirm the loss of efficiency and delay in maturation, as shortest path length measures are expected to decrease with age during childhood (Hagmann, Sporns, et al. 2010). Moreover, IUGR children showed a lower clustering index, indicating less local communities or hubs, and therefore less segregation. Since the clustering index does not usually change during development, this indicates a permanent change in IUGR subjects, rather than delayed maturation only.

Throughout development, the human brain tends to locally favor dense communication, minimize path lengths, and increase specialization and segregation of brain areas (Khundrakpam et al. 2013). Our graph analysis results show that extreme premature birth and/or prenatal growth restriction reduce this aforementioned tendency.

Local Connectivity Analysis

During development, major WM fiber systems display specific spatio-temporal maturation (Vasung et al. 2010). The maturation of thalamo-cortical fibers and striatal fibers of the CBTCL is followed by the maturation of the associational long (intrahemispheric and interhemispheric) and short cortico-cortical fibers (Kostovic and Jovanov-Milosevic 2006; Vasung et al. 2010; Kostovic et al. 2014).

Our results indicate that early maturing fiber systems (e.g., thalamo-cortical fibers, striatal fibers) have decreased FAw-SC at school age in EP and IUGR children (Figs 1 and 2). Contrarily, late maturing fiber systems (mostly the associational cortico-cortical fibers) have both decreased (Figs 1*A*–*C* and 2*A*–*C*; orange-colored connections) and increased FAw-SC (Figs 1*A*–*C* and 2*A*–*C*; blue-colored connections). Such differences in FAw-SC strength suggest different vulnerability and developmental trajectories of the aforementioned fiber systems.

Connections with Weaker FAw-SC

Cortico-Basal Ganglia-Thalamo-Cortical Loop

The CBTCL is a model of the functional and anatomical organization of cortico-basal ganglia-thalamo-cortical pathways (Cummings 1993) that play an important role in human behavior. In this study, connectivity alterations in the CBTCL connections were common in both groups (EP and IUGR) when compared with controls (see Figs 1*A*–*C* and 2*A*–*C*; red-colored connections, and Supplementary Tables 5*A*,*B* and 7*A*,*B*) and were linked with the level of their socio-cognitive performance (Figs 4 and 5).

The relationship between the cortex, the basal ganglia, and the thalamus in terms of information processing is complex and has been an area of scientific debate for years (Goldman-Rakic and Selemon 1990). Basal ganglia receive inputs from the majority of cortical areas. This flux of information is then transferred to the thalamus that serves as a relay for the basal ganglia projections back to the cortex (Alexander et al. 1986; Cummings 1993, 1995, 1998; Mega and Cummings 1994; Parent and Hazrati 1995; Takada et al. 1998; Gallay et al. 2008). Recent imaging data using probabilistic tractography demonstrated the structural basis of the CBTCL at the global level (Draganski et al. 2008). The parallel organization of cortico-striatal circuits belonging to the CBTCL allows simultaneous processing of cognitive, sensorimotor, and motivational information (Alexander and Crutcher 1990; Groenewegen et al. 2009). Our results suggest that weaker connections within this circuit might be a biological blueprint of less efficient simultaneous information processing seen in EP and IUGR children (Figs 1*D*, 2*D*, 4*B* and 5*B*). In addition, the connectivity alterations that we found in EP and IUGR suggest that the most vulnerable part of this loop consists of the components belonging to the prefronto-subcortical and limbic circuits (Figs 1*A*–*C* and 2*A*–*C*; red-colored connections, Supplementary Tables 5*A*, *B* and 7*A*,*B*). The prefronto-subcortical circuits are referred to as major mediators of the executive, social, and motivated human behavior (Cummings 1993, 1995, 1998; Parent and Hazrati 1995), shown to be affected by premature birth (Nosarti et al. 2010). Moreover, these circuits have also been implicated in psychiatric disorders (Mega and Cummings 1994) which are known to occur with higher prevalence in prematurely born children (Nosarti et al. 2010) and individuals with low BW.

Orbitofrontal Circuits of the CBTCL

Different connections belonging to orbital and medial network circuitry were found to be weaker in EP and IUGR children (Figs 1*A*–*C* and 2*A*–*C*; red-colored connections, Supplementary Tables 5*A* and 7*A*).

The orbital network serves as a system for sensory integration while the medial prefrontal network plays an important role in reward-related learning, extinction, and reality check and fantasies, or to keep thought and behavior in phase with reality (Ongur and Price 2000; Schnider 2008). A neuroimaging study in adolescents associated the alteration of orbitofrontal sulcal depth with prematurity (Gimenez et al. 2006), suggesting altered maturation of orbitofrontal cortex after premature birth. In recent years, alterations of the orbitofrontal cortex have further been associated with impaired social behavior, poor reward-based decision making and disturbances in emotional processing. Our results support these findings since in EP and IUGR children weaker strength of connections belonging to medial and orbital networks (Figs 1*A*–*C* and 2*A*–*C*) correlated with deficits in recognition of social context, social recognition abilities, simultaneous processing, and hyperactivity (Figs 4 and 5). Therefore, our results suggest that these networks might be responsible for lower social competences seen in prematurely born children (Ross et al. 1990).

CBTCL Alteration in Relation to Injury

Primary lesions from acquired insults that are associated with premature birth were extensively studied, for review see Volpe (2009). The predilection sights of these lesions are periventricular regions. "Periventricular crossroad areas", situated in periventricular regions, have been recently described as being crucial for proper navigation and growth of axonal pathways during human brain development (Judas et al. 2005). During fetal development, an abundant periventricular fiber pathway (PVP) (Vasung et al. 2011) is situated within these areas. Since the PVP is made of the fronto-occipital fascicle, the corpus callosum, the fronto-pontine pathway, and the Muratoff fascicle (major route for cortico-striatal fibers (Schmahmann and Pandya 2009)) (Vasung et al. 2011), we suspect that discrete injury in these "periventricular crossroad areas" might lead to altered callosal (Supplementary Tables 5*E* and 7*E*), brainstem (Supplementary Tables 5*D* and 7*D*), and cortico-striatal connectivity (CBTC, Supplementary Tables 5*A*,*B* and 7*A*,*B*).

Additionally, Pierson et al. (2007) reported that primary injury of the WM does not happen in isolation, but it is associated with significant neuronal loss and/or gliosis within the basal ganglia and thalamus. Neuroimaging studies have recently shown decreased volumes of thalamus and weaker thalamo-cortical connections in prematurely born infants (Ball et al. 2012). Therefore, discrete injury of periventricular regions affecting the major route for cortico-striatal fibres (the Murratoff fascicle) and neuronal loss within basal ganglia could partially explain the weaker connectivity within the CBTCL that we found in EP and IUGR preterm children (Figs 1*A*–*C* and 2*A*–*C*; red-colored connections, Supplementary Tables 5 and 7*B*).

Short Associational Cortico-Cortical Connections

Language-Associated Areas

Comparing IUGR to EP revealed that EP children display weaker FAw-SC in connections belonging to regions associated with language processing, namely pars opercularis and pars triangularis of inferior frontal gyrus (Fig. 3*A*–*C*; blue-colored connections, Supplementary Table 10).

It has been shown that low BW and extreme prematurity are associated with poorer language skills at almost all levels, from expressive to receptive language, phonological awareness, discourse, semantics, and pragmatics (Foster-Cohen et al. 2007; Marston et al. 2007; Wolke et al. 2008; Barre et al. 2011; Ramon-Casas et al. 2013). Furthermore, recent imaging findings, showing connectivity alterations of similar areas as in the current study, suggest that these children recruit alternate cortical regions for language processing (Gozzo et al. 2009). Thus, our results provide further evidence of altered (decreased) SC between cortical areas relevant for language processing (Figs 1*A*–*C* and 2*A*–*C*; orange-colored connections, Supplementary Tables 5*C* and 7*C*).

Precuneus

One of the most striking alterations was found in cortico-cortical connections between the precuneus and neighboring regions (Figs 1*A*–*C* and 2*A*–*C*; orange-colored connections, Supplementary Tables 5*C* and 7*C*). The precuneus has been reported to have a major role in a broad spectrum of complex cognitive tasks, including visuo-spatial imagery, episodic memory retrieval, and self-processing.

However, during the resting state of the brain, the precuneus and the posterior regions of the medio-sagittal cortex show synchronous activity patterns and have been referred to as being part of the "default mode network" (DMN) functionally linked to self-consciousness (Cavanna and Trimble 2006). DMN is known to appear later in development of preterm infants (Smyser et al. 2010). Our results of reduced connectivity between these 2 major hubs of the DMN at 6 years of life (posterior cingulate gyrus and posterior precuneus) suggests alteration of this basic structural and functional network important for functional integration of information processing (Hagmann et al. 2007, 2008). Significant correlation with the cognitive outcome provided evidence that weaker strength of connections belonging to these circuits might contribute to their less efficient simultaneous information processing, poor recognition of social context, and poor prosocial behavior (Figs 1*D*, 2*D*, 4, and 5).

Connections with Stronger FAw-SC

Short Associational Cortico-Cortical Connections

Although human brain develops in distinct stages of genetic activity (Pletikos et al. 2014), experience-dependent structural changes are generally described within the GM. These changes, associated with synaptogenesis and dendritic arborization (Petanjek et al. 2011), contribute to functional plasticity (Volkmar and Greenough 1972; Turner and Greenough 1985). Training and rehabilitation are further known to affect the cortico-cortical rewiring, and recent DTI data show that training induces changes in WM architecture (Scholz et al. 2009). In our study, all connections with significantly increased FAw-SC in EP and IUGR were short cortico-cortical connections (Figs 1*A*–*C* and 2*A*–*C*; blue-colored connections). Nevertheless, none of these connections were associated with improved measures of the socio-cognitive outcome. On the contrary, they were associated with less efficient simultaneous processing and higher rates of hyperactivity (Figs 1*D*, 2*D*, 4, and 5). Thus, our results indicate that this increase in connectivity strength does not necessarily mean a better socio-cognitive performance but might occur in order to compensate weaker parts of network circuitry.

Implications for Understanding Cognition and Behavior

When reaching school age, EP children show deficits in motor, sensory and executive functioning (Marlow et al. 2007). Moreover, they display problems in processing complex information that needs logical reasoning and spatial orientation abilities (Larroque et al. 2008). As these cognitive deficits have a similar incidence in EP and IUGR preterm infants (born between 29 and 32 weeks) (Guellec et al. 2011), similar connectivity alterations found in the EP and IUGR subjects speaks in favor of their similar neural substrate. The current analysis therefore suggests that the alterations in the CBTCL and the short cortico-cortical connections following preterm birth and IUGR might contribute to poorer prosocial behavior, recognition of social context, and simultaneous information processing (Figs 4 and 5).

Strengths and Limitations of the Study

Some limitations of the current study need to be taken into consideration. First, the small cohort of subjects, the higher variability between individuals, and the large number of comparisons were overcome using a new two-step methodology that exploits the data structure and information of positive dependence to increase power of testing. Second, DTI was chosen instead of other dMRI acquisition schemes (HARDI or DSI) because subjects were young children requiring shorter acquisition time. Third, DTI reconstruction and tractography are sensitive to motion artifacts and both present limitations for reconstruction of complex fiber configurations, like crossing-fibers or kissing-fibers. A threshold on the density values of each bundle (the mean FA value) was used to minimize possible artifacts due to the acquisition and tractography noise. In that way, we reduced the number of residual connection values. Validation of the tractography method and the construction of connectomes are not discussed here as both aspects are extensively discussed elsewhere (Hagmann et al. 2007; Cammoun et al. 2012).

Given the relatively small local cohort of extreme premature infants, the linear regression model testing the link between clinical risk factors and cognitive and behavioral measures has the inherent risk of Type I and Type II errors. Nevertheless, our results concur with published data from larger cohorts.

Although connectomics still present technical challenges, they remain an ideal complementary tool to assess structural co-variance between brain regions on a global brain network scale (Alexander-Bloch et al. 2013).

Conclusion

The new approach of whole-brain connectome analysis proposed here allowed to comprehensively study both long-ranging and short-ranging connectivity in preterm school-age children. The results suggest that EP and IUGR have altered SC of CBTCL connections that start their maturation early in development. SC alterations of the orbitofrontal cortex circuitry (responsible for reward learning, reality check, and socio-emotional processing) were evidenced by the whole-brain connectome approach. Specific short associational cortico-cortical connections, developing later and most likely influenced by environmental sensory inputs, showed both diminished and increased strength of connectivity between areas known to play an important role in language, problem solving, and social behavior. The strength of altered connections was associated with their socio-cognitive performance. In conclusion, the whole-brain connectivity analysis provides a link between early life events (extreme prematurity and IUGR), circuitry development, and specific socio-cognitive disabilities.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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