Pre- and postnatal maternal depressive symptoms associate with local connectivity of the left amygdala in 5-year-olds.

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Abstract

Maternal pre- and postnatal depressive symptoms influence brain development in offspring. Maternal symptoms may affect child brain development through intrauterine conditions as well as ways of parenting and mother–child interaction. This study investigated whether maternal pre- and postnatal depressive symptoms are associated with child's whole brain regional homogeneity (ReHo) and seed-based connectivity of the bilateral amygdala at 5 years of age based on the sample available from FinnBrain Birth Cohort Study (N = 68; 28 boys, 40 girls). Maternal depressive symptoms were assessed with the Edinburgh Postnatal Depression Scale (EPDS) at gestational week 24, 3 months, 6 months, and 12 months postnatal. Children's brain imaging data were acquired with task-free functional magnetic resonance imaging (fMRI) at the age of 5 years in 7 min scans while watching the *Inscapes* movie. The ReHo and seed-based connectivity maps of the bilateral amygdalae were created from the fMRI data. We found that maternal depressive symptoms were positively associated with ReHo values of the left amygdala. The association was strongest with the maternal depressive symptoms at three months postnatal. Seed-based connectivity analysis did not reveal associations between distal connectivity of the left amygdala region and maternal depressive symptoms. These results suggest that maternal depressive symptoms during pregnancy and especially soon after birth may influence offspring's neurodevelopment related to emotional processing in fundamental ways and may raise the risk of vulnerability of intergenerational transmission for depression and other affective disorders.

Keywords: brain development, fMRI, maternal depression, amygdala, ReHo, children

1. Introduction

Maternal psychological distress in pregnancy, such as depression, can affect fetal brain development in fundamental ways (Bergh et al., 2018; Lautarescu et al., 2020). The prevalence of clinically meaningful depression, including major and minor depressive disorder, in pregnancy is 11% in the first trimester and 8,5% in the second and third trimester (Gavin et al., 2005). Effects of prenatal maternal depressive symptoms have been observed especially in the structure and function of the offspring's amygdala (Qiu et al., 2015; Soe et al., 2018) which is largely responsible for emotional regulation (Constantinof et al., 2016). In some subjects with depression the hypothalamic–pituitary–adrenal (HPA) axis appears to be overactive (Keller et al., 2017) which leads to heightened levels of cortisol (Pearson Murphy, 1991). Cortisol passes through blood–placental barrier and is a key hormone in the regulation of fetal brain development and maturation (Constantinof et al., 2016; Kassotaki et al., 2021; Wood & Keller-Wood, 2016). Maternal prenatal depressive symptoms and therefore excess placental cortisol levels in fetus are associated with changes in the limbic brain areas (e.g. amygdala, hypothalamus, hippocampus) and frontotemporal networks (Kassotaki et al., 2021; Lautarescu et al., 2020). Further, prenatal exposure to stress-inducing conditions can possibly alter the child's HPA-axis (Bergh et al., 2018) and stimulate fetal biological stress pathways that increase the vulnerability of the risk for neuropsychiatric disorders such as depression (Nestler et al., 2002), anxiety (Kassotaki et al., 2021), schizophrenia (Koenig et al., 2002), and autism (Gillott & Standen, 2007).

Structural and diffusion MRI studies have indicated that maternal prenatal stress, including depression, is associated with changes in child brain morphology (Lautarescu et al., 2020; Rifkin-Graboi et al., 2013;

Wen et al., 2017). An association between prenatal stress and smaller grey matter volumes has been reported extending from prefrontal to occipital regions in 7-year-olds (Buss et al., 2010), right inferior frontal and middle temporal region in 3.5-year-olds (Lebel et al., 2016), superior frontal cortex in the left hemisphere in 8-year-olds (El Marroun et al., 2016) and frontal and temporal regions in 7-year-olds (Davis et al., 2020). In addition, other studies have focused on the correlation of prenatal stress with structure of amygdala. A positive association was found between maternal depressive symptoms during pregnancy and larger right amygdala volume in 4.5-year-old girls, but not in boys (Wen et al., 2017), whereas another study reported significantly greater left relative amygdala volume in 4-year-old girls compared to boys (Acosta et al., 2019). Maternal cortisol levels during pregnancy have also been shown to be associated with larger amygdala volumes in young 7.5-year-old girls (Buss et al., 2012). Prenatal maternal depressive symptoms have been linked to lower right and left amygdala fractional anisotropy (FA) as well as lower right amygdala axial diffusivity (Rifkin-Graboi et al., 2013). Maternal depressive symptoms during pregnancy have also been reported to associate with higher left amygdala mean diffusivity in infants (Hashempour et al., 2023) as well as with higher right amygdala FA in 4.5-year-old children (Wen et al., 2017). These findings affirm that the prenatal period is critical for fetus' neurodevelopment and poor maternal well-being during pregnancy may have profound long-lasting effects on the offspring. Effects of prenatal depressive symptoms are found in brain structures that are responsible for, e.g. emotional regulation, cognition, memory, and decision-making.

Resting-state functional magnetic resonance imaging (rs-fMRI) can provide novel information on maternal distress as a predictor of offspring's neurodevelopment (Bale et al., 2010; Posner et al., 2016; Qiu et al., 2015; Singh-Taylor et al., 2015). A recent rs-fMRI study on infant neurodevelopment showed that maternal prenatal depressive symptoms were associated with increased functional connectivity (FC) between medial prefrontal cortex (mPFC) and left amygdala in 6-month-old infants (Qiu et al., 2015).

Rajasilta et al. demonstrated that in infants approximately one moth of age maternal prenatal psychological distress was positively linked to rs-fMRI-derived fractional amplitude of low-frequency fluctuations (fALFF) in the neonate mPFC which indicates that prenatal stress may affect functional features of the maturing brain during gestation (Rajasilta et al., 2023). Children of mothers who experienced psychological distress during late pregnancy had increased amygdala functional connectivity with the ventromedial prefrontal cortex (vmPFC) and anterior insula (Marr et al., 2023). In comparison to prenatal maternal depressive symptoms, early postnatal maternal wellbeing and later child development have received significantly less attention in neuroimaging studies, even though the first years of life are crucially important time for parent-child bonding and child development.

To best of our knowledge, there is only one prior functional neuroimaging study linking both pre- and postnatal maternal depressive symptoms to adverse child brain connectivity outcomes in early childhood. This study by (Soe et al., 2018) investigated the effect of perinatal maternal depressive symptoms relation to bilateral amygdala of approximately 4.5-year-old children. They found significant positive associations between maternal prenatal depressive symptoms and the left amygdala functional connectivity with the right insula and putamen, bilateral subgenual anterior cingulate cortex (ACC) and caudate. Similar associations were found between the right amygdala and left orbitofrontal cortex (OFC) and temporal pole. Greater pre- than postnatal depressive symptoms had associations with lower functional connectivity of the left amygdala with the bilateral subgenual ACC and left caudate. Correspondingly, greater prenatal maternal depressive symptoms were associated with lower functional connectivity of the right amygdala with the left OFC, insula, and caudate. These were gender-specific to girls. However, the study did not find statistically significant interactions of gender with pre- or postnatal maternal depressive symptoms on amygdala functional connectivity (Soe et al., 2018). These findings that emerged from Soe et al. study are part of the cortico-amygdala-striatal circuitry which is largely

responsible for emotional perception and processing (Cho et al., 2013; Salzman & Fusi, 2010). The association between maternal perinatal depressive symptoms and child's amygdala functionality have not been explored by comparing depressive symptom levels at different timepoints with other voxel-wise measures such as ReHo. Thus, our study reveals novel information on offspring's amygdala's functional profile when exposed to pre- and/or postnatal maternal depressive symptoms.

Our aim was to investigate whether maternal pre- and postnatal depressive symptoms associate with 5-year-olds' local connectivity across the whole brain as assessed by regional homogeneity (ReHo), a measure derived from task-free fMRI while the participants were watching *Inscapes* movie (Vanderwal et al., 2015). Second, replicating the analyses in prior work (Soe et al., 2018), we mapped the association of maternal depressive symptoms to bilateral amygdala seed-based connectivity. Third, multiple regression analyses were performed to assess the associations between maternal depressive symptoms and bilateral amygdala ReHo values. This was an exploratory study and thus no explicit hypotheses were placed regarding the direction or strength of the associations.

2. Methods

This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Joint Ethics Committee of the University of Turku and the Hospital District of Southwest Finland (15.03.2011) §95, ETMK: 31/180/2011. Written informed consent was obtained from the participants, and parents gave consent on behalf of their children. We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines for cohort studies

(https://www.strobe-statement.org). The participant criteria, MRI scanning visits, image acquisition and preprocessing are identical to those used in our prior work (Copeland et al., 2022).

2.1 Participants

The participants are part of the large FinnBrain Birth Cohort Study, which prospectively examines the influence of genetic and environmental factors on child development and later mental and physical health outcomes (Karlsson et al., 2018). Pregnant women attending their first trimester ultrasound were recruited by research nurses in maternal welfare clinics in the Turku region of the Southwest Finland Hospital District and the Åland Islands between December 2011 and April 2015. Ultrasound-verified pregnancy and a sufficient knowledge of Finnish or Swedish were required for participation.

The exclusion criteria for the neuroimaging visit were: (1) born before gestational week 35 (week 32 for those with exposure to maternal prenatal synthetic glucocorticoid treatment), (2) developmental or major organ 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, (5) the child using continuous, daily medication (including oral medications, topical creams, and inhalants; desmopressin was allowed), (6) history of head trauma (defined as concussion necessitating clinical follow up in a health care setting), (7) metallic ear tubes, and (8) routine MRI contraindications.

Obstetric data was retrieved from the Finnish National Birth Register (National Institute for Health and Welfare, www.thl.fi). Other information was gathered using questionnaires on behalf FinnBrain Birth Cohort Study.

In total, 203 children participated in a neuroimaging visit at 5 years of age, and 77 of them had successful functional scans due to limited subject compliance (the fMRI data was acquired last), out of which 68 had the Edinburgh Postnatal Depression Scale (EPDS) questionnaires collected, and were included in the study after quality control steps outlined below. Participant characteristics are reported in Table 1A and 1B.

2.2 Maternal depressive and anxiety symptoms

Questionnaires assessing maternal psychological health were filled in by the mothers during the gestational week 24, 3 months, 6 months, and 12 months postnatal. We measured the prenatal EPDS scores at gestational week 24 because at this timepoint neurogenesis takes place, cortex begins to fold and myelin starts to develop (Bendersky et al., 2006; Garel et al., 2003; Leibovitz et al., 2022). Maternal depressive symptoms were assessed with the EPDS (Cox et al., 1987), which has been validated for use during pregnancy. This 10-item questionnaire is scaled from 0 to 30 points with a higher score denoting increased symptom severity. A score of 10 has been implicated as a clinically meaningful threshold for symptoms of depression in pregnancy (Vázquez & Míguez, 2019).

Pre- and postnatal maternal anxiety symptoms were evaluated using the anxiety scale of Symptom Checklist 90 (SCL-90) (Derogatis et al., 1973) at gestational week 24, 3 months and 6 months postnatal. The anxiety subscale of SCL-90 is a reliable and valid measure of anxiety symptoms in both clinical and research settings and the questionnaire consists of 10 items scaled from 0 to 5.

2.3 Magnetic resonance imaging visits

All MRI scans were performed for research purposes, and participants were scanned awake and without sedation. The imaging was performed at the Department of Radiology, Turku University Hospital between October 2017, and March 2021. Before scanning, a research staff member met with the families personally. Parents were advised to use familiarization methods, such as reading a story and showing a video describing the visit, playing audio of scanner sounds, encouraging the child to lie still like a statue, and practicing with a homemade mock scanner, e.g., a cardboard box.

On the scanning day, imaging was practiced with a wooden mock scanner using the child's own toy to "scan" and the effects of motion were illustrated by taking sharp and blurry pictures using a mobile phone camera. Participants were shown parts of the *Inscapes* movie beforehand on a tablet screen. At the end of the preparation, a light meal was served. The preparation phase lasted 1–2 h. To increase comfort and minimize head motion, foam paddings were positioned around the participant's head inside the head coil. A leg cushion under the knees and customized weighted blanket were provided if desired. Earplugs (Mack's Soft Moldable Silicone Putty Earplugs) and MRI safe headphones (Siemens Medical Solutions) were provided for noise attenuation. A parent and a member of the research staff stayed in the imaging room right next to the child throughout the whole session. Research personnel continuously monitored the scanning in the scanning room and from the control room through a window with a microphone contact.

2.4 Image acquisition

The MRI scans were conducted on a Siemens Magneton Skyra fit 3T scanner (Siemens Medical Solutions, Erlangen, Germany). A 20-element Head/Neck Matrix coil allowed the use of the generalized

autocalibrating partially parallel acquisition (GRAPPA) technique to accelerate acquisitions (parallel acquisition technique [PAT] factor of 2). The scans included a high-resolution T1 magnetization-prepared rapid gradient echo (MPRAGE), a T2 turbo-spin echo (TSE), diffusion tensor imaging (DTI), and a 7-min fMRI. The fMRI consisted of 170 volumes with voxel size 3.0 × 3.0 × 3.0 mm, TR 2500 ms, TE 30.0 ms, flip angle of 80°, and 42 axial slices without gaps. Full cerebellar coverage was not possible in all participants. Prior to fMRI acquisition, all children had rested by watching a movie or a TV show of their choice during the 30–45 min required for structural scanning. If the child had fallen asleep, they were gently awakened. During the fMRI sequence, participants were instructed to stay as still as possible with their eyes open. To minimize motion and reduce cognitive load, the *Inscapes* movie was played during fMRI data collection (Vanderwal et al., 2015). Visual stimuli were presented on an MRI-compatible 32" LCD monitor with full HD resolution (Nordic Neuro Lab) located at the foot of the bed of the scanner, where participants could watch via mirrors mounted on the head coil. The total scanning time was limited to 1 hour, and the imaging was discontinued if the child expressed unwillingness to continue at any point.

Anatomical images were screened by an experienced neuroradiologist for incidental findings (Kumpulainen et al., 2020). None of the participants included in the present study had clinically relevant incidental findings.

2.5 Image preprocessing and estimating regional homogeneity (ReHo)

Functional MRI data were slice-timing corrected and motion corrected in the FMRIB Software Library (FSL; Jenkinson et al., 2012) v6.00 relative to a manually chosen reference volume, free of major artifacts. Motion outliers were estimated using artifact detection tools (ART)

(https://www.nitrc.org/projects/artifact_detect). We tagged the images as outliers if they had composite motion threshold > 2 mm or DVARS > 9, which are default parameters in the ART toolbox and worked well for our current data. All children included in the final statistical analyses had a full fMRI sequence of 170 volumes, and a maximum of 50 volumes were tagged as outliers by ART. The descriptive statistics for motion were as follows (of full sample N = 77): motion outliers (mean 12, range 0–44), mean absolute displacement (mean 0.51, range 0.11–1.81, mm), and mean relative displacement (mean 0.21, range 0.03–0.83, mm). Anatomical masks for white matter and cerebrospinal fluid were defined in the Montreal Neurological Institute (MNI) standard space and registered to functional data with an affine transformation. Average signal in white matter and cerebrospinal fluid as well as 24 motion covariates (the six realignment parameters and their temporal derivatives and quadratic terms) were included as nuisance covariates. Taken together, denoising consisted of outlier rejection, nuisance regression, detrending, and high-pass filtering (0.008 Hz).

Regional homogeneity describes synchronization between timeseries of a given voxel in its neighbours (Zang et al., 2004) which can be a sign of synchronised activation or deactivation in blood-oxygen-level-dependent (BOLD) timeseries. The main derived brain metric was ReHo, which was estimated in a data-driven manner and provided a voxel-wise local connectivity measure across the whole brain. ReHo is based on calculating the Kendall's coefficient of concordance over a target voxel and neighbouring voxels. ReHo was computed as implemented in DPABI (number of voxels in a cluster; N = 27). For group analysis, ReHo maps were normalized non-linearly to $1.0 \times 1.0 \times 1.0$ mm^3 MNI space using FSL FNIRT. Finally, the data were smoothed with a Gaussian filter of 6 mm full width at half maximum (FWHM).

2.7 Seed-based connectivity analysis (SCA)

We decided to carry out seed-based connectivity analyses in line with prior work (Soe et al., 2018). Additionally, in line with our prior work (Copeland et al., 2022; Rajasilta et al., 2021), we had predefined plans to conduct complementary exploratory SCAs guided by the ReHo results. The SCA analyses were performed with FSL tools using the same preprocessing and nuisance regression as for the ReHo analyses except that the interquartile range (obtained via fsl_motion_outliers) of DVARS was used for removal of motion corrupted volumes after confirming that it matched the ReHo pipeline described above.

The amygdalae were set as the regions of interest (ROIs) and the average time series of the seed ROIs was extracted from normalized data using the "fslmeants" command after creating a binary amygdala mask for the left and right side from the AAL template (Tzourio-Mazoyer et al., 2002). Subject-level seed-based connectivity maps were generated using the FSL v6.00 fMRI expert analysis tool (FEAT; Woolrich et al., 2001). The resulting z-score maps for each participant were then normalized to MNI space, and statistical tests were conducted with FSL FEAT higher-level analysis.

2.8 Statistical analysis

Statistical analyses were performed with SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) with general linear models (GLM) and "multiple regression" design for ReHo. Analysis was performed to assess the association between maternal perinatal depressive symptoms and ReHo of the bilateral amygdala. Child age at scan and sex were set as the independent variables (IV) of no interest and EPDS sum score was set as the main explanatory variable (EV). Multiple regression models were performed for EPDS sum scores separately to determine the associations for maternal subjective experiences of depressive symptoms for each of the time points (gestational week 24, 3 months, 6 months, and 12 months postnatal). We performed the analysis with

EPDS sum score at 3 months postnatal as the EV also with added IVs including maternal socioeconomic status (SES) measured by maternal educational level, maternal pre-pregnancy BMI, and child's ponderal index (measured at MRI scan, relationship between body mass and height; mass/height^3, (Peterson et al., 2017)), and lastly with maternal anxiety symptom score (SCL-90 sum score) in addition. The final multiple regression analysis was for EPDS sum score at 12 months postnatal as the EV and maternal SES, maternal pre-pregnancy BMI, and ponderal index as the IVs. Prior to statistical testing we inclusively masked the ReHo maps with a binary grey matter mask. The *a priori* statistical threshold for clusters was set at $p < 0.001$ and secondarily at $p < 0.005$ and corrected with family-wise error (FWE) at cluster level at $p < 0.05$.

In addition, complementary regression models were performed for bilateral amygdala mean ReHo values with RStudio (R Core Team (2024). _R: A Language and Environment for Statistical Computing_. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.) to describe the effect sizes of the associations between the ReHo of the left and right amygdala, and the independent variables in line with the SPM12 models, and with other additional independent variables described below. The ReHo values were obtained by creating binary masks of bilateral amygdala from the AAL atlas and then using them to mask normalised ReHo maps and the mean was estimated with fslmaths.

All regression models were performed for left and right amygdala mean ReHo values separately. In the first regression model, independent variables were set as EPDS sum score (gestational week 24, 3 months, 6 months, and 12 months postnatal separately), child sex, and child age at scan. In the second model, independent variables were set as EPDS sum score (gestational week 24, 3 months, 6 months, and 12 months postnatal separately), child sex, child age at scan, maternal SES, maternal pre-pregnancy BMI, and ponderal index. Finally, we added maternal anxiety symptoms (SCL-90 sum score at

gestational week 24, 3 months, and 6 months separately) to the second model to test if the association was specific to depressive symptoms. Missing EPDS sum score, SCL-90 sum score and maternal educational level values were mean imputed for statistical analyses. We checked that the regression models met basic assumptions: multicollinearity through variation inflation factor (all variance inflation factors, VIF's < 2.3) and that the residuals were normally distributed through visual inspection of Q–Q plots and histograms of the residuals. We report uncorrected *p*-values throughout the manuscript but note that we performed eight statistical tests, 2 (left and right amygdala) x 4 (EPDS questionnaire timepoints), and the Bonferroni corrected *p*-values are below 0.00625.

3. Results

The sample characteristics are reported in Tables 1A and 1B. The sample included 28 boys and 40 girls. Maternal EPDS sum scores showed variability across different measurement points so that the mean scores were 5.12 (gestational week 24), 3.97 (3 months postnatal), 5.19 (6 months postnatal), and 4.39 (12 months postnatal). Correspondingly, SCL-90 sum scores were 3.41 (gestational week 24), 2.00 (3 months postnatal), and 3.21 (6 months postnatal).

Table 1A. Continuous variables

Descriptive Statistics

	Valid	**Missing**	**Mean**	**SD**	**Range**
Child age at scan (years)	68	0	5.39	0.12	0.51
Duration of gestation (weeks)	68	0	39.84	1.34	6.43
Child birthweight (grams)	67	1	20.60	3.08	17.10

Descriptive Statistics

	Valid	Missing	Mean	SD	Range
Maternal age at childbirth (years)	68	0	30.40	4.63	21.00
Maternal pre-pregnancy BMI (kg/m^2)	68	0	23.52	3.99	19.25
EPDS sum score at gestational week 24	65	3	5.12	4.23	21.00
EPDS sum score at 3 months postnatal	68	0	3.97	3.52	12.22
EPDS sum score at 6 months postnatal	60	8	5.19	4.63	19.00
EPDS sum score at 12 months postnatal	57	11	4.39	4.32	21.00
SCL-90 sum score at gestational week 24	65	3	3.41	3.55	14.00
SCL-90 sum score at 3 months postnatal	68	0	2.00	3.12	15.00
SCL-90 sum score at 6 months postnatal	60	8	3.21	4.75	24.00

Table 1B. Categorical variables

Child sex	Frequency	Percent
Boy	28	41.2%
Girl	40	58.8%
Missing	0	0

Maternal education level	Frequency	Percent
Upper secondary school or vocational school or lower	14	20.6%
University of applied sciences	17	25.0%
University	36	52.9%
Missing	1	1.5%

Maternal background	Frequency	Percent
Finnish	66	97.1%
Other	2	2.9%
Missing	0	0

Smoking during pregnancy	Frequency	Percent
No smoking	64	94.1%
During first trimester	2	2.9%
During third trimester	2	2.9%
Missing	0	0

Table 1A & 1B. Demographics of the mother and child participants. SD, standard deviation; BMI, pregnancy body mass index; EPDS, Edinburgh Postnatal Depression Scale; SCL-90, Symptom Checklist 90

3.1 Whole brain models

Multiple regression analyses did not reveal positive or negative associations between EDPS sum score at gestational week 24 and child brain ReHo map of left amygdala when child sex and age at scan were controlled.

Significant positive association between mothers' EPDS sum score at 3 months postnatal and child brain ReHo map of left amygdala region was found with multiple regression analysis when child sex and age at scan were controlled ($p < 0.001$, $p = 0.027$ FWE corrected, cluster size (kE) 407) (Figure 1). Association remained significant when maternal pre-pregnancy BMI, maternal SES and ponderal index were included as covariates ($p < 0.001$, $p = 0.044$ FWE corrected, cluster size (kE) 357), and when SCL-90 sum score was controlled in addition ($p < 0.001$, $p = 0.058$ FWE corrected, cluster size (kE) 327). There were no negative associations between mothers' EPDS sum score at 3 months postnatal and child brain ReHo map of the left amygdala region. We carried out a sensitivity analysis to test whether EDPS sum score at gestational week 24 had an impact to the significant positive association between EPDS

sum score at 3 months postnatal and child brain ReHo map of the left amygdala region. Results did not meaningfully change in the sensitivity analysis and our conclusions remained the same.

No associations were found with EPDS sum score at 6 months postnatal and child brain ReHo map of left amygdala region with the multiple regression analysis.

Analysis revealed positive association between mothers' EPDS sum score at 12 months postnatal and child brain ReHo map of the left amygdala region when child sex and age at scan were set as covariates ($p < 0.005$, $p = 0.011$ FWE corrected, cluster size (kE) 1152) as well as when maternal pre-pregnancy BMI, maternal SES and ponderal index were controlled in addition ($p < 0.005$, $p = 0.028$ FWE corrected, cluster size (kE) 958). There were no negative associations between child brain ReHo map of the left amygdala region and mothers' EPDS sum scores at 12 months postnatal.

We did not find significant associations in seed-based connectivity analysis of our seed ROI, left / right amygdala, to the rest of the brain, and the EPDS sum scores.

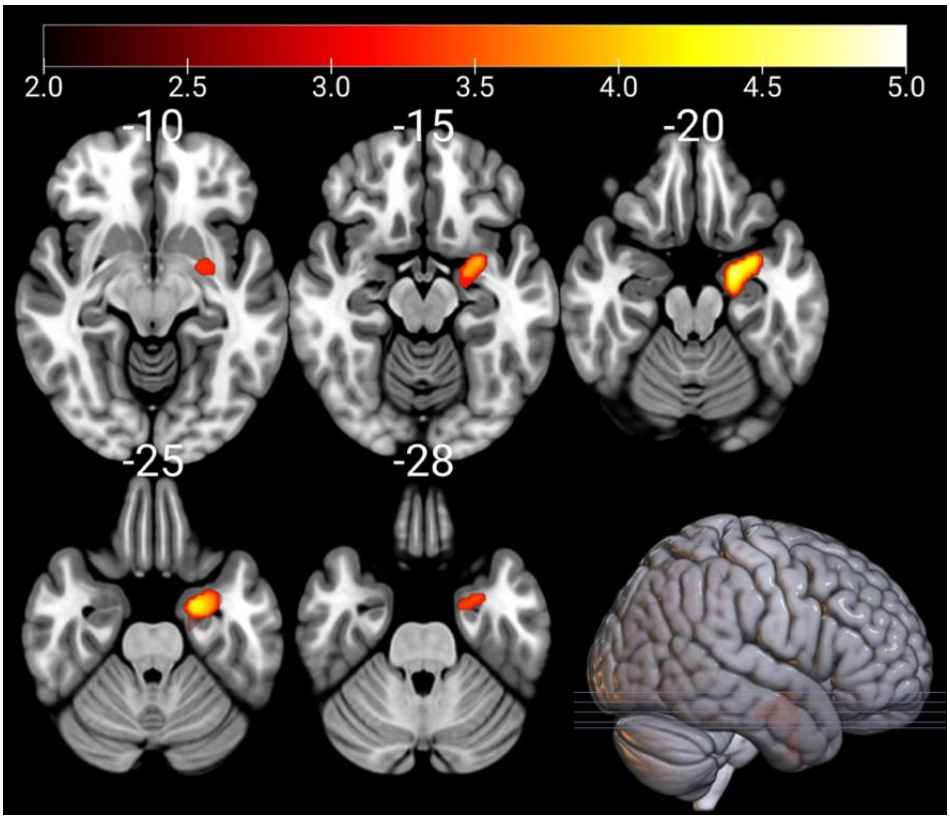

Figure 1. ReHo values associate positively with EPDS sum scores at 3 months postnatal; controlling for child sex and age at scan. The results have been thresholded at $p < 0.001$, FDR multiple comparisons corrected at the cluster level. The color bars depict t-values.

3.2 Region of interest regression analyses for bilateral amygdala

The linear regression model showed association at $p < 0.05$ between left amygdala mean ReHo value and EPDS sum score at gestational week 24 when child sex and age at scan were controlled. This association did not persist when maternal SES, maternal pre-pregnancy BMI, and ponderal index nor when SCL-90 sum score at gestational week 24 were controlled for in addition. There were no associations with the mean ReHo value of the right amygdala and EPDS sum score at gestational week 24 with the abovementioned covariates (Supplemental Table 1).

Significant association was found at $p < 0.001$ between mean ReHo value of the left amygdala and EPDS sum score at 3 months postnatal when child sex and age at scan were included as covariates. Same

association was found when maternal SES, maternal pre-pregnancy BMI and ponderal index were controlled in addition. When SCL-90 sum score at 3 months postnatal was additionally set as covariate the association was attenuated $p < 0.05$. Right amygdala mean ReHo value and EPDS sum score at 3 months postnatal had an association at $p < 0.05$ when child sex and age at scan were controlled, and the association remained significant when additionally controlling for maternal SES, maternal pre-pregnancy BMI and ponderal index, but did not remain when SCL-90 sum score at 3 months postnatal was controlled in addition (Supplemental Table 2). Right amygdala mean ReHo value and EPDS sum score at 3 months postnatal had association at $p < 0.05$ when child sex and age at scan were controlled and remained when maternal SES, maternal pre-pregnancy BMI, and ponderal index were controlled in addition.

Left amygdala mean ReHo value and EPDS sum score at 6 months postnatal had an association at $p < 0.01$ when sex and age were controlled. The same association was found when maternal SES, maternal pre-pregnancy BMI and ponderal index were controlled in addition (Supplemental Table 3). There were no associations with right amygdala mean ReHo value and EPDS sum score at 6 months.

Associations between left amygdala mean ReHo value and EPDS sum score at 12 months postnatal were observed at $p < 0.001$ when child sex and age at scan were controlled. This association did not persist when maternal SES, maternal pre-pregnancy BMI and ponderal index were controlled in addition, $p < 0.01$. No associations between right amygdala mean ReHo values and EPDS sum score at 12 months postnatal were found (Supplemental Table 4).

Lastly, when EPDS sum score at 6 months postnatal, child sex, age at scan, maternal SES, and ponderal index were controlled, we found association at $p < 0.05$ between left amygdala ReHo and maternal pre-

pregnancy BMI and remained when SCL-90 sum score at 6 months postnatal was controlled in addition (Supplemental Table 3).

Summary of all statistically significant results of the linear regression analyses for bilateral amygdala mean ReHo values are shown in Table 2.

Table 2. Summary of the statistically significant results of the regression analyses for bilateral amygdala mean ReHo values.

Relation	**Controlled covariates**	***β***	***p***
Left Amygdala ReHo and EPDS sum score at GA 24	Child sex, and age at scan	0.25	< 0.05
Left Amygdala ReHo and EPDS sum score at 3 mo.	Child sex, and age at scan	0.48	< 0.001
Left Amygdala ReHo and EPDS sum score at 3 mo.	Child sex, age at scan, maternal SES, maternal pre-pregnancy BMI, and ponderal index	0.47	< 0.001
Left Amygdala ReHo and EPDS sum score at 3 mo.	Child sex, age at scan, maternal SES, maternal pre-pregnancy BMI, ponderal index, and SCL-90 sum score at 3 mo.	0.34	< 0.05
Right Amygdala ReHo and EPDS sum score at 3 mo.	Child sex, and age at scan	0.28	< 0.05
Right Amygdala ReHo and EPDS sum score at 3 mo.	Child sex, age at scan, maternal SES, maternal pre-pregnancy BMI, and ponderal index	0.29	< 0.05
Left Amygdala ReHo and EPDS sum score at 6 mo.	Child sex, and age at scan	0.38	< 0.01
Left Amygdala ReHo and EPDS sum score at 6 mo.	Child sex, age at scan, maternal SES, maternal pre-pregnancy BMI, and ponderal index	0.37	< 0.01
Left Amygdala ReHo and EPDS sum score at 12 mo.	Child sex, and age at scan	0.42	< 0.001
Left Amygdala ReHo and EPDS sum score at 12 mo.	Child sex, age at scan, maternal SES, maternal pre-pregnancy BMI, and ponderal index	0.39	< 0.01
Left Amygdala ReHo and maternal pre-pregnancy BMI	Child sex, age at scan, maternal SES, ponderal index, and EPDS sum score at 6 mo.	-0.25	< 0.05
Left Amygdala ReHo and maternal pre-pregnancy BMI	Child sex, age at scan, maternal SES, ponderal index, EPDS sum score at 6 mo., and SCL-90 sum score at 6 mo.	-0.25	< 0.05

ReHo, regional homogeneity; EPDS, Edinburgh Postnatal Depression Scale; GA, gestational age; SES, socioeconomic status; BMI, body mass index; SCL-90, Symptom Checklist 90.

4. Discussion

In this study, we investigated whether maternal perinatal depressive symptoms associate with child's bilateral amygdala ReHo and seed-based functional connectivity. The voxel-wise analyses of ReHo implicated that the left amygdala has a strong positive association to EPDS sum scores obtained 3 months postnatally, and similar associations were detected for EPDS sum scores at 6 and 12 months postnatal albeit with smaller effect sizes.

Our study showed that perinatal maternal depressive symptoms were associated with heightened ReHo, i.e. heightened local functional activity, in the offspring's left amygdala region. Seed-based connectivity analysis did not reveal any significant connections from the left amygdala to the rest of the brain. ROI analyses of ReHo values were used in linear regression analysis which showed a significant positive association between maternal depressive symptoms at three months postnatal and with later time points with generally decreasing effects size. Association attenuated, but stayed significant, when maternal anxiety symptoms were controlled in addition to evaluating whether the association was specific to depressive symptoms. These findings are intriguing given that the association was relatively strong and particularly located in the left amygdala in the whole brain statistical models. Research of the mechanisms underlying depression have shown that left amygdala hyperactivity increases the risk for depression (Janiri et al., 2020; Li & Wang, 2021; McTeague et al., 2020). Considering the above-mentioned and that our finding suggests that the offspring of mothers experiencing perinatal depressive symptoms have heightened left amygdala activity, this may raise the question of intergenerational transmission of risk for depression and other affective disorders. However, further research on amygdala's contribution to depression and familial pathways of affective disorders should be done.

The effect of postnatal maternal depressive symptoms on child's developing brain mediates via parenting and mother–child interaction (Brummelte & Galea, 2016; Rifkin-Graboi et al., 2015). Infancy and

toddlerhood are crucial times for a child's development of self- and emotion-regulation, cognitive, language and motor skills (Eisenberg et al., 1998; Kolb et al., 2012; Madigan et al., 2019). A key feature of depression is dysfunction of self- and emotion-regulation (Joormann & Gotlib, 2010). Therefore, maternal depressive symptoms may affect the self-regulation and sensitivity of the mother. Sensitive interaction refers to mother's ability to interpret child's physical needs and emotional cues and to response appropriately towards the child (Ainsworth, 1997). Preschool-aged children of mothers experiencing postnatal depression had more internalizing and externalizing behavioural problems, i.e. altered self- and emotion-regulation (Cicchetti et al., 1998; Dawson et al., 2003). Kumpulainen et al. found that postnatal depression was associated negatively with white matter FA in vast areas in 5-year-olds, an effect which was only found in girls (Kumpulainen et al., 2023). Another DTI study found that postnatal depression had negative correlation to offspring's right frontal cortical thickness and the white matter mean diffusivity in that area (Lebel et al., 2016). The literature of postnatal depressive symptoms influence to child amygdalae functionality is sparce. Our results provide preliminary evidence of this relation and suggests that this association should be further investigated.

Findings of this study indicates that particularly offspring's left amygdala functionality is affected by mother's perinatal depressive symptoms. In patients with depression, the left amygdala has been reported to have decreased functional connectivity with the cognitive network, including the bilateral frontal gyri and the left insula, such effect was not observed in the right amygdala (Peng et al., 2020). In a review by Baas et al., the left amygdala appears to be more activated in emotional processing than the right amygdala (Baas et al., 2004). Greater grey matter volume of the left amygdala has been linked to later onset of depression and smaller grey matter volume with prolonged depression (Zavorotnyy et al., 2018). Considering our results and the congruence to these studies this supports the effect of intergenerational transmission of depression.

Previous neuroimaging research on this relation of perinatal, and especially postnatal, maternal depressive symptoms and offspring's brain functionality is sparse. Previous studies have mainly examined the associations of prenatal maternal depressive symptoms with child's brain functionality and controlled the postnatal depressive symptoms effect. However, our findings, in line with Soe et al. (2018), show that postnatal maternal depressive symptoms may also be linked brain functionality. During infancy, children are highly dependent on their caregiver(s), especially in emotional regulation and distress (Kopp, 1989). Maternal depression may reduce engagement and responsiveness towards the child and has been shown to increase offspring's risk for psychopathology later in life (Miguel et al., 2019). The current study focused on maternal symptoms and therefore offers limited information on the underlying mechanism behind the links between caregiving and brain development. However, based on previous literature and our findings it seems that for the benefit of child's healthy brain development it is important to monitor the parental well-being. In the future, further investigation of this effect should be made to understand the mechanisms and to develop potential interventions.

4.1 Limitations

Although our sample size is relatively small, our results are compatible with the few previously done studies investigating this similar effect with fMRI (Qiu et al., 2015; Soe et al., 2018). Nevertheless, studies with larger populations are needed in the future. Also, the children were scanned only at one time point so this effect should be further studied when the children are older to examine whether the amygdala functional changes stay similar, or are they related to further alterations in amygdala functional networks. The background/ethnicity of this study's population was restricted to Turku region of the Southwest Finland Hospital District and the Åland Islands and therefore it is needed to further study this association

in other populations. Regarding the limitations of fMRI acquisition, the use of a passive viewing paradigm to reduce head motion (Finn & Bandettini, 2021; Vanderwal et al., 2019) and the presence of the parent in the imaging room may have affected the measured fMRI signal. The EPDS and SCL-90 scores are self-reported measures and majority of the participating mothers did not have clinically meaningful or severe symptoms of perinatal depression. Child's neurodevelopment is rapid during the first years of life and the time gap between maternal depressive symptom assessment and child imaging was 4–5 years. It is not possible control all measures and events that influenced the children during the gestation and ages 0–5 years. Hence there is uncertainty how much solely the maternal pre- and postnatal depressive symptoms affect brain development at 5 years of age.

5. Conclusions

In conclusion, we found that maternal perinatal depressive symptoms were associated with heightened local functional connectivity of the left amygdala in 5-year-olds. We did not find associations in the patterns of the left amygdala connectivity to the rest of the brain. These findings suggest that maternal depressive symptoms during pregnancy and soon after giving birth may influence child brain functionality related to emotional regulation in fundamental ways. Left amygdala hyperreactivity is known to be associated with clinical depression and these results offer a possible pathway of intergenerational transmission of depression that should be further explored in future studies. Our results provide preliminary indication that maternal mental health during pregnancy and especially soon after birth may influence on offspring's neurodevelopment.

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Author contributions

- Elena Vartiainen, performed seed-based connectivity pre-processing, performed the statistical models and lead the writing of the manuscript.
- Anni Copeland, collected the MRI data, fMRI data quality control and pre-processing, performed the statistical models, wrote the initial draft of manuscript and supervised Elena Vartiainen.
- Elmo P. Pulli collected the MRI data and participated in the initial draft of manuscript, supervised Elena Vartiainen.
- Venla Kumpulainen, collected the MRI data.
- Eero Silver, collected the MRI data.
- Olli Rajasilta, supported the data preprocessing and analyses.
- Ashmeet Jolly, participated in the initial draft of the manuscript.
- Silja Luotonen, participated in the initial draft of the manuscript.
- Hilyatushalihah K. Audah, participated in the initial draft of the manuscript.
- Niloofar Hashempour, participated in the initial draft of the manuscript.
- Wajiha Bano, participated in the initial draft of the manuscript.
- Ilkka Suuronen, participated in the initial draft of the manuscript.
- Ekaterina Saukko, collected the MRI data.
- Suvi Häkkinen, designed the data processing pipelines.
- Hasse Karlsson, conceptualized the study and build the infrastructure of the FinnBrain Birth Cohort
- Linnea Karlsson, conceptualized the study and build the infrastructure of the FinnBrain Birth Cohort.

- Jetro J. Tuulari conceptualized the study, planned, and funded the measurements, designed the data processing pipelines, supervised Elena Vartiainen and Anni Copeland.
- All co-authors participated in editing the manuscript and accepted it in its final form.

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