Prenatal and Early-Life Environmental Factors, Family Demographics and Cortical Brain Anatomy in 5-Year-Olds: An MRI Study From FinnBrain Birth Cohort

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Abstract

The human brain develops dynamically during early childhood, when the child is sensitive to both genetic programming and extrinsic exposures. Recent studies have found links between prenatal and early life environmental factors, family demographics and the cortical brain morphology in newborns measured by surface area, volume and thickness. Here in this magnetic resonance imaging study, we evaluated whether a similar set of variables associates with cortical surface area and volumes measured in a sample of 170 healthy 5-year-olds from the FinnBrain Birth Cohort Study. We found that child sex, maternal pre-pregnancy body mass index, 5min APGAR score, neonatal intensive care admission and maternal smoking during pregnancy associated with surface areas. Furthermore, child sex, maternal age and maternal level of education associated with brain volumes. Expectedly, many variables deemed important for neonatal brain anatomy (such as birth weight and gestational age at birth) in earlier studies did not associate with brain metrics in our study group of 5-year-olds, which implies that their effects on brain anatomy are age-specific. Future research may benefit from including pre- and perinatal covariates in the analyses when such data are available. Finally, we provide evidence for right lateralization for surface area and volumes except for the temporal lobes. These subtle differences between hemispheres are variable across individuals and may be interesting brain metrics in future studies.

Introduction

The cortical brain development is fast during the first years of life (Knickmeyer et al., 2010), which is reflected in all typically used metrics such as cortical thickness (CT), surface area (SA), gyrification and cortical volumes (Remer et al., 2017). These metrics seem to capture distinct patterns of brain maturation, and indeed, are frequently discussed separately in recent studies (Kuhl et al., 2020; Lyall et al., 2015; Yang et al., 2016). Cortical development is sensitive to extrinsic factors starting from the perinatal period, and these exposures may have long-lasting and often adverse effects on the neurocognitive development among the vulnerable individuals later in life (Duan et al., 2019; Lehtola et al., 2019; Pulli et al., 2019). In a broader context, many psychiatric and neurocognitive disorders have been postulated to result from alterations in cortical and subcortical maturation in the early childhood (Hazlett et al., 2012; Li et al., 2016), and to capture such signals is of importance for both clinical and scientific purposes. For example, the ability to select an appropriate set of covariates for the data analyses, is dependent on the knowledge of important and potentially confounding factors.

A study by Jha et al. (2019) observed the effects of obstetric and prenatal environmental factors on CT and SA in the newborns. The average CT correlated positively with postnatal age at magnetic resonance imaging (MRI) and negatively with paternal education. In addition, maternal ethnicity associated with the average CT, with the offspring of African American mothers presenting larger CT than Caucasian mothers. The total SA showed positive correlations with birth weight, gestational age at birth and postnatal age at MRI. Furthermore, males were found to have significantly greater total SA than females. These results demonstrate the role of perinatal surroundings and family demographics for the early cortical anatomy (Sheridan et al., 2012; Wu et al., 2020). The results also suggest that the early

organization of cortical structure is affected by both maternal and paternal factors, that may be genetic. To which extent these environmentally associated structural features persist to later ages during childhood is still unclear.

In the current study, we quantified the associations between demographics and gross anatomy of cortical SA and volumes in healthy, typically developing 5-year-olds, and discussed how these results were in line with prior work (Jha et al., 2019). The study by Jha et al. was selected for the prior reference work due to its unique and large newborn dataset, which is a combination of comprehensive background information and quality MRI data of the participants. If the demographics that have been shown to associate to neonatal brain anatomy still explained later childhood brain features it would imply the presence of possible programme effect. It would also suggest that the perinatal timepoint has a crucial role in cortical development considering the following years of life, too. However, we generally expected to find that most of these factors that associated with newborn brain anatomy (e.g. birth weight, gestational age at birth and postnatal age at MRI) in the previous study do not explain structural features in 5-year-olds, which could mean that postnatal environment and genetics are prominent determinants of early childhood brain development. On the other hand, we expected to find sex differences and that demographics that are continuous exposures from the viewpoint of the child, such as maternal socioeconomic status (SES) would associate with brain morphology through the first five years of life. In addition, we provide descriptive statistics of the cortical lateralization.

Methods

The study was conducted according to the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK:31/180/2011).

Participants

The participants of the current MRI study are part of a larger FinnBrain Birth Cohort Study population (www.finnbrain.fi) (Karlsson et al., 2018). Initially, mothers and their spouses were recruited at three maternal welfare clinics in Southwest Finland during the first trimester ultrasound visits. The participating mothers of the current sample were mostly of Finnish background. Parental background information was gathered during pregnancy by questionnaires and included monthly income, educational level, diagnosed medical conditions, medications affecting central nervous system (CNS), and substance use during pregnancy. For CNS affecting medications, only serotonin reuptake inhibitors and norepinephrine reuptake inhibitors (SSRI/SNRI) or benzodiazepines were reported. No illicit drug use substance was reported in the current sample. Parental psychiatric history variables were determined based on questionnaires for mothers, that screened the parents for symptoms of depression, anxiety disorder and psychotic symptoms. Obstetric data (NICU admission, 5 min APGAR score, Maternal BMI before gestation, Diagnosis of gestation diabetes) were retrieved from the Finnish Medical Birth Register of the National Institute for Health and Welfare (www.thl.fi).

The inclusion criteria for the imaging measurements were a visit to *FinnBrain Child Development and Parental Functioning Lab*, including neuropsychological measurements, at 5 years of age. However, five participants were included without neuropsychological visits: three participants had an exposure to maternal prenatal synthetic glucocorticoid treatment (recruited separately for a nested case–control sub-study). In addition, two participants were enrolled for pilot scans. The exclusion criteria specific for this study were: 1) born before gestational week 35, 2) developmental anomaly or abnormalities in senses or communication (e.g. blindness, deafness, congenital heart disease), 3) known long-term medical diagnosis (e.g. epilepsy, autism), 4) ongoing medical examinations or clinical follow up in a hospital (meaning there has been a referral from primary care setting to special health care), 5) child use of continuous, daily medication (including per oral medications, topical creams and inhalants. Exceptions to this were desmopressin (®Minirin) medication and asthma inhalers during infection, which were allowed), 6) history of head trauma reported by parents (defined as concussion necessitating clinical follow up in a health care setting or worse), 7) metallic (golden) ear tubes, and routine MRI contraindications.

The MRI scans were performed between 29 October 2017 and 1 March 2021. Altogether 541 families were contacted and 478 (88%) of them reached. In total, 203 (42% of the reached families) participants attended imaging visits.

MRI data acquisition

All MRI scans were performed for research purposes by the research staff. Before the visit, each family was contacted and recruited via telephone calls by a research staff member. A written informed consent was acquired from both parents at the beginning of the MRI visit. Before the imaging, a research member met families personally to share information about the study visit and to bring practice materials for home rehearsal. During the study visit, a flexible timetable was reserved for the subjects to get familiar with the research staff. Imaging was practiced with a mock scanner (incl. wooden head coil) and a light meal was served before the scan.

The subjects were scanned during natural sleep or awake while they were watching a movie or TV show of their choice. Hearing protection included wax earplugs and headphones. Foam padding was applied to help the head stay still and assure comfortable position. A member of the research staff and a parent stayed in the scanner room throughout the scan. Subjects were given a “signal ball” to throw in case they needed or wanted to stop the scan at any point. The protocol of the preparations and the study visit are described in detail in our previous studies (Copeland et al., 2021; Pulli et al., 2021).

Subjects were scanned with a Siemens Magnetom Skyra fit 3T (Siemens Medical Solutions, Erlangen, Germany) using a 20-element head/neck coil. The Generalized Autocalibrating Partially Parallel Acquisition (GRAPPA) technique was used to accelerate image acquisition (Parallel acquisition techniques factor of 2 was used). The MRI data was acquired as a part of max. 60-minute scan protocol. For the purposes of the current study, we acquired high resolution 3D T1 images using magnetization prepared rapid gradient echo (MPRAGE) sequence with following sequence parameters: TR = 1900 ms, TE = 3.26 ms, TI = 900 ms, flip angle = 9 degrees, voxel size = 1.0 x 1.0 x 1.0 mm³, FOV 256 x 256 mm².

In addition, MRI protocol consisted of a T2 turbo spin echo (TSE), a 96-direction ($b = 1000 \text{ s/mm}^2$, 9 b0s, TR/TE = 9300/87.0ms) diffusion tensor imaging (DTI) sequences (Merisaari et al., 2019) and a 7-minute functional MRI acquisition.

Image analysis

Three out of the 203 participants that attended the imaging visit were born before 35 weeks of gestation and 13 subjects were excluded due to the failure or excess motion artefact in the T1-weighted images. Thereafter, 187 subjects' T1-weighted images entered the processing pipeline (Pulli et al., 2021) and after assessing the automated segmentation, 170 were qualified into the analyses. Cortical reconstruction and volumetric segmentation for all images that were included to the processing pipeline was performed with the FreeSurfer software suite, version 6.0.0 (<http://surfer.nmr.mgh.harvard.edu/>). We run the "recon-all" processing stream with default parameters, including the following steps: first transformation to Talaraich space, intensity inhomogeneity correction, bias field correction (Sled, Zijdenbos, & Evans, 1998), and skull-stripping (Ségonne et al., 2004). White matter (WM) was separated from everything else and the volume within the created WM–gray matter boundary was filled. After this, the surfaces were tessellated and smoothed. When these preprocessing steps were completed, the surfaces were inflated (Fischl, Sereno, & Dale, 1999) and registered to a spherical atlas.

Automatically segmented images were viewed and edited with the Freeview in line with the procedures recommended by the FreeSurfer instructions, with the addition of the Desikan–Killiany atlas that allowed us to correctly identify the areas where errors were found. Images with excess motion artefact or large unsegmented regions were excluded. The images that passed the initial quality check were then manually edited by two research staff members (authors ES and EPP, supervised by JJT) and after that the automated segmentation process was ran again as suggested by FreeSurfer instructions. The images were then inspected again for errors according to the FinnBrain quality control protocol, which is comprehensively presented in our recent article (Pulli et al., 2021).

The Freesurfer pipeline divides the cortex to 33 regions bilaterally. However, instead of analysing each region specifically, we were interested in the gross cortical anatomy and the regions of interests (ROIs) were determined for volumes and SA's as follows: total, left and right hemispheres, and lobe division bilaterally to four main lobes (frontal, temporal, parietal and occipital) according to the Freesurfer instructions (Supplementary Table 1). We included all the MRI data that passed the FinnBrain quality control protocol. Specifically, we did not exclude participants if they had minor issues in a single or few ROIs within the lobar measures as volumes and SA's in specific excluded regions are relatively small and are not likely to affect the measures of the main lobes and hemispheres (we also confirmed that typical errors in borders and cortical labelling were located inside main lobes instead of areas between lobes or between hemispheres). The ROI selection was justified by the notion that prior work (Jha et al., 2019) reported associations that reflected gross anatomy in the main results. In addition, expanding the approach to smaller ROI's would have aggravated the multiple comparison issues, and we did not pursue such analyses in the current study.

Statistical analysis

A total of 170 subjects' MR images passed the inclusion criteria and the FinnBrain quality control protocol (Pulli et al., 2021) and were selected for the statistical analyses. Brain variables included cortical volumes and surface area for the following regions: total cortex, both cortical hemispheres, and the aforementioned four main lobes bilaterally. The reference article by Jha et al., (2019) was set as a basis for selecting the variables. After careful consideration and matching of variables, 16 demographic variables were included in the analyses. Categorical variables included: sex, neonatal intensive care unit (NICU) admission, mode of delivery, maternal and paternal education level, maternal smoking during pregnancy, diagnosis of gestational diabetes during gestation and the use of SSRI/SNRI medication during pregnancy. Continuous variables included: birth weight, gestational age at birth, postnatal age at MRI, ponderal index at MRI, maternal age at child's birth, paternal age at child's birth, maternal BMI before gestation and 5min APGAR score. To aid interpretation of the results we have grouped the variables into three groups. 1) Fixed family factors and child features at scanning: child sex, maternal and paternal education level, maternal age at child's birth, paternal age at child's birth, postnatal age at MRI and ponderal index at MRI, 2) Incidental pregnancy and delivery related factors: mode of delivery, child birth weight and gestational age at birth as well as neonatal intensive care unit (NICU) admission and 5min APGAR score, 3) Maternal prenatal health features: maternal pre-pregnancy BMI, maternal smoking during pregnancy, diagnosis of gestational diabetes and the use of SSRI/SNRI medication during pregnancy. The following variables were considered too unreliable or otherwise suboptimal in our questionnaire data, and were excluded: maternal and paternal psychiatric history, household income, gestation number, and number of siblings. The descriptive statistics of the demographics and brain variables are presented in the Tables 1 and 2.

Statistical analyses were conducted using IBM SPSS Statistics 27.0. (IBM Corp., Armonk, NY, USA). The MRI data was confirmed to be normally distributed using JASP Statistics 0.14.1. (<https://jasp-stats.org/>), based on visual assessment, skewness, kurtosis and Shapiro-wilk p values (Supplementary Figure 1 and Supplementary Table 2). Correlation matrices with Pearson correlation were created for cortical volumes and surface areas with JASP Statistics. Lateralization calculations for hemispheres and lobes were carried out with JAPS statistics for descriptive purposes. Lateralization indices were also confirmed to be normally distributed based on the same criteria as the initial MRI data (Supplementary Figure 2, Supplementary Table 2).

Linear regression models were carried out using each brain variable separately as a dependent variable and the group of 16 demographics as independent variables. Stepwise linear regression models were applied. This study was exploratory in nature and therefore we decided (a priori) not to perform formal corrections for multiple comparisons and report raw p values throughout the manuscript. The Bonferroni corrected p value at alpha level 0.05 over the 22 comparisons over the 11 regression models x 2 brain measures (SA, volumes) was $p < 0.002$.

Results

Correlation and lateralization

The total SA correlated significantly positively with hemispheric lobular SA's (r_s range = 0.649- 0.940) (Figure 1A, Supplementary Table 3A). The SA correlations between occipital lobes and other ROI's were remarkably weaker (r_s range for the left occipital lobe = 0.44- 0.658 and for the right occipital lobe = 0.451- 0.659). Similar trends were quantified also in the cortical volumes (Figure 1B, Supplementary Table 3B), with total volume correlating positively with hemispheric lobular volumes (r_s range = 0.610- 0.932) and weaker correlations between occipital lobes and other ROI's (r_s range for the left occipital lobe = 0.398- 0.611 and for the right occipital lobe = 0.432- 0.636). Large interindividual variation in cortical anatomy (both volumes and SA) among 5-year-olds was observed.

The cortical SA's and volumes were right lateralized except for the temporal lobes that had greater volumetric and SA values on the left side (Figures 2 and 3). However, the degree of lateralization (the difference between hemispheres or lobes of interest divided by the total volume or SA) was relatively small in general and there was a considerable interindividual variation based on standard deviations (Supplementary Table 4).

Surface area

The results of the regression models for cortical surface areas are presented in the Table 3. Sex was a significant predictor for SA throughout the cortex bilaterally, with males having 8.5% larger total SA on average ($M = 187\,665$, $SD = 13\,881$) than females ($M = 172\,409$, $SD = 13\,065$). NICU admission predicted larger SA in total, both hemispheres and in the left parietal lobe. Maternal smoking during pregnancy predicted smaller SA values in the right hemisphere and particularly, in the right temporal, right parietal and left parietal lobes. In addition, two predictors were found for the right parietal lobe, with maternal BMI before gestation associating with larger SA and higher 5 min APGAR scores associating with smaller SA values.

Volumes

The results of the regression models for cortical volumes are presented in the Table 4. Sex was a significant predictor for volumes throughout the cortex bilaterally, with males having 6.3% larger volumes on average ($M = 623\,594$, $SD = 41\,419$) than females ($M = 585\,748$, $SD = 43\,212$). Higher maternal educational level predicted larger volumes in total, in the left hemisphere, left frontal, left temporal, left parietal, right temporal and in the right parietal lobes. Higher maternal age predicted larger volumes in the right hemisphere and particularly, in the right parietal lobe.

Discussion

In the current study, we quantified how 16 family demographics and pre-/perinatal factors associate with the cortical SA's and volumes at the age of 5 years. For further discussion we grouped the variables into three groups: 1) Fixed family factors and child characteristics at scanning: child's sex, maternal and

paternal education level, maternal age at child's birth, paternal age at child's birth, postnatal age at MRI and ponderal index at MRI, 2) Incidental pregnancy and delivery related factors: mode of delivery, child birth weight and gestational age at birth as well as neonatal intensive care unit (NICU) admission and 5min APGAR score, 3) Maternal prenatal health features: maternal pre-pregnancy BMI, maternal smoking during pregnancy, diagnosis of gestational diabetes and the use of SSRI/SNRI medication during pregnancy. Specifically, we compared the results to the ones in the previous newborn studies to evaluate whether the specific factors could have possible programming effects and on the other hand, quantify the effects of environmental factors on early cortical maturation.

Fixed family factors

Expectedly, child's sex was a significant predictor for both volumes and SA's, with males having larger brains, which is in line with earlier studies (Jha et al., 2019; Lehtola et al., 2019; Wilke et al., 2007). Significant predictors for cortical volumes in 5-year-olds were maternal education level and maternal age. In comparison with the findings from the previous work (Jha et al., 2019), parental factors were not detected in newborns, whereas delivery related factors (child's sex, birth weight, postnatal age at MRI and gestational age at birth) associated with the SA development. Hence, apart from child's sex, different predictors modulated SA growth in the newborns than in 5-year-olds. However, the average CT growth (that was not analyzed in our study) was associated with postnatal age at MRI, paternal education, and maternal ethnicity in the previous study.

Maternal education level during gestation correlated positively to volumetric growth of the cortex in total, in the left hemisphere and partially in specific lobes bilaterally. Similarly, maternal age at delivery had a positive correlation to volumetric development in the right hemisphere. This is interesting, since these variables are not transient, but constant factors that are likely to contribute the child's development throughout the childhood. Maternal education has been reported to correlate positively with cortical volumes also in newborns (Knickmeyer et al., 2017).

In our study, the average maternal age at the time of childbirth was 30.6 years (SD = 4.7 years), which is comparable to the previous work (mean = 29.9, SD = 5.6 years) (Jha et al., 2019). Previous clinical research has showed that advanced maternal age associates with reduced fertility and increased risk of offspring health problems (Jolly et al., 2000; Nassar & Usta, 2009). These conclusions of negative outcomes rely on physiological mechanisms and become more apparent at the maternal age over 35 years (Liu et al., 2011). On the other hand, epidemiologic studies have proposed that advanced maternal age (ranging from 25 to 35 years) could have positive outcome to child's health in terms of self-rated health status, height, obesity, diagnosed conditions and mortality (Myrskylä & Fenelon, 2012). These results are likely to be partly explained by maternal socioeconomic status (or other correlate of maternal age and education), which is also strongly associated with positive outcome to child's health profile (Erola et al., 2016). Other environmental factors naturally co-influence the child's health, too.

Maternal prenatal health profile and delivery related factors

NICU admission, 5min APGAR score, maternal BMI before gestation and maternal smoking during pregnancy associated with cortical SA's maturation at the age of 5 years. In comparison with these findings to the ones in the previous work (Jha et al., 2019), maternal health profile during gestation and incidental delivery related features did not associate with cortical development in the newborns.

Maternal smoking during pregnancy predicted smaller SA values comprehensively in the right hemisphere, with the exception of the right frontal lobe showing no significant associations. These results support the findings from previous studies, where pre/perinatal smoking exposure predicts smaller SA, CT and brain volumes (El Marroun et al., 2016; Liu et al., 2013; Salminen et al., 2019), likely due to the growth restriction caused by nicotine-induced hypoxemia (Lambers & Clark, 1996).

Patterns of lateralisation

The lateralization of the cortical anatomy was right sided, with only the temporal lobes showing greater values on the left hemisphere. However, the degree of lateralization was modest in general, which differed remarkably compared to what has been reported among newborns (Lehtola et al., 2019), where the right-sided lateralization was more prominent and present also in the temporal lobe. The age-related trends of the cortical asymmetry form a potentially interesting phenotype e.g. for language related studies.

Strengths and limitations

The strengths of this study include relatively large sample size with prospective design. The MRI data is analysed thoroughly with quality protocols carried out for every subject and hence, we provide state of art imaging data. Most demographics were collected from national birth registry that is built from records of clinical staff, which makes the variables reliable and standardized. Some variables were missing in our study compared to the previous work, but generally the environmental and obstetric variables matched satisfactorily.

There were a few limitations, too. Part of the demographics were obtained from questionnaires from mothers during pregnancy (including paternal information), which creates minor but important reliability considerations. The 5-year time gap between data collection and imaging sessions was intended as per study design as we were specifically interested if a set of demographics that have been shown to be important determinants of infant brain structure have similar association later in development. Full longitudinal data would be optimal for this purpose and such studies are warranted in the light of our results. In addition, some variables included a modest sample size both absolutely and in relation to the whole data (e.g. maternal smoking and the use of medication during pregnancy). Even though the demographics matched satisfactorily compared to the previous work (Jha et al., 2019), the brain variables differed partly between the studies, as we analyzed cortical SA and volume, whereas Jha et al. studied CT and SA, which is in our view age-appropriate. Most of these limitations can likely be addressed in data sets such as the developing and baby Human Connectome Project (Eggebrecht et al., 2018; Fenchel et al., 2020).

Conclusions

In summary, we aimed to add knowledge about the influence of environmental factors and family demographics on brain cortical development in healthy 5-year-olds. We wanted to inspect whether our current findings are in line with similar studies carried out with newborns in order to evaluate possible age-related and developmental differences in factors explaining the variance in brain cortical development. We found that apart from child sex, the predictors of cortical volume and SA that are typically detected among infant MRI studies, were not identified here at the child age of 5 years. This can be due to variation in methodology or study population characteristics but can also be interpreted as preliminary evidence on early childhood postnatal environmental factors influencing cortical development over prenatal factors as children grow up. Overall, despite the large variable pool, only few of the candidate variables were found to predict cortical maturation. Hence, it is worth mentioning, that the aim of the study was not to find the best predictive model for 5-year-olds, but to explore similarities and differences in patterns of maturation in comparison with earlier literature on infant studies. These findings demonstrate that although closely related to each other, cortical SA and volumes have different patterns of maturation with differential associations with observed variables. Overall, the effects of prenatal and early life variables on cortical maturation are not standardised in the current literature, and hence it is important to report these factors if they are available. In the future, researchers will likely benefit from including similar environmental, parental and delivery related variables to sensitivity analyses for analyses of cortical anatomy between 0-5 years of life either by carrying out longitudinal studies or obtaining data retrospectively.

Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

The study was conducted according to the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK:31/180/2011).

Consent to participate

A written informed consent was acquired from both parents at the beginning of the MRI visit.

Consent for publication

I, Eero Silver, on behalf of all other authors of this article, give my consent for the publication of the manuscript, tables and figures (including supplementary material) to be published in Journal Brain imaging and behaviour.

Data Availability

The data can not be made openly available due to restrictions by national law and local ethical permissions. Data sharing is possible via formal material transfer agreements for which interested investigators should contact the authors.

Code availability

Not applicable.

Author's contributions

Not applicable.

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Tables

Table 1. Descriptive statistics for brain variables.

Surface area (mm ²)	<i>N</i>	Mean	SD	Min	Max
170					
Total		180755,07	15481,36	148666	226766
Lh		89982,64	7627,79	74749	113230
Rh		90772,43	7924,54	73917	115308
Lh_Frontal		33440,15	3015,67	26272	43656
Rh_Frontal		33855,83	3244,34	26152	48106
Lh_Temporal		17296,24	1544,58	13980	21233
Rh_Temporal		16907,72	1616,30	13213	20880
Lh_Parietal		27300,94	2794,00	20793	36058
Rh_Parietal		27610,06	2844,47	21037	38824
Lh_Occipital		11945,31	1286,50	8981	15188
Rh_Occipital		12398,82	1414,54	8725	16626
Volumes (mm ³)	<i>N</i>	Mean	SD	Min	Max
170					
Total		606452,21	46159,53	497420	736409
Lh		302249,82	22672,50	250548	367289
Rh		304202,39	23703,97	246872	369120
Lh_Frontal		118277,27	9006,91	91088	139497
Rh_Frontal		118764,95	9571,09	87395	150397
Lh_Temporal		66867,79	5425,63	55329	80265
Rh_Temporal		65409,89	5921,49	53409	79327
Lh_Parietal		86491,25	8331,19	69212	109634
Rh_Parietal		87297,71	8285,69	70824	116491
Lh_Occipital		30613,5	3465,59	22948	40722
Rh_Occipital		32729,84	3867,42	23970	43800
Lh= Left hemisphere, Rh= Right hemisphere					

Table 2. Descriptive statistics for demographic and obstetric history variables

Categorical variables	N	%
Sex	170	
Male	93	54,7
Female	77	45,4
NICU admission	169	
Yes	23	13,6
No	146	86,4
Missing	1	
Mode of delivery	169	
Vaginal	138	81,7
C-section	31	18,3
Missing	1	
Maternal education*	164	
Low&Mid	83	50,6
High	81	49,4
Missing	6	
Paternal education*	111	
Low&Mid	74	66,7
High	37	33,3
Missing	59	
Maternal smoking during gestation**	170	
Yes	11	6,5
No	159	93,5
Diagnosis of gestation diabetes	169	
Yes	20	11,8
No	149	88,2
Missing	1	
SSRI/SNRI medication during gestation	155	
Yes	6	3,9

	No	149	96,1				
	Missing	15					
Maternal ethnicity	Finnish	165	97,1				
	Other	5	2,9				
Continuous variables	missing	N	Mean	SD	Min	Max	
Birth weight (g)	0	170	3550.55	477.07	2450.00	4980.00	
Gestational age at birth (weeks)	0	170	39.80	1.50	35.14	42.29	
Postnatal age at MRI (years)	0	170	5.40	0.13	5.09	5.79	
Ponderal Index at MRI	0	170	14.10	1.20	11.21	17.63	
Maternal age at child's birth (years)	0	170	30.55	4.74	19.00	41.00	
Paternal age at child's birth (years)	51	119	31.88	5.14	20.00	45.00	
Maternal BMI before gestation	1	169	24.27	4.33	17.48	41.95	
5min APGAR score	0	170	9.10	0.69	4	10	
BMI= body mass index, MRI= magnetic resonance imaging, NICU= neonatal intensive care unit, SSRI/SNRI= serotonin and norepinephrine reuptake inhibitors, *Educational levels: Low&Mid= Upper secondary school, vocational school or lower & University of applied sciences, High= University, **Maternal smoking during gestation= a combination variable of maternal smoking during early and late pregnancy.							

Table 3. Regression models for cortical surface areas

Region of interest		Unstandardized Coefficients		Standardized Coefficients		
		B	Std.error	Beta	t	p
Total	$\Delta R^2 = 0.242$					
	Intercept	186097.140	1721.157		108.123	<0.001
	Sex	-13180.327	2474.319	-0.463	-5.327	<0.001
	NICU stay	8766.857	4340.761	0.175	2.020	0.046
Lh	$\Delta R^2 = 0.233$					
	Intercept	92548.854			108.068	<0.001
	Sex	-6394.823	1231.148	-0.454	-5.194	<0.001
	NICU stay	4296.865	2159.834	0.174	1.989	0.049
Rh	$\Delta R^2 = 0.270$					
	Intercept	93898.948	878.226		106.919	<0.001
	Sex	-6870.241	1239.729	-0.473	-5.542	<0.001
	NICU stay	5220.45	2203.441	0.205	2.369	0.020
	Smoking	-4827.973	2320.645	-0.179	-2.080	0.040
Lh_Frontal	$\Delta R^2 = 0.198$					
	Intercept	34632.929	341.152		101.518	<0.001
	Sex	-2590.472	508.006	-0.454	-5.099	<0.001
Rh_Frontal	$\Delta R^2 = 0.167$					
	Intercept	35182.821	389.038		90.436	<0.001
	Sex	-2669.430	579.312	-0.418	-4.608	<0.001
Lh_Temporal	$\Delta R^2 = 0.136$					
	Intercept	17864.661	171.617		104.096	<0.001
	Sex	-1049.182	255.554	-0.380	-4.106	<0.001
Rh_Temporal	$\Delta R^2 = 0.212$					
	Intercept	17647.327	172.592		102.249	<0.01
	Sex	-1270.74	249.794	-0.450	-5.087	<0.001
	Smoking	-949.658	462.324	-0.182	-2.054	0.043
Lh_Parietal	$\Delta R^2 = 0.224$					

	Intercept	28221.694	307.444		91.795	<0.001
	Sex	-2011.924	433.996	-0.408	-4.636	<0.001
	NICU stay	2006.496	771.366	0.232	2.601	0.011
	Smoking	-1700.972	812.36	-0.186	-2.094	0.039
Rh_Parietal	$\Delta R^2 = 0.286$					
	Intercept	33269.109	2957.655		11.248	<0.001
	Sex	-2091.949	393.354	-0.448	-5.318	<0.001
	Maternal BMI before gestation	82.173	44.989	0.157	1.827	0.071
	Smoking	-2137.658	745.459	-0.247	-2.867	0.005
	5min APGAR score	-718.263	274.478	-0.229	-2.617	0.010
Lh_Occipital	$\Delta R^2 = 0.098$					
	Intercept	12226.839	170.999		71.502	0.010
	Sex	-880.209	254.633	-0.327	-3.457	0.010
Rh_Occipital	$\Delta R^2 = 0.113$					
	Intercept	12785.036	191.373		66.807	0.010
	Sex	-1060.541	284.972	-0.349	-3.721	0.010
BMI= body mass index, Lh= Left hemisphere, NICU= neonatal intensive care unit, Rh= Right hemisphere						

Table 4. Regression models for cortical volumes.

Region of interest	Predictor	Unstandardized Coefficients		Standardized Coefficients		
		B	Std.error	Beta	t	p
Total	$\Delta R^2 = 0.176$					
	Intercept	594860.313	13058.506		45.553	<0.001
	Sex	-31553.852	7745.375	-0.369	-4.074	<0.001
	Maternal education	18052.615	7713.996	0.212	2.340	0.021
Lh	$\Delta R^2 = 0.180$					
	Intercept	295874.645	6411.987		46.144	<0.001
	Sex	-15443.847	3803.134	-0.367	-4.061	<0.001
	Maternal education	9291.872	3787.726	0.222	2.453	0.016
Rh	$\Delta R^2 = 0.176$					
	Intercept	281648.405	13146.871		21.423	<0.001
	Sex	-16929.853	3973.653	-0.385	-4.261	<0.001
	Maternal age at child's birth	1020.654	424.560	0.217	2.404	0.018
Lh_Frontal	$\Delta R^2 = 0.211$					
	Intercept	116746.722	2566.493		45.489	<0.001
	Sex	-7205.936	1522.260	-0.419	-4.734	<0.001
	Maternal education	3367.145	1516.093	0.197	2.221	0.029
Rh_Frontal	$\Delta R^2 = 0.148$					
	Intercept	122564.875	1151.887		106.404	<0.001
	Sex	-7394.897	1715.264	-0.396	-4.311	<0.001
Lh_Temporal	$\Delta R^2 = 0.076$					
	Intercept	64528.682	1683.306		38.334	<0.001
	Maternal education	2348.389	994.372	0.226	2.362	0.020
	Sex	-2001.561	998.417	-0.192	-2.005	0.048
Rh_Temporal	$\Delta R^2 = 0.110$					

	Intercept	63038.236	1810.103		34.826	<0.001
	Sex	-2871.587	1073.624	-0.252	-2.675	0.009
	Maternal education	2682.296	1069.274	0.236	2.509	0.014
Lh_Parietal	$\Delta R^2 = 0.126$					
	Intercept	83938.651	2377.323		35.308	<0.001
	Sex	-4449.082	1410.059	-0.294	-3.155	0.002
	Maternal education	3273.144	1404.346	0.217	2.331	0.002
Rh_Parietal	$\Delta R^2 = 0.205$					
	Intercept	73520.942	4310.590		17.056	<0.001
	Sex	-4310.438	1248.428	-0.307	-3.453	<0.001
	Maternal age at child's birth	375.256	134.865	0.250	2.782	0.006
	Maternal education	3009.091	1260.523	0.215	2.387	0.019
Lh_Occipital	$\Delta R^2 = 0.057$					
	Intercept	31131.625	455.341		68.370	<0.001
	Sex	-1810.103	678.044	-0.258	-2.670	0.009
Rh_Occipital	$\Delta R^2 = 0.043$					
	Intercept	33251.786	517.972		64.196	<0.001
	Sex	-1823.090	771.307	-0.230	-2.364	0.020
Lh= Left hemisphere, Rh= Right hemisphere						

Figures

Figure 1A.

Figure 1B.

Figure 1

1A. Colour-coded correlation matrix of the cortical surface areas.

lh= left hemisphere, rh= right hemisphere, SA= Surface Area

1B. Colour-coded correlation matrix of the cortical volumes

lh=left hemisphere, rh= right hemisphere, Vol= volumes

Figure 2

Violin plots of the lateralization of the cortical surface areas.

LI= Lateralization Index (the difference between left hemisphere/lobe and right hemisphere/lobe), SA= Surface Area.

Figure 3

Violin plots of the lateralization of the cortical volumes.

LI= Lateralization Index (the difference between left hemisphere/lobe and right hemisphere/lobe), Vol= Volume

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