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Prenatal and Postnatal Maternal Depressive Symptoms Are Associated With White Matter Integrity in 5-Year-Olds in a Sex-Specific Manner

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ABSTRACT

BACKGROUND: Prenatal and postnatal maternal psychological distress predicts various detrimental consequences on social, behavioral, and cognitive development of offspring, especially in girls. Maturation of white matter (WM) continues from prenatal development into adulthood and is thus susceptible to exposures both before and after birth.

METHODS: WM microstructural features of 130 children (mean age, 5.36 years; range, 5.04–5.79 years; 63 girls) and their association with maternal prenatal and postnatal depressive and anxiety symptoms were investigated with diffusion tensor imaging, tract-based spatial statistics, and regression analyses. Maternal questionnaires were collected during first, second, and third trimesters and at 3, 6, and 12 months postpartum with the Edinburgh Postnatal Depression Scale (EPDS) for depressive symptoms and Symptom Checklist-90 for general anxiety. Covariates included child's sex; child's age; maternal prepregnancy body mass index; maternal age; socioeconomic status; and exposures to smoking, selective serotonin reuptake inhibitors, and synthetic glucocorticoids during pregnancy.

RESULTS: Prenatal second-trimester EPDS scores were positively associated with fractional anisotropy in boys ($p < .05$, 5000 permutations) after controlling for EPDS scores 3 months postpartum. In contrast, postpartum EPDS scores at 3 months correlated negatively with fractional anisotropy ($p < .01$, 5000 permutations) in widespread areas only in girls after controlling for prenatal second-trimester EPDS scores. Perinatal anxiety was not associated with WM structure.

CONCLUSIONS: These results suggest that prenatal and postnatal maternal psychological distress is associated with brain WM tract developmental alterations in a sex- and timing-dependent manner. Future studies including behavioral data are required to consolidate associative outcomes for these alterations.

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Prenatal and postnatal exposure to maternal stress is associated with increased risk for emotional, behavioral, cognitive, and executive-function problems in offspring. Estimates of the prevalence of perinatal maternal mental disorders range from 8% to 12% (1–3), identified with clinical diagnostic tools to over 30% of standardized self-report scales of pregnancy-related anxiety (4). As follows, maternal psychological distress forms both a significant and a potentially underdiagnosed early-life stressor for the child. The perinatal period represents a crucial juncture in family dynamics and in adaptation to parenthood. This epoch coincides with a highly plastic period in brain development, with the brain susceptible to environmental influences, and can inflict long-term programming changes in brain structure and function. The effects of prenatal distress on different brain metrics have been studied extensively in recent years (5); however, the postnatal period has received less attention (6,7).

The mechanisms transmitting the effects of prenatal and postnatal environmental factors are different. In utero, fetal programming includes exposure to a stress-activated increase in maternal cortisol levels and autonomic nervous system. Prior studies have detected a correlation between offspring hypothalamic-pituitary-adrenal axis activity and prenatal maternal stress (8), which has been suggested to set the baseline of function of the hypothalamic-pituitary-adrenal axis. The activity of the hypothalamic-pituitary-adrenal axis is positively correlated with depression later in life (9). Additionally, gut microbiome, immune system activation, and stress-induced epigenetic changes (10) mediate the effects of maternal mental health on the offspring.

After birth, the significance of the social environment and parent-infant interaction is frequently emphasized in research settings, i.e., instead of prenatal biological exposures. Maternal postnatal anxiety and depressive symptoms are related to several potentially adverse influences on infant care practices and maternal involvement, for example, through lower mother-child bonding, suggested to partly stem from avoidance behavior and social withdrawal (11). Mothers with

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general anxiety are less responsive to infant vocalization but simultaneously more controlling compared with healthy control mothers (12). Additionally, maternal postpartum depression has been associated with lower sensitivity (13) and less affectionate touching of the infant (14); less smiling and vocal and visual communication (15,16); less enrichment activity in forms of reading, telling stories, and playing (17); and increased risk for deprivation of health-promoting practices such as breastfeeding (18) and visits to preventive health care services (19). Lastly, depressed mothers experience lower self-confidence (20), pay more attention to negative information, and are prone to negative misinterpretations (21), which can be reflected as learned adverse behavioral manners in the child.

Recent neuroimaging studies have provided evidence of neural pathways conveying possible associations between perinatal exposure to maternal mental distress and adverse outcomes in the offspring. Diffusion tensor imaging (DTI) characterizes water diffusion properties and consequently provides estimates of axonal organization and myelination (22). Interpretation of DTI metrics requires certain cautions, but generally increased fractional anisotropy (FA) and decreased mean diffusivity are regarded to reflect higher axonal organization and myelination (and more advanced brain development). In neonates, prenatal exposure to maternal distress has been associated with white matter (WM) integrity in a range of areas (23–27). The antenatal effects are suggested to extend further, as associations between WM structure and prenatal stress are also detected in older children between 2.6 and 7 years of age (6,28–34), and these effects have also been shown to mediate the relationship between prenatal depression and child behavioral symptoms such as externalizing behavior (31). Drawing general conclusions from previous studies is challenging as the age ranges, analysis methods, and types of prenatal distress vary widely; prevalence of postnatal depressive symptoms is not always controlled for (30); and controlling for other confounding factors is partly lacking. [See Table S1 for a review of prior literature and Pulli *et al.* (35) for recommended covariates in brain developmental research.]

The postnatal period provides additional challenges in neurodevelopmental research in the form of various confounding factors and aspects of both supportive caregiving and adverse social interactions, which may both mitigate and exacerbate perinatal effects. Axonal myelination peaks during early postnatal development (36), rendering it an interesting period especially for WM trajectories. Few researchers have studied the relationship between postnatal depressive symptoms and offspring WM microstructure (6,7,33,37,38). There are some inconsistencies in the results, as two studies found no associations with postnatal depression, while one study (38) showed that postnatal depression measured 2 months postpartum was associated with lower FA in 10-year-olds. Further, negative correlation between postpartum depressive symptoms assessed 2 to 3 months postpartum and frontal WM mean diffusivity and radial diffusivity was detected in a population of 2.6- to 5.1-year-old children (7). Lastly, a positive association between maternal depressive symptoms 3 months postpartum and right amygdala FA was detected in 4-year-olds, but only in girls (6). In girls, brain developmental sensitivity to maternal distress has also been observed with other imaging modalities. Perinatal maternal depression was associated with functional connectivity of amygdala in girls (39), and elevated maternal cortisol levels predicted global connectome properties in 6- to 9-year-old girls, which further mediated the association between exposure to cortisol and internalizing symptoms (40).

The microstructure of WM differs between girls and boys during development. Generally, increase in WM integrity proceeds earlier in girls, even though the difference levels off during later development (41–48). Reflecting this, we previously observed that girls in the current cohort of 5-year-olds had higher FA values in widespread areas (49). Furthermore, maternal prenatal distress has been shown to induce sexually dimorphic outcomes in the offspring (6,39,40,50–53). While the exact mechanisms have remained unknown, researchers have suggested that sex-specific placental adaptation to stress exposure may affect the consequences of exposure to cortisol (54–56). Accumulating evidence has also suggested that prenatal stress exposure affects the risk for psychopathology in a sex-dependent manner, with, for example, more internalizing symptoms observed in exposed girls (57,58).

To further elucidate the neural features associated with maternal perinatal depression, we gathered data of self-reported depressive and anxiety symptoms from mothers during the prenatal period and the postnatal period up to 12 months after delivery. Subsequently, the microstructural changes of WM were assessed by DTI in offspring at 5 years of age in this study. As stress exposure has been suggested to accelerate brain development, we expected to find more advanced WM development in children exposed to maternal mental distress. We expected to detect sex differences based on prior knowledge of brain developmental trajectories.

METHODS AND MATERIALS

Study Design and Participants

The study population is a part of the FinnBrain Birth Cohort (https://sites.utu.fi/finnbrain/) (59) that was established in 2010 to prospectively study the effects of exposure to early-life stress. The participating families were followed during and after pregnancy, and data including questionnaires and other measurements such as brain magnetic resonance imaging (MRI) of the offspring were gathered. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland and performed in accordance with the Declaration of Helsinki. Both parents of the participating child signed a written informed consent form. Child assent was ensured before neuroimaging visits.

The brain MRI substudy of 5-year-olds included an initial population of 203 families. The participants were healthy, normally developing children. Exclusion criteria were as follows: 1) birth before gestational week 35 (week 32 for children with exposure to synthetic glucocorticoid treatment, resulting in one exception); 2) major developmental disorder; 3) other long-term diagnosis requiring regular follow-up visits in a hospital; 4) sensory abnormalities (including blindness or deafness); 5) use of daily regular medication (asthma inhalers during infections were allowed); and 6) head trauma that had required inpatient care (reported by parents). Additionally, routine MRI contraindications and metallic ear tubes prevented participation in the imaging.

Maternal Questionnaires

Maternal psychological distress was surveyed with self-report questionnaires during pregnancy at 14, 24, and 34 gestational weeks and 3, 6, and 12 months postpartum. The questionnaires included the Edinburgh Postnatal Depression Scale (EPDS) (60) for depressive symptoms and Symptom Checklist-90 (SCL-90) (61,62) (not collected at 12 months postpartum) for overall anxiety. We also formed aggregate variables of the prenatal period with a sum and a mean of all 3 time points.

Study Visits

Preparation for the MRI scans involved a home practice period (preceded by a home visit of a study member to provide detailed information) and a training session immediately before scanning, which also permitted the participating child to become familiar with the study personnel, scanner sounds, and lying still. Imaging was performed with the participants awake. One study member and the parent(s) stayed in the scanner room throughout the imaging. For a more thorough description of the study visits, see our previous studies (63,64).

MRI Data Acquisition

MRI was performed with a 3T MAGNETOM Skyra scanner (20-element head/neck matrix coil) (Siemens Healthineers) at Turku University Hospital. The generalized autocalibrating partially parallel acquisition technique was used. A DTI protocol was applied with a standard twice-refocused spin echo–echo-planar imaging sequence and the following parameters: repetition time/echo time = 9300/87.0 ms, field of view = 208 mm, isotropic voxels with 2.0 × 2.0 × 2.0 mm resolution, b value 1000 s/mm^2, and 96 noncollinear diffusion gradient directions divided into 3 scanning sets (31, 32, and 33 directions) with 9 b0 images. Additionally, structural T1- and T2-weighted images and functional resting-state MRI were obtained.

Image Processing

Data acquisition was successful in 163 children. DTIprep (https://nitrc.org/projects/dtiprep/) (65) with default settings and manual inspection was used for quality control of the volumes. Subsequently, 30 directions were chosen per each participant (66) by maximizing the angular resolution (67). After exclusion of participants with no maternal questionnaire data at second trimester and 3 months postpartum, the final number was 130 children (63 girls). The questionnaire data at time points 6 and 12 months postpartum were missing from 11 participants, and the regressions for those time points were performed with 119 participants.

Preprocessing of quality-controlled data with FSL 6.0 (FMRIB Software Library, University of Oxford, United Kingdom; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) included coregistration and averaging of b0 images (FLIRT), creation of brain mask (BET 1.0.0; settings -R -f 0.3) (68), motion and eddy current correction, and concurrent rotation of the b matrix. The scalar maps were computed with FSL dtifit. Tract-based spatial statistics pipeline of FSL (69) was used to estimate the WM skeleton. See our prior studies (66,67,70) for more detailed description and validation of used pipelines. Tractwise FA values were extracted with coregistration to the JHU-ICBM-DTI atlas (71). The background of the FinnBrain Birth Cohort, recruitment, study visits, data preprocessing, and quality control protocol are described in more detail in Supplemental Methods, with Figure S1 showing the workflow of the study and Table S2 showing the mean framewise head displacement.

Statistical Analyses

To assess potential selection bias, we compared included (n = 130) and excluded (n = 73) participants with independent samples t tests for continuous variables and analysis of variance for categorical variables (Table S3). Voxelwise analysis of association between FA and maternal psychological distress evaluated by questionnaire scores (EPDS and SCL-90) was performed with the general linear model (using FSL randomise). The analyses, conducted with all participants and for girls and boys separately, were performed with 5000 permutations, and multiple comparison correction with threshold-free cluster enhancement with two-dimensional optimization was used.

Participants' age at scan and sex were used as confounding factors in all analyses. Additionally, the following covariates were considered: maternal age at childbirth; maternal prepregnancy body mass index (BMI); maternal socioeconomic status (SES) (59) (educational level, categorized into 2 classes, low-middle and high); participant's ponderal index; prenatal exposures to smoking, selective serotonin/serotonin-noradrenaline reuptake inhibitors, and synthetic glucocorticoids (exposures were self-reported); and duration of full breastfeeding. To control for early-life stress, we used the following adverse life events during the preceding year and an aggregate variable of occurrence of any of these as covariates: parental divorce, parental severe disease or death, and parental unemployment. The data were collected from both parents, and we recorded a "yes" answer if either parent had responded. The categorical variables were dummy coded for suitability to regression analysis. None of the other covariates except age and sex showed significant correlations with FA. Maternal BMI and child's ponderal index showed correlation (β = 0.30, $p < .001$), and we excluded ponderal index from a regression model to avoid possible multicollinearity. No multicollinearity between other covariates was detected (variance inflation factor for all variables between 1.0 and 1.8). Missing covariate data were maternal BMI (n = 1, 0.7%), SES (n = 5, 3.8%), selective serotonin/serotonin-noradrenaline reuptake inhibitor exposure (n = 8, 6.2%), duration of full breastfeeding (n = 5, 3.8%), and information on adverse life events during preceding year (n = 5, 3.8%). The data points were missing completely at random (Little's test). The missing values were imputed with a regression method, and correlation of variables was calculated with IBM SPSS version 27.0.1.0 (IBM Corp.). The interactions between sex and maternal depressive symptoms were examined by forming interaction variables (sex × second-trimester EPDS score and sex × 3-month EPDS score).

Spearman and partial correlations (with same covariates as in multiple regression) between separate WM tract mean FA values and EPDS/SCL-90 scores were calculated with IBM SPSS. False discovery rate (72) correction for multiple comparison was applied post hoc by tract. Statistical differences between girls and boys were estimated with independent

samples *t* test (two-tailed) for continuous variables and analysis of variance for categorical variables. The sample size in the current study was not sufficient for modeling trajectories of maternal symptoms. We also considered modeling the maternal distress exposure by cumulative scores but opted for performing the analyses over individual time points because it gives the most detailed and reliable account of the associations. A correlation matrix reporting correlation of maternal distress scores for the time points is provided in Table S4.

RESULTS

Demographics

The study included 130 children (mean age, 5.36 years; range, 5.04–5.79 years; 63 girls). The participants in the imaged group were younger (mean [SD] = 5.37 [0.11] years) compared with the participants who were not imaged (5.45 [0.15], $p < .001$). Statistically significant differences between included ($n = 130$) and excluded ($n = 73$) participants were not observed in other considered variables (Table S3). Demographic data and group differences between girls and boys are presented in Table 1. There were no significant differences in confounding variables between girls and boys (for second-trimester EPDS score, mean score was higher in girls, 5.59 vs. 4.02 in boys, $p = .037$).

Second-trimester and 3-month postpartum EPDS and SCL-90 scores correlated significantly (Spearman's $r = 0.54$, $p < .001$ and $r = 0.59$, $p < .001$, respectively) (Table S4). Second-trimester EPDS and SCL-90 scores showed higher correlation compared with correlation between prenatal and postnatal EPDS ($r = 0.68$, $p < .001$ and $r = 0.54$, $p < .001$).

Association Between WM and Maternal Psychological Distress

Prenatal Maternal Distress. Prenatal exposure to maternal depressive symptoms in the second trimester was positively correlated with FA values in multiple areas ($p < .05$, 5000 permutations) in boys after controlling for postnatal EPDS score at 3 months, child's age, maternal age and BMI, SES, breastfeeding, stressful life events during previous year, and exposure to smoking, selective serotonin/serotonin-noradrenaline reuptake inhibitors, and glucocorticoids (Figure 1; Table S5 shows *p* values from regression analyses

Table 1. Demographics and Group Differences Between Girls and Boys

				Differences by Independent Sample *t* Test	
	Girls	Boys	All Participants	*t*	*p* Value
Age at Scan, Years	5.34 (0.12) [5.04–5.73]	5.37 (0.12) [5.04–5.79]	5.36 (0.12) [5.04–5.79]	0.068	.95
Gestational Age, Weeks	39.9 (1.39) [35.1–42.3]	39.6 (1.69) [33.9–42.3]	39.8 (1.55) [33.9–42.3]	1.13	.26
Ponderal Index	14.1 (1.32) [11.0–18.0]	14.1 (1.27) [12.0–18.0]	14.1 (1.29) [11.0–18.0]	−0.16	.87
Maternal Age, Years	30.1 (4.40) [22.0–41.0]	31.1 (5.0) [18.0–41.0]	30.6 (4.72) [18.0–41.0]	−1.01	.31
Maternal Prepregnancy BMI	24.1 (4.00) [17.5–36.7]	24.2 (4.26) [18.1–36.1]	24.2 (4.12) [17.5–36.7]	−0.20	.84
Duration of Full Breastfeeding, Months	4.03 (2.00) [0–7]	3.63 (2.23) [0–8]	3.84 (2.14) [0–8]	−1.50	.13
EPDS Score					
First trimester	4.94 (4.31) [0–22]	4.11 (3.19) [0–13]	4.53 (3.80) [0–13]	1.20	.23
Second trimester	5.59 (4.74) [0–21]	4.02 (3.61) [0–13]	4.77 (4.24) [0–21]	2.11	.037
Third trimester	5.29 (4.92) [0–19]	4.34 (3.94) [0–17]	4.81 (4.45) [0–19]	1.20	.23
3 months postpartum	4.03 (3.96) [0–19]	4.29 (3.72) [0–15]	4.16 (3.83) [0–19]	−0.72	.47
6 months postpartum	4.9 (5.04) [0–19]	4.9 (4.68) [0–19]	4.91 (4.83) [0–22]	−0.018	.99
12 months postpartum	4.3 (4.30) [0–21]	4.5 (4.07) [0–18]	4.4 (4.26) [0–21]	−0.28	.78
SCL-90 Score					
First trimester	3.03 (3.51) [0–17]	2.66 (3.22) [0–15]	2.85 (3.36) [0–17]	0.62	.54
Second trimester	3.66 (3.50) [0–14]	3.53 (4.14) [0–19]	3.59 (3.83) [0–19]	0.20	.84
Third trimester	3.03 (3.72) [0–19]	3.12 (3.66) [0–15]	3.08 (3.68) [0–19]	−0.14	.89
3 months postpartum	2.33 (3.29) [0–15]	2.66 (3.64) [0–17]	2.52 (3.46) [0–17]	−0.75	.45
6 months postpartum	3.0 (4.93) [0–24]	3.1 (3.80) [0–19]	3.0 (4.36) [0–24]	−0.14	.89
				Differences by ANOVA	
				F	*p* Value
SES, Low-Middle/High/NA	34/28/1	29/34/4	63/62/5	0.51	.48
Exposures During Pregnancy, Yes/No/NA					
Smoking	3/60/0	4/63/0	7/123/0	0.33	.57
SSRI/SNRI	2/59/2	2/59/6	4/118/8	0.17	.68
Glucocorticoid	5/58/0	5/62/0	10/120/0	0.030	.86

Values are mean (SD) [range] or *n*/*n*/*n*.

ANOVA, analysis of variance; BMI, body mass index; EPDS, Edinburgh Postnatal Depression Scale; NA, not available; SCL-90, Symptom Checklist-90; SES, socioeconomic status; SSRI/SNRI, selective serotonin/serotonin-noradrenaline reuptake inhibitor.

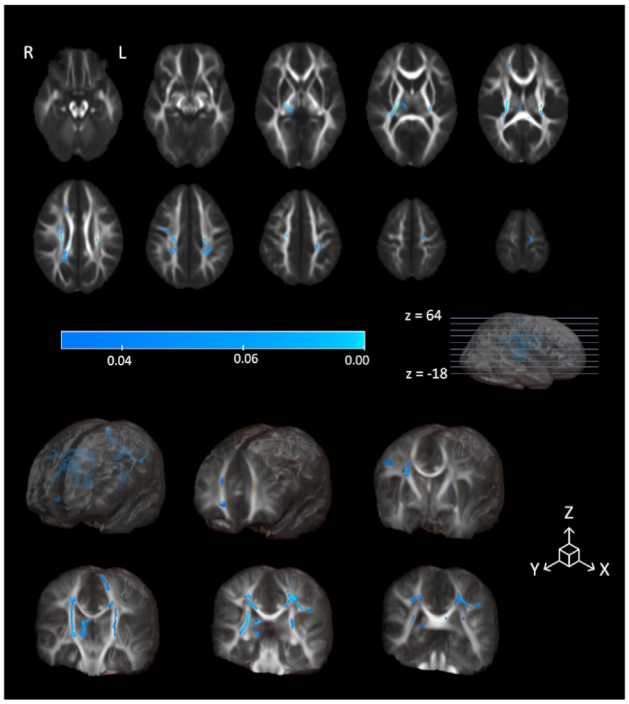

Figure 1. Statistically significant positive associations between fractional anisotropy values in boys and prenatal maternal depressive symptoms according to Edinburgh Postnatal Depression Scale score during the second trimester ($p < .05$, 5000 permutations, threshold-free cluster enhancement applied as multiple comparison correction). L, left; R, right.

with EPDS and SCL-90 scores at separate time points and separately for all participants, boys, and girls). The association with second-trimester EPDS score was detected only in boys. There were no statistically significant correlations between FA in boys and first- or third-trimester EPDS scores ($p = .14$ and $p = .18$) after controlling for postpartum scores and none between sum ($p = .29$) or mean ($p = .25$) of prenatal EPDS scores and FA. The association with second-trimester SCL-90 scores did not remain significant after controlling for covariates ($p = .10$ for all participants, age as a covariate, and $p = .61$ after controlling for 3-month SCL-90 score). No statistically significant associations between prenatal SCL-90 score and FA were found when girls and boys were inspected separately (Table S5). Interaction term of sex by second-trimester EPDS score showed more positive association with FA in boys ($p < .05$) after controlling for all covariates (Figure S2).

Postnatal Maternal Distress. After controlling for considered confounding variables and EPDS score at second trimester, 3-month postpartum EPDS scores showed significant negative correlation with FA in multiple WM clusters in girls ($p < .01$, 5000 permutations) (Figure 2) including clusters in corpus callosum, right corona radiata, right uncinate fasciculus, right internal capsule, and bilateral posterior thalamic radiations. The negative association with 3-month EPDS score was similar with categorizing depressive symptoms into 2 classes (high/low [≥10/<10]; $p < .04$, 5000 permutations) (Figure S3), but was not repeated with cutoff value ≥11 ($p = .09$). No regions with positive correlations were detected. Similar statistically significant correlations were not detected in boys ($p = .75$), and the correlations did not reach significance in the group of all participants ($p = .06$). The correlation between child's FA at 5 years of age and maternal EPDS score was also examined at later time points, 6 and 12 months postpartum. The results did not remain significant (Table S5).

The SCL-90 scores at 3 months postpartum showed a trend toward negative correlation with FA values in girls ($p = .08$); however, the result was not statistically significant after controlling for all covariates ($p = 0.29$) (Table S5; Figure S4). No statistically significant correlations between 3- or 6-month SCL-90 scores and FA were observed in boys or in all participants.

The partial correlations and Spearman correlations between whole WM tract FA values and EPDS questionnaire scores are provided in Table S6. The correlations with EPDS scores and whole-tract mean FA did not reach statistical significance after false discovery rate correction. However, the results show the maternal depressive symptoms × sex interaction with negative correlations detected in girls, but mainly positive correlations in boys. Statistically significant sex differences were detected in multiple tracts, with higher FA values in girls (Table S7). Scatter plots of the associations separately in girls and boys for chosen regions of interest are provided in Figure S5. Interaction term of sex by 3-month EPDS score showed more negative association with FA in girls ($p = .04$), but the association did not

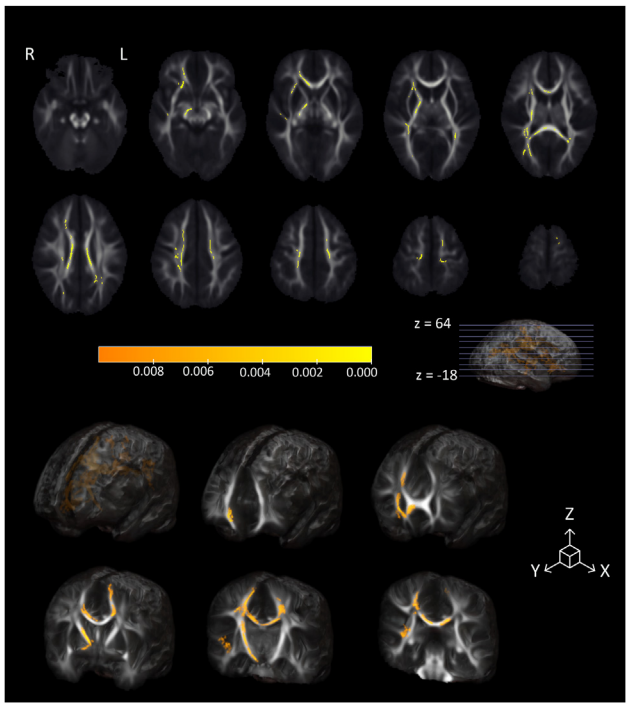

Figure 2. Statistically significant negative associations between fractional anisotropy values in girls and postnatal maternal depressive symptoms according to Edinburgh Postnatal Depression Scale score at 3 months postpartum ($p < .01$, 5000 permutations, threshold-free cluster enhancement applied as multiple comparison correction). L, left; R, right.

remain significant after controlling for all covariates (Figure S6). The correlations between 3-, 6-, and 12-month EPDS scores and mean FA in girls in selected WM tracts are shown in Table 2.

DISCUSSION

In the present study, we report a significant and widespread negative association between maternal postpartum depressive symptoms and WM microstructure in girls. Furthermore, we found that maternal prenatal depressive symptoms during midpregnancy predicted higher FA values in boys. Prior investigations have shown postnatal early-life adversities to inflict long-term effects, with exposed children showing adverse outcomes in multiple areas. Only a few studies have previously considered the relationship between maternal postnatal distress and changes in WM microstructure, even though the early postnatal period is known to be sensitive particularly regarding WM development. Our findings provide important new information about the timing- and sex-specific features of neural correlates that may participate in transmitting the effects of perinatal maternal depression on emotional, behavioral, and cognitive outcomes of offspring described widely in recent research literature.

According to our results, there was a positive association between maternal prenatal depressive symptoms and FA in 5-year-old boys, but the finding was limited to only the second trimester. Midpregnancy has been highlighted as a critical period of WM plasticity, during which the axons are formed and organized to long-distance bundles, and myelination begins (36). Maternal mental distress especially during that period has been associated with offspring brain morphology in multiple previous studies (6,7,51,52,73–75). In our earlier study of neonatal brain correlates of exposure to maternal mental distress (52), second-trimester maternal combined anxiety and depressive score was associated with reduced left amygdala volume only in infant boys. Thus, aligned with previous findings, we suggest that midpregnancy is a sensitive period during which exposure to maternal mental distress may have long-term impacts on WM structure. Further, we observed the prenatal association only in boys. Growing evidence has suggested intrauterine programming effects, such as cortisol levels, to be associated with different outcomes in boys and girls (40,50,74).

We observed that the associations between postnatal depressive symptoms and offspring WM structure were strongest during the first months after birth. This finding of a sensitive period is in line with prior literature. First, even though myelination begins during the prenatal period, it proceeds fastest during the first year of life (36). More precisely, myelination of the anterior limb of internal capsule, fornix, cingulum, and other association tracts begins during the first 1 to 3 months postpartum and renders it an extremely sensitive period (36,76). Second, significant relationships between maternal postpartum psychological distress and offspring WM microstructure have been successfully demonstrated only in previous studies evaluating the immediate 2 to 3 months after birth (6,7,38). Conversely, in studies by Borchers *et al.* (37) and El Marroun *et al.* (33), maternal mental health was evaluated at the child's age of 6 months and 3 years, and no associations with WM structure were detected. Third, the period around childbirth and transition to parenthood results in changes, for example, in lifestyle, sleeping patterns, couple relationship, and identity (77), and has been shown to increase the vulnerability to parental psychological distress (78). Thus, the peaking of postpartum maternal mental distress coincides with the highly plastic period of brain development, which may together have long-term effects on WM trajectories. Duration, timing, and cumulative maternal distress may have implications on outcomes and warrant further research.

Our results showed that the sensitivity for maternal perinatal depressive symptoms presents a sex-specific pattern. We observed WM in girls to be more sensitive to early postnatal exposure to maternal depressive symptoms, while in boys, prenatal depressive symptoms predicted higher FA values. Prenatal exposure to different types of maternal stress is associated with vulnerability to internalizing symptoms, greater distress in response to limitations, decreased smiling, lower soothability (79), poorer problem-solving skills during childhood (80), increased negative affectivity (81), and risk for depression (82), particularly in girls. One potential explanation for sex-specific consequences of early adversity involves the vulnerability-viability hypothesis (83,84). Accumulating evidence suggests that in utero, females are more responsive to stress signals and more adaptable according to environmental requirements, which provides an advantage in surviving but may also increase vulnerability to later adversities (55,85). Male fetuses, in contrast, show less adjustability, and environmental challenges may consequently threaten their survival, which

Table 2. Correlations Between EPDS Scores at 3, 6, and 12 Months Postpartum and White Matter Tract FA Values in Selected Tracts in Girls

		EPDS Score		
FA	Correlation	3 Months	6 Months	12 Months
GCC	R^2	0.038	5.1×10^{-4}	5.3×10^{-4}
	ρ	−0.25	−0.054	−0.10
	p	.052	.70	.45
Right SFOF	R^2	0.075	0.007	0.007
	ρ	−0.35	−0.18	−0.24
	p	.005	.20	.081
Right PLIC	R^2	0.055	0.025	0.10
	ρ	−0.24	−0.17	−0.29
	p	.057	.22	.038
Right ALIC	R^2	0.022	0.029	0.007
	ρ	−0.12	−0.15	−0.10
	p	.36	.27	.49
Right ACR	R^2	0.078	5.8×10^{-4}	4.0×10^{-4}
	ρ	−0.18	−0.060	0.040
	p	.17	.66	.77
Right SCR	R^2	0.16	0.050	8.3×10^{-4}
	ρ	−0.35	−0.24	0.004
	p	.005	.082	.93

ACR, anterior corona radiata; ALIC, anterior limb of internal capsule; EPDS, Edinburgh Postnatal Depression Scale; FA, fractional anisotropy; GCC, genu of corpus callosum; PLIC, posterior limb of internal capsule; SCR, superior corona radiata; SFOF, superior fronto-occipital fasciculus.

leads to creation of more stress-resistant individuals (i.e., survival of the fittest). There is some evidence in the previous neuroimaging literature that early adversity may indeed accelerate WM maturation in boys. In two studies detecting negative consequences in girls exposed to maternal stress, exposed boys had reduced risk for depression (82) and attenuated negative emotionality (81). Additionally, hormonal levels of gonadotropins vary between girls and boys in utero and during the first months after birth due to "minipuberty" and are suggested to affect sex specificity of cognitive and behavioral developmental features (86).

There are some inconsistencies regarding the direction of changes in FA associated with early-life stress. According to one hypothesis, early-life adversity accelerates the development that decreases brain plasticity and subsequently makes brain function less adaptable to different environmental requirements (87). One prior study observed reduction in FA values in girls and conversely increased FA in boys exposed to maternal distress during pregnancy (23), showing a similar trend of sex-specific associations in infants as we detected in 5-year-olds. Decrease in FA values has also been associated with exposure to early maltreatment (88,89) and social deprivation (90) during childhood. In the few prior studies resolving the influence of exposure to postpartum maternal depression on WM structure, decrease of FA in forceps minor, forceps major, and uncinate of 10-year-olds (38), but increase of FA in amygdala of 4-year-olds, was observed (6). Considering the aforementioned, early-life stress that is present postpartum appears to relate to reduction in WM integrity during later childhood, as was also detected in girls exposed to maternal postnatal depressive symptoms in our study population. Further, prenatal exposure to depressive symptoms predicted higher FA values in boys, which might relate to accelerated WM development and may, however, culminate later as less adaptive brain microstructure and thus negative outcomes.

While consequences of postpartum depression on WM structure have been rather understudied, multiple studies have indicated repeatable negative outcomes in social and behavioral contexts regarding exposure to maternal psychological distress. Longitudinal studies have observed children of depressed mothers to exhibit worse cognitive, neuropsychological, social, and emotional skills across childhood and up to adolescence (91–93). Postpartum psychological distress has been found to increase the tendency of more difficult temperament in infants (94,95) and to be associated with less social engagement (96,97), accelerated growth in infant fear reactivity between 4 and 12 months (98), more fearful behavior (96), and less mature regulatory behavior (97). During later childhood, behavioral problems (99,100) emerge more often in children exposed to parental stress with a sex-specific pattern: girls show more internalizing symptoms such as depression and anxiety (101), while boys seem to be more prone to externalizing disorders such as antisocial personality and conduct disorders (100,102). Lastly, maternal postnatal distress has been shown to predict increased problems in executive functions (only in girls) (103) and deteriorated fine and gross motor skills (104).

Many previous studies have focused on limbic and frontal structures (6,24,25,29,31,105), but maternal mental distress also predicts consequences affecting a variety of social, behavioral, cognitive, and motor functions. We examined associations between maternal psychological distress and WM microstructure prospectively across all tracts and observed maternal depressive symptoms to be associated with WM integrity in widespread areas. Previously observed associations between exposure to early stress and WM structure especially in emotion-processing circuits (23,24,25,27) give a plausible explanation for emotional changes, but purposeful concentration on limbic tracts with a priori assumptions (6,24,25,29,31,105) may lead to missing other possible changes.

In previous studies, WM changes across multiple regions have been associated with emergence of depression, anxiety, antisocial behavior, and problems with executive functions (Table S9). Abnormal structure of the uncinate has been associated with, e.g., anxiety (106–111), mood disorders (112–118), and antisocial behavior (119–124), and changes are also detected in children exposed to early adversity (90,125). Reduced FA is generally associated with internalizing symptoms (Table S9) and detected especially in girls (118), while increase of FA is related to better inhibitory abilities (126–128), working memory (129–132), reaction speed (131,133), and verbal performance (134), but also to conduct disorder (120,135) and antisocial personality (121,136), which are conversely more frequent in boys. Our results partly parallel these outcomes, as reduced FA in girls and increased FA in boys are observed after exposure to maternal depression.

In addition to the applied covariates, various factors, including parental interaction, responsiveness, and sensitivity, parental psychiatric history including effect of genetic predispositions, and environmental factors such as diet, can influence the development of WM, but have not been considered within the scope of the current study. The postnatal environment has been observed to modify the association between prenatal stress and brain development (137,138). Interventions during the postnatal period, including a supportive and enriched environment, age-appropriate cognitive training, linguistic stimulation, higher maternal sensitivity, and secure attachment, may reverse the consequences of prenatal adversity. More specifically, high parental bonding was observed to reverse the association between lower birth weight and smaller hippocampus (139), and maternal prenatal anxiety was observed to be associated with child externalizing symptoms only when maternal sensitivity was low (140). Further, higher SES has been observed to protect neurocognitive development in children born preterm or with lower birth weight (141–144). The influence of these supportive factors on WM development is to be addressed in future studies.

Several methodological and study technique questions, such as defining the accurate timing of exposure to depressive/anxiety symptoms and their comorbidity (145), affect the interpretation of the results. First, previous evidence suggests that depression and anxiety have unique effects on child development and should be studied separately (146,147). Additionally, psychological distress evaluated by diagnosis of depression/anxiety disorder may not correspond to current perceived stress—which is an advantage with self-report questionnaires that measure subjective experiences. Furthermore, dropout rate of depressed mothers is higher compared with healthy control mothers (107), which may distort the

prevalence of depressive symptoms. Second, confounding factors complicate resolving the effects of mental distress. The prevalence of several confounding factors, such as use of antidepressants, smoking, substance use (148), overweight, and educational level, is associated with depression hindering separation of their individual effects. Effects of positive and supportive environmental factors are difficult to specify, but simultaneously practices such as childcare have been shown to mitigate effects of parental depression on offspring outcomes (99). Third, child behavioral problems may induce maternal stress through difficulties in mother-child bonding (149) and thus induce reverse causality. Additionally, some study populations consist of children with wide age ranges (7,33); as the development of DTI metrics is fast during childhood, distribution of DTI scalar values in those populations is wider, decreasing power of statistical tests, and associations with timing-specific emergence may be missed.

The current study has limitations, including the moderate sample size and inclusion of only Finnish participants. While detecting associations, we cannot speak of causal effects, as other variables, such as genetic influences, may also convey apparent relationships between maternal well-being and offspring WM. Lastly, with a cross-sectional study setting, the exact timing and permanence of the effects remain elusive.

In conclusion, we showed that maternal perinatal depressive symptoms were associated with offspring WM integrity in multiple areas in a timing- and sex-specific manner. We suggest that WM development in girls is more prone to the effects of postpartum depressive symptoms, and we plan to address this association in future studies investigating the behavioral and emotional outcomes of exposure to maternal mental distress. In boys, exposure to prenatal stress in the form of depressive symptoms seems to accelerate the maturation of WM tracts. According to the stress-acceleration hypothesis, this may prepare the child for environmental stress after birth, but simultaneously lead to decreased WM plasticity. These observed changes may play a role in mediating the well-acknowledged associations of maternal mental distress with behavioral and social problems and increased risk for mental illnesses in offspring. However, considering the complex interaction between brain development and environmental and genetic factors, larger samples with longitudinal and multimodal research approaches are required to further investigate the causality between the observed associations.

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VK performed data collection (5-year-olds), data preprocessing, and formal analyses and wrote the manuscript draft. EPP, AC, and ESi performed data collection and wrote the manuscript. HM and JDL designed the data processing pipeline and wrote the manuscript. E-LK wrote the manuscript. ESa assisted with MRI sessions and wrote the manuscript. LK and HK established the cohort and built the infrastructure for carrying out the study. JJT was responsible for study conception, funding acquisition, supervision of VK, and building the preprocessing pipelines.

The Finnish law and ethical permissions do not allow open sharing of the data used in this study, but data access is possible via formal material transfer agreements. Investigators who wish to access the data are encouraged to contact the principal investigator of the FinnBrain Birth Cohort Study, HK, at hasse.karlsson@utu.fi.

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