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Longitudinal study of neonatal brain tissue volumes in preterm infants and their ability to predict neurodevelopmental outcome

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ABSTRACT

Premature birth has been associated with poor neurodevelopmental outcomes. However, the relation between such outcomes and brain growth in the neonatal period has not yet been fully elucidated. This study investigates longitudinal brain development between birth and term-equivalent age (TEA) by quantitative imaging in a cohort of premature infants born between 26 and 36 weeks gestational age (GA), to provide insight into the relation of brain growth with later neurodevelopmental outcomes.

Longitudinal T2-weighted magnetic resonance images (MRI) of 84 prematurely born infants acquired shortly after birth and TEA were automatically segmented into cortical gray matter (CGM), unmyelinated white matter (UWM), subcortical gray matter (SGM), cerebellum (CB) and cerebrospinal fluid (CSF). General linear models and correlation analysis were used to study the relation between brain volumes and their growth, and perinatal variables. To investigate the ability of the brain volumes to predict children's neurodevelopmental outcome at 18–24 months and at 5 years of age, a linear discriminant analysis classifier was tested and several general linear models were fitted and compared by statistical tests.

From birth to TEA, relative volumes of CGM, CB and CSF with respect to total intracranial volume increased, while relative volumes of UWM and SGM decreased. The fastest growing tissues between birth and TEA were found to be the CB and the CGM. Lower GA at birth was associated with lower growth rates of CGM, CB and total tissue. Among perinatal factors, persistent ductus arteriosus was associated with lower SGM, CB and IC growth rates, while sepsis was associated with lower CSF and intracranial volume growth rates.

Model comparisons showed that brain tissue volumes at birth and at TEA contributed to the prediction of motor outcomes at 18–24 months, while volumes at TEA and volume growth rates contributed to the prediction of cognitive scores at 5 years of age. The family socio-economic status (SES) was not correlated with brain volumes at birth or at TEA, but was strongly associated with the cognitive outcomes at 18–24 months and 5 years of age.

This study provides information about brain growth between birth and TEA in premature children with no focal brain lesions, and investigates their association with subsequent neurodevelopmental outcome. Parental SES was found to be a major determinant of neurodevelopmental outcome, unrelated to brain growth. However, further research is necessary in order to fully explain the variability of neurodevelopmental outcomes in this population.

Introduction

The last trimester of pregnancy is the stage of major brain growth and development (Volpe, 2008). Prematurely born children spend a part of this crucial period outside the womb, making them vulnerable to a multitude of risk factors susceptible to perturb their brain growth and development, and affect their motor and cognitive outcomes. Indeed, preterm (PT) birth has been associated with adverse neurodevelopmental outcomes, such as motor impairment, cognitive and language difficulties, and behavioral or attention problems (Larroque et al., 2004; Aarnoudse-Moens, 2009; Aarnoudse-Moens et al., 2009; Moore et al., 2012). Such adverse outcomes can occur even in the absence of significant brain lesions and can be related to subtle alterations in brain development (Wood et al., 2005; Ment et al., 2009). For some PT children, these difficulties may persist throughout childhood and adolescence and therefore have a significant impact on their school achievements and quality of life

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Abbreviations

TEA	term-equivalent age
MRI	magnetic resonance imaging
CSF	cerebrospinal fluid
UWM	unmyelinated white matter
CGM	cortical gray matter
SGM	subcortical gray matter
IC	intracranial
MDI	mental developmental index
PDI	psychomotor developmental index
MPC	mental processing composite
SES	socioeconomic status
LDA	Linear Discriminant Analysis
GLMs	General Linear models

(Aarnoudse-Moens, 2009; Mulder et al., 2009; Lindstrom et al., 2011; Jaekel et al., 2013; Wilson-Ching et al., 2013). In addition, these morbidities have important public health and economic implications. A key responsible for such poor outcomes seems to be a combination of antenatal conditions leading to PT birth, postnatal brain injury and impaired brain maturation (Ment et al., 2009; Volpe, 2009a; Xiong et al., 2012). In order to better understand and prevent these impairments, neonatologists need tools to help them identify the most vulnerable PT infants, and better prognosticate neurodevelopmental outcomes.

Recent advances in magnetic resonance imaging (MRI) have allowed the acquisition of good quality images of the newborn brain, which, together with the emergence of adequate post-processing tools, has allowed the extraction of global and regional tissue brain volumes. In turn, this has prompted research into the possible contribution of such information to understanding the relationship between impairments in brain development and the poor outcomes associated with prematurity. Several studies have shown that, in comparison with their term-born peers, PT born infants have altered brain tissue volumes at term-equivalent age (TEA) (Peterson et al., 2003; Inder et al., 2005; Mewes et al., 2006; Thompson et al., 2007; Keunen et al., 2012; Padilla et al., 2015), and also in childhood and adolescence (Peterson et al., 2000; de Kieviet et al., 2012). Additionally, several authors reported associations between neurodevelopmental outcomes and global and regional tissue volumes at TEA (Peterson et al., 2003; Inder et al., 2005; Woodward et al., 2005; Beauchamp et al., 2008; Lodygensky et al., 2008; Thompson et al., 2008; Van Kooij et al., 2012; Keunen et al., 2016; Monson et al., 2016). However, others did not find evidence of such associations, or found that the associations were weakened or not significant after adjustment for perinatal variables (Shah et al., 2006; Lind et al., 2010; Lind et al., 2011; Cheong et al., 2016; Lee et al., 2016). To improve our understanding of the brain maturation after PT birth, some authors performed longitudinal studies of volumetric brain tissue growth between birth and TEA (Mewes et al., 2006; Kersbergen et al., 2016a,b; Makropoulos et al., 2016), but only few investigated possible relationships between neonatal brain volumes and later neurodevelopmental outcomes (Kapellou et al., 2006; Rathbone et al., 2011; Kersbergen et al., 2016a,b; Lee et al., 2016; Moeskops et al., 2017). Furthermore, studies looking at associations between neonatal brain volumes and outcomes beyond 24 months of age are scarce (Thompson et al., 2008; Lind et al., 2010; Keunen et al., 2016; Lee et al., 2016; Monson et al., 2016). Therefore, recent reviews (Keunen et al., 2012; Anderson et al., 2015) concluded that up to date there is limited evidence regarding the value of neonatal brain volumetric information in predicting neurodevelopmental outcome in childhood.

In order to provide early prediction of neurodevelopmental outcome, it is crucial to be able to identify early perinatal markers of neurodevelopmental outcomes. In this context, the first objective of this study was to investigate longitudinal brain development between birth and TEA in a cohort of relatively healthy PT infants. Additionally, we also investigated whether brain asymmetries are already present at birth or at TEA. The second objective of this study was to investigate the ability of brain volumetric data to predict cognitive/motor outcomes at 18–24 months of corrected age and at 5 years of age.

Methods

Participants

The participants to our study were infants born PT before 36 weeks gestational age (GA) at the University Hospitals of Geneva between 2000 and 2011, who had undergone two MRI exams – one as soon as possible after birth and one at TEA. Exclusion criteria were the presence of congenital or chromosomal abnormalities, or major brain pathology such as intraventricular hemorrhage (grade 3 or higher) and/or parenchymal hemorrhagic infarction on early cerebral ultrasound. Infants who developed major lesions on MRI at TEA were also excluded from the study. Out of 125 infants who had two MRI scans, 41 were excluded because they did not fulfill inclusion criteria, or because image quality in one or both scans was not sufficient to enable automatic tissue segmentation. The remaining 84 infants born between 25 and 36 weeks GA (mean ± SD: 30.15 ± 2.5 weeks) were included in the study.

Perinatal data known from the literature to be associated with neurodevelopmental outcome was taken from the infants' medical records. GA was based on the last menstrual period or prenatal ultrasound. Birth weight z-scores were calculated based on the growth curves by Voigt et al. (2006). Persistent ductus arteriosus (PDA) was defined as a ductus arteriosus requiring medical or surgical closure. Birth asphyxia was diagnosed based on an Apgar score less than 6 at 5 min after birth, and umbilical cord blood pH less than 7.0. Presence of proven sepsis was defined as at least one positive blood culture during the hospital stay. Bronchopulmonary dysplasia (BPD) was defined as a need for supplemental oxygen or ventilatory support at 36 weeks postmenstrual age (Jobe and Bancalari, 2001).

Parental socioeconomic status (SES) was rated according to Largo et al. (1989), based on recorded mother's education and father's occupation. The scores are distributed from 2 to 12, with 2 indicating higher SES.

MRI acquisition and processing

A first MRI examination of all PT infants was performed as soon as possible after birth (GA at scan = 31.78 ± 2.55 weeks, range: 26.6–36.1 weeks) and a second longitudinal scan was acquired at TEA (GA at scan = 40.35 ± 1.03 weeks, range: 38.4–44.4 weeks). Both scans were acquired without sedation, during infants' natural sleep. Infants were positioned inside the scanner wrapped in a vacuum pillow and monitored with electrocardiography and pulse oximetry. Earmuffs were used for noise attenuation. The scans were performed on four different machines because of scanner upgrades throughout the study period: Philips Eclipse (1.5T), Philips Achieva (1.5T), Siemens Avanto (1.5T), and Siemens Trio Tim (3T). Adequate signal-to-noise ratio (SNR) and absence of geometric distortions were verified on each scanner using regular phantom-based quality control programs provided by the vendors. To obtain comparable images, scanning protocols were harmonized among the machines during the study period. Since infant cortex can be as thin as 1–2 mm in some areas, we used the smallest slice thickness possible in order to capture and allow the segmentation of such fine anatomical details (1.5 mm for the older scanners, and 1.2 mm for the more recent scanners).

In-plane resolution was set so as to obtain similar voxel volumes, and thus similar SNR among scanners, namely to 0.7 mm × 0.7 mm on the older scanners, and 0.8 mm × 0.8 mm on the more recent scanners, yielding voxel volumes of 0.735 mm^3, and 0.768 mm^3 respectively. To obtain similar contrast on all scanners, the values of echo times, repetition times, and echo train lengths were chosen to be as close as possible among scanners. Acquisition parameters and number of infants scanned on each of the MRI scanners are presented in the Appendix (Table A).

All scans were automatically segmented into cortical gray matter (CGM), unmyelinated white matter (UWM), subcortical gray matter (SGM), cerebellum (CB), brainstem, and cerebrospinal fluid (CSF) with the method of Gui et al. (2012), which is a segmentation pipeline based on mathematical morphology. The SGM segmentation step of the method was modified by employing a multi-atlas label fusion method (Heckemann et al., 2006), which provided more accurate segmentation. The atlases consisted of SGM segmentations obtained with the original method of (Gui et al., 2012) and manually corrected where necessary. A total of 20 atlases were used (10 for each MRI examination), and they were chosen to represent all scanner types from the study. All segmentations were visually inspected and small manual corrections were applied where necessary (Fig. 1). The automatic phase of the segmentation took about 90 min on an iMac computer (3.4 GHz Intel Core i7, 32 GB RAM) and the manual corrections required an average of 15 min per exam. This allowed the automatic extraction of global and hemispheric tissue volumes. The volume of the brainstem was not considered for statistical analysis since imaged brainstem length varied among scans because of differences in image plane positioning. The volume growth rate (GR) between the birth and TEA scans was calculated as the ratio of the volume difference and the age difference between the two scans. Total brain tissue volume was computed as the sum of all brain tissue volumes, and total intracranial (IC) brain volume was computed as the sum between the total brain tissue volume and the volume of CSF.

Neurodevelopmental outcome data

Children underwent structured neurological and developmental assessments at 18–24 months of age (corrected for the prematurity) and at 5 years of age. The standardized neurological examination was completed by a developmental pediatrician and the developmental assessment was performed by a developmental psychologist, both blinded to children's clinical details as well as possible in a clinical situation. All children had normal neurologic examinations at both time points. Developmental outcomes at 18–24 months were the mental and psychomotor developmental indices (MDI and PDI, respectively) of the Bayley Scales of Infant Development II (Bayley, 1993). Cognitive outcome at 5 years of age was assessed with the French version of the Kaufman Assessment Battery for Children (K-ABC) (Kaufman and Kaufman, 1983), yielding a cognitive score, the mental processing composite (MPC), comparable to the one found in general intelligence tests. All these scores have an expected mean of 100 and a standard deviation (SD) of 15. Thus, at 18–24 months of age, delayed mental development was defined as a MDI score <85, and delayed motor development was defined as a PDI score <85. Normal development was defined as a MDI/PDI score ≥ 85. At 5 years of age, low cognitive outcome was defined as an MPC score <85, and good cognitive outcome was defined as an MPC score ≥ 85. Mental/motor outcome at 18–24 months of age was assessed in 74 out of the 84 children (88.1%) included in the study (5 children moved, 3 refused and 2 were unable to be tracked), whereas cognitive outcome at 5 years of age was available for 56 out of the 84 children (66.7%) included in the study (4 children moved, 7 refused to come back for the follow up, 1 was ill the day of the assessment and 6 were unable to be tracked).

Data collection and evaluation for this study were approved by the Ethics Committee of the Geneva University Hospitals and written consent was obtained from all participating families.

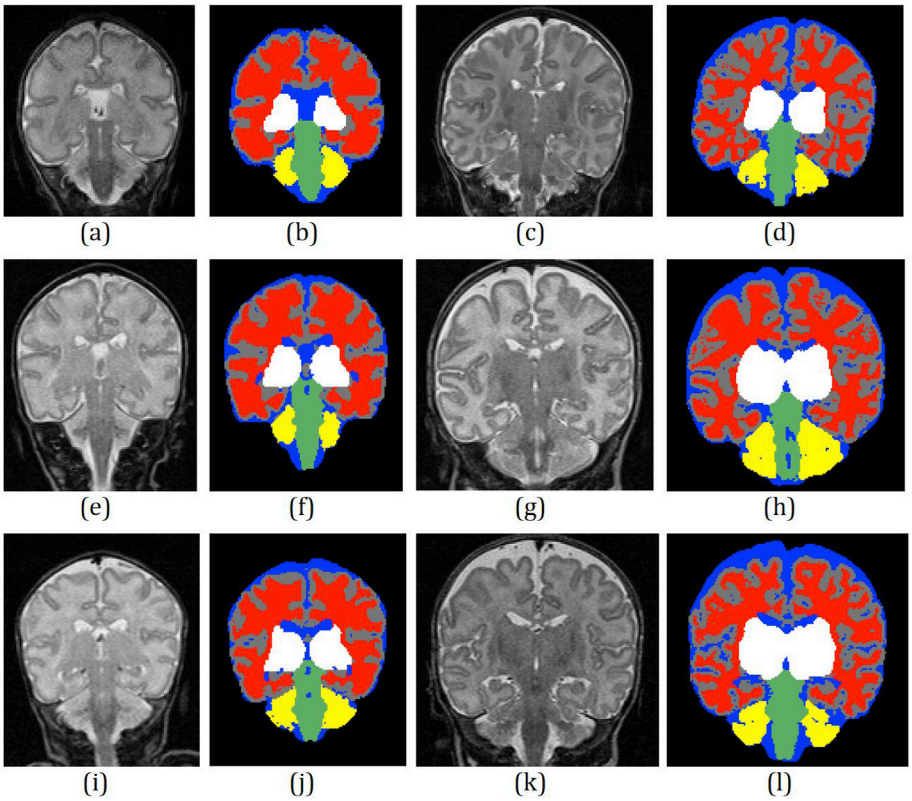

Fig. 1. Automatic segmentation of longitudinal T2-weighted images acquired at birth and TEA of three infants, each corresponding to one line. Gestational ages at acquisition were 30 4/7 GW and 41 3/7 GW for the first infant (a, c), 33 5/7 GW and 39 5/7 GW for the second infant (e, g), and 32 6/7 GW and 40 6/7 GW for the third infant (i, k). Image acquisition was performed on the following scanners: Siemens Avanto (a), Siemens Trio (c), Philips Eclipse (e, g), Philips Achieva (i, k). Segmented tissues: CGM (gray), UWM (red), SGM (white), CB (yellow), brainstem (green), and CSF (blue).

Statistical analysis

Differences between the children included and excluded from the study, as well as between the children who had and those who did not have a cognitive assessment at 5 years of age were evaluated using Student t-tests for continuous variables, and chi-square tests or Fisher exact tests, as appropriate, for categorical variables.

Analysis of covariance revealed no significant effects of scanner type on tissue volumes controlled for GA at birth (Appendix, Table B); therefore, scanner type was not included as a covariate in the following analyzes. Moreover, since correlation analysis showed that none of the volumes or volumes GR was significantly correlated with the SES, we did not adjust the volumetric analyses for SES.

Correlation analysis was used to investigate associations between GA at birth and tissue volumes (absolute and relative to the total intracranial volume) at birth and at TEA, as well as between absolute tissue volumes at birth and at TEA. Correlations of tissue volumes at birth with GA at birth were adjusted for gender, while correlations of tissue volumes at TEA with GA at birth were adjusted for gender and GA at the TEA MRI. Correlations between tissue volumes at birth and at TEA were adjusted for gender, GA at birth and GA at the TEA MRI.

Since factors such as asphyxia, BPD, sepsis and PDA are expected to have an impact on brain development, we evaluated their associations with tissues GR. Thus, multiple general linear models (GLMs) were used to study the associations between tissue volumes GR and the presence of asphyxia, BPD, sepsis and PDA, adjusting for gender and GA at birth, according to the following equation:

$$Volume\ GR = Asphyxia + BPD + Sepsis + PDA + Gender + GA\ birth.$$

Inter-hemispheric asymmetries of CGM, UWM, SGM and CB were assessed at birth and at TEA using paired t-tests.

Furthermore, we investigated the predictive ability of brain volumetric data for the identification of infants with normal or low mental/motor outcome at 18–24 months and normal or low cognitive outcome at 5 years of age, using Linear Discriminant Analysis (LDA) (implemented via R software). In order to build a classifier for the two groups, the brain volumes at birth and at TEA were normalized by birth weight. Then, LDA was applied on the normalized longitudinal volumetric data (CGM, UWM, SGM, CSF, CB, total IC and total brain tissue volume) to classify children into two classes: those with scores < 85 and those with scores ≥ 85. Classifications were performed using the following sets of features: (i) volumetric data at birth, (ii) volumetric data at TEA, (iii) volumetric data at birth and TEA, and (iv) brain volume GR. All cases were considered with and without the addition of GA at birth and SES as features. Leave-one-out cross-validation (LOOCV) was considered in order to avoid overfitting issues. The prediction power of classifiers was assessed by receiver operating characteristic (ROC) curves and evaluated by the area under the curve (AUC) of ROC curves. The same procedure was repeated using different normalization schemes (normalization by brain volume or without normalization).

In order to better understand the ability of brain tissue volumes (at birth or TEA), or GR to predict the developmental outcomes at 18–24 months or 5 years of age, we compared (via F-tests) adjusted R^2 values of different GLMs of the outcomes with either gender, GA at birth, and SES as independent variables or with models obtained by adding volumes (at birth and TEA) and tissue GR. The R^2, which indicates the variance explained by a model increases as long as we add more variables in the model and hence, it is not a good indicator of a better model. However, the adjusted R^2 takes into account the number of variables in the model and favors ease of interpretability. We therefore used this indicator to compare different models.

Statistical analysis was performed with SPSS Statistics and R software. A two-tailed p-value ≤ 0.05 was considered significant for all analyses.

Results

Cohort characteristics

GA at birth, birth weight, birth weight z-score and parental SES were similar between the 84 infants included in the study and the 41 infants not included in the study (Table 1). Moreover, there were no significant differences in gender distribution, rates of BPD, asphyxia and PDA between the two groups. The incidence of sepsis was significantly higher in infants included in the study compared to the infants excluded from the study (16.7% versus 2.4%, p 0.021). No significant differences between neurodevelopmental outcomes at 18–24 months corrected age and 5 years of age were found between groups.

Among children included in the study, there were no significant differences in perinatal characteristics, nor in mental/motor development at

Table 1
Comparison between children included and excluded from the study.

Variables	Children included in the study	Children excluded from the study	*P-value*[a]
Perinatal data	N = 84	N = 41	
Male gender, No. (%)	38 (45.2)	22 (53.7)	0.783
GA, weeks, mean (±SD), range	30.16 (2.56), [25.57, 35.57]	31.02 (2.82), [24.71, 36.57]	0.092
Birth Weight, g, mean (±SD)	1305.77 (405.45), [510, 2730]	1422.56 (485.42), [580, 2680]	0.159
BW z-score, mean (±SD), range	−0.37 (1.13), [-3.06, 2.06]	−0.57 (1.01) [-2.11, 2.38]	0.346
Birth height, cm, mean (±SD), range	38.83 (3.34), [29, 47.5]	39.59 (4.36), [31, 48]	0.301
Birth head circumference, cm, mean (±SD), range	26.93 (2.57), [21.5, 33.6]	27.34 (3.03), [20.5, 32.5]	0.431
Asphyxia, No. (%)	9 (10.7)	5 (12.2)	0.061
BPD, No. (%)	14 (16.7)	9 (22)	0.512
Sepsis, No. (%)	14 (16.7)	1 (2.4)	**0.021**
PDA, No. (%)	16 (19)	7 (17.1)	0.072
Mental/motor development at 18–24 months	**N = 74**	**N = 34**	
MDI, mean (±SD), range	92.22 (14.88), [50, 119]	87.09 (14.93), [57, 128]	0.100
MDI < 85, No. (%)	20 (27)	11 (32.4)	0.570
PDI, mean (±SD), range	85.61 (14.80), [50, 121]	81.68 (18.64), [50, 113]	0.284
PDI < 85, No. (%)	27 (36.5)	14 (41.2)	0.641
Cognitive outcome at 5 years	**N = 56**	**N = 26**	
MPC, mean (±SD), range	100.07 (15.38), [50, 133]	98.11 (15.66), [64, 126]	0.585
MPC < 85, No. (%)	6 (10.7)	3 (10.7)	1.000
Parental socioeconomic status			
SES, mean (±SD), range	5.88 (3.23), [2, 12]	5.85 (2.8), [2, 11]	0.961

SD – standard deviation.

[a] Group characteristics were compared using independent sample t-tests for continuous variables, and chi-square or Fisher's exact test for categorical variables, as appropriate.

Table 2
Comparison between children who had and those who did not have cognitive assessment at 5 years of age.

Variables	Children assessed at 5 years N = 56	Children not assessed at 5 years N = 28	P-value[a]
Perinatal data			
Male gender, No. (%)	24 (42.9)	14 (50)	0.535
GA, weeks, mean (±SD)	30.18 (2.60)	30.11 (2.5)	0.905
Birt h Weight, g, mean (±SD)	1282.95 (432.98)	1351.43 (346.73)	0.469
BW z-score, mean (±SD)	−0.45 (1.16)	−0.23 (1.09)	0.401
Birth height, cm, mean (±SD)	38.61 (3.63)	39.29 (2.64)	0.392
Birth head circumference, cm, mean (±SD)	26.9 (2.66)	26.97 (2.41)	0.912
Asphyxia, No. (%)	6 (10.7)	3 (10.7)	1.000
BPD, No. (%)	9 (16.1)	5 (17.9)	1.000
Sepsis, No. (%)	7 (12.5)	7 (25)	0.213
PDA, No. (%)	10 (17.9)	6 (21.4)	0.694
Mental/motor development at 18–24 months			
MDI, mean (±SD)	92.66 (15.89)	90.95 (11.79)	0.669
PDI, mean (±SD)	86.1 (15.01)	84.21 (14.51)	0.636
Parental socioeconomic status			
SES, mean (±SD)	5.93 (3.17)	5.75 (3.46)	0.835

SD – standard deviation.
[a] Group characteristics were compared using independent sample t-tests for continuous variables, and chi-square or Fisher's exact test for categorical variables, as appropriate.

18–24 months, between children who had and those who did not have a cognitive assessment at 5 years of age (Table 2).

Brain development between birth and TEA

Absolute and relative tissue volumes

Fig. 2 illustrates infant's absolute and relative tissue volumes at birth and TEA. Absolute volumes of all tissue classes increase between the two scans. While the relative volumes of CGM, CB and CSF increase from birth to TEA, we observe a reduction of the relative volumes of UWM (which was found to be the most prominent brain tissue at birth) and of SGM from birth to TEA.

Absolute tissue volumes at birth adjusted for gender showed a significant positive association of all brain tissues with GA at birth (Table 3).

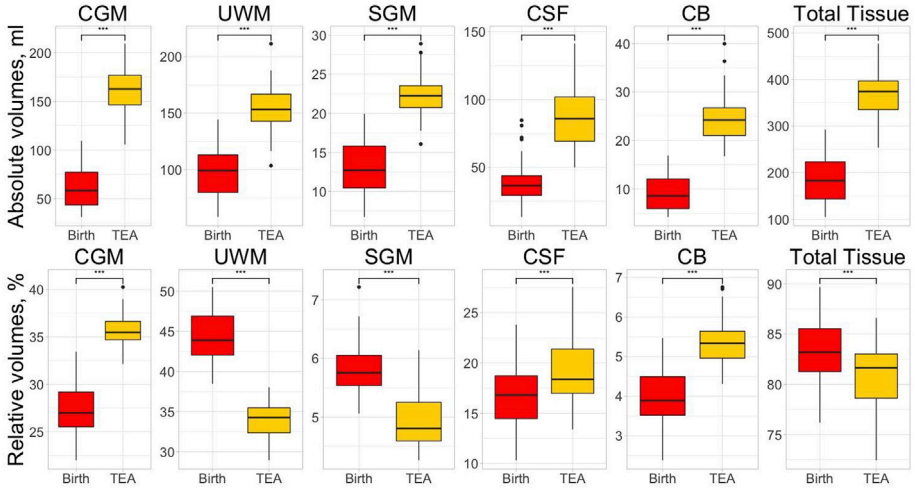

Fig. 2. Absolute and relative cerebral tissue volumes measured at birth and at TEA (expressed as medians with 25/75 centile box, 10th/90th centile error bars, and outliers).

Table 3
Correlations between GA at birth and absolute/relative tissue volumes at birth on one hand and between GA and absolute/relative tissue volumes at TEA on the other hand.

Tissue type	Birth				TEA			
	Absolute volume		Relative volume		Absolute volume		Relative volume	
	r	P-value[a]	r	P-value[a]	r	P-value[b]	r	P-value[b]
CGM	.884	**< .001**	.765	**< .001**	-.041	.718	.037	.738
UWM	.796	**< .001**	-.678	**< .001**	.103	.356	.322	**.003**
SGM	.845	**< .001**	.058	.601	-.008	.940	.089	.424
CB	.863	**< .001**	.730	**< .001**	-.002	.984	.045	.688
CSF	.543	**< .001**	-.075	.500	-.235	**.034**	-.277	**.012**
Total tissue	.855	**< .001**	.075	.500	.026	.816	.277	**.012**
IC	.825	**< .001**			-.066	.558		

[a] Correlations between absolute and relative tissue volumes at birth and GA at birth were adjusted for gender.
[b] Correlations between absolute and relative tissue volumes at TEA and GA at birth were adjusted for gender and for GA at 2nd MRI.

Table 4
Averages of tissue absolute and relative GRs.

Variable	Tissue type						
	CGM	UWM	SGM	CB	CSF	Total tissue	IC
Absolute GR[a], mean (SD) in ml/week	11.94 (2.1)	6.51 (1.3)	1.05 (0.2)	1.76 (0.3)	5.77 (1.9)	21.44 (3)	27.22 (3.7)
Relative GR[b], mean (SD) in %/week	21 (5)	7 (2)	9 (3)	22 (7)	17 (9)	12 (3)	13 (3)

[a] Tissue absolute growth rates were computed as: (TEA volume – birth volume)/(GA TEA – GA birth).
[b] Tissue relative growth rates were computed as: absolute growth rates x 100/birth volume.

The repetition of the analysis using relative tissue volumes at birth (in percentages of IC volumes at birth) showed that only CGM and CB volumes at birth were significantly positively associated with GA at birth, while relative UWM at birth was significantly negatively associated with GA at birth. Associations with GA at birth were no longer significant for relative SGM, CSF and total tissue volumes.

Correlations between GA at birth and absolute volumes at TEA adjusted for gender and GA at 2nd MRI showed that only CSF volumes were significantly negatively correlated with GA at birth (Table 3). The repetition of the analysis using relative tissue volumes (in percentages of IC volumes) at TEA showed positive correlations of relative volumes of UWM and total tissue with GA at birth, and negative correlations of relative CSF volumes with GA at birth. There was no significant correlation between the relative volumes of CGM, SGM and CB and GA at birth.

Moreover, our cohort presented moderate to strong positive correlations between absolute tissue volumes at birth and absolute tissue volumes at TEA, adjusted for gender, GA at birth and GA at the 2nd MRI: CGM: r .526, $p < .001$; UWM: r .707, $p < .001$; SGM: r .452, $p < .001$; CB: r .629, $p < .001$; CSF: r .489, $p < .001$; total tissue: r .662, $p < .001$; IC: r .655, $p < .001$).

Tissue volume GR

Table 4 presents average absolute tissue GR, and tissue GR relative to birth volumes, the latter allowing the comparison of growth rates among

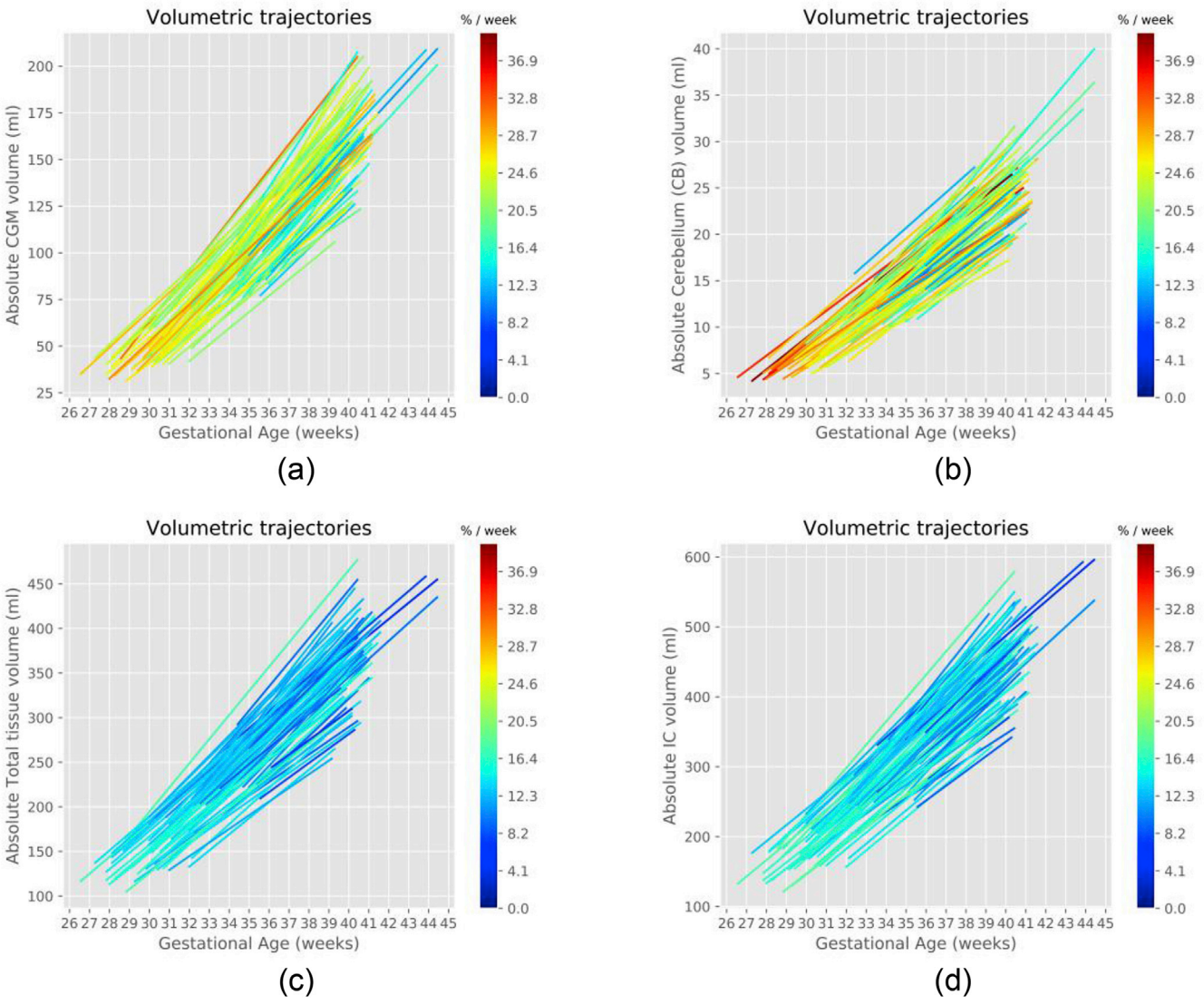

Fig. 3. Individual volume growth trajectories from birth to TEA: (a) CGM volume; (b) CB volume; (c) Total tissue volume; (d) Total IC volume. Line colors indicate tissue growth rates relative to birth volumes (faster and slower growth are represented by red and blue colors, respectively).

tissues. We observe that the fastest growing tissues are the CB (22 ± 7% of its birth volume/week) and the CGM (21 ± 5% of its birth volume/week), followed by the CSF (17 ± 9% of its birth volume/week).

In Fig. 3 we display individual tissue volume trajectories from birth to TEA in our PT born children. Line colors indicate relative tissue growth rates, with red lines depicting faster growth, and blue lines – slower growth.

GLM analysis of tissue volume GR showed a significant positive association of CGM, CB, and total brain tissue GR with GA at birth (Table 5). On the other hand, SGM volume GR was negatively associated with GA at birth. Infants that had suffered from sepsis had significantly lower CSF (mean difference [MD] 1.55 ml/week, 95% CI, 0.26–2.84) and IC GR (MD 3.01 ml/week, 95% CI, 0.64–5.39) than infants who did not suffer from sepsis. Neither BPD nor asphyxia had significant effects on volumes GR. Infants that were suffering from PDA had significantly lower SGM (MD 0.21 ml/week, 95% CI, 0.07–0.35), CB (MD 0.30 ml/week, 95% CI, 0.13–0.47) and IC GR (MD 2.54 ml/week, 95% CI, 0.18–4.89) compared to infants who did not suffer from PDA. Finally, males had significantly higher CB GR (MD 0.21 ml/week, 95% CI, 0.10–0.32) than females.

Table 5
General linear model analysis of tissue volume GR and perinatal factors.

Dependent variables	Model R^2	B (95% CI)	P-value
CGM GR			
Gender	.281	-.63 (−1.50, .23)	.149
GA		.33 (.14, .52)	.001
BPD		.83 (−.40, 2.06)	.183
Asphyxia		-.65 (−1.96, .67)	.330
Sepsis		−1.05 (−2.37, .27	.116
PDA		-.82 (−2.12, .49)	.215
UWM GR			
Gender	.091	-.18 (−.77, .42)	.553
GA		-.04 (−.17, .09)	.573
BPD		.38 (−.46, 1.22)	.374
Asphyxia		-.90 (−1.80, .004)	.051
Sepsis		-.49 (−1.49, .41)	280
PDA		-.42 (−1.32, .48)	.353
SGM GR			
Gender	.202	-.05 (−.14, .05)	.338
GA		-.03 (−.05, −.01)	.005
BPD		.087 (−.044, .217)	.191
Asphyxia		-.02 (−.16, .12)	.769
Sepsis		.02 (−.12, .16)	.804
PDA		-.21 (−.35, −.07)	.004
CSF GR			
Gender	.155	-.19 (−1.04, .66)	.659
GA		-.06 (−.24, .13)	.538
BPD		.49 (−.72, 1.69)	.423
Asphyxia		.91 (−.38, 2.20)	.162
Sepsis		−1.55 (−2.84, −.26)	.019
PDA		-.73 (−2.01, .55)	.258
CB GR			
Gender	.313	-.21 (−.32, −.10)	.000
GA		.04 (.02, .06)	.002
BPD		.15 (−.004, .31)	.056
Asphyxia		-.01 (−.18, .16)	.931
Sepsis		.07 (−.10, .24)	.424
PDA		-.30 (−.47, −.13)	.001
Total tissue GR			
Gender	.226	−1.07 (−2.34, .21)	.099
GA		.30 (.01, .58)	.040
BPD		1.47 (−.35, 3.28)	.111
Asphyxia		−1.58 (−3.51, .36)	.110
Sepsis		−1.47 (−3.41, .48)	.137
PDA		−1.81 (−3.73, .12)	.065
Total IC GR			
Gender	.270	−1.26 (−2.82, .30)	.113
GA		.24 (−.11, .58)	.173
BPD		1.95 (−.26, 4.17)	.083
Asphyxia		-.66 (−3.03, 1.71)	.579
Sepsis		−3.01 (−5.39, −.64)	.014
PDA		−2.54 (−4.89, −.18)	.035

Volume asymmetries

The comparison of tissue volumes between hemispheres (Table 6) revealed that at birth, CGM and SGM volumes were significantly higher in the left hemisphere than in the right hemisphere (MD 0.42 ml for CGM, 0.06 ml for SGM), while UWM volumes were significantly lower in the left hemisphere than in the right hemisphere (MD 0.28 ml). At TEA only the UWM asymmetry was maintained, with UWM volumes significantly lower in the left hemisphere than in the right hemisphere (MD 0.61 ml).

Neurodevelopmental outcome in relation with neonatal brain volumes

Neurodevelopmental outcome was assessed in 74 of the 84 PT children (88.1%) at 18–24 months of corrected age (Table 1). At 18–24 months of age, mean mental scores were 92 ± 15 for MDI and 86 ± 15 for PDI. Of these children, 20 (27%) exhibited mental delay (MDI < 85) and 27 (36%) exhibited motor delay (PDI < 85). At 5 years of age, cognitive development was assessed in 56 out of 84 children (66.7%). Mean MPC scores were 100 ± 15; 6 children (11%) had cognitive MPC scores below the normal range.

Classification of neurodevelopmental outcomes

Fig. 4 presents the ROC curves of the LDA classification of the children into two classes: those with outcome scores <85 and those with outcome scores ≥85 at 18–24 months and 5 years of age using the four sets of birth weight normalized features, as well as the GA at birth and the SES. Among the three outcome scores (MDI, PDI and MPC), the classification of MDI scores at 18–24 months had the highest predictive power evaluated by the AUC (AUC = 0.77 using the birth volumetric data, AUC = 0.73 using TEA volumetric data, AUC = 0.7 using the combination of birth and TEA data, and AUC = 0.72 using volume GR). However, this predictive power may be influenced by the inclusion of GA and SES as features, since the predictive power for GA and SES alone were similar (AUC = 0.78). For the PDI score at 18–24 months, the predictive performance was lower than in the MDI case (AUC = 0.63, 0.64, 0.6 and 0.62 for birth, TEA, birth and TEA, and GR, respectively), however GA and SES seem to contribute less in this case (AUC = 0.57 for the prediction based solely on GA and SES). Finally, for predicting the MPC outcome at 5 years of age, the highest AUC was obtained by using only GA and SES as features (AUC = 0.77), while the addition of volumetric features did not improve the performance of the classifier (AUC = 0.63, 0.71, 0.64, and 0.76, for birth, TEA, birth and TEA, and volume GR, respectively). Classification performance was not changed when the data was not normalized, or normalized by the total IC volume (instead of the birth weight). Lower classification performance was obtained when using only brain volumes as features (without GA at birth or SES); corresponding ROC curves are shown in the Appendix (Fig. A).

The classification suffers from the small number of subjects in the abnormal group, especially for the MPC score, with only 6 abnormal scores vs. 50 normal scores. This is one of the limitations of this study that we will discuss later. Furthermore, the classification may have suffered from over fitting and low rank issues in some cases. For these reasons, we explored the ability of volumetric data to predict neurodevelopmental

Table 6
Volume asymmetries.

Tissue volume difference	Mean (ml) (95% CI)	SD	*P-value*[a]
CGM birth left – CGM birth right	.42 (.24, .60)	.83	< .001
UWM birth left – UWM birth right	-.28 (−.46, −.10)	.84	.003
SGM birth left – SGM birth right	.06 (.03, .09)	.14	< .001
CB birth left – CB birth right	-.03 (−.09, .03)	.28	.396
CGM TEA left – CGM TEA right	.42 (−.24, 1.08)	3.05	.206
UWM TEA left – UWM TEA right	-.61 (−1.04, −.18)	2.00	.006
SGM TEA left – SGM TEA right	.004 (−.04, .05)	.22	.883
CB TEA left – CB TEA right	.14 (−.03, .31)	.77	.097

SD – standard deviation.
[a] Paired samples *t*-test.

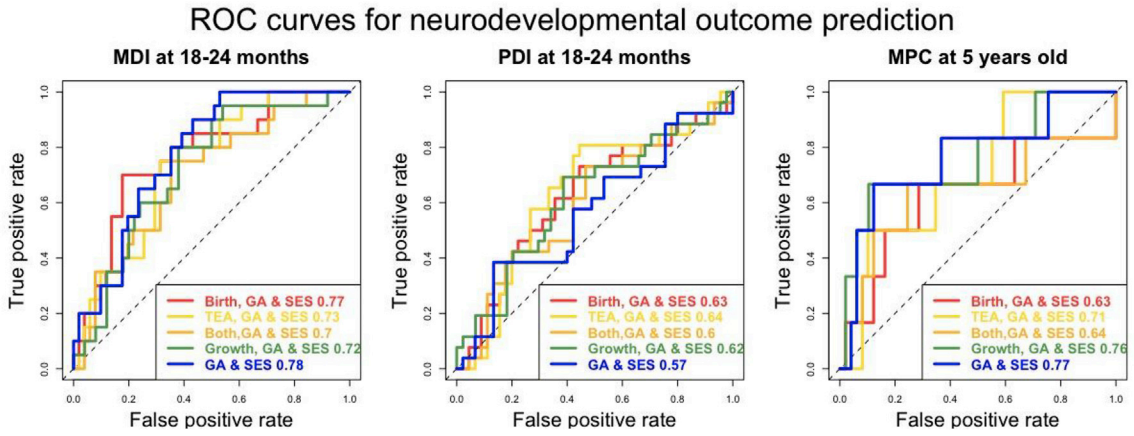

Fig. 4. Classification ROC curves using the following four sets of birth weight normalized features, together with GA and SES: (i) birth data, GA and SES (red lines), (ii) TEA data, GA and SES (yellow lines), (iii) both birth and TEA data, GA and SES (orange lines), (iv) brain volume GR, GA and SES (green lines), and (v) only GA and SES.

Table 7
General linear model analysis of neurodevelopmental outcomes (model 1).

Variables	MDI 18–24 months	*P-value*	PDI 18–24 months	*P-value*	MPC 5 years	*P-value*
	B (95% CI)		B (95% CI)		B (95% CI)	
SES[a]	−2.15 (−3.11, −1.19)	**< .001**	-.34 (−1.40, .71)	.519	−2.07 (−3.31, −.83)	**.001**
GA at birth	.72 (−1.97, .52)	.251	−1.18 (−2.56, .19)	.092	.27 (−1.23, 1.77)	.718
Gender	2.96 (−3.44, 9.36)	.360	7.74 (.66, 14.83)	**.033**	1.82 (−6.08, 9.73)	.646

[a] SES: Parental socioeconomic status.

outcomes by using GLMs and F-tests, whose results are presented in the next section.

General linear models for the prediction of the neurodevelopmental outcome

The analysis of outcomes by GLM with gender, GA at birth and SES showed that low parental SES was associated with poorer cognitive development at 18–24 months and 5 years of age, reflected by lower MDI and MPC scores, but not with motor development (PDI score) at 18–24 months of age (Table 7). At that age, males had significantly lower motor scores compared to females (PDI score: mean ± SD: 82 ± 16 versus 89 ± 13, p .043). GA at birth was not significantly associated with outcome in our cohort.

Associations between neurodevelopmental outcome and perinatal factors, tissue volumes and GR were investigated by comparing (F-test) R^2 values of six GLMs. Table 8 shows that the MDI score at 18–24 months is predicted mainly by model 1 (GA, Gender and SES) (adjusted-$R^2 = 0.22$). Adding the perinatal data (model 2) in the analysis does not improve the prediction of outcomes ($p = 0.45$, 0.23, 0.57 for MDI, PDI and MPC, respectively). MRI volumetric data (either at birth, at TEA, both at birth and at TEA, or volume GR) do not contribute to the prediction power of the MDI score ($p = 0.73$, 0.43, 0.53, 0.38, respectively). For the PDI score, model 1 has a lower predictive power (adjusted-$R^2 = 0.055$) compared to MDI outcome. This lack of predictive power is compensated by the volumetric data, especially at birth ($p = 0.0029$) (model 3). The combination of birth volumetric data and TEA volumetric data also contributes to the predictive power for the motor outcome (adjusted-$R^2 = 0.25$, $p = 0.0026$) (model 5). However, volumetric data at TEA only (model 4) seems to contribute more to the predictive power of the MPC ($p = 0.037$) at 5 years. The best model for predicting the cognitive outcome at 5 years of age is achieved when the volume GR (model 6) is added to model 1 (adjusted-$R^2 = 0.27$, $p = 0.021$). Over all, the models do not have a high predictive power as the adjusted-R^2 is lower than 0.3 in all cases. Finally, the adjusted-R^2 cannot be negative in theory, but it can be in practice, in which case it is an indication of a badly fitted model.

Discussion

There are currently only few studies that investigated longitudinal brain tissue volume growth in PT infants in the neonatal period and its association with later neurodevelopmental outcomes (Kapellou et al., 2006; Rathbone et al., 2011; Kersbergen et al., 2016a,b; Lee et al., 2016), and even fewer such studies that considered outcomes beyond 24 months of age (Lee et al., 2016). This study evaluated longitudinal brain tissue growth between birth and TEA, and its relation with perinatal factors and neurodevelopmental outcomes at 18–24 months of corrected age, and at five years of age, in a cohort of PT children free of major brain injury.

Relative volumes of CGM and CB were found to increase with GA at birth, while relative volumes of UWM decreased with GA at birth. The trend continued in the longitudinal evolution of the cohort, with higher relative volumes of CGM, CB and CSF at TEA compared to birth, and lower relative volumes of UWM and SGM at TEA than at birth. Increasing prematurity at birth was associated with lower relative volumes of UWM and total brain tissue at TEA, as well as higher absolute and relative volumes of CSF at TEA. Moreover, increasing prematurity was associated with lower growth rates of CGM, CB and total tissue. Among perinatal factors, neither BPD nor asphyxia had significant effects on tissue GR; PDA was associated with lower SGM, CB and IC GR, while sepsis was associated with lower CSF and IC GR. The fastest growing tissues were found to be the CB and the CGM (22% of birth volume/week, and 21% of birth volume/week, respectively).

An exploratory analysis was performed using LDA for the classification of children's neurodevelopmental outcomes into normal and abnormal, based on perinatal brain volumes and their growth. Cognitive outcomes at 18–24 months (MDI) and at 5 years of age (MPC) were best predicted by the LDA based solely on GA and SES, while the addition of volumetric features did not improve the performance of the classifier. Motor outcome at 18–24 months (PDI) was best predicted by combining GA and SES with volumetric data measured at birth and at TEA.

To analyze the contributions of either perinatal factors, parental SES and brain volumetric factors to the prediction of neurodevelopmental

Table 8
Predictive power (R^2/ R^2 adjusted) and model comparison (p value) for MDI, PDI, MPC scores.

Model/Model comparison	MDI 18–24 months (R^2/R^2 adjusted; *p value*)	PDI 18–24 months (R^2/R^2 adjusted; *p value*)	MPC 5 years (R^2/R^2 adjusted; *p value*)
1	0.2543/**0.2209**	0.09631/**0.05585**	0.1899/**0.1422**
1 + 2	0.319/0.2185	0.2032/0.08562	.268/0.1216
1 + 2/1 (2 contribution)	0.4461	0.2251	0.5695
3	0.04103/-0.04888	0.2296/0.1574	0.05961/-0.05794
1 + 3	0.2964/0.1926	0.3187/**0.2181**	0.2823/0.1388
1 + 3/1 (3 contribution)	0.723	0.002878**	0.4464
1 + 3/3 (1 contribution)	6.083e-05***	0.04664*	0.002954**
4	0.1053/0.02137	0.1473/0.06732	0.202/0.1023
1 + 4	0.3208/0.2206	0.2226/0.1079	0.3757/0.2508
1 + 4/1 (4 contribution)	0.4263	0.1285	0.03721*
1 + 4/4 (1 contribution)	0.0002309***	0.116	0.005806**
5	0.1458/-0.03094	0.3194/0.1785	0.4444/0.2308
1 + 5	0.3789/0.2095	0.4167/**0.2576**	0.2349/0.02142
1 + 5/1 (5 contribution)	0.526	0.002602**	0.1197
1 + 5/5 (1 contribution)	0.0001251***	0.02706*	0.001712**
6	0.06175/-0.02621	0.09551/0.01071	0.2107/0.1121
1 + 6	0.3252/0.2256	0.2125/0.09633	0.3909/**0.269**
1 + 6/1 (6 contribution)	0.3789	0.1735	0.02148*
1 + 6/6 (1 contribution)	2.735e-05***	0.02845*	0.004018**

1 Gender, GA birth, SES.
2 Asphyxia, BPD, Sepsis, PDA.
3 Absolute volumes at birth: CGM, UWM, SGM, CB, CSF, Total IC.
4 Absolute volumes at TEA: CGM, UWM, SGM, CB, CSF, Total IC.
5 Absolute volumes at birth + Absolute volumes at TEA: CGM, UWM, SGM, CB, CSF, Total IC.
6 Absolute volumes GR: CGM, UWM, SGM, CB, CSF, Total IC.

outcomes, statistical models comparison was performed, confirming that cognitive outcomes at 18–24 months and 5 years of age are predicted mainly by GA at birth and SE. Brain volumetric data at birth and at TEA contributed significantly to the variability of motor outcome at 18–24 months, whereas brain tissue volumes at TEA and tissue volume GR significantly influenced cognitive outcome at 5 years of age.

Longitudinal brain tissue volumes growth and volumes asymmetry

Several studies performed in PT born infants have demonstrated reductions in brain volumes at TEA in comparison with their term-born peers, (Peterson et al., 2003; Inder et al., 2005; Mewes et al., 2006; Thompson et al., 2007; Keunen et al., 2012; Padilla et al., 2015), but only few authors performed longitudinal studies of volumetric brain tissue growth between birth and TEA (Mewes et al., 2006; Kersbergen et al., 2016a,b; Makropoulos et al., 2016). Our data shows an effect of GA at birth on all cerebral tissue volumes measured early after birth. Relative volumes of CGM and CB as percentages of total IC were positively correlated with GA at birth, while relative UWM at birth was significantly negatively associated with GA at birth. At TEA, only UWM and relative total brain tissue volume were positively associated with GA at birth, while relative CSF was negatively correlated with GA at birth. Regarding tissue volume changes between birth and TEA, we observed an increase of the relative volume of CGM as percentage of total IC volume and, on the other hand, a decrease in relative volume of UWM, which is consistent with the cross-sectional study of Hüppi et al. (1998). Moreover, the increase of relative CGM, CB and CSF volumes, and decrease of relative UWM and SGM volumes between birth and TEA demonstrated in our cohort confirm the findings of Mewes et al. (2006), Makropoulos et al. (2016). The increase in relative CSF between birth and TEA revealed by our study and corroborated by Makropoulos et al. (2016) explains the slight decrease in relative total brain tissue between birth and TEA indicated by our data. Furthermore, in line with Dubois et al. (2008), our data revealed moderate to strong correlations between tissue volumes at TEA and tissue volumes at birth (after adjustment for gender, GA at birth and GA at 2nd MRI), suggesting that structural measurements at birth contribute to explaining brain development at TEA.

Additionally, tissue volumes GR of CGM, SGM, CB, adjusted for gender, also showed a significant positive association with GA at birth. This is in line with other studies that found that gestational age at birth is a major predictor of cerebral volume growth rates (Inder et al., 2005), meaning that the longitudinal brain growth trajectory is influenced by GA at birth. In the absence of major cerebral lesions, this may suggest delayed or impaired cerebral development, either due to postnatal factors after PT birth, or as a consequence of the processes leading to PT birth. Hüppi, Warfield et al. (1998) were the first to quantitatively assess in vivo of early human brain development using 3D-MRI and tissue segmentation techniques. This cross-sectional study showed a fourfold increase in CGM and a fivefold increase in myelinated white matter in 78 prematurely born infants from 29 to 41 weeks GA. In line with these findings, our longitudinal study showed a relatively rapid increase of CGM between birth and TEA, of 21% per week relative to birth volume (almost 12 ml/week in absolute volume). UWM, which accounts for nearly 98% of the total WM during this period of brain development, was shown to increase with 7% per week relative to birth volume (6.5 ml/week in absolute volume), while CSF volumes were shown to increase with 17% per week relative to birth volume (5.7 ml/week in absolute volume). SGM, which represents the volume of basal ganglia and thalamus together, showed a growth rate of 9% per week relative to birth volume (1 ml/week in absolute volume). In line with other studies (Mewes et al., 2006; Kersbergen et al., 2016a,b), we found that the CB displayed the fastest growth between birth and TEA of 22% per week relative to birth volume (1.76 ml/week in absolute volume. Considering the rapid evolution of brain differentiation in this critical period of development, a neonatal intensive care unit (NICU) environment might negatively impact the vulnerable PT brain, causing abnormal development.

When looking at the individual growth trajectories of brain tissue volumes, we observed a great inter-individual variability, which reflects the fact that, even in the absence of brain injury, tissue volume growth from birth to TEA might be influenced by various clinical factors, such as gender, intrauterine growth restriction, asphyxia, BPD, neonatal sepsis and PDA (Tolsa et al., 2004, Boardman et al., 2007, Thompson et al., 2007, Keunen et al., 2012, Skiold et al., 2014, Bouyssi-Kobar et al., 2016). In our study, the effect of several perinatal risk factors on brain volumes growth was modest. Males had significantly higher CB GR (MD 0.21 ml/week, 95% CI, 0.10–0.32) than females. In this study, sepsis was associated with lower CSF and IC GR. Lee, Neil et al. (2014) found infants suffering from necrotizing enterocolitis with sepsis to have reduced *trans*-cerebellar diameter and increased left ventricles, while Padilla, Alexandrou et al. (2015) did not find significant differences in global or

regional brain volumes between infants with and without sepsis. Differently from the report of Thompson et al. (2007), in our study BPD had no significant effect on brain tissue volume growth. PDA on the other hand was associated with lower GR of SGM and CB. Indeed, it has been shown that PDA can affect perfusion and oxygenation in the premature brain (Lemmers et al., 2016), which might lead to impaired growth in rapidly growing brain structures. Moreover, PDA has been shown to be associated with reduced volumes of the CB (Limperopoulos et al., 2005; Padilla et al., 2015) and several gray matter areas (Padilla et al., 2015), while others (Kersbergen et al. (2016a,b) reported that surgery (including PDA-related surgery) was associated with volume reductions in several brain areas, but not the CB. As also confirmed by our results, the CB has been shown to be one of the fastest growing tissues in the last trimester of pregnancy (Limperopoulos et al., 2005; Volpe, 2009b, Andescavage et al., 2016; Kersbergen et al., 2016a,b), which could explain its greater vulnerability to a lack of oxygenation caused by PDA.

Regarding brain asymmetry, we found small but statistically significant inter-hemispheric differences: CGM and SGM volumes were higher, and UWM lower in the left hemisphere at birth, while at TEA only the UWM asymmetry was maintained. In a study of the fetal brain, Andescavage et al. (2016) also reported larger volumes of left hemisphere CGM and SGM in early gestation, followed by left-right volume equalization by TEA. However, in their study white matter asymmetries were not significant. Gilmore, Lin et al. (2007) studied infants born at term in the first few weeks after birth, and found left-greater-than-right asymmetries in the CGM, SGM and UWM, with gray matter asymmetries more pronounced. Thus, our study confirms the accumulating evidence that brain asymmetry evolves during lifespan, and that the well-known rightwards asymmetry of the adult brain is not yet present at birth, but develops later in life.

Relationship to neurodevelopmental outcome

Of the 84 children who had 2 MRI scans, 74 children were evaluated for mental and motor development with the BSID II (MDI and PDI scores respectively) at 18–24 months of corrected age and 56 children were assessed for cognitive development with the K-ABC (MPC score) at 5 years of age. These follow-up rates with some dropouts are mostly due to high migration rates in the area. In this cohort of relatively healthy children, with no major cerebral lesions, spanning a wide range of GA from extreme to late prematurity, mean MDI, PDI and MPC scores were all in the normal range.

To study the relationship between brain tissue volumes measured in the neonatal period and subsequent neurodevelopmental outcome, we first performed an exploratory analysis using LDA to classify neurodevelopmental outcomes of PT children into normal and abnormal as defined by standardized tests. Cognitive outcomes (MDI scores) at 18–24 months and at 5 years of age (MPC scores) were predicted with highest AUC by the LDA based solely on GA and SES (AUC = 0.78 for MDI and AUC = 0.77 for MPC). The addition of tissue volumes at birth, TEA or tissue GR as features of the classifier did not improve its performance. Motor outcome (PDI scores) at 18–24 months was predicted with lower AUC values than the cognitive scores (MDI and MPC), with the highest AUC obtained by combining GA and SES with brain volumes at TEA (AUC = 0.64). For the prediction of the PDI and MPC scores, the specificity was found to be very high vs. the sensitivity due to the small number of subjects considered as having abnormal scores (<85) was low. Interestingly, the classification performance increased when using the GA at birth and SES as features when predicting MDI and MPC scores, but not for the PDI score. This is in line with Moeskops et al. (2017), who also performed classification of PT children's neurodevelopmental scores based on brain structural features (including volumes) and reported that the GA at birth improves their classification performance. Furthermore, in our study the prediction of PDI and MPC outcomes suffered from the small number of subjects in the abnormal range, which yielded low prediction ability for these two scores. This corroborates the results of Moeskops et al. (2017), whose ROC curves indicated that high specificity was achieved by paying the price of a large false discovery rate, and therefore a reduced ability to predict abnormal neurodevelopmental outcomes.

In order to better understand and prognosticate neurodevelopmental outcomes associated with preterm birth, we then used a GLM of outcomes including the parent SES, gender and GA at birth (model 1). The main finding of this simple model was that cognitive scores (MDI and MPC) at 18–24 months of corrected age and at 5 years old were associated with the SES of the family, which confirms evidence from the literature. High-risk environments have been shown to negatively impact the cognitive trajectories of both PT and term born children (Bradley and Corwyn, 2002; Wong and Edwards, 2013). Child SES, characterized by parental educational attainment and parental occupation, has been shown to be strongly associated with global cognitive development (Farah et al., 2006), but also with language and memory (Fluss et al., 2009; Jednoróg et al., 2012; Noble et al., 2015), executive functions development (Stevens et al., 2009) and school achievement. Mangin, Horwood et al. (2017), who performed a longitudinal analysis describing cognitive development of very PT children over time, reported that the combination of PT birth and family high social risk is particularly detrimental, resulting in PT children to have the poorest developmental trajectory from early age to 12 years. There are also several recent studies looking at brain structural relations with SES in childhood. Jednoróg, Altarelli et al. (2012) examined the influence of the family SES on brain anatomy through MRI in a group of 10-year-old children. They found that unfavorable environmental conditions were associated with smaller hippocampal volume and with smaller volumes of CGM in regions related to language and executive function development. Recent data from the large "Pediatric Imaging, Neurocognition and Genetics" (PING) study has confirmed the effect of SES on childhood cortical thickness changes, which in turn are associated with cognitive performance (Piccolo et al., 2016). Our analyses in the newborn period did not yield any association between tissue volumes measured at birth or at TEA and parental SES. These results suggest that the effects of SES are related to environmental factors postnatally, rather than genetically influenced and present at birth.

Furthermore, we investigated whether the addition to this model of perinatal factors, brain tissue volumes or growth rates significantly increases the R^2 of the model. A variety of neonatal risk factors have been associated with adverse outcome in PT children, such as BPD (Short et al., 2003; Anderson and Doyle, 2006), PDA (Bourgoin et al., 2016) and sepsis (Miller et al., 2005; Lee et al., 2014). Although in the literature alterations in brain tissue volumes and several perinatal morbidities associated with preterm birth seem to be related to later neurodevelopmental impairments, in this study perinatal risk factors such as asphyxia, sepsis, BPD and PDA do not consistently improve the prediction of outcomes until 5 years of age.

Concerning possible associations between reduced neonatal brain volumes and unfavorable neurodevelopmental outcomes, the evidence in the literature is mixed, with several authors reporting such associations (Peterson et al., 2003; Inder et al., 2005; Woodward et al., 2005; Beauchamp et al., 2008; Lodygensky et al., 2008; Thompson et al., 2008; Van Kooij, Benders et al., 2012; Keunen et al., 2016; Monson et al., 2016), and a few reporting the lack of significant associations, or a weakening of such associations after adjustment for perinatal variables (Shah et al., 2006; Lind et al., 2010; Lind et al., 2011; Cheong et al., 2016; Lee et al., 2016). In our subset of preterm born children with no brain lesions, adding the MRI volumetric data (either at birth, at TEA, both at birth and at TEA, or volume GR) does not contribute to the prediction power for the mental outcome at 18–24 months of corrected age. However, model 1 has a lower predictive power for the motor outcome at 18–24 months,

compared to mental outcome. This lack of predictive power is compensated by adding tissue volumes segmented at birth. The prediction of the motor outcomes is further improved by using the combination of brain volumes measured at birth and TEA. At 5 years of age, volumetric measurements at TEA contributed to the predictive power of the cognitive outcome. The best model was achieved by adding volumes GR to model 1. These results suggest that the volumetric assessments at birth and TEA contribute to the prediction of outcomes, but their relevance is limited, as the adjusted-R^2 is lower than 0.3. However, this lack of evidence needs to be carefully considered in the light of its possible explanations. First of all, our cohort was a relatively healthy one, exhibiting no major brain injury, spanning a wide range of gestational ages from extreme to late prematurity, and with few children whose outcomes indicated neurodevelopmental delay. The cohorts investigated in most studies reporting significant associations between neonatal tissue volumes and later outcomes had lower mean GA-s than our cohort, and several included cases of moderate to severe brain injury, factor not always adjusted for in statistical tests (Inder et al., 2005; Woodward et al., 2005; Beauchamp et al., 2008; Thompson et al., 2008; Van Kooij, Benders et al., 2012; Keunen et al., 2016; Monson et al., 2016). The other differences to be mentioned between our study and the others were related to MRI parameters, volume extraction methodologies or the use of more specific neuropsychological assessment tools for outcome evaluation.

Limitations

A few limitations of this study need to be mentioned. First, the MRI scans were performed on four different scanners because of scanner upgrades throughout the study period. Despite the fact that protocols were harmonized in order to obtain similar quality images, subtle differences might subsist among images acquired on different machines, and these might be reflected in the positioning of segmentation boundaries, and thus also in the final extracted tissue volumes. In order to mitigate this limitation, systematic visual inspection and manual correction of visible segmentation errors was performed. Moreover, analysis of covariance showed no effect of scanner type on brain tissue volumes corrected for GA at birth.

Secondly, we evaluated global tissue volumes, while several other studies looked at finer divisions of the brain, by performing parcellations (Peterson et al., 2003; Woodward et al., 2005), or studying specific structures, such as the hippocampus (Isaacs et al., 2000; Beauchamp et al., 2008; Lodygensky et al., 2008; Thompson et al., 2008). Indeed, we speculate that segmentations into finer anatomical divisions might improve our understanding of associations between early brain structure and later outcomes, and envisage performing such segmentations in our future work. In the same line of thought, it seems that investigations of brain cortical surface and folding (Kapellou et al., 2006; Dubois et al., 2008; Rathbone et al., 2011; Kersbergen et al., 2016a,b), structural connectivity (Thompson et al., 2016), and functional connectivity (Rogers et al., 2017) constitute promising investigation paths for the detection of MRI neonatal biomarkers associated with future outcomes.

Thirdly, dropout rates of our cohort were quite high, especially for the 5 years examination, where only 56 out of 84 children (66.7%) could be evaluated, thus limiting the power available for statistical testing. Furthermore, the groups where unbalanced for the LDA classification, which resulted in high specificity vs. low sensitivity. Finally, we could not perform a comparison with term-born neonates, since such data was not available.

Conclusion

This is one of the few longitudinal studies of premature infants from a wide spectrum of gestational ages, looking at neonatal brain structure and growth between birth and TEA, and their relation to neurodevelopmental outcomes at 18–24 months of corrected age and 5 years of age.

Increasing prematurity, as well as several perinatal risk factors were found to have an impact on brain tissue volumes and their growth between birth and TEA. By fitting and comparing several GLMs and testing an LDA classifier, we demonstrated that children's cognitive outcomes at 18–24 months and 5 years of age were strongly associated with parental SES – a well-known potent modifier of childhood brain development. Moreover, volumetric data at birth and at TEA contributed to explaining the variability of children's motor outcomes at 18–24 months, while brain volumes at TEA and tissue growth rates between birth and TEA contributed to explaining the variability of children's cognitive outcome at 5 years of age. These results suggest that perinatal brain characteristics in PT infants may influence later functional development. However, since the overall predictive power of our models was relatively low, further research is required to elucidate the factors that affect brain development after premature birth.

Promising directions for future research include investigations of finer regional brain divisions, brain cortical surface, structural and functional brain connectivity as other possible biomarkers for neurodevelopmental outcomes.

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Appendix

MRI acquisition parameters

The parameters used for the acquisition of the T2-weighted images in this study are summarized in the following table.

Table A
MRI acquisition parameters for T2-weighted images.

Machine	Field strength (T)	Echo time (ms)	Repetition time (ms)	Echo train length	Voxel size (mm^3)	Birth scans	TEA scans
Philips Eclipse	1.5	156	4000	16	$0.7 \times 0.7 \times 1.5$	11	8
Philips Achieva	1.5	150	4000	16	$0.7 \times 0.7 \times 1.5$	39	41
Siemens Avanto	1.5	150	5700	15	$0.8 \times 0.8 \times 1.2$	31	2
Siemens Trio Tim	3	150	4600	15	$0.8 \times 0.8 \times 1.2$	3	33

Data dependency on scanner type

Table B
Effect of scanner type on tissue volumes, controlling for GA at birth (analysis of covariance).

Tissue volume	At birth				At TEA			
	Scanner type		GA birth		Scanner type		GA birth	
	F	P-value	F	P-value	F	P-value	F	P-value
GM	.94	.426	202.24	<.001	.71	.552	.10	.758
UWM	1.64	.186	96.54	<.001	.48	.700	.11	.742
SGM	2.31	.083	158.14	<.001	.82	.489	.05	.825
CSF	1.80	.153	28.03	<.001	1.82	.151	.70	.404
CB	.89	.453	173.89	<.001	1.09	.360	.13	.716
IC	1.61	.193	123.74	<.001	.59	.625	.00	.992

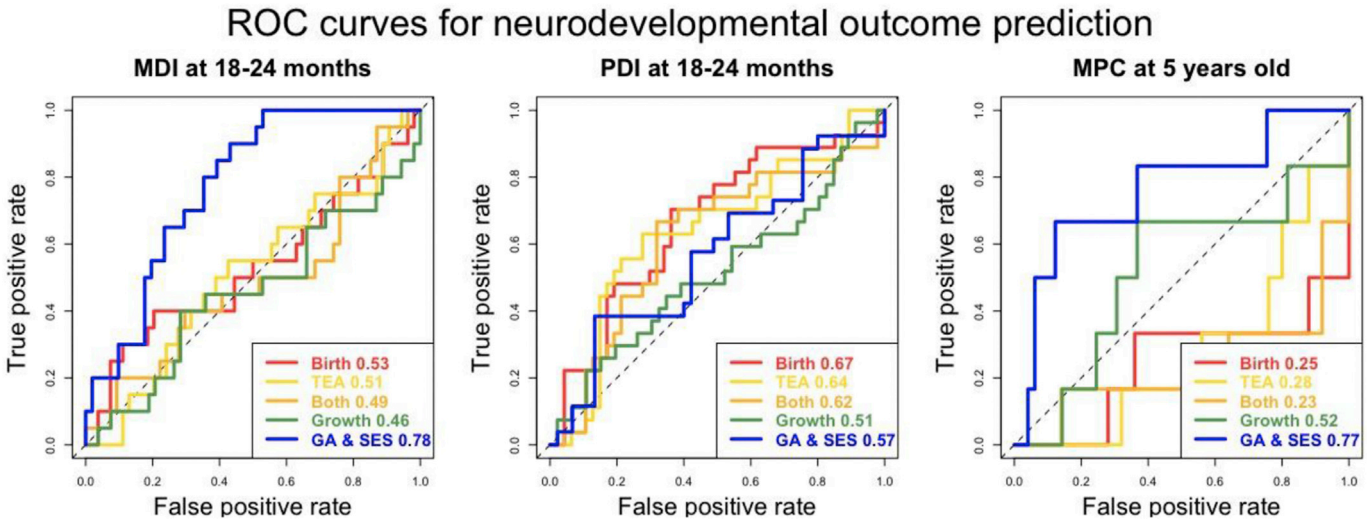

Fig. A. Classification ROC curves using the following four sets of birth weight normalized features (without GA and SES) (i) only the birth data (red lines), (ii) only the TEA data (yellow lines), (iii) both birth and TEA data (orange lines), (iv) brain volume GR, and, for comparison, (v) only GA and SES.

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