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Original Article

Cortical alterations after very preterm birth and the association with socio-emotional abilities from childhood to early adolescence

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Very preterm birth (VPT; <32 weeks' gestation) leads to a situation where crucial steps of brain development occur in an abnormal ex utero environment, translating to vulnerable cortical and subcortical development. Associated with this atypical brain development, children and adolescents born VPT are at a high risk of socio-emotional difficulties. In the current study, we unravel developmental changes in cortical gray matter (GM) concentration in VPT and term-born controls aged 6–14 years, together with their associations with socio-emotional abilities. T1-weighted images were used to estimate signal intensities of brain tissue types in a single voxel (GM, white matter, and cortico-spinal fluid) and extract GM concentration disentangled from the presence of partial volume effects (PVEs). General linear model analysis was used to compare groups. Socio-emotional abilities were assessed and associations with GM concentration were explored using univariate and multivariate analyses. The effects of prematurity were far-reaching, with intricated patterns of increases and decreases of GM concentration mainly in frontal, temporal, parietal, and cingular regions. Better socio-emotional abilities were associated with increased GM concentration in regions known to be involved in such process for both groups. Our findings suggest that the trajectory of brain development following VPT birth may be fundamentally distinctive and impact socio-emotional abilities.

Key words: cortical alterations; gray matter; prematurity; preterm birth; socio-emotional abilities.

Introduction

The genesis of the human cerebral cortex occurs through precise spatiotemporal gene expression controlling cell proliferation, cell migration, morphogenesis, dendritic differentiation, synaptogenesis, apoptosis, and myelination (Kostovic and Judas 2007). In addition, these developmental mechanisms take place in specific critical periods and are, in part, sensory input dependent. Perturbations in any of these timed processes lead to abnormalities either in cortical structure, layering, and/or number of neurons and axonal projections, which translate at their turn to altered neurodevelopment and long-lasting behavioral consequences (Dimitrova et al. 2021). Increasingly, many neurodevelopmental disorders find their origins early in life, when the architecture of the neuronal networks is being established and cortex formation is specifically vulnerable. Preterm birth occurs specifically during key periods of these interrelated neurobiological processes underlying brain development.

To explore both the structure and architecture of the brain in vivo, magnetic resonance imaging (MRI) has proven to be a valuable, non-invasive tool with improved combined spatial and temporal resolution. In the case of preterm birth, MRI has indeed been widely used to detect structural brain alteration. In addition to common periventricular white matter (WM) damage (Volpe 2003; Khwaja and Volpe 2008), prematurity has been associated with alteration in whole-brain structural connectivity and a brain's network organization (Sa de Almeida et al. 2021) as early as birth, with the effects lasting until late childhood and adolescence (Fischi et al. 2014; Fischi-Gomez et al. 2016; Muñoz-Moreno et al. 2016; Siffredi et al. 2022a). Other than WM alterations, preterm birth has also been linked to whole-brain and regional cortical, as well as subcortical, gray matter (GM) alterations (Hüppi et al. 1998; Inder et al. 1999; Ball et al. 2012; Ball et al. 2013). These GM alterations have not only been observed not only at birth and term-equivalent age (Peterson et al. 2000; Inder et al. 2005; Boardman et al. 2006; Srinivasan et al. 2007)

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but also during childhood and adolescence (Isaacs et al. 2004; Kesler et al. 2004, 2008; Ment et al. 2009; Soria-Pastor et al. 2009; Botellero et al. 2017), persisting into adulthood (Nosarti et al. 2014; Karolis et al. 2017).

The study of GM alteration in individuals born preterm have traditionally been conducted using volumetric measurements based on the binary classification of signal intensities of the T1-weighted image (Kesler et al. 2004, 2008; Ment et al. 2009; Soria–Pastor et al. 2009; Botellero et al. 2017). However, the complexity of GM properties might not be fully captured using such volumetric measures. The cortical plate in early brain development is composed of GM and WM. The later cortex is populated by neurons that migrate with guidance of radial glial cells toward the pial surface (the boundary between GM and cerebrospinal fluid (CSF)) (Bystron et al. 2008). Following this migration, cross-connections develop, with dendrites and axons obscuring the early radial structure (McKinstry et al. 2002; Vasung et al. 2016). Hence, the tissue architecture of cortical GM is composed by a characteristic organization of neurons, glia cells, and more or less myelinated axons. This combination of different tissue characteristics in a single voxel makes the estimation of GM and WM volumes based on signal intensities challenging, especially when dealing with neonatal data (where the MRI contrast is inverted due to the largely unmyelinated WM) or pediatric data (due to smaller structures compared to adult brains). Indeed, one of the major challenges in detecting cortical GM structure using MRI is the presence of partial volume effects (PVEs). PVEs occur when an imaging voxel contains more than one tissue type, yielding a signal equal to the weighted average of its components. The main caveat is that in regions with spatially varying intensities such as the cortical surface, the PVE can shift the apparent position of abnormalities detected by multiple voxels. By describing the intensity within each voxel as the sum of GM, WM, and CSF characteristic intensities (weighted by their respective local concentrations), one can estimate the signal intensities of several tissue types in a single voxel (Roche and Forbes 2014), in contrast of a binary classification based on global signal averaging, as previously used when exploring GM volumes in preterm children and adolescents. In this context, PVE estimation algorithms allowing for the extraction of cortical GM concentration might provide valuable information on GM structural morphometry and tissue's properties in a vulnerable population, such as preterm born individuals (Fischi et al. 2021).

In recent years, several studies have highlighted the role of subtle and widespread GM damage for increased risk of neurodevelopmental difficulties in the preterm population (Peterson et al. 2000; Inder et al. 2005; Soria-Pastor et al. 2009; Zubiaurre-Elorza et al. 2012; Botellero et al. 2017; Dimitrova et al. 2021). Of particular interest, GM alteration in different brain regions has been associated with socio-emotional outcomes in preterm children and adolescents, especially in frontal, temporal, and fusiform regions (Rogers et al. 2012; Zubiaurre-Elorza et al. 2012; Healy et al. 2013; Montagna and Nosarti 2016). Socio-emotional difficulties are observed as early as the first year of life in premature children and extend from difficulties in emotional information processing, emotion regulation, social understanding, socializing, peer relationship, and internalizing problems (Spittle et al. 2009; Johnson et al. 2010; Langerock et al. 2013; Montagna and Nosarti 2016). Importantly, deficits in socio-emotional processing and regulation in early life are considered precursors of later psychiatric and mental health problems (Carter et al. 2004; Briggs-Gowan and Carter 2008). In preterm children, these difficulties have indeed been found to be long-lasting, with subsequent consequences observed in social, occupational, and family functioning through adolescence and adulthood (Montagna and Nosarti 2016; Saigal et al. 2016; Mendonça et al. 2019). Increased risk of developing psychiatric disorders, including depression, bipolar affective disorder, anxiety disorder, and schizophrenia, have also been observed in preterm-born adults (Nosarti et al. 2012; Walshe et al. 2008; Mendonça et al. 2019). Studies show that the magnitude of the effect of preterm birth on socio-emotional outcomes is directly proportional to their immaturity at birth, with children born very preterm (VPT, born <32 weeks of gestation) being particularly vulnerable (Spittle et al. 2011; Serenius et al. 2016).

The present study aimed to unravel developmental changes in cortical GM concentration (i.e. the distribution of voxels segmented as GM) by considering the presence of PVE in VPT- born children to young adolescents compared with their term-born peers and to relate these changes to socio-emotional outcomes. Building up on previous studies examining GM alterations after a VPT birth, we leveraged recent advances in the extraction of GM characteristics and applied a data-driven multivariate approach to explore the association with socio-emotional outcomes in a cross-sectional developmental cohort aged 6–14 years. We hypothesize that understanding GM concentration after preterm birth across childhood and adolescence might further inform on the developmental course of GM development and its associations with socio-emotional abilities in this population.

Material and methods

Participants

Participants of the current study were recruited as part of the "Geneva Preterm Cohort Study," at the age of 6–14 years (including two substudies completed in children and adolescents from 6 to 14 years of age, i.e. the "Mindful preterm teens" study (Siffredi et al. 2021a) and "Vis-à-Vis" study). Participants were recruited between January 2017 and July 2019. About, 392 VPT children and adolescents born before 32 gestational weeks between 2003 January 1 and 2012 December 31, in the Neonatal Unit at the Geneva University Hospital (Switzerland) and followed up at the Division of Child Development and Growth, were invited to participate. Participants were excluded from the study if they had an intelligence quotient below 70, sensory or physical disabilities (cerebral palsy, blindness, and hearing loss), or an insufficient understanding of French. Moreover, 40 full-term (FT) control participants aged between 6 and 14 years old were recruited through the community. For consistency with our previous study on the same dataset (Siffredi et al. 2022b), the final sample size included 65 VPT and 35 FT participants aged 6–14 years (see Table 1).

All experimental protocols were approved by the Swiss Ethics Committees on research involving humans, ID: 2015–00175. All methods were carried out in accordance with relevant guidelines and regulations. Written informed consent was obtained from primary caregivers and participants.

Neonatal and demographic measures

Neonatal characteristics were documented from medical records. Socio-economic status (SES) of the parents was estimated using the Largo scale, a validated 12-point score based on maternal education and paternal occupation (Largo et al. 1989). Higher largo scores reflect lower SES.

General intellectual functioning was assessed using two different test batteries according to the age of the participants. For participants from 6 to 9 years and 11 months old, the Kaufman Assessment Battery for Children—2nd Edition (K-ABC-II;

Table 1. Neonatal and demographic characteristics of the FT and VPT groups. Data are presented as mean (standard deviation) [range] for continuous variables and count (percentage) for categorical variables. Sex here refers to the individual's physical characteristics at birth associated with a male or female. Independent-sample *t*-test or chi-square, as appropriate, were used to compare the VPT and the FT groups, with statistical significance set to $P < 0.05$.

	Full term, FT ($n = 35$)	Very preterm, VPT ($n = 65$)	*P*-value
Neonatal characteristics			
Birth weight (BW) [g]	3,402.43 (406.95) [2,620; 4,110]	1,278.52 (377.41) [510; 1,990]	$2.2\ 10^{-16}$
Gestational age (GA) [days]	39.76 (1.56) [35.85; 42.43]	29.55 (1.76) [25.71; 31.85]	$2.2\ 10^{-16}$
Head circumference [cm]	-	26.90 (3.13) [21; 40]	-
Length of hospitalization [days]	-	55.46 (24.67) [17; 131]	-
Multiple births, *n* (%)	0 (0%)	21 (36.84%)	-
cPVL, *n* (%)	0 (0%)	0 (0%)	-
IVH—Grades III and IV, *n* (%)	0 (0%)	0 (0%)	-
BPD, *n* (%)	0 (0%)	19 (32.75%)	-
Demographic characteristics			
Female, *n* (%)	19 (54.28%)	33 (50.7%)	ns
Male, *n* (%)	16 (45.71%)	32 (49.3%)	ns
Age at assessment [years]	12.05 (1.23) [10.08; 14.24]	10.07 (2.36) [6.08; 14.41]	ns
General Intellectual Functioning	113.56 (11.46) [93; 142]	107.54 (11.48) [82; 142]	ns
Socio-economic status (SES)	4.78 (2.62) [2; 12]	4.37 (2.43) [2; 12]	0.0002

cPVL, cystic periventricular leukomalacia; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; ns, not significant.

(Kaufman and Kaufman 2014)) was used to evaluate the Fluid-Crystallized Index (FCI) as a measure of general intellectual functioning. The FCI is derived from a linear combination of 10 core subtests that composed five first-order scale scores (i.e. short-term memory, long-term storage and retrieval, visual processing, fluid reasoning, and crystallized ability). For children younger than 7 years of age, a different subset combination is administered to calculate the FCI. For participants from 10 to 14 years of age, the Wechsler Intelligence Scale for Children—4th Edition (WISC-IV; (Weschler 2003)) was used to evaluate the General Ability Index (GAI) as a measure of general intellectual functioning. The GAI is derived from the core verbal comprehension and perceptual reasoning subtests. Index scores of these measures of general intellectual functioning, FCI and GAI, have been found to correlate strongly (Naglieri and Jensen 1987; Reynolds et al. 1989; Oliver 2010). Both measures of general intellectual functioning, i.e. FCI and GAI, have a mean of 100 and a standard deviation of 15.

Socio-emotional measures

Socio-emotional abilities were assessed at the time of the MRI scan in all participants using neuropsychological testing as well as parent-reported questionnaires specifically testing socio-emotional abilities (Siffredi et al. 2022b):

- The total score of the Theory of Mind subtest of the Developmental Neuropsychological Assessment—2nd Edition (NEPSY-II (Kemp 2011)) was used to assess the ability to understand mental contents such as belief, intention, or deception. As the Theory of Mind subtest does not provide a standard score, raw scores were regressed on age at assessment and standardized residuals was used as a Theory of Mind score.
- The total score of the Affect Recognition subtest of the NEPSY-II (Kemp 2011) was used to assess facial emotional recognition. For consistency with the Theory of Mind score of the NEPSY-II, the Affect Recognition raw scores were regressed on age at assessment and standardized residuals was used as an Affect Recognition score.
- Internalized Score of the Strength and Difficulties Questionnaire—parent version (Goodman 1997) was used as a specific measure of socio-emotional abilities. The Internalized Score is scored on a Likert scale and is the sum of the emotional and peer problems scales. As standardized scores are not available for this measure, raw scores were regressed on age at assessment and the standardized residuals were used as an internalized score. Higher internalized scores reflect increased internalized difficulties in daily life as rated by parents.
- Emotional Control Scale of the Behavior Rating Inventory of Executive Function, parent version (BRIEF (Gioia and Isquith 2011)) was used to measure the extent to which the child is able to mediate emotional responses in daily life. As standardized scores are available for this measure, standardized scores were used as an emotional control score (mean = 50, SD = 10). Higher emotional control scores reflect increased difficulties in emotional control in daily life, as rated by parents.

MR acquisition protocol

All participants were scanned with the same acquisition protocol in the same 3 Tesla Siemens Prisma scanner (Siemens, Erlangen, Germany) located at the Campus Biotech, Geneva. High-resolution T1-weighted (T1w) MRI (0.9 mm isotropic resolution) were acquired for all subjects with the Magnetization Prepared RApid Gradient-Echo (MPRAGE) imaging sequence (Marques et al. 2010) (TE = 2.3 s; 256 × 256 matrix, 192 sagittal slices).

GM concentration extraction

Total intracranial volume (TIV) extraction and tissue segmentation were performed over the T1w image using Freesurfer image analysis suite (FS, version 6.0.0), freely available for download online (http://surfer.nmr.mgh.harvard.edu/). FS was also used to extract the cortical regions of interest (ROIs), obtained by parcellating the cerebral cortex into units with respect to gyral and sulcal structure (Desikan et al. 2006). Whole brain tissue concentration maps were computed over the T1w image by estimating the concentration of GM, WM, and CSF in each voxel. This was done by assigning values computed as a mixture of tissues instead of assigning them a single tissue type as in Bonnier et al. (2016). We used the algorithm proposed by Roche and Forbes (Roche and Forbes 2014), which models the intensity of each voxel (y)

as the sum of GM, WM, and CSF characteristic intensities in a given region, weighted by their respective local concentrations, with additive Gaussian noise, following

$$y = C_{GM}\mu_{GM} + C_{WM}\mu_{WM} + C_{CSF}\mu_{CSF} + \varepsilon$$

- with C_{GM}, C_{WM}, and C_{CSF} tissue's concentrations for GM, WM, and CSF, respectively, μ_{GM}, μ_{WM}, and μ_{CSF} the characteristic intensities of each tissue and $\xi = N(0, \mu)$ the additive Gaussian noise.

For each subject, the corresponding GM concentration map was projected to the pial surface using FS. For each vertex of the pial-surface mesh, the corresponding GM concentration was calculated as the averaged GM concentration sampled at three cortical locations: the WM-GM interface, the middle cortical surface, and the outer surface (pial). In order to allow group comparisons and draw population-specific inferences, the resulting individual GM concentration surfaces were resampled to the FS standard average cortical surface template (FSaverage). We used a nonlinear procedure that aligns cortical folding patterns to the template with several deformable procedures including surface inflation and spherical registration minimizing cortical geometry mismatch. All individual GM concentration surfaces were combined into a single dataset.

Visual quality control of the original T1 image, the FS parcellated image (aparc image), and the GM concentration map were completed for all participants. More specifically, for each participant, the T1 anatomical image was examined for potential motion artifacts. The original T1 image was then registered to the FS parcellated image. The quality of the parcellation of the T1 image was evaluated by both a master student in neuroscience and the first author (VS). Finally, the GM concentration maps were coregistered to the FS parcellated images using the affine transform matrix. The quality of both the coregistration and the GM concentration map was evaluated by the senior author (EFG).

Statistical analysis

Sample characteristics

The independent-sample *t*-test was used to compare the VPT and the FT control group for continuous variables, and chi-square was used for categorical variables.

Group-wise GM concentration differences: general linear model analysis

Group-wise differences in cortical GM concentration between the VPT and FT groups were evaluated using a general linear model (GLM) as implemented in Freesurfer. Before the GLM fitting, normalized GM concentration measures were smoothed using a full width half maximum (FWHM) Gaussian kernel of 8 mm. For each hemisphere, the GLM was computed at each cortical vertex. The number of mesh vertices ranged from 31,000 vertices for the biggest ROI to 2,630 vertices for the smallest. The design matrix consisted of two discrete groups, i.e. VPT and FT control, with age at assessment, birth weight, and sex as covariates, with the Different Offset, Different Slope (DODS) method implemented in Freesurfer. DODS assumes different GM concentration measures for both groups as well as different developmental trajectories of cortical maturation, i.e. different slopes. The contrast matrix used investigated the average differences between cortical GM concentration, while regressing out the effect of age at assessment, birth weight, and sex, using a two-tailed *t*-test. In order to correct for multiple comparisons, we used the false discovery rate (FDR) at $P < 0.05$. For visualization of the results, the statistically significant maps obtained were overlaid onto the inflated surface of the corresponding hemisphere.

Univariate association with socio-emotional scores: GLM analysis

The mean GM concentration was computed over the ROIs that appeared significantly different on the GLM analysis between the VPT and FT control groups. For each ROI, the averaged GM concentration was then used to evaluate the association between GM concentration measures and socio-emotional scores, along with the effect of gestational age (GA), SES, and age at assessment in both the VPT and the FT participants. We ran a GLM analysis in R (version 1.1–23), using an iteratively reweighted least square (IWLS) method. SES was introduced as a fixed effect as several studies have shown that the SES of the family plays an important role in socio-emotional outcomes in children. In particular, it has been recently shown that at school age children from households with lower socio-economic positions have higher odds for daily emotional symptoms and lower levels of social competence, with respect to their peers coming from higher socioeconomic status (Meilstrup et al. 2020). Significance was calculated using the *lmerTest* package (Kuznetsova, Brockhoff, and Christensen, 2017). *lmerTest* applies Satterthwaite's method to estimate degrees of freedom and generate *P*-values for mixed models. Formally, the model specification was as follows:

$$y = 1 + \mu_{GM}^{ROI} + \mathrm{GA} + \mathrm{SES} + \text{age at assessment}$$

- where μ_{GM}^{ROI} is the mean GM concentration within mesh vertex of the projection of the GM map to the pial surface in each specific ROI (see section GM Concentration Extraction).

Multivariate association of GM concentration with socio-emotional scores: partial least square correlations

Similar to the previous GLM analysis, the ROI-based averaged GM concentration was used to evaluate the multivariate patterns of correlation between the GM concentration measures and socio-emotional scores. Instead of using a univariate analysis as in the previous section, here, we specifically seek to evaluate the multivariate relationship between the different socio-emotional scores and GM concentration in the ROIs. We used a multivariate partial least squares correlation (PLSC), instead of a mass univariate approach. Mass univariate analysis is very limited by the multiple comparison problem, hence providing less power when dealing with a large number of measures. More importantly, PLSC has the advantage of allowing for the exploration of the relationship of brain imaging variables (and hence the multivariability pattern of the brain's ROIs) with multiple external variables at the same time. PLSC measures the multivariate relationship between two sets of variables (here: mean GM concentration in the ROIs and socio-emotional scores). More specifically and following previous studies (Zöller et al. 2019; Kebets et al. 2019; Bolton et al. 2020; Anthony R. McIntosh and Mišić 2013; Anthony Randal McIntosh and Lobaugh 2004; Siffredi et al. 2021b), the analysis used the mean GM concentration over the ROIs showing statistically significant differences between the VPT and the FT control group as brain variables and all socio-emotional scores and SES (i.e. Largo scale) as behavioral variables.

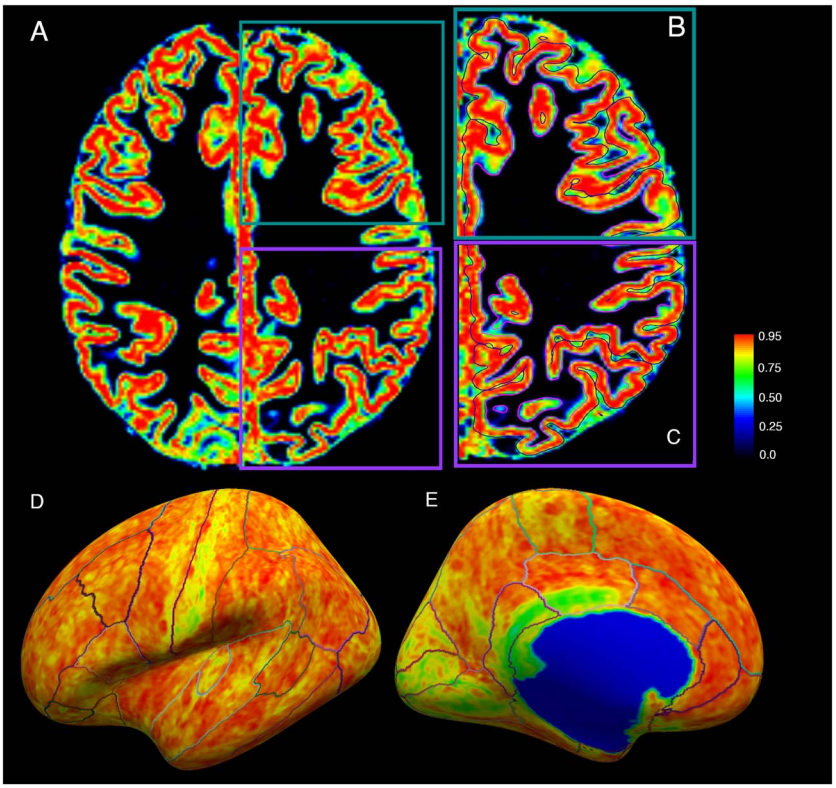

Fig. 1. Example of a GM concentration map of a representative control participant and its projection to the inflated surface. a) Axial view of the GM concentration map for a control participant. b) and c) Anterior and posterior zoom of the same maps (green and grape colors, resp.) with pia (dark blue) and WM (pink) surfaces overlaid. d) and e) Lateral and medial views, resp., of the projection of the GM concentration map over the FS average inflated surface on the left hemisphere. The color bar corresponds to the GM concentration for both the axial and zoomed views and the inflated surfaces.

We used an openly available Matlab code (https://miplab.epfl.ch/index.php/software/PLS) published in Kebets et al. (2019), running in MATLAB vR2019b version (The MathWorks, Inc., Natick, MA). In short, this method first computes a correlation matrix between behavioral variables and brain variables while concatenating group-specific correlation matrices of VPT and FT participants. Computing the singular value decomposition of this matrix provides several latent components, each of them composed of a set of behavior weights and mean GM concentration weights, indicating how strongly each variable contributes to the multivariate correlation. Permutation testing with 1,000 permutations was used to assess the significance of each latent components. Stability of brain and behavior weights was estimated using bootstrapping (500 bootstrap samples with replacement). Bootstrap ratio z-scores for each brain and behavior variables were obtained by dividing each brain and behavior weight by its bootstrap-estimated standard deviation, and a *P*-value was obtained for each bootstrap ratio z-score. The contribution of brain and behavior weights for a given latent component was considered robust at $P < 0.01$ (i.e. absolute bootstrap ratio z-scores above 3, corresponding to a confidence interval of approximately 99%) (Bolton et al. 2020; Siffredi et al. 2021b).

Results

Sample characteristics

Demographic and neonatal characteristics of the participants are presented in Table 1. As expected, the VPT and FT control groups were statistically different in terms of GA and birth weight ($P < 0.005$). There were no significant group differences neither in proportion of male/female nor in the mean age at assessment. No significant difference was found in terms of general intellectual functioning between the VPT and FT groups either. FT participants showed a significantly lower SES compared to VPT ($P < 0.005$). *P*-values for group comparisons are summarized in Table 1.

Qualitative evaluation of GM concentration maps

Figure 1 shows the GM concentration map of a representative (and randomly chosen) control participant (A) with two zoomed views (B, C). In the zoomed views, we have overlaid the corresponding pia and WM surfaces extracted by FS. These surfaces are used to map project the GM concentration to the inflated FS average surface (panels D and E). The final GM concentration value is computed (for each vertex of the mesh) averaging the values of the GM concentration sampled at the pial and WM surfaces and the middle point between these two. GM values range from 0.71 to 0.95.

Group-wise GM concentration differences: GLM

The voxel-based GLM analysis demonstrates significant alterations in GM concentration in VPT children and adolescents when compared to FT controls mainly in frontal, temporal, parietal, and cingular regions. Decreased GM concentrations were found in VPT compared to FT controls in the posterior, caudal anterior, and isthmus cingulate cortices (PCC, cACC, and ICC) as well as the lateroccipital cortex (LOCC) bilaterally. Further decreased GM concentration in the VPT compared to the FT group was found in the left inferior and middle (ITG and MTG) temporal gyri. In the right hemisphere, VPT children and adolescents displayed lower GM concentration than FT controls in the superior temporal gyrus (STG), fusiform gyrus (FFG), and inferior parietal cortex

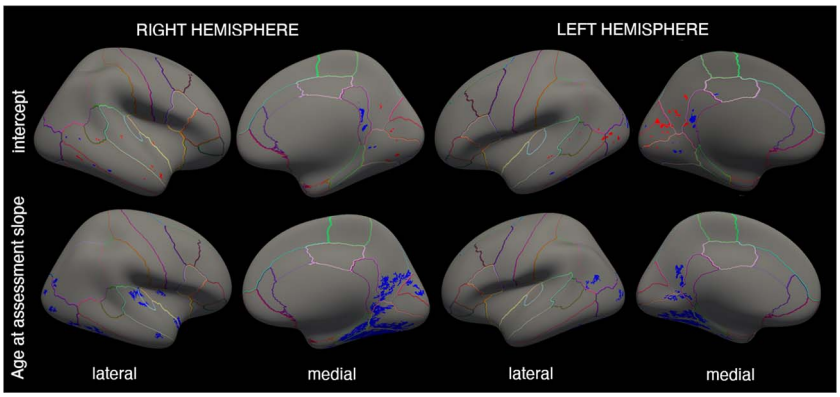

Fig. 2. GLM results for the cortical GM concentration comparisons between the VPT and FT control groups. Significant increase in GM concentration in the VPT group compared the FT group is shown in blue; significant increase in GM concentration in the FT control group compared to the VPT group is shown in red. VPT participants showed decreased GM concentrations bilaterally in the PCC, cACC, ICC, and LOCC; in the left ITG and MTG; and in the right STG, FFG, and IPC. Increased GM concentration in the VPT group compared to the FT control group was found bilaterally in the PCUN, CUN, PCAL, and bnkSTS; in the left STG; and in the right MTG. Both increased and decreased concentration was found in the LING and LOCC, bilaterally (first row: Intercept). With respect to age at assessment, VPT participants displayed lower GM concentration bilaterally in the CUN, LOCC, FFG, ITG, MTG, and STG; in the left PHC; and in the right IPG, PCUN, PCAL, LING, and INS (bottom row: Age at assessment slope).

(IPC). Additionally, increased GM concentration was seen in the VPT compared to the FT control group bilaterally in the precuneus (PCUN), cuneus (CUN), and pericalcarine (PCAL) cortices as well as in the banks of the superior temporal sulci (bnkSTS). The left STG as well as the right middle temporal gyrus (MTG) also displayed increased GM concentration in VPT compared to FT controls. Both increased and decreased concentration was found in the LOCC and the lingual gyrus (LING), bilaterally (see Fig. 2, Intercept).

With respect to age at assessment, VPT children and adolescents displayed lower GM concentration compared to FT controls bilaterally in the CUN; LOCC; FFG; and ITG, MTG, and STG. Additionally, decreased GM concentration was also found in the VPT group compared to FT controls in the right inferior parietal gyrus (IPG), PCUN, PCAL, LING, insula (INS), and left parahippocampal cortices (PHCs) (Fig. 2, Age at assessment slope).

Univariate association with socio-emotional scores: GLM

Results for the GLM are summarized in Table 3. In all ROIs under analysis, for the Emotional Control score, there was a significant main effect of GA ($P < 0.005$), with higher Emotional Control scores associated with smaller GA; reflecting increased emotional control difficulties in daily life for VPT children and adolescents with smaller GA. The same main effect of GA was found for Internalized scores in all regions of interest ($P < 0.005$) except for the CUN and PCAL bilaterally and for the right LOCC. Bilaterally in the LOCC and PCAL, we found an additional effect of SES ($P < 0.05$) indicating an association between lower SES with reduced Internalized scores. The Affect Recognition scores had a significant main effect of GM concentration bilaterally in the ICC (left, $P < 0.05$; right, $P < 0.01$) and in the LOFC ($P < 0.05$); in the left ITG, PHC and STG ($P < 0.05$); as well as in the right CUN, LOCC ($P < 0.01$), MTG, PCC, and PCUN ($P < 0.05$). In these cases, no main effect was found with GA and SES, reflecting that reduced scores in Affect Recognition are linked to subtle GM alterations in these regions irrespective to GA and SES. No significant main effect was found for the Theory of Mind scores.

Altogether, the GLM results show a clear association of Emotional Control and Internalized scores with GA, while GM concentration was mainly linked to the children's abilities in the Affect Recognition scores (Table 2).

Multivariate association with socio-emotional scores: PLSCs

The PLSC analysis for the multivariate patterns of correlation between the mean GM concentration in the ROIs with altered concentration in VPT children and adolescents and socio-emotional scores gave one significant latent component (latent component 1 (LC1), $P = 0.012$) and is shown in Fig. 3.

Overall, LC1 revealed comparable patterns of associations in the VPT and FT group with better socio-emotional abilities associated with increased GM concentration (Fig. 3). Both in the VPT and FT groups, results show an association between increased Affect Recognition scores with increased GM concentration means bilaterally in the FFG, PCUN, and PCC; in the left STG, MTG, ITG and LOFC; and in the right CUN, ICC, LOCC, and IPC. In the VPT group, this same pattern of increased GM concentration means in the same ROIs was also associated with increased Theory of Mind scores. Environmental factors have been found to be closely related to brain development, including WM development (Bick et al. 2015). In VPT children and adolescents, environmental factors, such as socioeconomic status, have indeed been increasingly recognized as an important determinant of neurodevelopmental outcomes (Benavente et al. 2019). In the current study, socio-economic status was not significantly associated with GM concentration alterations neither in the VPT group nor in the FT group. Salience, bootstrap-estimated standard deviations, and bootstrap ratio z-scores for all socio-emotional measures and GM concentration means for each ROI are reported in Supplementary Table S1. See online supplementary material for a color version of this figure.

Discussion

The present study aimed to unravel the effects of subtle GM alterations in cortical development in VPT children and adolescents aged 6–14 years old and its association with socio-emotional abilities. To this end, we applied advanced neuroimaging and statistical approaches to a cross-sectional cohort covering a large developmental period over childhood and adolescence in

Table 2. GLM results for the association between socio-emotional measures and mean GM concentration or each ROI.

LEFT HEMISPHERE						RIGHT HEMISPHERE					
ROIs		EMO	INT	AR	ToM	ROIs		EMO	INT	AR	ToM
cCAG	GA	*	*			cCAG	GA	*	*		
	SES						SES				
	GM						GM				
CUN	GA	*				CUN	GA	*			
	SES						SES				
	GM						GM			**	
FFG	GA	*	*			FFG	GA	*	*		
	SES						SES				
	GM						GM			*	
ICC	GA	*	*			ICC	GA	*	*		
	SES						SES				
	GM			*			GM			**	
ITG	GA	*	*			INS	GA	*	*		
	SES						SES				
	GM			*			GM				
LOCC	GA	*	*			IPC	GA	*	*		
	SES		*				SES				
	GM						GM				
LOFC	GA	*	*			ITG	GA	*	*		
	SES						SES				
	GM			*			GM				
LING	GA	*	*			LOFC	GA	*	*		
	SES						SES				
	GM						GM			*	
MTG	GA	*	*			LING	GA	*	*		
	SES						SES				
	GM						GM				
PHC	GA	*	*			MTG	GA	*	*		
	SES						SES				
	GM			*			GM			*	
PCAL	GA	*				PCAL	GA	*			
	SES		*				SES		*		
	GM						GM				
PCC	GA	*	*			PCC	GA	*	*		
	SES						SES				
	GM						GM			*	
PCUN	GA	*	*			PCUN	GA	*	*		
	SES						SES				
	GM						GM			*	
STG	GA	*	*			STG	GA	*	*		
	SES						SES				
	GM			*			GM				

Significance: *P-value < 0.05; **P-value < 0.01. ROIs are arranged in rows. Columns correspond to socio-emotional scores; EMO: Emotional control; INT: Internalized; AR: Affect recognition; ToM: Theory of Mind.

both VPT and FT participants. By describing the intensity of each voxel as the sum of GM, WM, and CSF characteristic intensities (weighted by their respective local concentrations), cortical tissue characteristics were disentangled from the presence of PVE in the cortical mantle, providing a more in-depth insight in the cortical microstructure at the voxel level. The association of GM concentration with socio-emotional abilities was studied using not only a univariate analysis but also an advanced data-driven multivariate approach.

GM concentration in VPT children and adolescents

Our findings show that the effects of prematurity were far-reaching, with atypical GM concentration in a range of cortical brain regions. Consistent with previous studies, alteration in GM concentration following VPT birth seems to not simply result in overall GM tissue loss but in specific patterns of cortical alterations (Allin et al. 2004; Nosarti et al. 2008).

In the occipital lobes, regions showed both a decrease (i.e. lingual, latero-occipital, and fusiform cortex) and an increase (i.e. CUN, PCUN, and PCAL) in GM concentration in the VPT group compared to FT controls. This variability in the occipital regions observed in our study is in line with previous results. While reduced GM volume, surface, and cortical thickness have been reported in different occipital regions in VPT children (Kesler et al. 2004; Zubiaurre-Elorza et al. 2012; Vandewouw et al. 2020), adolescents (Nosarti et al. 2008; Karolis et al. 2017), and adults (Nosarti et al. 2014; Meng et al. 2016), increased GM volume and cortical thickness have also been found in children (Lean et al. 2017; Vandewouw et al. 2020) and adults (Shang et al. 2019). With a particular focus on socio-emotional processing, the right fusiform

area, found to be reduced in the VPT group in our study, has been continually mentioned as having differential GM volume in VPT compared to their FT peers. Similar to other occipital regions, the direction of these differences was found inconsistent with a loss of GM in VPT infants (Makropoulos et al. 2016) and a gain of GM and cortical thickness in VPT children (Vandewouw et al. 2020), adolescents (Nosarti et al. 2008), and adults (Bäuml et al. 2015; Meng et al. 2016; Shang et al. 2019).

In the temporal lobes, contrasting findings were found with increased and decreased GM concentration in the VPT group compared to the FT controls across the left and the right hemispheres (i.e. a decrease in left inferior and middle as well as in right superior temporal sulci; an increase in right middle as well as left superior temporal and bank of the superior temporal sulci). Once again, the high variability in temporal alteration observed in the current study is consistent with the contrasting results in the literature. Reduced GM volume, cortical surface area, and cortical thickness were found in children (Peterson et al. 2000; Kesler et al. 2004; Zhang et al. 2015; Lean et al. 2017), adolescents (Nagy et al. 2009) and young adults (Bjuland et al. 2013; Skranes et al. 2013; Meng et al. 2016); increased GM volume and surface area were also observed in children (Vandewouw et al. 2020) and adolescents (Nosarti et al. 2008). In the current study, it is possible that the opposite pattern of alteration found in left and right temporal areas is related to different degrees of symmetry in the VPT and FT groups (Dubois et al. 2010).

Additionally, our findings show GM concentration loss in the lateral orbitofrontal regions bilaterally. Similarly, previous results found a reduction in GM volume in preterm infants (Thompson et al. 2007) as well as in children and adolescents (Nagy et al. 2009; Zubiaurre-Elorza et al. 2012; Lean et al. 2017). Nevertheless, conflicting results were also found in children from 7 to 11 years of age and in adults with increased GM volume in orbitofrontal regions (Kesler et al. 2004; Bäuml et al. 2015). This region is of interest as it is known to be sensitive to stress and mediates emotional responses (Stuss and Knight 2002). Thus, impairment in the cerebral development of this region may contribute to socio-emotional difficulties of VPT children and adolescents.

Moreover, GM concentration in the right inferior parietal cortex was reduced in the VPT group compared to the FT group. Previous studies were consistent with this finding with a decreased GM volume in children and adolescents (Lean et al. 2017; Nagy et al. 2009; Kesler et al. 2004; Zubiaurre-Elorza et al. 2012).

Finally, reduced GM concentration was observed in the VPT group compared to FT controls in the cingulate cortex bilaterally, including the isthmus, caudal anterior, and posterior cingulate. Studies conducted in infants and children are consistent with these results and show a reduction in GM volume, mostly in the posterior cingulate cortex (Ball et al. 2013; Lean et al. 2017). Nevertheless, in VPT adolescents from 15 years of age and adults, previous studies mostly reported an increase in GM volume in the different portions of the cingulate cortex (Nosarti et al. 2008; Bäuml et al. 2015; Meng et al. 2016).

Developmental trajectory of GM concentration in VPT children and adolescents

When exploring developmental trajectories of GM concentration from 6 to 14 years of age, the VPT group showed significant reductions in the development of GM concentration compared to the FT group for all regions, especially in regions showing overall group differences in GM concentration. This decrease in GM development over time was observed in temporal and occipital regions, as well as in the right INS and the left parahippocampal regions. Therefore, these findings fail to find evidence for a developmental "catch-up" in VPT children and adolescents that was previously suggested in the literature (Nam et al. 2015). One possibility is that this "catch-up" occurs later in development, during late adolescence. However, these findings are also in line with other studies exploring GM developmental trajectories (Nosarti et al. 2014; Karolis et al. 2017), suggesting that the trajectory of brain development following VPT birth may not only be delayed but also fundamentally distinctive.

Overall, our results demonstrated that VPT birth is associated with extensive alterations in cortical brain structure in children and adolescence, which seems particularly widespread in occipital and temporal regions. As illustrated above and already reported in the literature, the complex pattern of both increases and decreases in cortical GM concentration, GM volume, thickness, and surface areas in the different regions compared to FT controls defy easy generalization with respect to their developmental significance. As described by Nosarti and colleagues (Nosarti et al. 2014), this complex pattern of GM distribution can be interpreted within a "neuroplastic" framework, which proposed that developmental changes in any brain region may result in a cascade of alterations in many other regions. Nevertheless, this study adds to the evidence that perinatal complications occurring at critical periods of development, such as VPT birth, disrupt maturation and have a long-lasting effect on subsequent brain development (Petanjek and Kostović 2012; Raznahan et al. 2012). VPT birth occurs during the third trimester of gestation that is a critical window of neurodevelopment characterized by the final stages of neuronal differentiation and maturation driven by synapse formation. This neural maturation process is paralleled by the loss of radial projection and the increase of tangential extensions of cortico-cortical connections, mirrored by the early stages of cortical myelination (Fleiss et al. 2020). Volpe (2009) proposed the concept of an "encephalopathy of prematurity" for which the cerebral GM of preterm individuals may involve both destructive and developmental disturbances (Volpe 2009). Even if the relative contributions of destructive and developmental processes in contemporary preterm population is not yet clear, neuroimaging studies, including the present study, support that premature individuals have extensive GM abnormalities rather than "injuries" as identified by signal abnormalities on conventional MRI.

Association between GM concentration and socio-emotional outcomes

Given the involvement of GM characteristics for socio-emotional outcomes, we explored the association between GM abnormalities observed in VPT children and socio-emotional abilities both in the VPT and FT control groups. Linear mixed model and multivariate analyses gave coherent and overlapping findings. Better affect recognition abilities were associated with an increase in GM concentration for both the VPT and the FT control groups in several regions, including bilaterally the lateral orbitofrontal, fusiform, precuneus, posterior cingulate, and inferior temporal cortices, as well as left-lateralized caudal anterior cingulate, middle, and superior temporal regions and right-lateralized cuneus, lateral occipital, inferior parietal, and isthmus cingulate regions. This pattern of increase in GM concentration was also significantly associated with better theory of mind abilities in the VPT group only. The orbitofrontal and fusiform cortices are two main brain areas recognized to be involved in

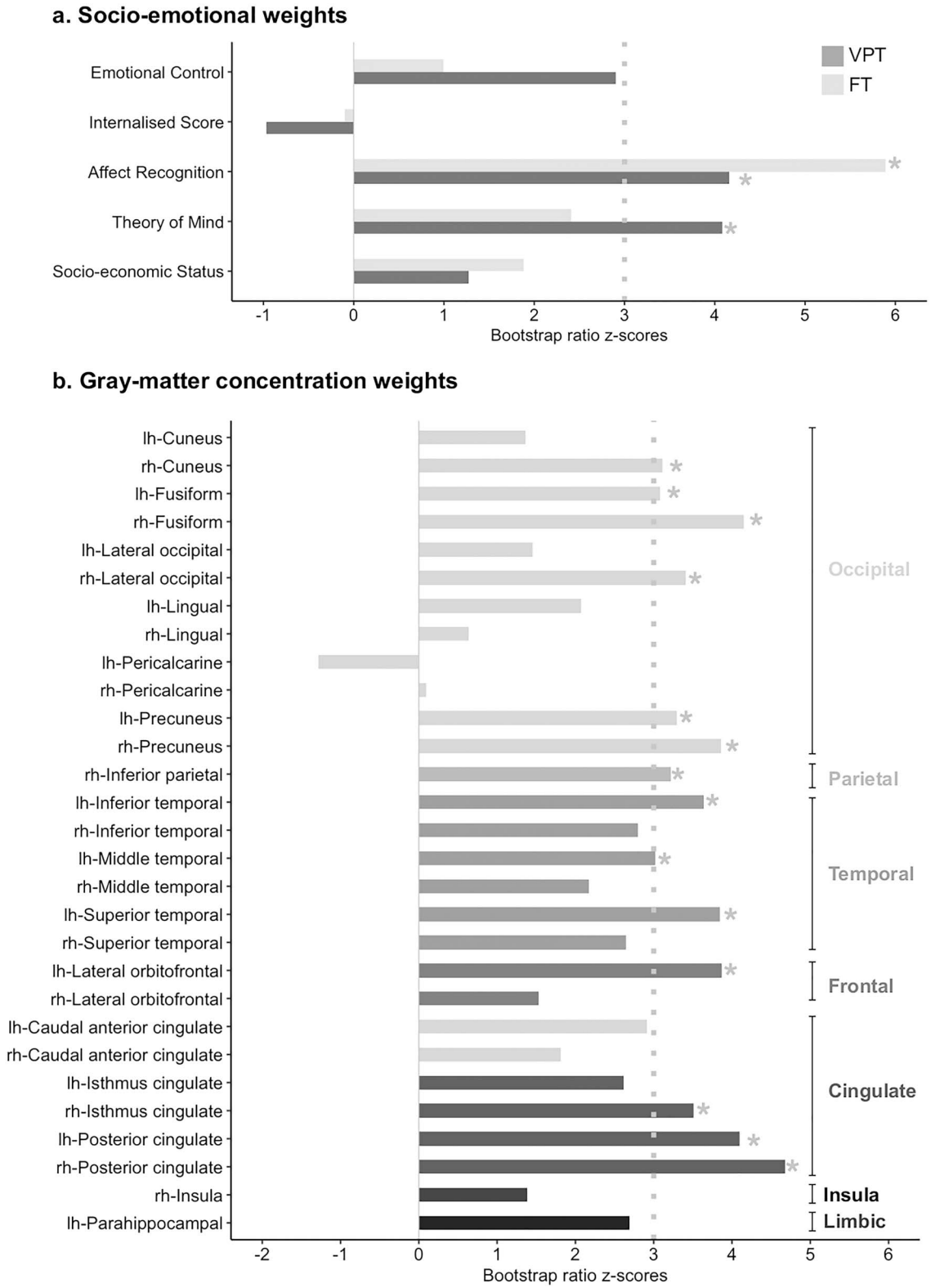

Fig. 3. PLSC results of LC1 showing associations between socio-emotional scores and GM concentration for each ROI. a) Socio-emotional weights: the diverging graph shows bootstrap ratio z-scores (x-axis) for each socio-emotional measure (y-axis). b) Gray-matter concentration weights: the diverging graph shows bootstrap ratio z-scores (x-axis) for GM concentration means for each ROI (y-axis). For both socio-emotional and GM concentration weights, bootstrap ratio z-scores above or equal to 3 are specified by an dash-dotted line and stars on the graph indicate a robust positive correlation.

Table 3. Abbreviations (in alphabetical order).

BPD	Bronchopulmonary dysplasia	GM	Gray matter
BW	Birth weight	IVH	Intraventricular hemorrhage
cPVL	Cystic periventricular leukomalacia	MRI	Magnetic resonance imaging
CSF	Cerebrospinal fluid	PLSC	Partial least square correlation
FCI	Fluid-Crystallized Index	PVE	Partial volume effects
FDR	False discovery rate	ROI	Region of interest
FT	Full term	SES	Socioeconomic status
GA	Gestational age	TIV	Total intracranial volume
GAI	General Ability Index	VPT	Very preterm
GLM	General linear model	WM	White matter
Cortical regions			
cACC	Caudal anterior cingulate cortex	LOCC	Lateroccipital cortex
CUN	Cuneus	LOFC	Laterorbitofrontal cortex
FFG	Fusiform gyrus	MTG	Middle temporal gyrus
ICC	Isthmuscingulate cortex	PCAL	Pericalcarine cortex
INS	Insula	PCC	Posterior cingulate cortex
IPC	Inferior parietal cortex	PCUN	Precuneus
ITG	Inferior temporal gyrus	STG	Superior temporal gyrus
LING	Lingual gyrus		

socio-emotional processing. The current findings are consistent with previous studies showing associations between GM alteration in orbitofrontal and fusiform cortices with prosocial difficulties and social immaturity in VPT children and adolescents (Rogers et al. 2012; Healy et al. 2013). In addition to orbitofrontal and fusiform areas, we also found an association between socio-emotional abilities with a general increase in GM concentration for both groups in a range of regions that are known to be part of the social brain network, including the cingulate, middle, and superior temporal as well as inferior parietal regions (Blakemore 2008; Beauchamp and Anderson 2010).

Strengths and limitations of the study

Our study benefits from cross-sectional data of VPT children and adolescents from 6 to 14 years of age. The estimation of signal intensities of brain tissue types in a single voxel (i.e. GM, WM, and CSF) in contrast of a traditional binary classification based on global signal averaging allowed for a better characterization of GM concentration in this population. PVE methods generally estimate partial volume in a conventional discrete segmentation framework, and represent mixed tissue classes by modelling by intensity distributions that may physically reflect PV effects. This framework has the potential to pinpoint voxels affected by strong PVE but often underestimate the overall PVE. The PVE method used in this work, on the contrary, revisit methods that rely on continuous MRFs and formulate tissue concentration estimation as a Bayesian maximum a posteriori problem alleviating two main drawbacks of "mixed models." First, tissue concentration maps and global intensity parameters are simultaneously updated at each iteration, allowing for a faster and more accurate convergence. Second, it includes a tissue homogeneity prior, drastically reducing the overestimation of PV effects. Nevertheless, potential remaining confounders that may affect the brain surfaces extracted from MRI can be (i) the high variability of intracranial vessel anatomy that pierce through the pia and (ii) the increase in subarachnoid space following premature birth. Also, the use of longitudinal data could inform more precisely on the developmental trajectories and maturation of GM concentration in VPT and its association with socio-emotional abilities during childhood and adolescence.

Conclusion

This study explored GM concentration and its developmental trajectory in VPT children and adolescents aged 6–14 years compared to FT peers. Widespread abnormal GM concentration with altered maturation was found with specific patterns of increases and decreases of GM concentration across cortical regions. Socio-emotional abilities were associated with GM concentration in regions known to be involved in such process for both VPT and FT children and adolescents.

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Author contributions

Vanessa Siffredi (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing—original draft, Writing—review & editing), Maria Chiara Liverani (Conceptualization, Data curation, Project administration, Writing—review & editing), Cristina Borradori-Tolsa (Conceptualization, Investigation, Project administration), Russia Ha-Vinh Leuchter (Conceptualization, Investigation, Project administration, Resources), Jean-Philippe Thiran (Resources, Software), Petra S. Huppi (Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Validation, Writing—review & editing), and Elda Fischi-Gomez (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing—original draft, Writing—review & editing)

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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Conflict of interest statement: Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

The datasets presented in this article are not readily available because requires a formal data sharing agreement. Requests to access the datasets should be directed to Petra.Huppi@hcuge.ch.

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