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Prenatal maternal depressive symptoms are associated with smaller amygdalar volumes of four-year-old children

Acosta H[a,i,*], Tuulari JJ[a,b,c,j], Scheinin NM[a], Hashempour N[a], Rajasilta O[a], Lavonius TI[a], Pelto J[a], Saunavaara V[d,h], Parkkola R[e], Lähdesmäki T[f], Karlsson L[a,g], Karlsson H[a,b,g]

[a] The FinnBrain Birth Cohort Study, Turku Brain and Mind Center, Department of Clinical Medicine, University of Turku, Turku, Finland
[b] Department of Psychiatry, University of Turku and Turku University Hospital, Turku, Finland
[c] Turku Collegium for Science and Medicine, University of Turku, Turku, Finland
[d] Department of Medical Physics, Turku University Hospital, Turku, Finland
[e] Department of Radiology, University of Turku and Turku University Hospital, Turku, Finland
[f] Department of Pediatric Neurology, University of Turku and Turku University Hospital, Turku, Finland
[g] Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland
[h] Turku PET Center, University of Turku and Turku University Hospital, Turku, Finland
[i] Department of Psychiatry and Psychotherapy, Philipps University of Marburg, Rudolf-Bultmann-St. 8, 35039, Marburg, Germany
[j] Department of Psychiatry, University of Oxford, Oxford, UK

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ABSTRACT

Prenatal maternal depressive symptoms are related to an increased offspring susceptibility to psychiatric disorders over the life course. Alterations in fetal brain development might partly mediate this association. The relation of prenatal depressive symptoms with child's amygdalar volumes is still underexplored, and this study aimed to address this gap. We explored the association of prenatal maternal depressive symptoms with amygdalar volumes in 28 4-year-old children (14 female). Amygdalar volumes were assessed using the volBrain pipeline and manual segmentation. Prenatal depressive symptoms were self-reported by mothers at gestational weeks 14, 24 and 34 (Edinburgh Postnatal Depression Scale). Sex differences were probed, and possible pre- and postnatal confounders, such as maternal general anxiety, were controlled for. We observed that elevated depressive symptoms of the early second trimester, after controlling for prenatal maternal general anxiety, were significantly related to smaller right amygdalar volumes in the whole sample. Higher depressive symptoms of the third trimester were associated with significantly smaller right amygdalar volumes in boys compared to girls. Altogether, our data suggest that offspring limbic brain development might be affected by maternal depressive symptoms in early pregnancy, and might also be more vulnerable to depressive symptoms in late pregnancy in boys compared to girls.

1. Introduction

The prevalence of maternal prenatal depression is high worldwide, varying in studies from 5% to 74%, depending on the diagnostic instrument and country (Gelaye et al., 2016; Woody et al., 2017; Field, 2011). Prenatal depression often continues into postnatal depression whose prevalence is usually comparably lower (Field, 2011; Underwood et al., 2016). For many years, research focused on the effects of maternal postnatal depression on mother-child interaction and offspring development. Meanwhile, evidence is mounting that prenatal depression has long-lasting effects on offspring health over and above the effects of maternal postnatal depression (e.g., Pearson et al., 2013; Davis et al., 2004). Higher levels of prenatal depressive symptoms have been associated with preterm delivery, infant behavioral problems, higher infant stress hormone levels (Grigoriadis et al., 2013; Grote et al., 2010; Lundy et al., 1999; Stroud et al., 2016; Field, 2011; Davis et al., 2004; Field et al., 2010), as well as with internalizing and externalizing behavior in children (Gentile, 2017; Field, 2011), and with depression and male criminality in adolescents and adults (Gentile, 2017; Pearson et al., 2013; Plant et al., 2015; Mäki et al., 2003). The underlying mechanisms are not yet fully understood and likely involve genetic, epigenetic, inflammatory, stress-related and behavioral mechanisms (Sohr-Preston and Scaramella, 2006; Non et al., 2014; Sullivan et al., 2000; Plant et al., 2015; Kim et al., 2015). Prenatal

* Corresponding author.
E-mail addresses: hschas@utu.fi, schneid5@staff.uni-marburg.de (A. H), schneid5@staff.uni-marburg.de (S. NM).

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depression compromises maternal health-related behavior and has been associated with higher maternal subjective stress (Gentile, 2017; Sohr-Preston and Scaramella, 2006). It has been proposed that the association between offspring outcomes and prenatal maternal adversity such as depression are partly mediated by stress-related effects on fetal brain development (Bock et al., 2015; Andersen, 2003). The intrauterine period is regarded as a sensitive time window for brain development, and the effects of prenatal stress on fetal brain development likely vary depending on the timing of stress exposure, its chronicity, and on offspring sex. Animal studies have revealed that the most prominent changes related to prenatal stress target prefrontal and limbic brain areas including the amygdala (Bock et al., 2015; Andersen 2003). In humans, recent studies have shown that prenatal depression is linked to atypical functional and /or structural amygdalar connectivity in infants (Posner et al., 2016; Qiu et al., 2015) and in young girls, but not boys (Soe et al., 2018), to altered cortical gray matter volumes in children (Lebel et al., 2016; El Marroun et al., 2016; Sandman et al., 2015), and to increased amygdalar responses to negative emotional faces in school-aged children (van der Knaap et al., 2018). The amygdala plays a central role in salience processing, stress physiology, and, in humans, in anxiety disorders and depression (Yilmazer-Hanke, 2012; Lindquist et al., 2012). To the best of our knowledge, only a few studies have investigated the relation between maternal prenatal depressive symptoms and offspring amygdalar volumes, and these studies assessed prenatal depression only once in late pregnancy: In neonates, no association between prenatal depressive symptoms and amygdalar volumes has been found (Rifkin-Graboi et al., 2013), even though an interaction between prenatal depression and genetic factors on amygdalar volumes has been revealed (Qiu et al., 2017). However, in 4.5-year-olds, a positive association between prenatal depressive symptoms of the late second trimester and right amygdalar volumes has been reported in girls, but not boys (Wen et al., 2017). In summary, the association between maternal prenatal depression and amygdalar volume is yet underexplored, as is the possible role of the timing of exposure and its chronicity.

With this study, we aimed to explore the association of maternal prenatal depressive symptoms with amygdalar volumes in four-year old children, taking into account timing and chronicity of prenatal exposure, child's sex, and other pre- and postnatal factors. Given the results of Wen and coworkers (2017), we hypothesized prenatal depressive symptoms of the late second trimester to be more positively related to right amygdalar volumes in girls than in boys.

2. Methods

2.1. Participants

Participants were mother-child-dyads recruited from the FinnBrain Birth Cohort Study [www.finnbrain.fi] (Karlsson et al., 2018). Neuroimaging data was collected from 33 four-year-old children. The inclusion criterion was child's age of ca. 4 years (47 – 54 months). Exclusion criteria for the children were significant developmental abnormalities of major organs (e.g., heart, limbs) and sensory systems (e.g., blindness, deafness), a diagnosis of a neurodevelopmental disorder such as autism or epilepsy, need for daily medication at the time of the scan, lifetime experience of a severe head trauma or concussion (with unconsciousness or clinical MRI scans post trauma), and other clinical investigations, all assessed by self-report from the parents. The parent(s) gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the South-Western Hospital District of Finland.

One subject was excluded from the analyses due to a technical failure of the MRI data acquisition. Four further subjects were excluded because of low quality of the brain structural data due to motion as assessed by visual inspection. In the final sample, 28 mother-child-dyads were included [mean age of children (at MRI scan time) = 50.8 months (SD = 1.6, range = 47.7 - 54.0), mean age of mothers (at term) = 30.4 years (SD = 4.0), and 14 of the children were boys (50%)]. Data from an overlapping sample have been published elsewhere (Acosta et al. 2019).

2.2. Measures and Procedures

2.2.1. Maternal prenatal depressive symptoms

For the assessment of maternal prenatal depressive symptoms the Finnish version of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) was administered at gestational weeks (gwk) 14, 24 and 34. The EPDS is a 10-item self-report questionnaire assessing typical symptoms of depression during the last two weeks. Each item is scored on a 4-point scale, and sum scores range from 0 to 30. Missing values (at maximum 3 items per time point) were imputed with the mean value of the existing ones. EPDS questionnaire data were not available for one of the mothers at gwk24 and data were imputed by the MissForest method (Stekhoven and Bühlmann, 2012). The EPDS has been validated in several studies and is regarded as a valid instrument for assessing both pre- and postnatal depressive symptoms (Eberhard-Gran et al., 2001; Cox et al., 1996; Kozinszky and Dudas, 2015). In this study, the sum scores of each time point (EPDS gwk14, EPDS gwk24, EPDS gwk34) were investigated. Additionally, the individual sum scores of all three time points were combined to form a total EPDS sum score (EPDS Sum) as a proxy for the chronicity of prenatal depressive symptoms.

2.2.2. Prenatal maternal control variables

To control for general and pregnancy-related anxiety, the Finnish versions of the anxiety subscale of the revised Symptom Checklist 90 (SCL-90-R) (Holi et al., 1998; Derogatis, 1983) and the PRAQ-R2 questionnaire (Huizink et al., 2016) were administered. General anxiety (SCL) was assessed at gwk 14, 24 and 34, and pregnancy-related anxiety (PRAQ) was assessed at gwk 24 and 34. Missing values (at maximum 3 items per time point for SCL and at maximum 1 item for PRAQ) were imputed with the mean value of the existing ones. No questionnaire data was available for one of the mothers at gwk 24, and the SCL data was imputed by the MissForest method (Stekhoven and Bühlmann, 2012). Individual sum scores were computed for prenatal maternal anxiety (SCL Sum) and pregnancy-related anxiety (PRAQ Sum; missing: $n = 1$) over pregnancy.

The Trauma and Distress Scale (TADS) (Salokangas et al., 2016) was administered to mothers at gwk 14 to assess childhood stress exposure and maltreatment. It has been shown that childhood maltreatment increases the risk for depression (Li, D'Arcy, and Meng, 2016) and is related to reduced gray matter volumes of the fetal brain (Moog et al., 2018). Missing values (at maximum 1 item per subscale and time point) were imputed with the mean value of the existing ones, and an individual sum score (TADS sum) was created.

Furthermore, the following maternal variables were assessed via mothers' self-report at gwk 14 and/or 34: maternal education, maternal age, prenatal medication, and prenatal alcohol, nicotine and illicit drug consumption. Obstetric data was retrieved from the Finnish Medical Birth Register of the National Institute for Health and Welfare (http://www.thl.fi), and included gestational complications (diabetes: $n = 6$, hypertension: $n = 1$), maternal prepregnancy body mass index (BMI) and previous miscarriages or abortions. We dichotomized BMI (BMI < 25, BMI >= 25) given that maternal obesity has been associated with alterations in the infant brain (Pulli et al., 2019). We further dichotomized medication use (thyroxine and corticosteroids; yes/no), alcohol and/or nicotine exposure (yes/no), gestational complications and previous miscarriages and/or abortions (yes/no). No significant use of antidepressants or illicit drugs was reported (four missing values at the first time point: medication: $n = 2$, alcohol exposure: $n = 1$; illicit

Table 1.
The mean scores (*M*), standard deviations (*SD*) and frequencies, respectively, are listed for maternal prenatal EPDS scores, child's amygdalar volumes and control variables, for the whole sample and for girls and boys separately. In the right column *p*-values for sex differences in the sample are listed.

Variable	Whole sample	Boys (n= 14)	Girls (n= 14)	*p*
M ± SD (range)				
Child's age [mo]	50.8 ± 1.6 (47.7-54.0)	50.8 ± 1.2 (48.7-53.1)	50.8 ± 2.0 (47.7-54.0)	0.949
Gestational weeks at birth	39.9 ± 1.1 (38.0-42.1)	39.9 ± 1.1 (38.0-42.0)	39.9 ± 1.1 (38.0-42.1)	0.901
Birth weight [g]	3620.0 ± 386.1 (2750-4225)	3540.1 ± 431.9 (2750-4025)	3700.0 ± 330.7 (2950-4225)	0.281
EPDS gwk14	4.18 ± 3.31 (0-12)	5.64 ± 3.56 (0-12)	2.71 ± 2.33 (0-8)	0.016*
EPDS gwk24	4.80 ± 3.06 (0-13)	5.36 ± 2.59 (1-9)	4.25 ± 3.48 (0-13)	0.347
EPDS gwk34	4.93 ± 4.52 (0-17)	5.36 ± 3.67 (1-13)	4.50 ± 5.35 (0-17)	0.625
EPDS Sum	13.91 ± 8.96 (0-31)	16.36 ± 8.54 (6-31)	11.46 ± 9.00 (0-31)	0.152
Left amygdala volume [mm^3]	1157.6 ± 107.8 (908-1330)	1115.4 ± 104.9 (908-1273)	1199.7 ± 96.6 (1028-1330)	0.036*
Right amygdala volume [mm^3]	1186.5 ± 117.3 (935-1480)	1164.6 ± 127.5 (935-1379)	1208.4 ± 106.2 (1091-1480)	0.333
Total intracranial volume [cm^3]	1400.8 ± 135.5 (1137.4-1720.1)	1485.9 ± 120.0 (1315.4-1720.1)	1315.7 ± 90.0 (1137.4-1459.5)	<0.001*
Prenatal SCL Sum	7.69 ± 8.41 (0-32)	8.30 ± 9.06 (0-32)	7.08 ± 8.01 (0-23)	0.709
PRAQ Sum (n=27)	43.81 ± 9.72 (28-61)	46.57 ± 8.73 (32-61)	40.85 ± 10.17 (28-59)	0.128
Postnatal EPDS Sum (n=13)	24.17 ± 20.88 (4-83)	28.03 ± 27.52 (4-83)	19.67 ± 9.64 (8-34)	0.496
Postnatal SCL Sum (n=13)	12.62 ± 16.76 (1-60)	16.86 ± 21.38 (2-60)	7.67 ± 8.50 (1-22)	0.346
TADS Sum	10.72 ± 10.94 (0-43)	9.09 ± 8.43 (0-28)	12.36 ± 13.10 (0-43)	0.440
Frequencies				
Maternal pre-pregnancy BMI (<25 / >=25)	17/11	7/7	10/4	0.246
Prenatal alcohol and/or nicotine consumption (no/yes) (n=27)	19/8	9/5	10/3	0.472
Prenatal medication – thyroxine (no/yes)	26/2	13/1	13/1	1.000
Prenatal medication – corticosteroids (no/yes)	26/2	13/1	13/1	1.000
Gestational complications (no/yes)	21/7	8/6	13/1	0.029*
Miscarriages and/or abortions (no/yes)	21/7	11/3	10/4	0.663
Maternal education (low/middle/high)	5/5/18	1/3/10	4/2/8	0.329

*p<0.05; **Abbr:** EPDS= Edinburgh Postnatal Depression Scale, PRAQ=pregnancy-related anxiety questionnaire, SCL= anxiety subscale of the revised Symptom Checklist 90

drugs: n=1). Education was trichotomized [low: high school or vocational education (9 years), middle: (career) college (12 years), high: university (+12 years)].

2.2.3. Postnatal maternal control variables

Maternal postnatal depressive symptoms were assessed by use of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) at 3 months (n= 28) and 6 months (n= 23), and at 1 year (n= 24), 2 years (n= 18) and 4 years (n= 22) post-partum. Maternal postnatal anxiety was assessed using the anxiety subscale of the revised Symptom Checklist 90 (SCL-90-R) (Derogatis, 1983; Holi et al., 1998) at 3 and 6 months, and at 2 and 4 years post-partum. Individual sum scores for postnatal maternal depressive symptoms and for general anxiety were created by summing up the scores of all postnatal time points, for depressive symptoms and for anxiety separately.

2.2.4. MRI acquisition

Magnetic resonance imaging was performed using a 3 T Philips Ingenuity TF PET/MR (Philips, Amsterdam, Netherlands) and a SenseHead-32 channel coil. The 3D T1 turbo field echo (TFE) sequence was imaged in sagittal orientation. The Field of view was 256 × 256 mm. Data was acquired and reconstructed with 1mm isotropic voxels. Parallel imaging was used with a SENSE factor of 2 and a flip angle of 7 degree. Repetition time was 8.1 ms and echo time was 3.7 ms. The sequence duration was 4 minutes 23 seconds.

2.2.5. Volume segmentation of the amygdala

The native anatomical images were preprocessed and segmented applying the volBrain pipeline (Manjón and Coupé, 2016). The segmentation of the amygdala volumes was amended by two raters according to the segmentation protocol by Hashempour and colleagues (Hashempour et al., 2019) that has been developed in our research group for the segmentation of young children's data. For the manual segmentation, the software ITK-SNAP (version 3.6.0; http://www.itksnap.org) (Yushkevich et al., 2006) and MNI Display (http://www.bic.mni.mcgill.ca/software/ Display/Display.html) were used (inter-rater reliability [ICC(2,1)](Koo and Li, 2016): ICC (right amygdala)= 0.93, ICC (left amygdala)= 0.94). Total intracranial volume was assessed by use of volBrain.

2.2.6. Statistical analyses

Statistical analyses of behavioral and brain volume data were performed using R 3.4.4 (R Core Team, 2016) (http://www.r-project.org/). Packages in use were “Hmisc” (Harrell, 2017), “psych” (Revelle, 2018), “nortest” (Gross and Ligges, 2015), “ggplot2” (Wickham, 2009), “missForest” (Stekhoven, 2013) and “car” (Fox and Weisberg, 2011) among others. Missing values of postnatal control variables were imputed by means of multiple imputation (Van Buuren, 2018; Rubio, 1987) using the package “mice” (Van Buuren and Groothuis-Oudshoorn, 2011), and the results given from these analyses are the pooled results.

Standard multiple linear regression analyses were performed to

investigate the associations between bilateral amygdala volumes and a) the individual EPDS scores and b) the interaction between EPDS scores and child's sex. Individual EPDS scores of all three time points (gwk14, gwk24, gwk34) and the EPDS Sum score were analyzed in independent analyses. All analyses included child's age at MRI scan time, child's sex and child's intracranial volume as (control) variables. In sensitivity analyses, we repeated all the multiple regression analyses by subsequently adding and removing each of the following control variables to/from the model in order to test if the observed results were explained by these covariates: maternal prenatal medication, prenatal alcohol and/or nicotine exposure, postnatal depressive symptoms, pre-/postnatal maternal general anxiety, pregnancy-related anxiety, maternal education, maternal BMI, gestational complications, previous miscarriages and/or abortions, maternal childhood trauma, child's birth weight and gestational age. We performed post-hoc analyses for the results that were either significant or related to our hypothesis, probing the association between amygdalar volumes and EPDS scores by means of partial correlation analyses. In all correlational analyses, Pearson Product Moment correlation coefficients (*r*) and, for non-normally distributed data, Spearman correlation coefficients (*rho*) are reported.

We chose a statistical threshold of $p < 0.05$. Given the exploratory nature of the study, no correction for multiple testing was carried out.

3. Results

3.1. Description of the sample

Descriptive information on EPDS scores, amygdalar volumes and control variables is listed for the whole sample and for boys and girls separately in Table 1. In the whole sample, the EPDS scores of different time points were highly intercorrelated (gwk14-gwk24: *rho* = 0.56, gwk14-gwk34: *rho* = 0.73; gwk24-gwk34: *rho* = 0.37). Mothers of girls compared to those of boys reported significantly lower depressive symptoms at gwk14. EPDS scores were also significantly positively correlated with SCL sum scores (gwk14: *rho* = 0.55; gwk24: *rho* = 0.49; gwk34: *rho* = 0.57, Sum: *rho* = 0.67) and with postnatal EPDS scores (gwk14: *W* = 5.6; gwk34: *W* = 3.3; Sum: *W* = 4.7). Left amygdalar volumes were significantly larger in girls compared to boys (Table 1).

3.2. Association between maternal prenatal depressive symptoms and child's amygdalar volumes

3.2.1. Higher EPDS gwk14 scores were associated with smaller bilateral amygdalar volumes after controlling for prenatal anxiety

In the multiple linear regression analyses of the whole sample, we did not find significant associations between EPDS scores and amygdalar volumes if we only controlled for child's sex, age and total intracranial volume (Table 2). However, in the sensitivity analyses we observed that higher EPDS gwk14 scores were significantly associated with smaller right amygdalar volumes after controlling for prenatal general anxiety (see Methods, 2.2.6) (Fig. 1). Multicollinearity in this analysis did not exceed recommended thresholds (variance inflation factor of all predictors <2.2). Post hoc partial correlation analyses revealed that right amygdalar volumes were negatively correlated with EPDS gwk14 scores in the whole sample (*rho*: -0.46, $p = 0.016$), and both in boys ($r = -0.54$, $p = 0.046$) as well as weakly in girls ($r = -0.39$, $p = 0.164$) (controlling for child's age, total intracranial volume, prenatal SCL Sum score and in the whole sample additionally for sex). Postnatal depressive symptoms were not significantly related to bilateral amygdalar volumes in the sensitivity analyses (all $p > 0.32$).

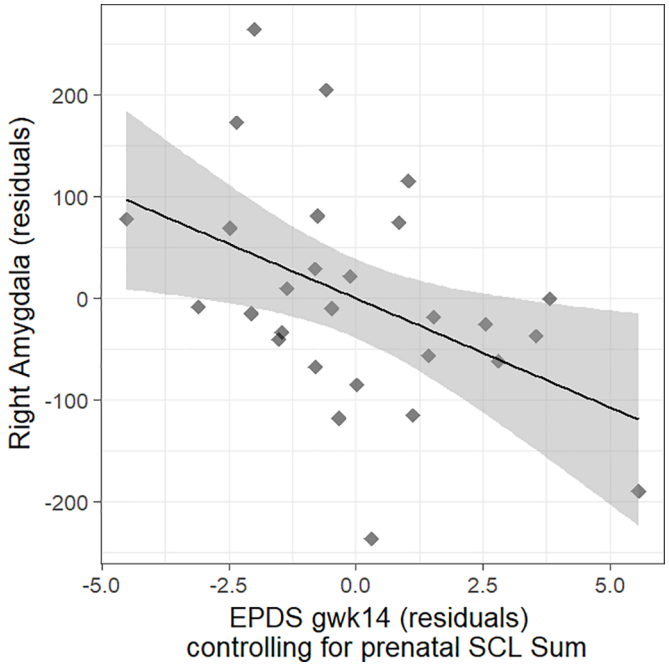

Fig. 1.. Association between EPDS gwk14 scores and right amygdalar volumes Higher EPDS gwk14 scores were significantly correlated with smaller right amygdalar volumes (*rho* = -0.46, $p = 0.016$) after controlling for child's sex, age and intracranial volume, and for maternal prenatal SCLSum scores (residuals are displayed).

3.2.2. Higher EPDS gwk34 scores were associated with smaller right amygdalar volumes in boys compared to girls

In multiple linear regression analyses, investigating the interaction between EPDS scores and child's sex on amygdalar volumes, we

Table 2.
The association between amygdalar volumes, prenatal EPDS scores and child's sex. The results or the multiple linear regression analyses with amygdalar volumes as dependent variable are listed. In the upper part of the table prenatal EPDS is the predictor. In the lower part the interaction term of EPDS and child's sex is the predictor.

Volumes	EPDS gwk14 β ± SE	p	EPDS gwk24 β ± SE	p	EPDS gwk34 β ± SE	p	EPDS Sum β ± SE	p
L amygdala	-7.21 ± 7.11	0.321	3.90 ± 6.86	0.575	-4.30 ± 4.39	0.337	-1.56 ± 2.39	0.519
R amygdala	-10.77 ± 8.05	0.194[a]	5.98 ± 7.85	0.454	-5.54 ± 5.02	0.281	-2.06 ± 2.74	0.460
Interaction between EPDS and child's sex (0 = female, 1 = male) on amygdalar volumes:								
	EPDS gwk14 x sex		EPDS gwk24 x sex		EPDS gwk34 x sex		EPDS Sum x sex	
L amygdala	0.59 ± 15.48	0.970	-5.33 ± 14.24	0.712	-3.49 ± 9.78	0.724	-1.54 ± 4.83	0.752
R amygdala	-12.18 ± 17.33	0.489	-10.87 ± 16.17	0.509	-22.11 ± 10.18	0.041[b]	-8.06 ± 5.27	0.140

Abbr.: L = left, R = right, EPDS = Edinburgh Postnatal Depression Scale, *SE* = standard error, gwk = gestational week

[a] $p < 0.05$ when controlling for prenatal SCL Sum

[b] $p < 0.05$ when controlling for birth weight, TADS Sum, postnatal depressive symptoms, $p < 0.06$ with PRAQ Sum ($n = 27$), medication (thyroxine), maternal education, previous miscarriages and/or abortions, $p < 0.07$ with gestational weeks, alcohol and/or nicotine exposure ($n = 27$), medication (corticosteroids), $p < 0.08$ with pre- and postnatal SCL Sum, $p < 0.10$ with maternal BMI, and $p < 0.12$ with gestational complications

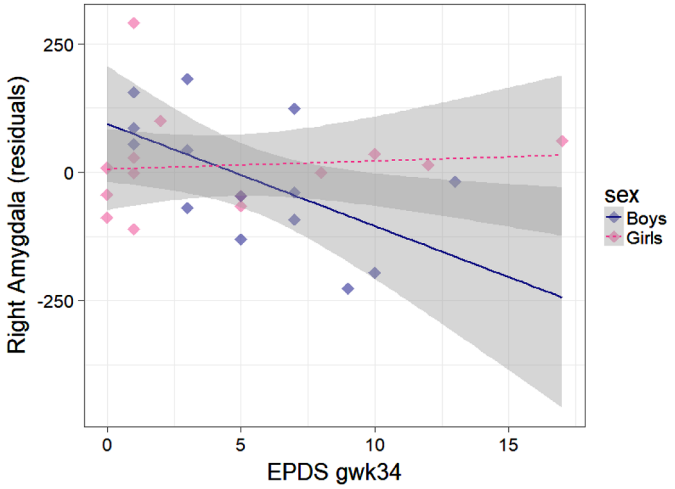

Fig. 2.. The association between EPDS gwk34 scores, child's sex and right amygdalar volumes EPDS gwk34 scores and child's sex showed a significant interaction on right amygdalar volumes ($\beta \pm SE = -22.11 \pm 10.18$, $p = 0.041$). Controlling for child's age and total intracranial volume, right amygdalar volumes were significantly negatively correlated with EPDS gwk34 scores in boys ($r = -0.62$, $p = 0.018$), but no association was observed in girls ($rho = 0.26$, $p = 0.366$). The residuals of right amygdalar volumes are displayed, controlling for child's age and total intracranial volume.

observed that EPDS gwk34 scores were significantly more negatively associated with right amygdalar volumes in boys compared to girls (Table 2, Fig. 2). In the sensitivity analyses, testing potential confounders, the association stayed significant after controlling for birth weight, maternal postnatal depressive symptoms and maternal childhood maltreatment experiences, but was reduced to nonsignificance by the other control variables (Table 2). Post hoc partial correlation analyses (controlling for child's age and total intracranial volume) yielded that right amygdalar volumes were significantly negatively correlated with EPDS gwk34 scores in boys ($r = -0.62$, $p = 0.018$), but no association was observed in girls ($rho = 0.26$, $p = 0.366$).

We found no evidence for interactions between EPDS gwk24 scores and sex on amygdalar volumes (Table 2). Post hoc partial correlation analyses showed no associations between EPDS gwk24 scores and right or left amygdalar volume in girls (all $p > 0.24$) or boys (all $p > 0.87$).

4. Discussion

With this study, we explored the association between maternal prenatal depressive symptoms and amygdalar gray matter volumes in four-year-olds. We observed that higher maternal depressive symptoms in the early second trimester (gwk 14) were related to smaller right amygdalar volumes after controlling for prenatal maternal anxiety. Postnatal depressive symptoms were not significantly associated with child's amygdalar volumes.

Furthermore, we detected a sexually dimorphic association between maternal depressive symptoms of the third trimester and right amygdalar volumes: Higher prenatal depressive symptoms were significantly related to smaller amygdalar volumes in boys compared to girls. This sex-specific association remained significant after controlling for postnatal depressive symptoms, but was reduced to nonsignificance by control variables such as gestational complications and maternal BMI.

In our study, maternal pre- and postnatal depressive symptoms were moderately to highly intercorrelated, and a high comorbidity with anxiety symptoms was observed. The course of depression during pregnancy is still poorly investigated (Gentile, 2017), but might be decomposable into different symptom trajectories during pregnancy (Korja et al., 2018). Prenatal depression has evolved to be a strong predictor for postnatal depression (Field, 2011), and the incidence of comorbid anxiety and depression in patients amounts to 50% on average, ranging between 33 and 90% (Gorman, 1996).

Controversy still continues as to whether depression and anxiety should be considered as separate or unitary disorders. Depression and anxiety share some, but not all neurobiological disturbances (Hranov, 2007). Importantly, Field et al. (2010) have shown that prenatal anxiety and depression exert partly distinct physiological effects on neonates, such as lowered versus heightened neonatal cortisol levels, respectively (Field et al., 2010). Neonates of mothers with comorbid anxiety and depression have exhibited physiological profiles resembling the attenuated profiles of depressed mothers' offspring (Field et al., 2010). In our study, control for maternal prenatal anxiety strengthened the association between EPDS gwk14 and right amygdalar volumes, suggesting that maternal anxiety weakens the effects of maternal depression on neonatal outcomes, thereby paralleling the findings of Field et al. (2010).

To the best of our knowledge, this study is the first to investigate the association between maternal depression of the early second trimester with amygdalar volumes, and our study revealed a negative association between EPDS gwk14 scores and right amygdalar volumes after controlling for maternal general anxiety. Amygdalar development starts early in embryonic life: All three main amygdalar subdivisions are detectable around the fifth week, and amygdalar neuronal migration, neuronal differentiation, axonal outgrowth and synaptogenesis continue during the second trimester until the early third trimester (Müller and O'Rahilly, 2006; Ulfig et al., 2003; Humphrey, 1968).

However, our hypothesis that maternal depressive symptoms of the late second trimester would be related to significantly larger right amygdalar volumes in girls compared to boys was only partly supported by our data: EPDS gwk24 scores were not significantly associated with amygdalar volumes in our sample, and while EPDS gwk34 scores showed a sex-specific interaction on right amygdalar volumes, post hoc analyses revealed, contrary to our expectations, a significant negative association for boys and no association for girls. It has been proposed that neurodevelopmental trajectories vary between sexes leading to different time windows of vulnerability (Entringer et al., 2015; Bock et al., 2015). Evidence is growing that prenatal stress exerts sexually dimorphic effects on the human fetus (Hicks et al., 2019), and neuroimaging studies have revealed sex-specific associations of maternal prenatal stress with neonatal functional amygdalar connectivity (Graham et al., 2019), and neonatal and child's amygdalar volumes (Buss et al., 2012; Lehtola et al., n.d.; Acosta et al. 2019). Sex-specific placental responses to prenatal stress might underly the observed sexually dimorphic effects: For instance, human studies have shown that the female placenta reacts with multiple adaptations of placental gene expression to prenatal challenges compared to minimal adaptations in male placentas (Clifton, 2010). Therefore, sex differences in the developmental timing of the amygdala and/or in placental functions might explain why maternal depressive symptoms of the third trimester associate with amygdalar volumes in boys and girls differently, suggesting a higher vulnerability of boys compared to girls in late pregnancy.

In animal studies, smaller offspring amygdalar volumes have been associated with in utero synthetic glucocorticoid exposure (Miranda and Sousa, 2018; Oliveira et al., 2012). In humans, reduced amygdalar volumes, especially of the left hemisphere, have been linked to hypercortisolism in children diagnosed with Cushing's syndrome (Merke et al., 2005) and to chronic corticosteroid therapy in adults (Brown et al., 2008). As mentioned above, significantly higher cortisol levels and a higher stress reactivity have been observed in neonates of prenatally depressed mothers compared to those of anxious mothers or controls (Field et al., 2010; Lundy et al., 1999; Stroud et al., 2016). The effects of maternal depression on offsping development are presumably not directly mediated by elevated maternal prenatal cortisol levels (O'Donnell and Meaney, 2017) which have not consistently been associated with maternal depression during pregnancy, although data

regarding the first trimester is scarce (Salacz et al., 2012; Field et al., 2010; Hellgren et al., 2016; O'Donnell and Meaney, 2017). Fetal exposure to maternal cortisol is regulated by a placental enzyme, the 11beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2). Acute maternal stress up-regulates the enzyme's activity protecting the fetus from rising cortisol concentrations (Welberg et al., 2005). However, chronic maternal stress has been associated with a lower activity of 11beta-HSD2 in animal and human studies resulting in a higher fetal cortisol exposure (O'Donnell et al., 2012; Mairesse et al., 2007; Welberg et al., 2005). Maternal depressive symptoms might be related to a reduced activity of 11beta-HSD2 (Seth et al., 2015; O'Donnell et al., 2012; Hellgren et al., 2016), even though findings have been, to some extent, inconsistent (Reynolds et al., 2015), and to an increased placental glucocorticoid sensitivity (Reynolds et al., 2015). Importantly, in typically progressing pregnancies, maternal psychophysiological stress responses are less attenuated in early compared to late pregnancy (Entringer et al., 2010; O'Donnell and Meaney, 2017).

We assume that maternal depressive symptoms alter placental functions resulting in less protection of the fetus from maternal stress responses, and this, along with a higher maternal stress reactivity in early compared to late pregnancy, might explain the association of maternal depressive symptoms in early pregnancy with smaller child's amygdalar volumes in our study. By contrast, higher maternal cortisol levels in early pregnancy without depression have been linked to larger amygdalar volumes in girls (Buss et al., 2012), and, based on these and our findings, we speculate that the effects of prenatal depression on fetal brain development are not directly mediated by maternal prenatal cortisol levels, but involve other pathways.

Smaller amygdalar volumes might facilitate unfavorable behavioral outcomes in children and adults: Behavioral problems, such as proactive aggression and conduct problems (Rogers and De Brito, 2016; Naaijen et al., 2018), emotional difficulties and peer relationship problems (Acosta et al. 2019), and a diagnosis of schizophrenia (Fischer et al., 2012). have been associated with smaller bilateral or left amygdalar volumes. However, conflicting findings exist: Better emotion regulation skills (Pagliaccio et al., 2014) have been associated with smaller bilateral amygdalar volumes, and smaller right amygdalar volumes have been related to a higher impulse control in toddlers (Graham et al., 2018), and a lower fearfulness in girls (van der Plas et al., 2010). Hence, the repercussions of the volume alterations remain to be determined.

In summary, the results of our exploratory study suggest that maternal EPDS scores of the early second trimester are related to smaller amygdalar volumes in boys and girls, controlling for prenatal maternal anxiety. Amygdalar development in boys compared to girls might be more vulnerable to depressive symptoms in the third trimester. The predictive value of depressive symptoms in the late second trimester was limited in our sample, as reflected in comparably weak associations not only with amygdalar volumes, but also with maternal postnatal depression. No significant associations with the chronicity of exposure to depressive symptoms were detected.

Our results are in contrast to findings observed for pregnancy-related anxiety in an overlapping sample where pregnancy-related anxiety of the late second trimester was associated with significantly larger amygdalar volumes in girls compared to boys (Acosta et al. 2019). Altogether, our current data together with previous work suggest that the effects of maternal prenatal anxiety, depression and cortisol on offspring brain development are potentially different. Future studies should elucidate the underlying biological pathways.

4.1. Limitations

The sample size of our study was rather small, reducing statistical power, limiting the generalizability and interpretation of our results. The sample size also did not allow us to investigate different trajectories of pre- and postnatal depressive symptoms. A replication of our study results is warranted. While we controlled for postnatal depressive symptoms and anxiety, other aspects of the postnatal environment such as the early caregiving behavior can shape child's development (e.g.,Tyrka et al., 2013). Furthermore, a recent study revealed that maternal prenatal depressive symptoms interact with infant genotype on amygdalar volumes (Qiu et al., 2017). However, it was beyond the scope of this study to take genetic factors and caregiving behavior into account.

Contributors

HA performed the data analyses (preprocessing, manual segmentation of the amygdala, statistical analyses), interpreted the data and drafted the manuscript. NH performed the manual segmentation and JP supported the statistical analyses. VS, RP and TL provided the technical and clinical support for the MRI data acquisition, and VS provided the description of the MRI data acquisition methods. JT and NS were involved in the planning and funding of the study, and JT, OR and TIL collected the MRI data. HK planned and established the Cohort and provided funding and infrastructure for the collection of the questionnaire data and the brain imaging. LK co-planned and established the Cohort with HK and participated in providing funding for the data collection. All co-authors revised the manuscript and accepted the final manuscript version.

Declaration of Competing Interest

The authors declare no competing financial interests.

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