Exposure to Maternal Pre- and Postnatal Psychological Distress: Associations with Brain Structure in 5-year-old Children

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Early life maternal distress and 5-year brain structure

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Abstract

Background: Maternal mental health is an important contributor to child neurodevelopment. While there are multiple studies on prenatal exposure, early postnatal exposure has received little attention in neuroimaging research.

Methods: 5-year-old children (n = 173) were recruited from the FinnBrain Birth Cohort study. Maternal distress was assessed using questionnaires on depressive and anxiety symptoms at 14, 24 and 34 gestational weeks and postnatally at 3, 6 and 24 months. T1-weighted structural images were processed using a voxel-based morphometry pipeline to map associations between maternal distress exposure and regional gray matter (GM) volumes, while accounting for potential confounders.

Results: We found widespread associations between maternal distress symptoms and offspring brain morphology. Higher prenatal distress at 14 gestational weeks was positively associated with regional GM volume in the right superior parietal lobe and precuneus. In contrast, postnatal distress at 3 months was negative associated with GM volumes in multiple motor regions, the left anterior insula, right superior frontal areas and supramarginal gyrus. Postnatal distress at 6 months demonstrated a positive relationship with GM volumes in the right calcarine and lingual gyri, while distress at 24 months was negatively associated with GM volumes in the left supramarginal and right superior frontal gyri.

Conclusions: This study provides support for hypotheses proposing that fetal and early life exposure to maternal distress can influence the structural development of the brain. Furthermore, it highlights the role of early postnatal period and calls for further research into this so far overlooked period and pathways that explain the associations.

Introduction

Maternal pre- and postnatal mental distress (e.g., depressive or anxiety symptoms), may present significant, enduring, and potentially irreversible effects on offspring development (1–4). Both pre- and postnatal distress share similarities in their potential long-term outcomes (5) which could reflect increased genetic vulnerability, as the role of genetics is well-established in major depression (6,7). It is still useful to study the timing of exposure, as pre- and postnatal distress exposure involve different mechanisms. Prenatal distress can affect fetal development via biological pathways such as perturbation of the hypothalamic–pituitary–adrenal axis function, increased inflammation (8), and epigenetic modifications of the placenta (9), while postnatal maternal distress can affect the offspring through psychosocial and environmental factors, such as maternal sensitivity (10) and attachment patterns (11). The environment can affect the brain through neural mechanisms such as activation-dependent plasticity, mediated by brain-derived neurotropic factor (12–14). As some of the mediating mechanisms are different, pre- and postnatal exposures could have different effects on offspring structural brain development, which can be studied using magnetic resonance imaging (MRI).

Prior neuroimaging research has put much focus on maternal prenatal as opposed to postnatal distress. Common measures include maternal depressive, anxiety, and stress symptoms based on questionnaires (2). Furthermore, structural neuroimaging studies have typically focused on subcortical structures (15–18), especially the amygdala (16,19–27) and the hippocampus (16,24,28). Previous amygdala studies have found positive (21,29) and negative (16,25,26) associations between prenatal maternal distress and amygdala volume as well as different association based on child sex (21–23), nonlinear relationships (15), or no associations at all (24,30). Hippocampal findings have been similarly inconsistent. Some studies reported smaller left (24), smaller right (31), and larger bilateral (29) hippocampal volume in newborns associated with maternal prenatal stress. Other studies have focused on gene–environment interactions influencing right hippocampal volume (28,32), while other studies found no significant hippocampal volume differences (16,22,30). Prenatal distress has also been associated with white matter structure (33) and brain function in the offspring (34).

Associations between prenatal distress exposure and structural cortical brain development in children have been examined in a few studies. Wei et al. (35) found that prenatal maternal depressive symptoms associated positively with areas in the prefrontal cortex, superior temporal gyrus, and superior parietal lobe in 4–6-year-old males, while the opposite pattern was observed in females. El Marroun et al. (36) found positive associations between prenatal maternal depressive symptoms and offspring surface area in the left caudal middle frontal, left superior frontal, and left lateral occipital regions in 6–10-year-olds. Additionally, they found a negative association between prenatal maternal depressive symptoms and cortical thickness (CT) in the left superior frontal gyrus. Davis et al. (37) found lower CT in 7-year-olds in multiple clusters throughout the cortex associated depressive symptoms in adolescence, and many frontal and temporal regions were associated with both stress exposure and future depressive symptoms. Sandman et al. (38) found negative associations between maternal prenatal depressive symptoms and CT in widespread clusters across the cortex in 6–9-year-olds. Finally, one study utilized voxel-based morphometry (VBM) to explore the effects of pregnancy-related anxiety on offspring brain development in 6–9-year-old children (39). They found significant associations between regional reductions in gray matter (GM) volume and higher pregnancy-related anxiety. Stress at 19 gestational weeks (GW) exhibited a significant negative association with GM volumes in regions including the prefrontal cortex, premotor cortex, lateral temporal cortex, medial temporal lobe, postcentral gyrus, and the cerebellum. Findings at 25 and 31 GW did not survive correction for false discovery rate (FDR). These findings suggest that the timing of the distress exposure may be of great importance, potentially due to neurodevelopmental stages of the fetus, i.e., neurogenesis and neural migration in early to mid-

pregnancy, synaptogenesis in mid-to late pregnancy (40), or the expecting mothers' changing reactivity to distress (41,42).

Postnatal maternal mental health has received less attention in neuroimaging studies, although it has adverse effects on child development comparable to prenatal exposure (5). To our knowledge, only one study has examined the effects of early life exposure to maternal distress and cortical structure in preschool-age children (43). They found that both pre- and postnatal depressive symptoms were negatively associated with local CT values at age 2.6–51 years: prenatal symptoms correlated negatively with right inferior frontal and superior/middle temporal CT, and postnatal symptoms correlated negatively with right superior frontal CT. El Marroun et al. (36) found no significant associations between postnatal maternal depressive symptoms (at age 3 years) and either CT or surface area. In 10-year-old children, Zou et al. (44) found a negative association between maternal depressive symptoms at 2 months postpartum and total GM volume. Overall, the cortical structural neuroimaging literature on the effects of early life postnatal maternal distress exposure is limited and particularly studies with both pre- and postnatal findings are missing.

The aim of this study was to investigate the associations between pre- and postnatal maternal stress and brain structure in 5-year-old children. Distress was measured longitudinally utilizing questionnaire data on depressive and anxiety symptoms from GWs 14, 24, and 34 as well as from 3, 6, and 24 months of child age postnatally. We expected to find: 1) significant differences in GM volumes in fronto–temporal regions; and 2) alterations in amygdalar and hippocampal volumes in those exposed to pre- and/or postnatal stress. As previous studies combining pre- and postnatal distress symptoms are scarce, we reported exploratory whole-brain VBM analyses.

Methods and Materials

This study adheres to the ethical guidelines and principles outlined in the 1975 Declaration of Helsinki and has undergone a thorough review and approval process by the joint Ethics Committee of the University of Turku and the Hospital District of Southwest Finland (ETMK:31/180/2011). This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (45), checklist in Table S1.

Participants

The participants of the present study are mother–child dyads (n = 173) drawn from the FinnBrain Birth Cohort study (www.finnbrain.fi)(46). Children who underwent neuroimaging during their 5-year follow-up visit (n = 203, 55.7% boys [n = 113], mean age 5.39 [SD 0.13], range 5.08–5.79 years) were eligible to participate. Exclusion criteria for the MRI included the following: premature birth (< 35 GW, or < 32 GW for those with exposure to maternal prenatal synthetic glucocorticoid treatment); developmental sensory anomaly or disability (e.g., blindness); long-term medical conditions (e.g., epilepsy, autism spectrum disorders); current ongoing medical examinations or clinical follow-ups; usage of daily medications; history of head trauma; routine MRI contraindications. More details on the cohort and recruitment process in Supplementary Materials.

The final sample consisted of 173 participants with high-quality structural imaging data. Participant characteristics are presented in Table 1.

Table 1 Demographic variables and distress scores of participating mothers and children

	Mean	***SD***	**Min**	**Max**
Maternal age at term (years)	31.12	4.70	19.10	41.95
Maternal body mass index before pregnancy	24.23	4.31	17.48	41.95
Child gestational age at birth (weeks)	39.69	1.68	33.57	42.29
Child age at scan (years)	5.41	0.13	5.09	5.79
Ponderal Index	14.05	1.19	11.21	17.63
14 gestational weeks composite distress score	7.53	6.94	0	39
24 gestational weeks composite distress score	8.04	7.05	0	34
34 gestational weeks composite distress score	7.76	7.53	0	39
3 months composite distress score	6.58	6.38	0	30
6 months composite distress score	7.70	7.40	0	43
24 months composite distress score	7.36	6.91	0	43
14 gestational weeks depressive symptoms score	4. 53	3.98	0	22
24 gestational weeks depressive symptoms score	4.64	4.07	0	21
34 gestational weeks depressive symptoms score	4.74	4.47	0	20
3 months depressive symptoms score	4.21	3.86	0	19

6 months depressive symptoms score	4.78	4.55	0	22
24 months depressive symptoms score	4.66	4.68	0	21
14 gestational weeks anxiety symptoms score	3.01	3.60	0	17
24 gestational weeks anxiety symptoms score	3.40	3.75	0	19
34 gestational weeks anxiety symptoms score	3.02	4.05	0	19
3 months anxiety symptoms score	2.37	3.44	0	17
6 months anxiety symptoms score	2.92	4.28	0	24
24 months anxiety symptoms score	2.70	4.13	0	26.67

	N	*%*
MOTHER		
Education level		
Low	37	21.4
Middle	48	27.7
High	88	50.9
Maternal monthly income (in €)		
< 1500	55	31.8
1501-2500	93	53.8
2501-3500	15	8.7
> 3501	3	1.7

Missing	7	4
Alcohol use during pregnancy		
Yes, before learning about pregnancy	23	13.3
Yes, continued after learning about pregnancy	24	13.9
No	123	71.1
Not reported / missing	3	1.7
Tobacco product use during pregnancy		
Yes	11	6.3
No	162	93.6
Illicit drug use during pregnancy		
No	162	93.6
Not reported / missing	11	6.4
SSRI or SNRI use during first trimester		
Yes	3	1.7
No	159	91.7
Missing	11	6.4
Community of origin		
Finnish	164	94.8
Other or mixed	3	1.7
Missing	6	3.5
CHILD		
Sex		

Female	95	54.9
Male	78	45.1
Gestational age at birth, weeks		
≥ 37 (Term)	164	94.8
< 37 (Preterm)	9	5.2
NICU Admission		
Yes	26	15
No	146	99.4
Not reported / missing	1	.6
Obstetric Risk		
Present	26	15
Absent	146	99.4
Not reported / missing	1	.6

Table 1 footnotes. SSRI = Selective Serotonin Reuptake Inhibitor, SNRI = Serotonin and Norepinephrine Reuptake Inhibitor, NICU = Neonatal Intensive Care Unit. Ponderal index was calculated using the following formula: weight in kilograms divided by height in meters cubed. Height and weight were acquired during the neuroimaging visit. The participants kept indoor clothes on during the weighing. Maternal education data was combined from questionnaire data from gestational week 14 or 5 years of child age by choosing the highest degree reported. The three classes are: Low = Upper secondary school or vocational school or lower, Middle = University of applied sciences, High = University. The data for maternal monthly income estimate, SSRI/SNRI and illicit drug use are from questionnaires at gestational week 14. Obstetric risk was defined as diagnosis (according to ICD-10, during pregnancy) for O12 (Gestational edema and proteinuria without hypertension), O13 (Gestational hypertension without significant proteinuria), O14 (Severe pre-eclampsia), O24 (Diabetes mellitus in pregnancy, childbirth, and the puerperium), O46 (Antepartum hemorrhage, not elsewhere classified), or O99.0 (Anemia complicating pregnancy, childbirth and the puerperium). Sex, birth weight, maternal body mass index before pregnancy, and smoking data (combined with questionnaire data) were retrieved from the wellbeing services county of Southwest Finland (VARHA) records.

Procedures

Following recruitment, participating mothers provided demographic information and completed a set of standardized and internationally validated self-report questionnaires regarding depressive and anxiety symptoms three times during pregnancy (14, 24 and 34 GW), and three times in the postnatal period (3, 6 and 24 months). MRI data was collected at age 5 years.

Measures

Maternal depressive symptoms were assessed using the Finnish version of the Edinburgh Postnatal Depression Scale (EPDS)(47). The clinical cut-off threshold for potential depression is ≥ 10 points. Maternal anxiety symptoms were evaluated using the Finnish version of the Symptom Checklist-90-Revised (SCL)(48). For the purposes of this study, only the anxiety subscale was utilized. The 10-item scale assesses signs of nervousness, tension, and feelings of panic. The questionnaires are described in more detail in Supplementary Materials.

Scores from both the EPDS and SCL were added together to create a unified measure of maternal psychological distress, the composite distress score (CDS). The rationale behind creating a combined, overall measure of distress is twofold: (1) study population were drawn from the general population and consequently, individual scores were relatively low, and (2) symptoms of anxiety and depression are often comorbid (49,50). A correlation matrix of EPDS and SCL scores is presented in Table S2. Thus, combining the measurements may provide a more robust tool to measure overall distress. Previous authors have used composite scores (22,51,52) or principal component approaches (53) in attempt to grasp the overlap of various distress measures. The EPDS and SCL scores were not standardized while calculating the CDS, as that would make the effect sizes not comparable with other studies (Pearson correlations between non-standardized and standardized CDS = 1.000 at each timepoint; Spearman correlation > 0.998 at each timepoint). For transparency, we additionally report the results of main analyses with the standardized scores.

There were missing maternal questionnaire data at various follow-up points (14 GW n = 9, 24 GW n = 8, 34 GW n = 8; 3 months n = 17, 6 months n = 32, 24 months n = 47), mean imputation of overall sum scores was used to replace the missing data in such cases (mean of the final sample used in analyses). With missing covariate data, mean imputation was used for maternal pre-pregnancy body mass index (one missing case) and mode imputation with categorical variables (missing data indicated in Table 1). Missing data is visualized in Figure S1.

Image acquisition

The neuroimaging visit is described in our earlier publications (54,55) and in the Supplementary Materials.

Participants were scanned on a 3T MRI system (MAGNETOM Skyra fit; Siemens Medical Solutions, Erlangen, Germany) equipped with a 20-channel head/neck coil. To speed up the acquisition process, the Generalized Auto-calibrating Partially Parallel Acquisition technique was employed, with a parallel acquisition technique factor of two applied to all image acquisitions. The MRI data collection was completed within a scan protocol lasting < 60 minutes. For the purposes of the current study, high-resolution 3D T1-weighted images using the magnetization prepared rapid gradient echo technique were acquired. This acquisition used the following sequence parameters: repetition time = 1,900 ms, echo time = 3.26 ms, inversion time = 900 ms, flip angle = 9 degrees, voxel size = 1.0 × 1.0 × 1.0 mm^3, and field of view 256 × 256 mm^2.

Data preprocessing and statistical analyses

Voxel-based morphometry

VBM is a method that enables researchers to study regional GM volume differences between various groups of participants on a voxel-by-voxel basis. In our study, the Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) software running on MATLAB R2016b (MathWorks, MA) was used to identify alterations in regional GM volumes associated with maternal pre- and postnatal distress.

Preprocessing of the data was done with the Computational Anatomy Toolbox (CAT12, version r1363)(56). A standard preprocessing pipeline, encompassing normalization, segmentation, modulation, quality assessment, and smoothing, was applied with the following specifications: the default tissue probability map provided in SPM was used, affine regularization was done with the European brains template, inhomogeneity correction was medium, affine preprocessing option was "rough", local adaptive segmentation was performed at medium, skull-stripping was done via the Graph cuts (GCUT) approach, voxel size for normalized images was set to 1.5 mm and internal resampling for preprocessing was fixed at 1.0 mm. Dartel was used for spatial registration and the MNI152 template (MNI = Montreal Neurological Institute) was used for both Dartel and Shooting templates.

Statistics

Correlation analyses performed using IBM SPSS for Mac (Version 29.0; IBM Corporation), and regression models with region of interest (ROI) data were performed using RStudio (Version 2022.07.1+554)(57). All analyses were performed two-tailed.

Following data preprocessing, we performed whole-brain general linear models in SPM12 with the CDS at 14, 24, and 34 GW and at 3, 6, and 24 months postpartum as covariates of interest. Based on findings of previous FinnBrain publications on the same age group (58), the following covariates were accounted for in our analyses: child age at the time of the scan, sex, and ponderal index, along with maternal age at term and education level (two classes: (1) any university degree, and (2) other degrees). Analyses were performed with a voxel-wise threshold of $p < 0.005$ uncorrected. However, we only report clusters that remained significant ($p < 0.05$) after correction for multiple comparisons using FDR approach. In addition to CDS, we performed the same VBM analyses for EPDS scores to test whether the effects of exposure to depressive symptoms, specifically, differ from exposure to distress in general (with same voxel and cluster thresholds).

The MarsBaR toolbox (59) within SPM12 was used to extract significant clusters of GM and their corresponding eigenvalues for ROI analyses. Partial correlations were calculated between the eigenvalues of each cluster and each of the CDS time points, while accounting for the same models as in the VBM model. The sole purpose of this analysis is to provide further information on whether the other timepoints show similar results that just did not reach the required level of significance.

Sensitivity analyses: ROI eigenvalues were extracted using MarsBaR. This approach allowed us to explore the significant clusters from the main analyses while adding potential confounders related to pregnancy and perinatal period. The linear regression model was:

ROI eigenvalue ~ CDS from the time point in which the ROI was significant + Age at scan + Sex + Ponderal Index + Maternal age at term + Maternal education + Prenatal alcohol exposure + Prenatal smoking exposure + Prenatal selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake

inhibitor exposure + Obstetric risk + Maternal pre-pregnancy body mass index + Neonatal intensive care unit admission

Additionally, we performed VBM analyses in a which we used all the same covariates as in the main CDS analyses and additionally included the CDS scores from all other timepoints in order to better differentiate the unique contribution of the specific measurement point. Full regression models presented in Supplementary Materials.

Results

Voxel-based morphometry results – distress

The VBM analysis examined the effect of maternal stress on child brain development. We observed several significant associations between maternal distress symptoms at various time points during the offspring's early life and regional GM volumes at 5 years of age. More maternal symptoms at the ages of 3 months and 24 months were associated with smaller volumes, while symptoms at 14 GW and 6 months postpartum were associated with larger volumes. The results are presented in Figures 1–5 and Table 2.

Same analyses with a CDS based on standardized values resulted in the same number of significant clusters at all same age points, with the same peak coordinates (one exception: cluster (-34, 8, 19) changed to (-33, 8, 12) at 3 months postpartum). Largest difference in cluster size compared to the unstandardized scores was 8%.

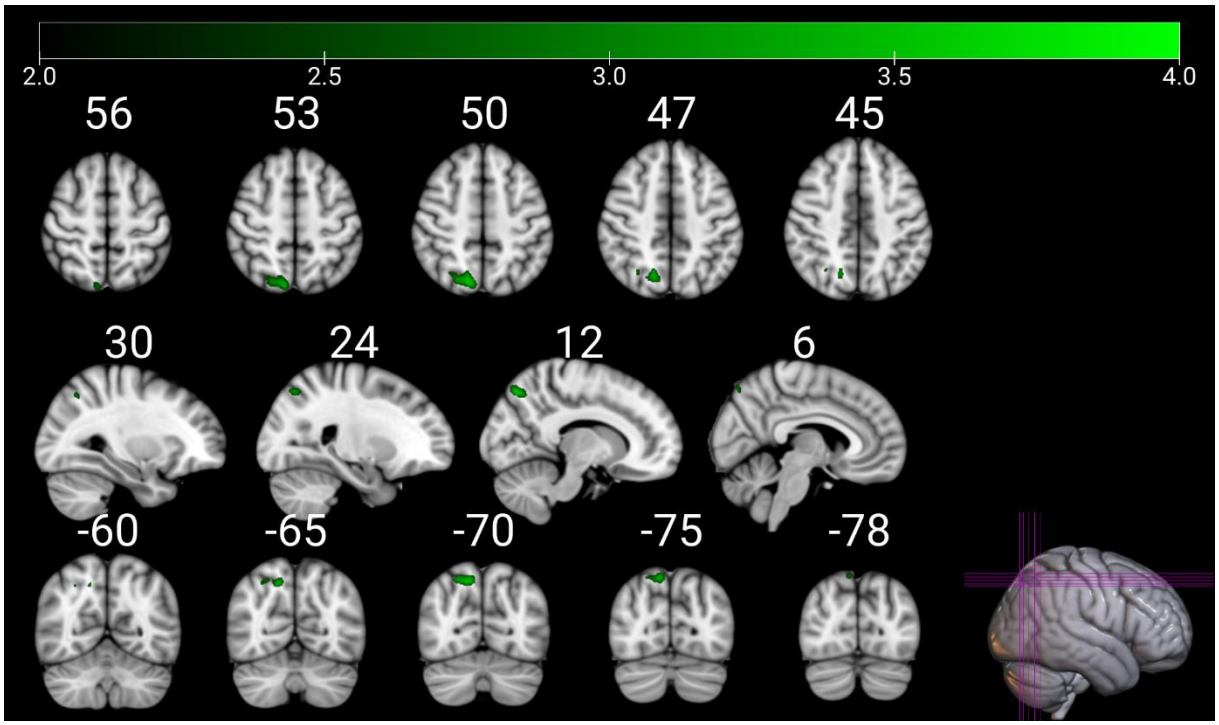

Figure 1. Positive association between maternal distress symptoms at 14 gestational weeks and regional volume in right superior parietal areas, including the parietal lobule and precuneus. Only statistically significant regions at $p < 0.005$, false discovery rate corrected at cluster level are displayed. Color indicates t-value. Images are in radiological orientation. Coordinates (indicated with white numbers) are in MNI space. The figure was created with MRIcroGL.

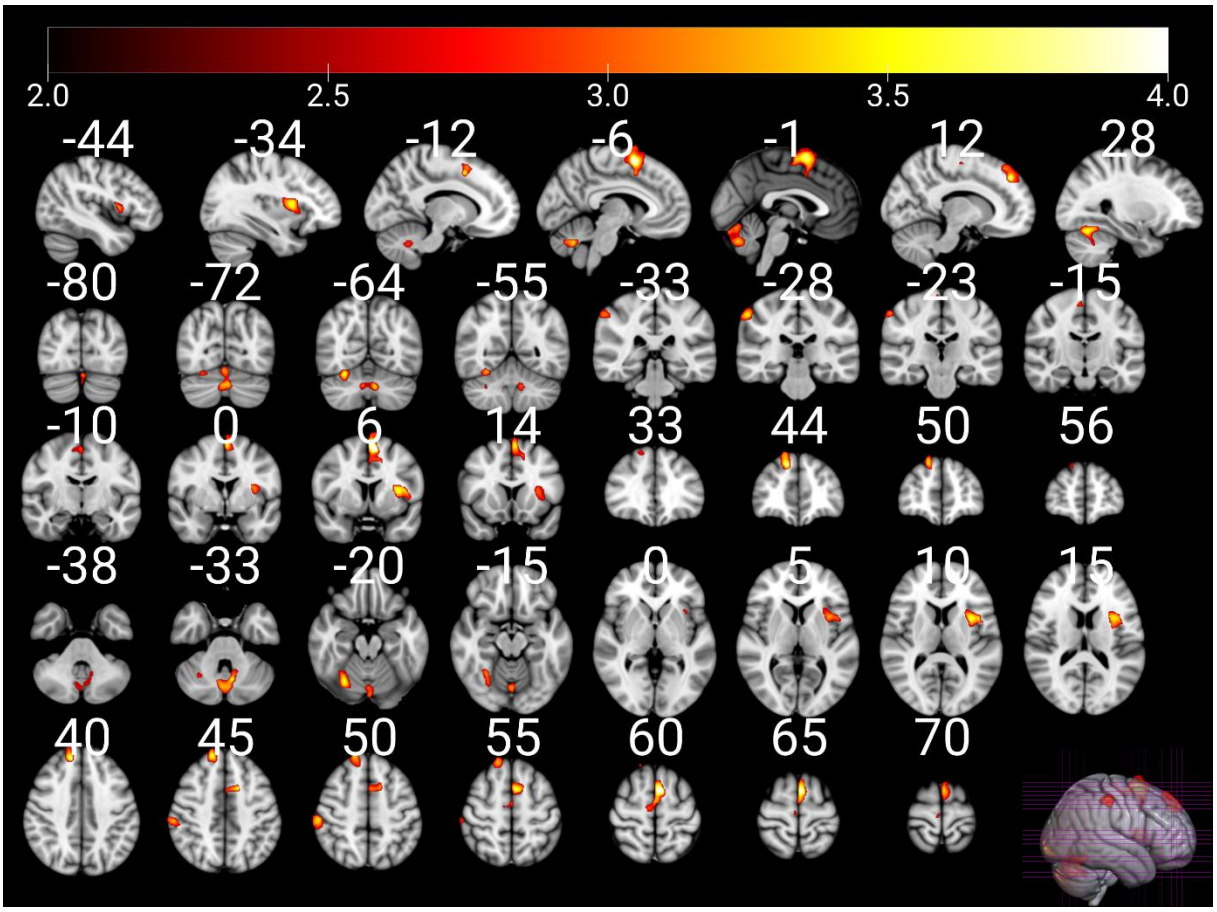

Figure 2. Negative associations between maternal distress symptoms at 3 months postpartum and regional volume in six clusters: right superior frontal gyrus; right cerebellum; right supramarginal gyrus; left cerebellum and cerebellar vermal lobules VIII-X; left supplementary motor cortex; left anterior insula. Only statistically significant regions at p < 0.005, false discovery rate corrected at cluster level are displayed. Color indicates t-value. Images are in radiological orientation. Coordinates (indicated with white numbers) are in MNI space. The figure was created with MRIcroGL.

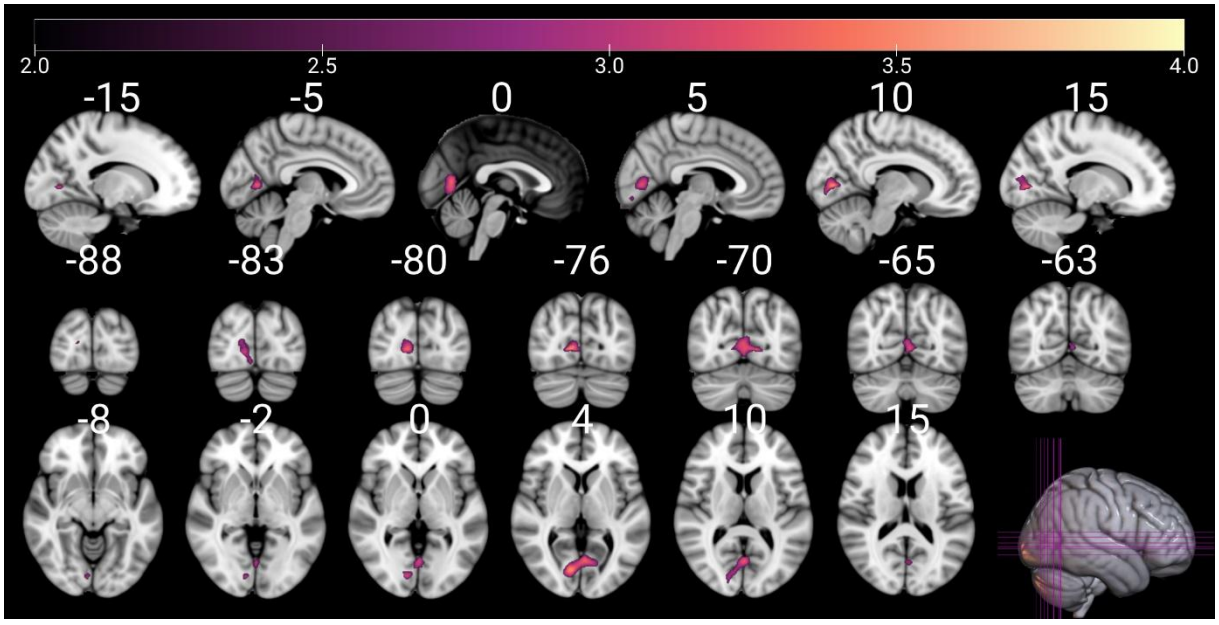

Figure 3. Positive association between maternal distress symptoms at 6 months postpartum and regional volume in the occipital lobe, including the right calcarine cortex and bilateral lingual gyrus. Only statistically significant regions at p < 0.005, false discovery rate corrected at cluster level are displayed. Color indicates t-value. Images are in radiological orientation.

Coordinates (indicated with white numbers) are in MNI space. The figure was created with MRIcroGL.

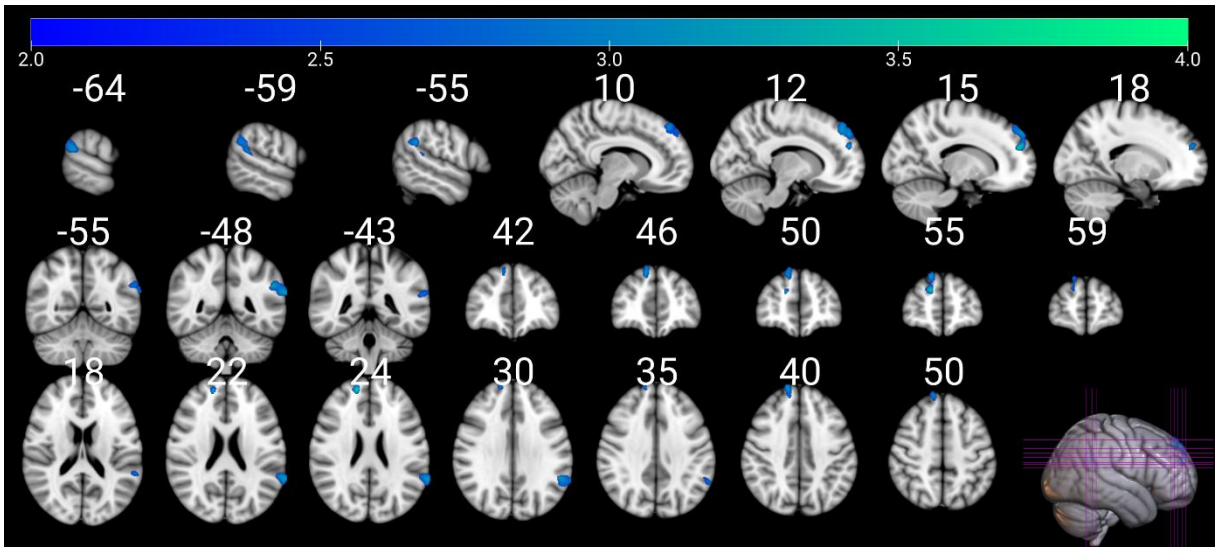

Figure 4. Negative associations between maternal distress symptoms at 24 months postpartum and regional volume in two clusters: the right superior frontal gyrus and left supramarginal gyrus. Only statistically significant regions at $p < 0.005$, false discovery rate corrected at cluster level are displayed. Color indicates t-value. Images are in radiological orientation. Coordinates (indicated with white numbers) are in MNI space. The figure was created with MRIcroGL.

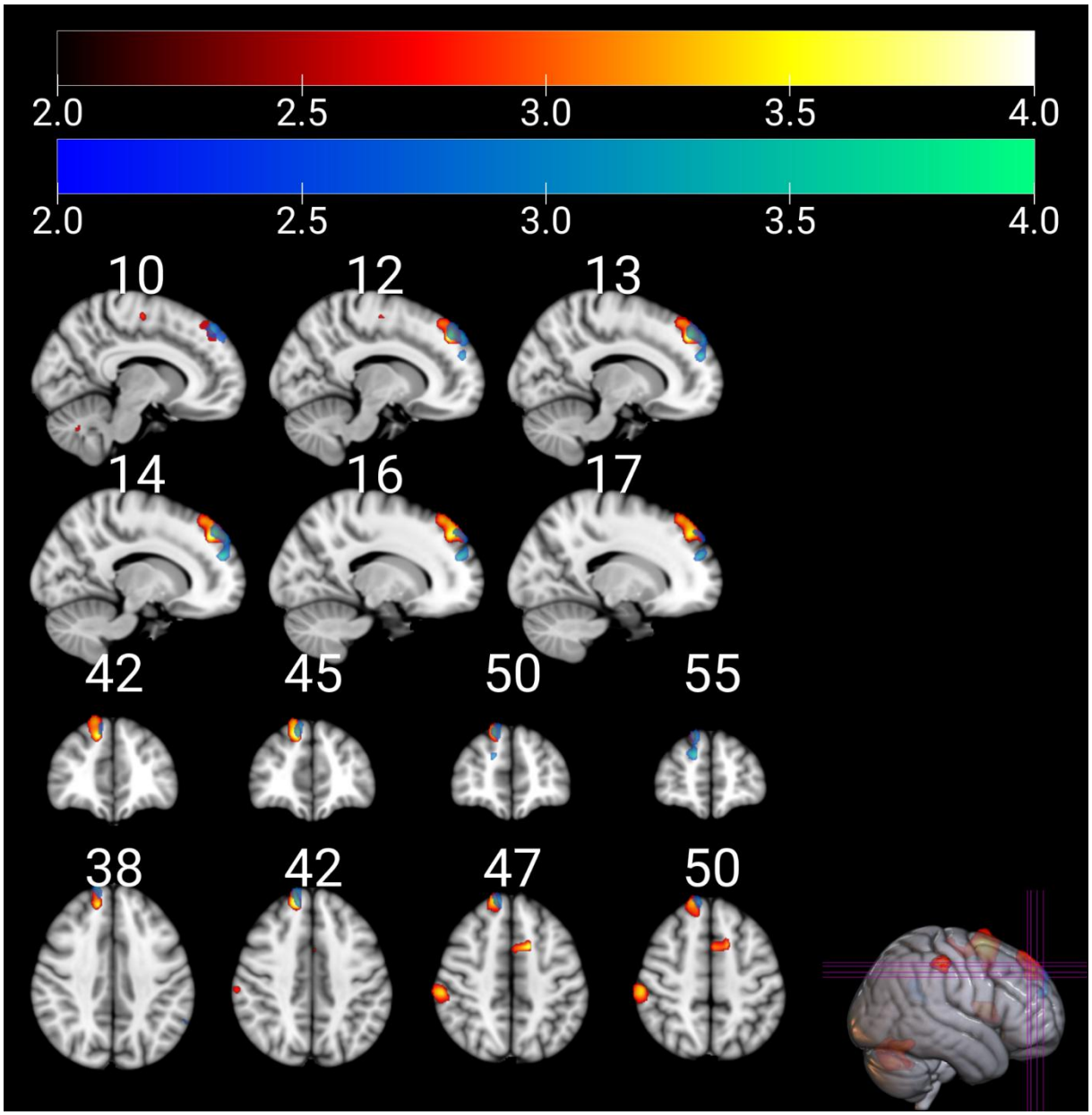

Figure 5. Negative associations between maternal distress symptoms at 3 (hot colormap) and 24 months postpartum (blue–green colormap), highlighting the overlap in superior frontal regions. Only statistically significant regions at p < 0.005, false discovery rate corrected at cluster level are displayed. Color indicates t-value. Images are in radiological orientation. Coordinates (indicated with white numbers) are in MNI space. The figure was created with MRIcroGL.

Table 2. Clusters from the voxel-based morphometry analysis.

Region	x	y	z	Cluster size	p (FDR-corrected)	Peak z
14 gestational weeks (positive association)						
Right precuneus/ superior parietal lobule	12	-72	50	524	0.025	3.48
3 months postpartum (negative association)						
Left supplementary motor cortex	-6	6	60	1893	< 0.001	4.14

Right superior frontal gyrus	12	44	40	875	0.006	3.75
Right cerebellum	28	-64	-20	638	0.021	3.54
Left anterior insula	-34	8	10	1001	0.004	3.52
Cerebellar vermal lobules VIII-X/left cerebellum	-8	-62	-33	1124	0.003	3.49
Right supramarginal gyrus	58	-28	48	500	0.046	3.43
6 months postpartum (positive association)						
Right calcarine cortex/ lingual gyrus	10	-76	4	1237	0.001	3.48
24 months postpartum (negative association)						
Left supramarginal gyrus	14	54	24	582	0.034	3.57
Right superior frontal	-66	-48	22	708	0.030	3.22

Abbreviations: FDR = false discovery rate

Partial correlation analysis

The partial correlation analysis found significant partial correlations between maternal symptoms and clusters identified in the VBM analysis. Partial correlations are presented in Table 3.

Table 3 Partial correlation coefficients (no correction for multiple comparisons) between significant clusters and maternal symptoms at different age points controlling for age at scan, sex, ponderal index, maternal age at term and maternal education.

	CDS 14 GW	**CDS 24 GW**	**CDS 34 GW**	**CDS 3 months**	**CDS 6 months**	**CDS 24 months**
14 gwks Right precuneus/ superior parietal lobule **(12, -72, 50)**	.29***	.17*	.24**	.09	.08	.08
3 months Left supplementary motor cortex **(-6, 6, 60)**	-.12	-.17*	-.06	-.32***	-.13	-.18*
3 months Cerebellar vermal lobules VIII-X/left cerebellum **(-8, -62, -33)**	-.16*	-.18*	-.08	-.29***	-.19*	-.16*
3 months Left anterior insula	-.09	-.16*	-.05	-.27***	-.07	-.11

(-34, 8, 10)						
3 months Right superior frontal gyrus **(12, 44, 40)**	-.18*	-.11	-.11	-.27***	-.22**	-.19*
3 months Right cerebellum **(28, -64, -20)**	-.06	-.12	-.02	-.26***	-.03	-.12
3 months Right supramarginal gyrus **(58, -28, 48)**	-.13	-.16*	-.06	-.25***	-.12	-.18*
6 months Right calcarine cortex/ lingual gyrus **(10, -76, 4)**	.04	.05	.13	.02	.28***	.10
24 months Left supramarginal gyrus **(-66, -48, 22)**	-.08	-.14	-.13	-.18*	-.13	-.25**
24 months Right superior frontal gyrus **(14, 54, 24)**	-.15	-.07	-.06	-.24**	-.16*	-.27***

*** = p ≤ 0.001, ** = p ≤ 0.01, * = p ≤ 0.05
CDS = Composite Distress Score, GW = gestational weeks, () = coordinates (x, y, z)

Voxel-based morphometry results – depressive symptoms

Results for 3 and 6 months of postnatal age were mostly similar to those seen in CDS analyses (Figures S2 and S3). At 34 GW, there were multiple positive associations between maternal depressive symptoms and regional brain volumes: the left cerebellum, right occipital pole, right precentral gyrus, right superior parietal lobule (Figure 6). In contrast to CDS results, using only EPDS score did not yield results at 14 GW or 24 months.

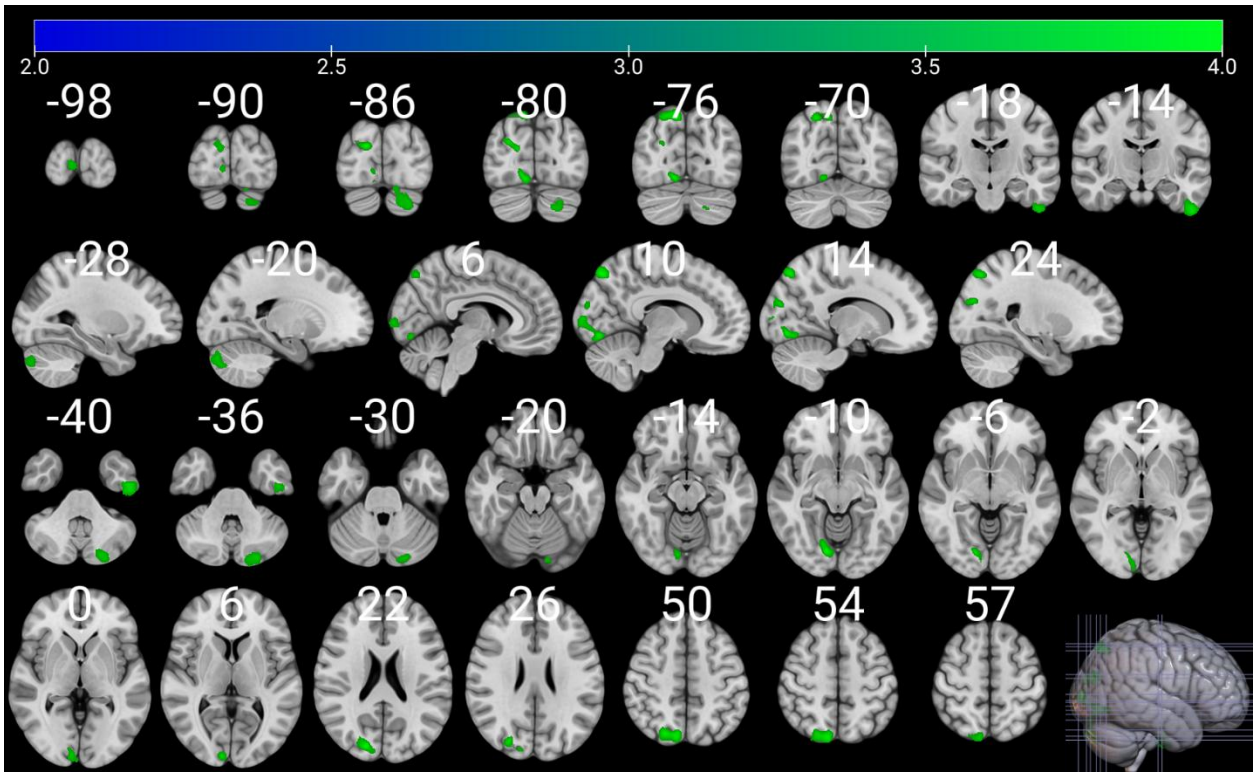

Figure 6. Positive associations between maternal depressive symptoms at 34 gestational weeks and regional volume in four clusters: the left cerebellum, right occipital pole, right precentral gyrus, and right superior parietal lobule. Color indicates t-value. Images are in radiological orientation. Coordinates (indicated with white numbers) are in MNI space. The figure was created with MRIcroGL.

Sensitivity analyses

When potential confounders from pregnancy and early life were added to the model, CDS remained significant for each cluster ($p \leq .003$ in all cases). All regression models are presented in Tables S3–S13.

In the model in which all CDS timepoints were controlled, multiple significant positive results were observed between brain volume and CDS at 34 GW and 6 months postpartum, and multiple negative results between brain volume and 3 months postpartum. Results from 3 and 6 months postpartum partially overlap with the main VBM models. Results are presented in Table S14 and Figure S4.

Discussion

This study investigated the association between pre- and postnatal maternal distress and child brain development at 5 years of age in the FinnBrain Birth Cohort study. We found that prenatal and particularly early postnatal symptoms of depression and anxiety were associated with offspring brain morphology. The most prominent findings were found at 3 months postnatal age. The associations with maternal distress were negative at 3 and 24 months, and positive at 14 GW and 6 months. At 34 GW, significant results were only found for depressive symptoms, not overall distress exposure. Contrary to our hypotheses, no significant results were found in the hippocampus or amygdala.

Prenatally, only 14 GW showed significant associations with distress, located in the right superior parietal regions, including the precuneus. The superior parietal region is involved in various cognitive functions, including visuospatial processing and working memory (60), while the precuneus is involved in memory retrieval and attentional processing (61). The right superior parietal region (35,62) and precuneus (62) surface area and CT have been associated with prenatal distress exposure before. Overall, the regions associated with early gestation exposure are important for cognitive functions (63), and our earlier study in the same population found an association between non-verbal cognitive ability and cortical volume and surface in a cluster involving the precuneus (64). Finally, the scarcity of prenatal findings in our study was surprising, considering the extent of previous studies finding associations between exposure to prenatal distress and brain structure (2).

Postnatal exposure to maternal distress was associated with widespread structural changes in the offspring's brain. The superior frontal and supramarginal gyrus are regions involved in a range of cognitive processes (65), including semantic processing and social cognition (66). Notably, the fronto–parietal model of cognition is mostly based on adult studies (63). The cerebellum is well-known for its role in motor functions (67) but recently there has been an increasing recognition of its role in cognitive and language functions (68–70). The cerebellar findings in this study involved both motor and non-motor regions (71). Together with the prenatal results, these findings indicate a possible connection between prenatal and early life distress exposure and cognitive development. This connection has been studied following the 1998 ice storm in Québec, Canada (72). Laplante et al. (72) found that prenatal distress exposure explained over 10% of the variance in general cognitive ability and language skills in toddlerhood. Motor control is another aspect that connects to many of the regions in our study: the left supplementary motor cortex, left anterior insula (73), and cerebellum. Motor development has also been studied in the context of the Québec ice storm and there is some evidence of prenatal distress exposure affecting motor development in children (74). In conclusion, our results indicate a potential connection between prenatal and early life distress exposure with cognitive and motor development, which will be important questions for future studies.

The hippocampus and amygdala have been associated with prenatal distress in multiple prior studies. Postnatal distress literature is more limited (17,21,27). We found no significant clusters in either one associated with distress or depressive symptoms at any timepoint. The previous results have been inconsistent, and might be affected by timing of exposure, or the research questions (e.g., association only when looking at different genetic profiles (32) or sexes (22) separately). Furthermore, hippocampus and particularly the amygdala are small structures that are challenging to segment accurately (75,76), and methodological variation could also explain some of the inconsistent results. Our chosen method, VBM, is unbiased to any GM structures and is not reliant on the accuracy of GM parcellation. Our results show the benefit of a whole-brain approach in identifying sensitive periods in child brain development.

The timing of the exposure at which most findings were seen is one of the key findings of this study. Three months postnatal age was the time for most findings for both distress and depressive symptoms, specifically. This study provides preliminary evidence that early postnatal distress, which may affect the child through mechanisms such as altered mother–child interaction, may have a particularly important role for future outcomes. It is important to note that neural structural associations of pre- and postnatal distress were not directly compared to each other, and as such we cannot draw a conclusion that postnatal timepoints had a larger importance than prenatal ones. Three months is the earliest postnatal measurement we have, and as such we cannot speculate on the importance of the three-month age, specifically, compared to the first two months of life. The early postnatal life is a potential sensitive period for neural development, as it is characterized by neural processes like myelination and

synaptogenesis (40) as well as quick increase in cerebral GM volume (77). Nevertheless, our results highlight the need to study the early postnatal period further, rather than just pregnancy.

In this study, we tested the brain associations of distress and depressive symptoms separately. For postnatal analyses, the results were quite similar: multiple significant negative associations at 3 months and one cluster in the calcarine and lingual regions at 6 months. The were no clusters in new regions and the decrease in significant results was expected as the variance decreased – particularly considering that the symptoms were mostly in the normal range in our sample. For the prenatal analyses, there was a meaningful difference between distress and depressive symptoms. In the third trimester, depressive symptoms were associated with brain volumes in multiple clusters, while distress was not. The results were similar in the sense that postnatal age points produced more results than prenatal ones, and the seemingly large difference could be partially related to thresholding.

This study has some limitations. Questionnaire data was collected longitudinally, with slightly increasing amount of missing data towards later measurements. Another limitation is that we relied on self-report questionnaires to assess maternal anxiety and depressive symptoms, which can be subject to measurement errors. Despite the potential issues, self-report remains the most common and widely accepted method for collecting data on subjective experiences, such as feelings of depression and anxiety. The questionnaire data was analyzed at multiple cross-sectional timepoints and not as longitudinal trajectories. This approach was considered but based on our prior research (78) we know that trajectories showing mostly prenatal or mostly postnatal symptoms are rare in the FinnBrain Birth Cohort, which was incompatible with our aim of highlighting the pre- and postnatal period separately. To mitigate this limitation, we performed supplementary analyses in which the other time points were added as covariates. The significant regions partially changed, however the importance of the early postnatal period remained regardless of the modeling approach. The neuroimaging method also brings some limitations. While VBM is an unbiased approach to regional volumes in whole brain GM, the interpretation of the findings is difficult. Decreased local volume could reflect multiple different underlying biological processes, such as apparent thinning due to more myelin in surrounding white matter, or a smaller number of neurons in the GM region. Finally, the homogeneity of our sample, consisting of FinnBrain participants mainly of Finnish origin from a specific region (i.e., Southwestern Finland), with a generally higher level of education, limits the generalizability of our findings to other populations and contexts.

Conclusion

This study investigated the effect of maternal distress during the pre- and postnatal periods on the brain development of offspring at the age of 5 years. A particular strength of our work is the collection of distress measurements from multiple timepoints both pre- and postnatally. Our findings revealed connections between exposure to maternal distress at various developmental stages and structural alterations in widespread brain regions, particularly those associated with cognitive and motor functions. In contrast to prior literature, this study highlights the importance of the early postnatal period as a sensitive window for structural brain development. Importantly, structural associations with early life distress do not automatically indicate maladaptive development. These results form a basis for hypothesis creation for developmental pathways from early distress exposure to cognitive or behavioral outcomes. In conclusion, future studies should always consider the effects of the timing of the exposure, including the postnatal period, to the extent that they have available data.

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Disclosures

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References

1. Pulli EP, Kumpulainen V, Kasurinen JH, Korja R, Merisaari H, Karlsson L, *et al.* (2019): Prenatal exposures and infant brain: Review of magnetic resonance imaging studies and a population description analysis. *Hum Brain Mapp* 40: 1987–2000.

2. Lautarescu A, Craig MC, Glover V (2020): Prenatal stress: Effects on fetal and child brain development. *Int Rev Neurobiol* 150: 17–40.

3. Van den Bergh BRH, van den Heuvel MI, Lahti M, Braeken M, de Rooij SR, Entringer S, *et al.* (2020): Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. *Neurosci Biobehav Rev* 117: 26–64.

4. Meaney MJ (2018): Perinatal maternal depressive symptoms as an issue for population health. *American Journal of Psychiatry* 175: 1084–1093.

5. Rogers A, Obst S, Teague SJ, Rossen L, Spry EA, MacDonald JA, *et al.* (2020): Association Between Maternal Perinatal Depression and Anxiety and Child and Adolescent Development: A Meta-analysis. *JAMA Pediatr* 174: 1082–1092.

6. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, *et al.* (2018): Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 50: 668–681.

7. Meng X, Navoly G, Giannakopoulou O, Levey DF, Koller D, Pathak GA, *et al.* (2024): Multi-ancestry genome-wide association study of major depression aids locus discovery, fine mapping, gene prioritization and causal inference. *Nature Genetics 2024 56:2* 56: 222–233.

8. Graham AM, Doyle O, Tilden EL, Sullivan EL, Gustafsson HC, Marr M, *et al.* (2022): Effects of Maternal Psychological Stress During Pregnancy on Offspring Brain Development: Considering the Role of Inflammation and Potential for Preventive Intervention. *Biol Psychiatry Cogn Neurosci Neuroimaging* 7: 461–470.

9. Bind RH (2022): Immunological and other biological correlates of the impact of antenatal depression on the mother-infant relationship. *Brain Behav Immun Health* 20: 100413.

10. Lefkovics E, Baji I, Rigó J (2014): Impact of Maternal Depression on Pregnancies and on Early Attachment. *Infant Ment Health J* 35: 354–365.

11. Barnes J, Theule J (2019): Maternal depression and infant attachment security: A meta-analysis. *Infant Ment Health J* 40: 817–834.

12. Miranda M, Morici JF, Zanoni MB, Bekinschtein P (2019): Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. *Front Cell Neurosci* 13: 472800.

13. Fahnestock M, Marchese M, Head E, Pop V, Michalski B, Milgram WN, Cotman CW (2012): BDNF increases with behavioral enrichment and an antioxidant diet in the aged dog. *Neurobiol Aging* 33: 546–554.

14. Hsiao YH, Hung HC, Chen SH, Gean PW (2014): Social Interaction Rescues Memory Deficit in an Animal Model of Alzheimer's Disease by Increasing BDNF-Dependent Hippocampal Neurogenesis. *Journal of Neuroscience* 34: 16207–16219.

15. Donnici C, Long X, Reynolds J, Giesbrecht GF, Dewey D, Letourneau N, *et al.* (2023): Prenatal depressive symptoms and childhood development of brain limbic and default mode network structure. *Hum Brain Mapp* 44: 2380–2394.

16. Favaro A, Tenconi E, Degortes D, Manara R, Santonastaso P (2015): Neural correlates of prenatal stress in young women. *Psychol Med* 45: 2533–2543.

17. Bezanson S, Nichols ES, Duerden EG (2023): Postnatal maternal distress, infant subcortical brain macrostructure and emotional regulation. *Psychiatry Res Neuroimaging* 328: 111577.

18. Qiu A, Rifkin-Graboi A, Chen H, Chong Y-S, Kwek K, Gluckman PD, *et al.* (2013): Maternal anxiety and infants' hippocampal development: timing matters. *Transl Psychiatry* 3: e306.

19. Lupien SJ, Parent S, Evans AC, Tremblay RE, Zelazo PD, Corbo V, *et al.* (2011): Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proc Natl Acad Sci U S A* 108: 14324–14329.

20. Lee A, Poh JS, Wen DJ, Guillaume B, Chong YS, Shek LP, *et al.* (2019): Long-term Influences of Prenatal Maternal Depressive Symptoms on the Amygdala–Prefrontal Circuitry of the Offspring From Birth to Early Childhood. *Biol Psychiatry Cogn Neurosci Neuroimaging* 4: 940–947.

21. Wen DJ, Poh JS, Ni SN, Chong YS, Chen H, Kwek K, *et al.* (2017): Influences of prenatal and postnatal maternal depression on amygdala volume and microstructure in young children. *Translational Psychiatry 2017 7:4* 7: e1103–e1103.

22. Lehtola SJ, Tuulari JJ, Scheinin NM, Karlsson L, Parkkola R, Merisaari H, *et al.* (2020): Newborn amygdalar volumes are associated with maternal prenatal psychological distress in a sex-dependent way. *Neuroimage Clin* 28: 102380.

23. Acosta H, Tuulari JJ, Scheinin NM, Hashempour N, Rajasilta O, Lavonius TI, *et al.* (2019): Maternal Pregnancy-Related Anxiety Is Associated With Sexually Dimorphic Alterations in Amygdala Volume in 4-Year-Old Children. *Front Behav Neurosci* 13: 175.

24. Moog NK, Nolvi S, Kleih TS, Styner M, Gilmore JH, Rasmussen JM, *et al.* (2021): Prospective association of maternal psychosocial stress in pregnancy with newborn hippocampal volume and implications for infant social-emotional development. *Neurobiol Stress* 15: 100368.

25. Acosta H, Tuulari JJ, Scheinin NM, Hashempour N, Rajasilta O, Lavonius TI, *et al.* (2020): Prenatal maternal depressive symptoms are associated with smaller amygdalar volumes of four-year-old children. *Psychiatry Res Neuroimaging* 304: 111153.

26. Wu Y, Kapse A, Espinosa K, Kapse K, Lopez C, Quistorff JL, *et al.* (2021): Prenatal maternal mental distress impairs newborn amygdala growth and infant neurodevelopment at 18 months. *Am J Obstet Gynecol* 224: S61.

27. Donnici C, Long X, Dewey D, Letourneau N, Landman B, Huo Y, Lebel C (2021): Prenatal and postnatal maternal anxiety and amygdala structure and function in young children. *Scientific Reports 2021 11:1* 11: 1–12.

28. Wang C, Shen M, Guillaume B, Chong Y-S, Chen H, Fortier M V, *et al.* (2018): FKBP5 Moderates the Association between Antenatal Maternal Depressive Symptoms and Neonatal Brain Morphology. *Neuropsychopharmacology* 43: 564–570.

29. Groenewold NA, Wedderburn CJ, Pellowski JA, Fouché J-P, Michalak L, Roos A, *et al.* (2022): Subcortical brain volumes in young infants exposed to antenatal maternal depression: Findings from a South African birth cohort. *Neuroimage Clin* 36: 103206.

30. Triplett RL, Lean RE, Parikh A, Miller JP, Alexopoulos D, Kaplan S, *et al.* (2022): Association of Prenatal Exposure to Early-Life Adversity With Neonatal Brain Volumes at Birth. *JAMA Netw Open* 5: e227045–e227045.

31. Weiner S, Wu Y, Kapse K, Vozar T, Cheng JJ, Murnick J, *et al.* (2024): Prenatal Maternal Psychological Distress During the COVID-19 Pandemic and Newborn Brain Development. *JAMA Netw Open* 7: e2417924–e2417924.

32. Qiu A, Shen M, Buss C, Chong Y-S, Kwek K, Saw S-M, *et al.* (2017): Effects of Antenatal Maternal Depressive Symptoms and Socio-Economic Status on Neonatal Brain Development are Modulated by Genetic Risk. *Cerebral Cortex* 27: 3080–3092.

33. Kumpulainen V, Copeland A, Pulli EP, Silver E, Kataja E-L, Saukko E, *et al.* (2023): Prenatal and Postnatal Maternal Depressive Symptoms Are Associated With White Matter Integrity in 5-Year-Olds in a Sex-Specific Manner. *Biol Psychiatry* 94: 924–935.

34. Wu Y, De Asis-Cruz J, Limperopoulos C (2024): Brain structural and functional outcomes in the offspring of women experiencing psychological distress during pregnancy. *Molecular Psychiatry 2024 29:7* 29: 2223–2240.

35. Wei D, Zhang H, Broekman BFP, Chong YS, Shek LP, Yap F, *et al.* (2022): Cortical Development Mediates Association of Prenatal Maternal Depressive Symptoms and Child Reward Sensitivity: A Longitudinal Study. *J Am Acad Child Adolesc Psychiatry* 61: 392–401.

36. El Marroun H, Tiemeier H, Muetzel RL, Thijssen S, van der Knaap NJF, Jaddoe VWV, *et al.* (2016): Prenatal Exposure to Maternal and Paternal Depressive Symptoms and Brain Morphology: A Population-based Prospective Neuroimaging Study in Young Children. *Depress Anxiety* 33: 658–666.

37. Davis EP, Hankin BL, Glynn LM, Head K, Kim DJ, Sandman CA (2020): Prenatal Maternal Stress, Child Cortical Thickness, and Adolescent Depressive Symptoms. *Child Dev* 91: e432–e450.

38. Sandman CA, Buss C, Head K, Davis EP (2015): Fetal Exposure to Maternal Depressive Symptoms Is Associated With Cortical Thickness in Late Childhood. *Biol Psychiatry* 77: 324–334.

39. Buss C, Davis EP, Muftuler LT, Head K, Sandman CA (2010): High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6-9 year-old children. *Psychoneuroendocrinology* 35: 141.

40. Silbereis JC, Pochareddy S, Zhu Y, Li M, Sestan N (2016): The Cellular and Molecular Landscapes of the Developing Human Central Nervous System. *Neuron* 89: 248–268.

41. Glynn LM, Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, Sandman CA (2001): When stress happens matters: Effects of earthquake timing on stress responsivity in pregnancy. *Am J Obstet Gynecol* 184: 637–642.

42. De Weerth C, Buitelaar JK (2005): Physiological stress reactivity in human pregnancy—a review. *Neurosci Biobehav Rev* 29: 295–312.

43. Lebel C, Walton M, Letourneau N, Giesbrecht GF, Kaplan BJ, Dewey D (2016): Prepartum and Postpartum Maternal Depressive Symptoms Are Related to Children's Brain Structure in Preschool. *Biol Psychiatry* 80: 859–868.

44. Zou R, Tiemeier H, Van Der Ende J, Verhulst FC, Muetzel RL, White T, *et al.* (2019): Exposure to maternal depressive symptoms in fetal life or childhood and offspring brain development: A population-based imaging study. *American Journal of Psychiatry* 176: 702–710.

45. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, *et al.* (2014): Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *International Journal of Surgery* 12: 1500–1524.

46. Karlsson L, Tolvanen M, Scheinin NM, Uusitupa H-M, Korja R, Ekholm E, *et al.* (2018): Cohort Profile: The FinnBrain Birth Cohort Study (FinnBrain). *Int J Epidemiol* 47: 15–16j.

47. Cox JL, Holden JM, Sagovsky R (1987): Detection of Postnatal Depression. *British Journal of Psychiatry* 150: 782–786.

48. Derogatis LR (1994): SCL-90-R: Administration, scoring and procedures manual (3rd ed.). *NCS Pearson*.

49. Kessler RC, Sampson NA, Berglund P, Gruber MJ, Al-Hamzawi A, Andrade L, *et al.* (2015): Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. *Epidemiol Psychiatr Sci* 24: 210–226.

50. Lamers F, Van Oppen P, Comijs HC, Smit JH, Spinhoven P, Van Balkom AJLM, *et al.* (2011): Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA). *J Clin Psychiatry* 72: 342–348.

51. Rajasilta O, Häkkinen S, Malin Björnsdotter |, Scheinin NM, Lehtola SJ, Saunavaara J, *et al.* (2023): Maternal psychological distress associates with alterations in resting-state low-frequency fluctuations and distal functional connectivity of the neonate medial prefrontal cortex. *European Journal of Neuroscience* 57: 242–257.

52. Tervahartiala K, Korja R, Sarelius V, Autere TA, Karlsson H, Carter AS, *et al.* (2025): Participation in early childhood education and care in Finland mitigates the associations between maternal psychological distress and child social and emotional problems at age two. *Eur Child Adolesc Psychiatry* 1–11.

53. Lahti-Pulkkinen M, Lähdepuro A, Lahti J, Girchenko P, Pyhälä R, Reynolds RM, *et al.* (2024): Maternal psychological distress and temperament traits in children from infancy to late childhood. *JCPP Advances* 4: e12242.

54. Copeland A, Korja R, Nolvi S, Rajasilta O, Pulli EP, Kumpulainen V, *et al.* (2022): Maternal sensitivity at the age of 8 months associates with local connectivity of the medial prefrontal cortex in children at 5 years of age. *Front Neurosci* 16: 1560.

55. Pulli EP, Silver E, Kumpulainen V, Copeland A, Merisaari H, Saunavaara J, *et al.* (2022): Feasibility of FreeSurfer Processing for T1-Weighted Brain Images of 5-Year-Olds: Semiautomated Protocol of FinnBrain Neuroimaging Lab. *Front Neurosci* 16: 640.

56. Gaser C, Dahnke R, Thompson PM, Kurth F, Luders E (2024): CAT: a computational anatomy toolbox for the analysis of structural MRI data. *Gigascience* 13: 1–13.

57. RStudio Team (2020): RStudio: Integrated Development for R. *RStudio, PBC, Boston*. Retrieved from http://www.rstudio.com/

58. Silver E, Pulli EP, Kataja E-L, Kumpulainen V, Copeland A, Saukko E, *et al.* (2022): Prenatal and early-life environmental factors, family demographics and cortical brain anatomy in 5-year-olds: an MRI study from FinnBrain Birth Cohort. *Brain Imaging and Behavior 2022* 1: 1–13.

59. Brett M, Anton J-L, Valabregue R, Poline J-B (2002): Region of interest analysis using an SPM toolbox [abstract]. Presented at the 8th International Conferance on Functional Mapping of the Human Brain, June 2-6, 2002, Sendai, Japan. *Neuroimage* 16. https://doi.org/10.1016/S1053-8119(02)90013-3

60. Koenigs M, Barbey AK, Postle BR, Grafman J (2009): Superior Parietal Cortex Is Critical for the Manipulation of Information in Working Memory. *Journal of Neuroscience* 29: 14980–14986.

61. Cavanna AE, Trimble MR (2006): The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* 129: 564–583.

62. Qiu A, Tuan TA, Ong ML, Li Y, Chen H, Rifkin-Graboi A, *et al.* (2014): COMT Haplotypes Modulate Associations of Antenatal Maternal Anxiety and Neonatal Cortical Morphology. *American Journal of Psychiatry* 172: 163–172.

63. Jung RE, Haier RJ (2007): The Parieto-Frontal Integration Theory (P-FIT) of intelligence: Converging neuroimaging evidence. *Behavioral and Brain Sciences* 30: 135–154.

64. Pulli EP, Nolvi S, Eskola E, Nordenswan E, Holmberg E, Copeland A, *et al.* (2023): Structural brain correlates of non-verbal cognitive ability in 5-year-old children: Findings from the FinnBrain birth cohort study. *Hum Brain Mapp* 44: 5582–5601.

65. Li W, Qin W, Liu H, Fan L, Wang J, Jiang T, Yu C (2013): Subregions of the human superior frontal gyrus and their connections. *Neuroimage* 78: 46–58.

66. Seghier ML (2013): The angular gyrus: Multiple functions and multiple subdivisions. *Neuroscientist* 19: 43–61.

67. Lara-Aparicio SY, Laureani-Fierro AJ, Morgado-Valle C, Beltrán-Parrazal L, Rojas-Durán F, García LI, *et al.* (2022): Latest research on the anatomy and physiology of the cerebellum. *Neurology Perspectives* 2: 34–46.

68. Vlasova RM, Panikratova YR, Pechenkova E V. (2023): Systematic Review and Meta-analysis of Language Symptoms due to Cerebellar Injury. *Cerebellum* 22: 1274–1286.

69. Buckner RL (2013): The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. *Neuron* 80: 807–815.

70. Zhang P, Duan L, Ou Y, Ling Q, Cao L, Qian H, *et al.* (2023): The cerebellum and cognitive neural networks. *Front Hum Neurosci* 17: 1197459.

71. Guell X, Schmahmann J (2020): Cerebellar Functional Anatomy: a Didactic Summary Based on Human fMRI Evidence. *Cerebellum* 19: 1–5.

72. Laplante DP, Barr RG, Brunet A, Du Fort GG, Meaney ML, Saucier JF, *et al.* (2004): Stress During Pregnancy Affects General Intellectual and Language Functioning in Human Toddlers. *Pediatric Research 2004 56:3* 56: 400–410.

73. Ackermann H, Riecker A (2004): The contribution of the insula to motor aspects of speech production: A review and a hypothesis. *Brain Lang* 89: 320–328.

74. Cao X, Laplante DP, Brunet A, Ciampi A, King S (2014): Prenatal maternal stress affects motor function in 5½-year-old children: Project Ice Storm. *Dev Psychobiol* 56: 117–125.

75. Lidauer K, Pulli EP, Copeland A, Silver E, Kumpulainen V, Hashempour N, *et al.* (2022): Subcortical and hippocampal brain segmentation in 5-year-old children: Validation of FSL-FIRST and FreeSurfer against manual segmentation. *European Journal of Neuroscience* 56: 4619–4641.

76. Hashempour N, Tuulari JJ, Merisaari H, Lidauer K, Luukkonen I, Saunavaara J, *et al.* (2019): A Novel Approach for Manual Segmentation of the Amygdala and Hippocampus in Neonate MRI. *Front Neurosci* 13: 1025.

77. Bethlehem RAI, Seidlitz J, White SR, Vogel JW, Anderson KM, Adamson C, *et al.* (2022): Brain charts for the human lifespan. *Nature* 604: 525–533.

78. Korja R, Nolvi S, Scheinin NM, Tervahartiala K, Carter A, Karlsson H, *et al.* (2024): Trajectories of maternal depressive and anxiety symptoms and child's socio-emotional outcome during early childhood. *J Affect Disord* 349: 625–634.