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Motor and cortico-striatal-thalamic connectivity alterations in intrauterine growth restriction

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Condensation: This study demonstrated altered microstructure in specific brain networks (motor and cortico-striatal-thalamic), which is specifically related with its respective functional outcome.

Short title: Altered structural connectivity in IUGR

ABSTRACT

Background: Intrauterine growth restriction is associated with short- and long-term neurodevelopmental problems. Structural brain changes underlying these alterations have been described using different magnetic resonance based methodologies, including changes in whole structural brain networks. However, evaluation of specific brain circuits and its correlation with related functions has not been investigated in intrauterine growth restriction.

Objectives: In this study we aimed to investigate differences in tractography-related metrics in cortico-striatal-thalamic and motor networks in intrauterine growth restricted children and whether these parameters were related with their specific function in order to explore its potential use as imaging biomarker of altered neurodevelopment.

Methods: We included a group of 24 intrauterine growth restriction and 27 controls that were scanned at one year of age acquiring T1-weighted and 30 directions diffusion MR images. Each subject brain was segmented in 93 regions using Anatomical Automatic Labeling atlas and deterministic tractography was performed. Brain regions included in motor and cortico-striatal-thalamic networks were defined based in functional and anatomical criteria. Within the streamlines resulting from the whole brain tractography, those belonging to each specific circuit were selected and tractography-related metrics including number of streamlines, fractional anisotropy, and integrity were calculated for each network. We evaluated differences between both groups and further explored the correlation of these parameters with the results of socio-emotional, cognitive, and motor scales from Bayley Scale at two years of age.

Results: Reduced fractional anisotropy (cortico-striatal-thalamic 0.319 (0.018) vs 0.315 (0.015), p= 0.010; motor 0.322 (0.019) vs 0.319 (0.020), p=0.019) and integrity cortico-striatal-thalamic 0.407 (0.040) vs 0.399 (0.034), p= 0.018; motor 0.417 (0.044) vs 0.409 (0.046), p=0.016) in both networks were observed in intrauterine growth restriction group with no differences in number of streamlines. More importantly, strong specific correlation was found between tractography-related metrics and its relative function in both networks in IUGR children. Motor network metrics were specifically correlated with motor scale results (fractional anisotropy rho= 0.857, integrity rho= 0.740) and cortico-striatal-thalamic network metrics were correlated with cognitive (fractional anisotropy rho= 0.793, integrity rho= 0.762) and socio-emotional scale (fractional anisotropy rho= 0.850, integrity rho= 0.877)

Conclusions: These results support the existence of altered brain connectivity in intrauterine growth restriction demonstrated by altered connectivity in motor and cortico-striatal-thalamic networks, with reduced fractional anisotropy and integrity. The specific correlation between tractography-related metrics and neurodevelopmental outcomes in IUGR shows the potential to use this approach in order to develop imaging biomarkers to predict specific neurodevelopmental outcome in infants at risk due to intrauterine growth restriction and other prenatal diseases.

KEYWORDS: Intrauterine growth restriction, Connectivity, Tractography-related metrics, Integrity, Fractional anisotropy, Magnetic resonance imaging, Brain networks

1. INTRODUCTION

Intrauterine growth restriction (IUGR) is a prevalent condition that affects 5-10% of all pregnancies in developed countries, being associated with short- and long-term neurodevelopmental problems, including motor and cognitive delay[1-3]. IUGR has been proposed, together with prematurity, as the cause of one-quarter of cases of special educational need due to sensory, motor and intellectual disabilities [4]. Moreover, IUGR has been proposed as a risk factor for developing autism spectrum disorders (ASD) [5]and attention deficit hyperactivity disorder (ADHD)[6]. Structural brain changes underlying altered neurodevelopment have been described using magnetic resonance imaging (MRI), starting in prenatal period [7-11], persisting at neonatal and early infancy [12-17] and at adolescence [18, 19]. However, we are still far from identifying those individuals at high risk of abnormal neurodevelopment, which are the potential target for early therapeutic interventions. Being a crucial clinical and experimental need the development of imaging biomarkers[20], it is extremely important to better characterize the brain reorganization underlying neurodevelopmental and cognitive dysfunctions in IUGR.

Several brain regions have been demonstrated to be affected by IUGR, including both gray and white mater [7, 12-15, 17, 21]. Specifically, global reduction of white matter (WM) volume [18, 19], but also changes in specific regions such as thinning of corpus callosum [18]have been reported, being part of these changes already present in prenatal period[22]. Recently, diffusion MRI, which provides indirect information about brain microstructure [23], has been used to detect changes occurring in IUGR [24-27] and other fetal conditions associated with reduced brain oxygen supply such as cardiac defects [28]. Aside from assessing changes in diffusivity parameters, diffusion MRI allows to

reconstruct the trajectory of the WM tracts within the brain by means of tractography, which combined with brain segmentation, allows to build brain networks. In this line, structural brain networks of one-year-old IUGR infants have been reported to have reduced level of organization together with a pattern of regional network features that is associated with latter neurodevelopmental outcomes [29, 30]. However, to the best of our knowledge, evaluation of specific brain circuits and its correlation with related functions has not been investigated in IUGR. Tractography-related metrics can be obtained in order to estimate features along the WM pathways among brain regions regulating specific brain functions. This approach has been used to identify changes in diseases of neurodevelopment such as ADHD [31], ASD [32] and periventricular leukomalacia [33, 34]. Several metrics have been proposed to be used to describe WM characteristics within specific networks, such as number of fibers, fractional anisotropy (FA) [31, 35], and radial diffusivity [36, 37]. Recently, INT has been proposed as a parameter to further evaluate intrinsic properties of WM tracts [38], which considers both anisotropy and radial diffusivity, being more sensitive to lack of linear diffusion into the tissue. Applying tractography-related metrics to IUGR could provide additional relevant information for a better understanding of the problem and its consequences, since it could bring straightforward information in relation to the identification of specific disorders in IUGR population.

In the present study we investigated tractography-related metrics in cortico-striatal-thalamic and motor networks obtained from a group of one-year-old infants with and without IUGR. We computed the number of streamlines obtained by tractography, mean FA and INT of each network and evaluated differences between both groups. We

also explored the correlation of these parameters with the results of socio-emotional, cognitive, and motor scales of Bayley's test at two years of age.

2. MATERIAL AND METHODS

2.1. Subjects

In this study we included part of prospective cohort of IUGR included in a previous study of our group [29]. From an original sample size of 83 fetuses (42 IUGR and 41 controls) recruited consecutively we excluded 5 controls that were born below 28 weeks of pregnancy. We also excluded 8 IUGR and in 5 controls based on structural MRI findings (four increased cisterna magna, seven ventricular dilatations and two WM lesions). In addition, 10 IUGR and 4 controls did not pass quality criteria due to motion artifacts hampering proper tractrography reconstruction, comprising a final sample of 24 IUGR and 27 controls. Following well-established criteria[39], IUGR was defined as a fetal estimated weight below 10th centile confirmed at birth, both according to local reference standards[40]. Control subjects were defined as fetuses with fetal estimated weight between the 10th and 90th customized centiles according to local reference [40] confirmed at birth. Pregnancies were dated according to the first-trimester crown-rump length measurements [41]. Infants with chromosomal, genetic, or structural defects and signs of intrauterine infection or neonatal early onset sepsis were excluded from this study. Neonatal data were prospectively recorded including: gestational age (GA), birth weight, gender, Apgar at 5 min, umbilical artery pH and neonatal complications. Maternal education was recorded as low, intermediate or high educational level. Maternal smoking status during pregnancy and breastfeeding were also recorded. Growth parameters (weight, length, body mass index and head circumference) were recorded at 12 months and were normalized for local standards [42]. The study protocol was approved by the local Ethics Committee, and written

informed consent was obtained from the parents or legal guardians of all participants (2008/4422).

2.2. Neurodevelopmental assessment

Neurodevelopmental outcome was assessed at 21 months of corrected age (±3 months) with the Bayley Scale for Infant and Toddler Development, Third edition (BSID-III), which evaluates five distinct scales of development [43]. For this study we considered results in cognitive, socio-emotional behavior, and motor scales. The scales have scores with a mean of 100 and S.D. of 15. All developmental examinations were performed by a blinded single trained psychologist examiner with previous experience with the BSID-III.

2.3. MRI data acquisition

Children were scanned at 12±2 months, during natural sleep using a TIM TRIO 3.0 T whole body MR scanner (Siemens, Germany). High resolution structural T1 and T2 weighted images and 30 diffusion volumes were acquired as previously described [29]. Structural T1 and T2 weighted images were evaluate in order to exclude brain abnormalities. All acquired MRI structural and diffusion images were visually inspected for apparent or aberrant artifacts and subjects excluded accordingly.

2.4. MRI processing

The methodology performed to process MRI was previously described in [29, 30]. Briefly, the acquired images of each subject were skull-stripped [44], segmented into WM, GM and cerebrospinal fluid (CSF) [45] using specific probability maps [46]. Each subject brain was regionally parcellated in the native space with a version of the AAL atlas of 116 regions [47], adapted to one-year-old infants [46]. Cerebellar regions were merged into vermis, right and left cerebellum, resulting in a total of 93 regions per subject. Whole-

brain deterministic tractography was performed for each subject using a Diffusion Tensor Imaging (DTI) based Fiber Tracking algorithm with Log-Euclidean Metrics [48], available on MedINRIA 1. FA threshold of 0.2 was chosen as stopping criterion for the tractography algorithm [49] and streamlines were confined to the WM mask.

2.5. Tractography metrics

Definition of circuits of interest

In this study two specific brain circuits were studied: motor and cortico-striatal-thalamic (CST). Motor network was defined as those fibers starting at the motor cortex (primary motor cortex or supplementary motor area) and passing through one of the following regions: post-central gyrus, superior parietal gyrus, cerebellum, nucleus palidus, caudate nucleus, putamen nucleus, and thalami [50, 51]. CST network was defined as those fibers starting in frontal cortex (superior frontal gyrus, medial superior frontal gyrus, middle frontal gyrus, and inferior frontal gyrus opercular and triangular part) and passing through the striatum or nucleus pallidus and the thalami [31]. Within the streamlines resulting from the whole brain tractography, those belonging to each specific circuit were selected and described by a set of parameters described below (Figure 1, Table S1).

Tractography metrics

Three different measures were considered for the quantitative analysis of brain circuits previously defined: number of streamlines belonging to each circuit, FA, and INT.

Number of stream lines was obtained counting those belonging to defined circuits. FA describes the diffusion anisotropy [23], which has been related with the presence, organization and/or maturation of fibers. The mean FA along each streamlines in the circuit was computed, and the resulting values averaged on the whole circuit obtaining

a single value. INT was defined in [38] as the relationship between FA and radial diffusivity, being higher values related to a high level of myelination, and being more sensitive to lack of linear diffusion into the tissue. INT was computed in each streamline and averaged in all the streamlines of the circuit as:

$$I = \frac{FA}{D_{rad}}$$

where D_{rad} is the radial diffusivity $D_{rad} = \frac{1}{2}(\lambda_2 + \lambda_3)$, being λ_2 y λ_3 the second and third eigenvalues of the matrix representing the diffusion tensor.

2.6. Statistical analysis

Statistical comparisons among groups were performed by general linear models with gender, maternal education level, smoking during pregnancy, and breastfeeding as cofactors and GA at delivery as a covariate. When analyzing tractography-related metrics, brain volume was added as covariate. For categorical variables, chi-squared test was used. Partial correlations between tractography metrics and BSID-III results were also performed with gender, GA at delivery, maternal education level, smoking during pregnancy, breastfeeding and brain volume as controlling variables. Due to the exploratory nature of this analysis, significance was declared at $p<0.05$ (uncorrected). The software package SPSS 19.0 (SPSS, Chicago, IL) was used for the statistical analyses.

3. RESULTS

Neonatal data, demographic characteristics and BSID-III scores are included in Table 1. No difference was found in the proportion of preterm infants between groups (<37 weeks: control 10 (37%) and IUGR 8 (33.3%)) No significant differences were found in neonatal results among groups.

At the time of MR, IUGR babies were significantly lighter and shorter, but no differences were found neither in cephalic perimeter, nor body mass index. Regarding BSID-III test, IUGR infants showed a trend to present lower score in the three scales, reaching statistical significance in motor scale. It should be noted that we only have available data about cognitive and motor scale in 68.8% of cases and socio-emotional scale in 62.7%. No differences were observed between those with and without neurodevelopmental information (mean GA at delivery 38.1(2.7) vs 36.0(4.6) weeks and proportion of IUGR 43.8% vs 48.6%, respectively).

By means of MRI analysis, no significant differences were found in brain (8.44 (0.90) $\times 10^5 mm^3$ vs 8.04 (0.77) $\times$ $10^5 mm^3$, p=0.085) and WM volume (3.52 (0.38) $\times 10^5 mm^3$ vs 3.45 (0.34) $\times$ $10^5 mm^3$, p=0.508). Quantitative metrics results showed significant reduction in mean FA and INT in both brain networks, with no differences in number of streamlines (Figure 2). When correlation between these parameters and BSID-III scores were evaluated in IUGR group, a specific correlation was found between each circuit and their associated test outcome. On the contrary, correlations between motor network and cognitive socio-emotional scales and between CTS network and motor BSID-III outcome were not significant (Table 2).

4. COMMENT

Although differences in brain development of IUGR babies have already been described using different approaches [7, 8, 10, 12-19, 21, 22], to the best of our knowledge, this issue had not been tackled from the analysis of specific brain circuits associated to a given function. The results obtained demonstrated a significant reduction in mean FA and INT of both motor and CST networks, suggesting the existence of altered maturation and organization of the fiber tracts within these networks in IUGR infants. In addition, we demonstrated that these parameters were highly and specifically correlated with related neurodevelopmental outcomes at two years of age supporting the notion that tractography related metrics in specific circuits could be used as imaging biomarkers to predict neurodevelopmental outcome of IUGR infants.

The group of babies included in our study did not showed differences in GA at delivery or neonatal morbidity, which allow us to exclude the impact of these parameters in the neurodevelopmental outcome obtained at two-year-old infants. Additionally, no differences were identified in the proportion of babies that were breastfeed at least 3 months after birth, which have been related to positive effects on WM development and maturation [52] and neurodevelopment, especially in IUGR babies [53]. However, mother smoking during pregnancy status, which has been previously described to increase IUGR risk [54, 55], was found significantly increased in IUGR group. We acknowledge that just including this variable as a co-factor in the statistical analysis could not be completely disentangling the real effect of smoking on neurodevelopment, but it certainly would reduce its effect on the analysis. In our population, despite being all averaged scores within normal range in both populations,

IUGR infants showed lower averaged performance in cognitive and socio-emotional areas with significant decrease in motor scale, which is in line with previous data showing poorer neurodevelopment in IUGR [1-3]. Impaired motor performance has been described in IUGR as soon as in neonatal period [56], persisting during childhood [57] and in adulthood[58], involving both gross and fine motor. Effects on socio-emotional development have also been documented after growth restriction with a reduction of social interaction in neonatal period [56], decreased performance in personal-social and communication areas at two years [59] and behavioral effects in adulthood[58]. Finally, cognitive delay has been extensively reported during childhood, which partially determines poor performance at school [57]. It has been reported that, at 14 years of age, up to 27% of the children with IUGR attended special education or private education compared to 5% in the general population [58]. Lack of statistical significance in cognitive and socio-emotional areas when comparing neurodevelopmental outcomes in our study could be related with small sample size, since part of this population has been included in a previous study in which significant differences were found [29].

Analysis of quantitative metrics showed significant reduction in mean FA and INT in motor and CST networks of IUGR babies, with no differences in number of streamlines reconstructed. Analysis of specific WM tracts have been previously applied in babies with focal brain lesions and congenital hemiparesia, demonstrating that diffusion parameters in corticospinal tract were different in those babies with hemiplegia, being correlated with severity of motor outcome [60, 61]. Corticospinal tract has also been analyzed in children with spastic cerebral palsy demonstrating that those with worst motor functioning have decreased number and volume of fibers with no differences in

diffusion parameters [34]. In contrast with our results, metrics based in number or volume of WM tracts was significantly different in these studies. This could be explained by the fact that population included were severely affected children that have suffered serious brain damage including ischemic or hemorrhagic damage and periventricular leukomalacia, two conditions that imply WM damage *per se*. However, this metric should be taken with caution, since is highly influenced by several parameters such as fiber length, curvature, and acquisition quality [62], while parameters based in anisotropic characteristics of the tissue are more reliable[63]. Reduction of FA in specific WM circuits have been demonstrated in neurodevelopmental disorders such as ADHD [31, 64] and ASD [32]. This change has been suggested to reflect axonal degeneration or less well-organized tract [35], as demonstrated in ADHD children with reduction in FA with no changes in magnetization transfer ratio [31], which is a marker of myelin content [65]. In our study, reduction of FA in both circuits in IUGR was associated with decreased INT, a parameter that provide information about organization of fibber bundles within a WM tract [38]. This parameter takes into account the radial diffusivity, which is highly related with myelin density and have been demonstrated to be increased after hypoxic-ischemic encephalopathy[66] and in children with focal brain injury with mild asymmetry in motor function [60]. Reduction in both FA and INT for IUGR children suggested that WM tracts within these specific brain networks are less organized and myelinated, leading to an altered structural connectivity.

Regarding structural-functional correlates in IUGR, we showed a specific association of each network tractography metrics with related neurodevelopmental outcome. These results are in line with previous data on ADHD, where reduction of FA in the frontostriatal WM tracts was specifically correlated with different particular

symptoms: orbitofrontal tract was correlated with inattention whereas left dorsolateral and right medial prefrontal were correlated with hyperactivity-impulsivity symptoms[64]. This specificity was also found in a rabbit model of IUGR, in which left anxiety network correlate with neurobehavioral performance in an open-field test [25]. Overall, the results presented are in line with previous data demonstrating changes in structural connectivity after IUGR [29, 67]and support the evidence of altered structural connectivity being involved in the functional impairment associated with IUGR. Importantly, the specificity demonstrated between tractography-related metrics at one-year period and later performance, supports the idea that these parameters could be used not only to identify those babies with abnormal neurodevelopment, but to identify specific neurodevelopmental delays.

Our study has some issues that deserve some discussion. Firstly, the use of generic neurodevelopmental tests instead of specific tests to evaluate motor performance and ADHD. Since this study was part of a larger prospective cohort of IUGR in which postnatal long-term follow-up was done with BSID-III[68], we found appropriate to use the selected scales for the objective of this study. In addition, the period between MRI acquisition and BSID-III could have some effects on the robustness of correlations between tractography-related metrics and Bayley results since different factors can have an influence in neurodevelopment. However, the evidence of these correlations even after one year should be considered as a positive characteristic in terms characteristic in terms of obtaining potential imaging biomarkers. Secondly, definition of motor and CST network was based in previous knowledge, but, since there is not a standard criteria in their definition, we acknowledge that some supplementary regions could be included or missed. In addition, in spite of using region of interest analysis we

decided to apply specific networks analysis, since tract based analysis has showed more robustness and reproducibility [69]. Thirdly, FA values in obtained in our study are lower compared with those reported in previous studies using preterm population [70]. This difference could be explained by the selection cortico-spinal tract and corpus callosum, both tracts being those with higher FA [71] while motor networks computed in this study not only included cortico-spinal, but also some short-range tracts that could have more crossing-fibers areas (which involves lower FA areas) and can have an effect on mean FA on the whole circuit. In addition, differences in acquisition protocol and tractography processing could have some effect on this respect [72]. Regarding other technical considerations, the proposed analysis is based on the streamlines obtained by means of a deterministic DTI-based tractography algorithm that is less robust than other techniques to detect fibers crossing. However, due to acquisition protocol including only 30 gradient directions, the use of other kind of techniques as Q-ball or spherical deconvolution is limited. Besides the case-control design, the use of tract metrics averaged across circuits makes these measures independent on the number of streamlines assessed by the tractography algorithm and less vulnerable to variability in the streamlines pathways. Despite the fact that number of streamlines has been extensively used in literature as a direct measure of quantification of white matter tracts, there are a lot of concerns regarding its use since is a parameter that is highly influenced by a lot of factors [62]. In our study, the lack of differences in this parameter together with small but significant changes in relative metrics such as mean FA and INT, support the use of these relative parameters in further studies.

In conclusion, analysis of quantitative tractography metrics in IUGR children demonstrated altered connectivity in motor and CST networks, as demonstrated with

reduced FA and INT, specifically correlated with neurodevelopmental outcomes. Further studies using different populations of children at risk after suffering perinatal insults and more specific test will be of help to support this data. Nevertheless, the results presented show the potential to use this approach in order to develop imaging biomarkers to predict specific neurodevelopmental outcome, opening the opportunity to apply individualized early therapeutic interventions to infants at high risk of suffering neurodevelopmental problems of a prenatal origin.

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TABLES

Table 1. Neonatal data, demographic characteristics, and BSID-III scores in the study groups.

	Controls n=27	IUGR n=24	p
Neonatal data			
Gestational age at delivery (weeks)	36.6 (5.0)	36.7 (3.2)	0.91
Birth-weight (gr)	2699 (989)	2053 (608)	0.008
Birth-weight centile	52.8 (26.4)	1.9 (2.8)	<0.001
Gender distribution (male/female)	17/15	15/9	0.48
Demographic characteristics			
Maternal education less than high school	26%	33%	0.56
Breastfeeding longer than 3 months	74%	59%	0.27
Smoking during pregnancy	15 %	46%	0.015
Corrected age at MR (months)	12.9 (1.6)	13.2 (1.6)	0.59
Corrected age at BSID-III (months)	20.1 (3.2)	21.7 (3.0)	0.12
Population characteristics at MR			
Weight z-score	-0.47 (0.86)	-1.06 (0.85)	0.018
Height z-score	-0.08 (1.21)	-1.01 (0.97)	0.006
Body mass index z-score	17.03 (1.51)	17.07 (1.57)	0.93
Cephalic perimeter z-score	-0.51 (1.04)	-1.09 (1.30)	0.10
BSID-III scores			
Cognitive [a]	109.7 (12.7)	105.9 (12.7)	0.58*
Socio-emotional [b]	119.1 (30.3)	110.3 (24.0)	0.50*
Motor [a]	106.6 (14.7)	101.1 (9.3)	0.042*

BSID-III: Bayley Scale for Infant and Toddler Development, Third edition; IUGR: Intrauterine growth restriction

[a] Available only in 18 controls and 17 IUGR, [b] Available only in 16 controls and 16 IUGR

* Adjusted by gender, maternal education level, smoking during pregnancy, breastfeeding, and GA at delivery.

Table 2. Mean correlation coefficients between quantitative tractography metrics and cognitive, socio-emotional behaviour, and motor scales of BSID-III in the IUGR group.

	Cognitive	Socio-emotional	Motor
Cortico-striatal-thalamic network			
Number of fibers (n)	-0.536	-0.441	-0.472
Fractional anisotropy	0.793*	0.850**	-0.256
Integrity	0.762*	0.877**	-0.143
Motor network			
Number of fibers (n)	0.242	-0.081	0.427
Fractional anisotropy	0.430	0.129	0.857**
Integrity	0.217	0.069	0.740*

Gender, GA at delivery, maternal education level, smoking during pregnancy, breastfeeding, and brain volume were included as controlling variables

*<p 0.05, **<p 0.001

FIGURES CAPTIONS AND LEGENDS

Figure 1. Motor and cortico-striatal-thalamic networks definition.

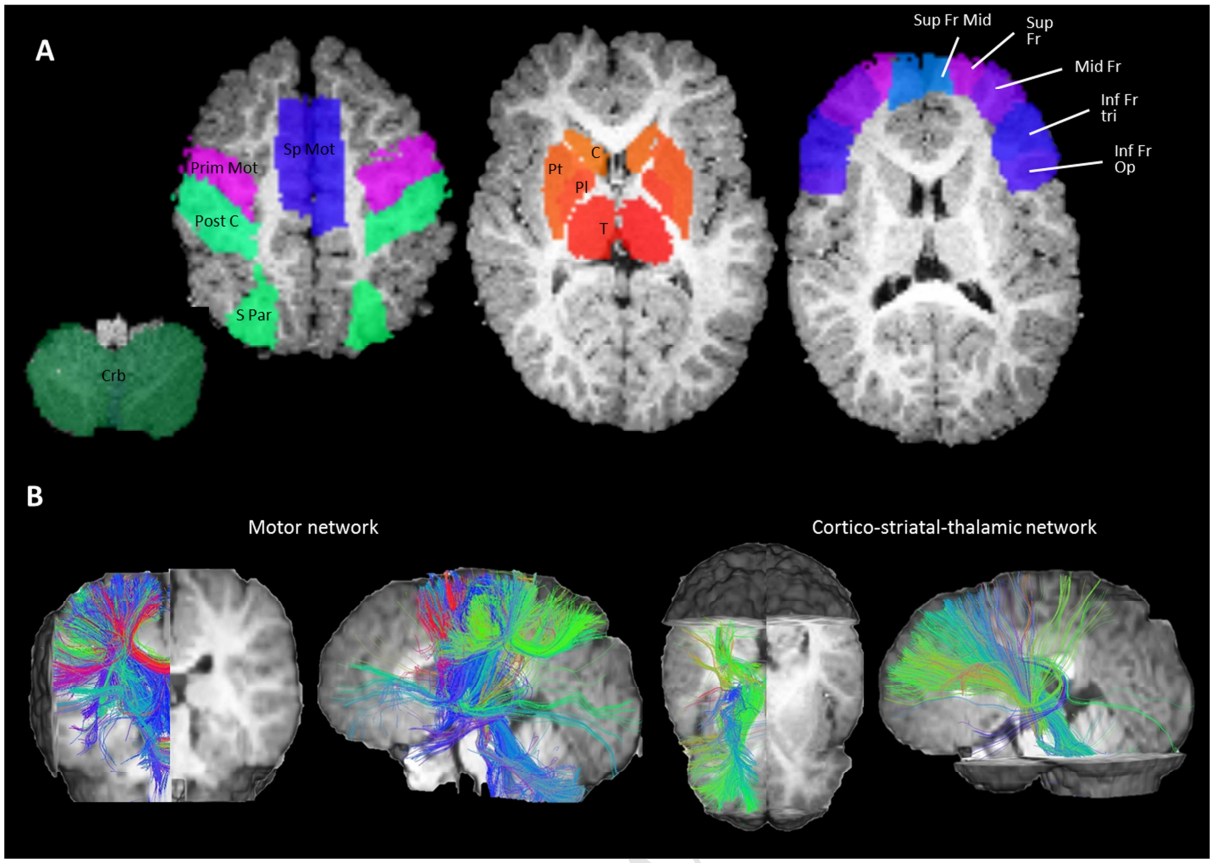
Motor network: (A) brain regions included (motor cortex, post-central gyrus, superior parietal gyrus, cerebellum, nucleus palidus, caudate nucleus, putamen nucleus, and thalami) and (B) white matter tracts reconstructed

Cortico-striatal-thalamic network: (C) brain regions included (frontal cortex, striatum, pallidus and thalami) and (D) white matter tracts reconstructed.

Figure 2. Quantitative tractography metrics of cortico-striatal-thalamic and motor networks in study groups

Values are mean and standard deviation.

p values are General Lineal Model significance among groups corrected for brain volume, education, smoking, gender, breastfeeding and GA at delivery



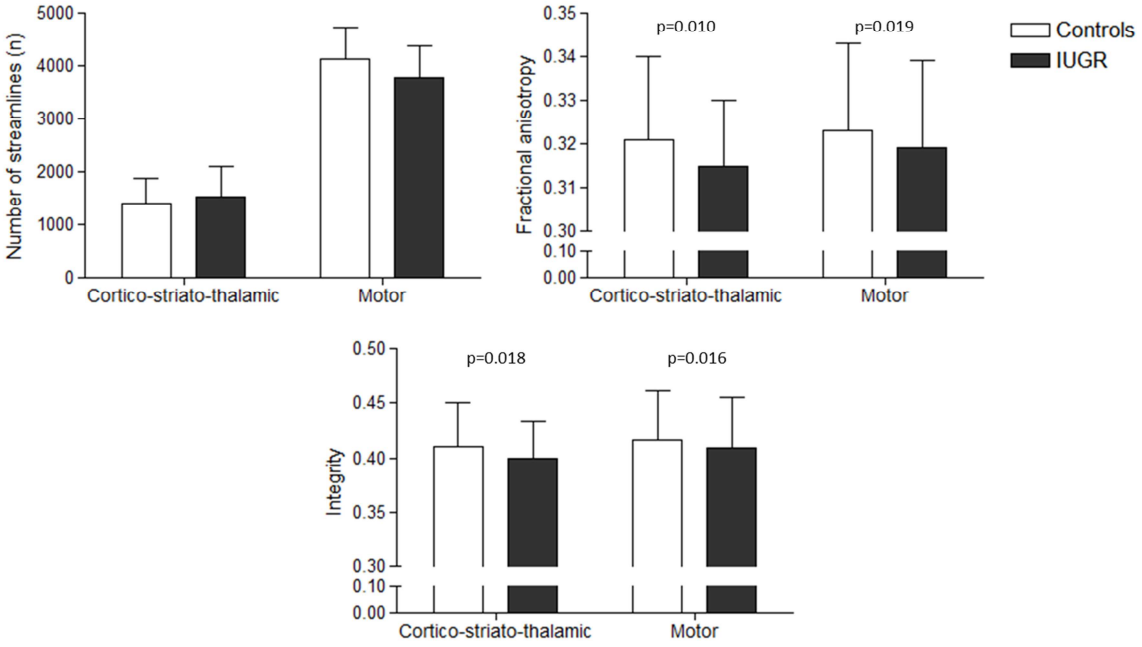


Table S1- Regions of AAL of motor and cortico-striato-thalamic networks

	AAL regions
Motor network	
Primary motor cortex	1,2
Supplementary motor área	19,20
Post-central gyrus	57,58
Superior parietal gyrus	59,60
Cerebellum	91 and 115, 92 and 116
Globus pallidus	75,76
Caudate nucleus	71,72
Putamen	73,74
Thalamus	77,78
Cortico-striatal-thalamic network	
Superior frontal gyrus	3,4
Medial superior frontal gyrus	23,24
Middle frontal gyrus	7,8
Inferior frontal gyrus opercular part	11,12
Inferior frontal gyrus triangular part	13,14
Caudate nucleus	71,72
Putamen	73,74
Globus pallidus	75,76
Thalamus	77,78