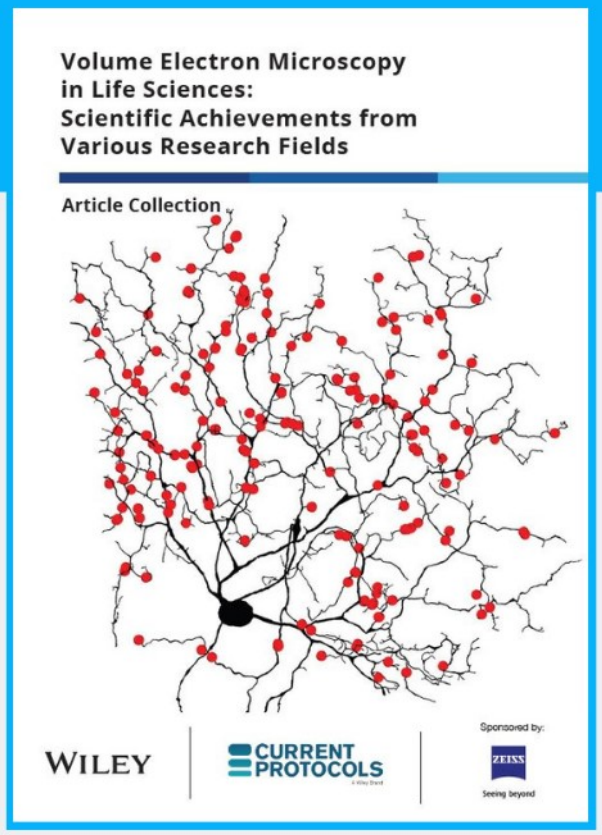
Volume Electron Microscopy in Life Sciences



A New Article Collection. Download for free.

Even though life exists in 3D, until the beginning of this century, most electron microscopy methods provided only 2D image data. Thanks to recent advances, electron microscopy can now go deeper into the structure of cells and tissues. Volume electron microscopy (vEM) is a group of techniques that encompasses high-resolution imaging methods used to reveal the 3D structure of cells, tissues, and small model organisms at nanometer resolution. Lately, vEM has been widely employed to investigate cell structure and tissues in multiple fields, such as neuroscience immunology, cancer research, developmental biology, plant biology, and biomaterials.

Through this article collection, we hope to provide researchers with more information on the application of volume electron microscopy techniques, allowing them to further their research in this field.

ZEISS

Seeing beyond

WILEY

Received: 7 January 2022 | Revised: 24 March 2023 | Accepted: 3 April 2023

DOI: 10.1111/ejn.15989

RESEARCH REPORT

EJN European Journal of Neuroscience FENS WILEY

Prenatal maternal depressive symptoms are associated with neonatal left amygdala microstructure in a sex-dependent way

Niloofar Hashempour[1] | Jetro J. Tuulari[1,2,3,4] | Harri Merisaari[1,9] | Henriette Acosta[1,5] | John D. Lewis[6] | Juho Pelto[1] | Noora M. Scheinin[1,2] | Vladimir S. Fonov[6] | D. Louis Collins[6] | Satu J. Lehtola[1] | Jani Saunavaara[7] | Tuire Lähdesmäki[8] | Riitta Parkkola[9] | Linnea Karlsson[1,2,10,11] | Hasse Karlsson[1,2,10]

[1]FinnBrain Birth Cohort Study, Turku Brain and Mind Center, Department of Clinical Medicine, University of Turku, Turku, Finland

[2]Department of Psychiatry, Turku University Hospital & University of Turku, Turku, Finland

[3]Turku Collegium for Science and Medicine, University of Turku, Turku, Finland

[4]Department of Psychiatry, University of Oxford, Oxford, UK

[5]Department of Psychiatry and Psychotherapy, Philipps University of Marburg, Marburg, Germany

[6]Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

[7]Department of Medical Physics, Turku University Hospital, Turku, Finland

[8]Department of Pediatric Neurology, Turku University Hospital & University of Turku, Turku, Finland

[9]Department of Radiology, Turku University Hospital & University of Turku, Turku, Finland

[10]Centre for Population Health Research, Turku University Hospital and University of Turku, Turku, Finland

[11]Department of Pediatrics and Adolescent Medicine, Turku University Hospital and University of Turku, Turku, Finland

Correspondence
Niloofar Hashempour, FinnBrain Birth Cohort Study, Turku Brain and Mind Center, Department of Clinical Medicine, University of Turku, Kiinamyllynkatu 8-10, Turku, FI-20014, Finland.
Email: niloofar.hashempour@utu.fi

Funding information
The Azrieli Neurodevelopmental Research Program; The Canadian Institutes of

Abstract

Exposures to prenatal maternal depressive symptoms (PMDS) may lead to neurodevelopmental changes in the offspring in a sex-dependent way. Although a connection between PMDS and infant brain development has been established by earlier studies, the relationship between PMDS exposures measured at various prenatal stages and microstructural alterations in fundamental subcortical structures such as the amygdala remains unknown. In this study, we investigated the associations between PMDS measured during

Abbreviations: 11ß–HSD2, 11beta hydroxysteroid dehydrogenase 2; 3D, three-dimensional; 4D, four-dimensional; AD, axial diffusivity; BMI, body mass index; CNS, central nervous system; CRH, corticotropin-releasing hormone; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; EPDS, Edinburgh Postnatal Depression Scale; FA, fractional anisotropy; FDR, false-discovery rate; FOV, field-of-view; FSL, FMRIB Software Library; GM, grey matter; GW, gestational week; HPA, hypothalamic–pituitary–adrenal; MD, mean diffusivity; MRI, magnetic resonance imaging; PMDS, prenatal maternal depressive symptoms; ROI, region-of-interest; SSRI, selective serotonin reuptake inhibitor; TE, echo time; TR, repetition time; WM, white matter.

Health Research; The Emil Aaltonen Foundation; The Hospital District of Southwest Finland State Research Grants; The Jane and Aatos Erkko Foundation; The Juho Vainio Foundation; The Maire Taponen Foundation; The NARSAD Brain and Behavior Research Foundation; The Natural Sciences and Engineering Research Council of Canada; The Orion Research Foundation; The Signe and Ane Gyllenberg Foundation; The Sigrid Juselius Foundation; University of Turku Graduate School; Orion Research Foundation; Sigrid Juselius Foundation; Emil Aaltonen Foundation; Juho Vainio Foundation; Hospital District of Southwest Finland State Research Grants, Grant/Award Numbers: K3562, P3654, P3498, P3003, P3006; Jane and Aatos Erkko Foundation; Maire Taponen Foundation; Azrieli Neurodevelopmental Research Program, Grant/Award Number: ANRP-MIRI13–3388; Canadian Institutes of Health Research; Natural Sciences and Engineering Research Council of Canada; NARSAD Brain and Behavior Research Foundation, Grant/Award Number: 1956; Signe and Ane Gyllenberg Foundation; Academy of Finland, Grant/Award Numbers: 134950, 253270, 264363 (HK), 308176 (LK), 26080983 (HM)

Edited by: John Foxe

gestational weeks 14, 24 and 34 and infant amygdala microstructural properties using diffusion tensor imaging. We explored amygdala mean diffusivity (MD) alterations in response to PMDS in infants aged 11 to 54 days from birth. PMDS had no significant main effect on the amygdala MD metrics. However, there was a significant interaction effect for PMDS and infant sex in the left amygdala MD. Compared with girls, boys exposed to greater PMDS during gestational week 14 showed significantly higher left amygdala MD. These results indicate that PMDS are linked to infants' amygdala microstructure in boys. These associations may be relevant to later neuropsychiatric outcomes in the offspring. Further research is required to better understand the mechanisms underlying these associations and to develop effective interventions to counteract any potential adverse consequences.

KEYWORDS
amygdala, diffusion tensor imaging, gray matter, mean diffusivity, prenatal maternal depression

1 | INTRODUCTION

Exposures to prenatal maternal depressive symptoms (PMDS) may predict the risk of developing long-term adverse physical and mental health outcomes in children (Bennett et al., 2004; Douros et al., 2017; Goodman et al., 2011; Lupien et al., 2009; Nazzari et al., 2019; Sidebottom et al., 2021). The risk of mothers developing depressive symptoms ranges from 7.4%, 12.8% and 12% during the first, second and third trimesters of pregnancy, respectively (Bennett et al., 2004; Sidebottom et al., 2021). PMDS have been associated with various negative health outcomes, including low birth weight (Bonari et al., 2004; Davalos et al., 2012), premature birth (Diego et al., 2009; Sandman et al., 1994), neurodevelopmental disorders such as autism and an increased risk for attention deficit hyperactivity disorder later in life (Kinney et al., 2008; Ronald et al., 2011). PMDS have also been linked with negative emotional, behavioural and cognitive outcomes with impacts that may extend into adolescence and adulthood (Markham & Koenig, 2011; Nolvi et al., 2016; O'Connor et al., 2002; Sandman et al., 1994).

Studies have shown that the amygdala undergoes significant growth during the embryonic stage and continues to develop throughout infancy (Humphrey, 1968; Uematsu et al., 2012).

PMDS exposures in offspring can result in changes in the structure of the amygdala. These changes occur in offspring not only at the macrostructural level, such as volume (Acosta, Kantojärvi, et al., 2020; Favaro et al., 2015; Lehtola et al., 2020; Lugo-Candelas et al., 2018; Wen et al., 2017) but also at the microstructural level (Rifkin-Graboi et al., 2013; Wen et al., 2017). The amygdala's structural and functional changes are associated with mental health disorders and depressive symptoms (Rosso et al., 2005; Straub et al., 2017). Therefore, it is a critical structure for understanding the biological mechanisms of PMDS on mental health and brain development in the offspring (Wen et al., 2017).

Microscopic features of brain structures can be assessed using diffusion tensor imaging (DTI) (Salo et al., 2018). DTI allows the mapping of tissue architecture based on the diffusion of hydrogen molecules, which generates a three-dimensional (3D) model of each voxel

using a 3×3 matrix, called a diffusion tensor (Stebbins, 2010). In each voxel, the diffusion tensor can be used to characterize the magnitude of diffusion and its direction using three eigenvectors (λ_1,λ_2,λ_3) (Stebbins, 2010). To the best of our knowledge, the amygdala diffusivity changes in response to PMDS in infants are limited to one study (Rifkin-Graboi et al., 2013). Rifkin-Graboi et al. (2013) reported that in 6- to 14-day-old infants, elevated PMDS were associated with decreased right and left amygdala fractional anisotropy (FA) and reduced right amygdala axial diffusivity (AD). The FA metrics measure the directionality of molecular displacement of water molecules and are sensitive to axonal diameter, myelin sheath thickness, fibre density and directionality (Tao et al., 2017). The AD metrics measure the movements of water molecules parallel to the axonal tracts, representing the longest observed eigenvector (Klawiter et al., 2011). FA and AD metrics can be difficult and misleading to interpret in the analysis of grey matter (GM) structures such as the amygdala, as diffusivity in GM is isotropic, meaning that diffusion in all three directions shows similar changes (Gillespie et al., 2017; Jeurissen et al., 2013; Yrondi et al., 2019). Thus, measurement of the mean diffusivity (MD) may be more accurate in providing information on the microstructure of the amygdala and other GM structures. The MD is an average of the three eigenvalues, which measures the overall amount of water diffusion regardless of its directionality (Stebbins, 2010). The MD metrics are affected by the number of barriers and restrictions to water motion in tissues, where high values indicate fewer restrictions and low values indicate more barriers in the underlying tissues (Clark et al., 2011; Tao et al., 2017). To date, the associations between PMDS and amygdala MD changes during infancy are still unknown.

PMDS at different stages of pregnancy have been shown to have a significant impact on fetal development. Investigating the effects of PMDS at different stages of pregnancy can provide valuable insights into the specific timing involved in fetal development, as well as the potential mechanisms that underlie these effects (Rifkin-Graboi et al., 2013). PMDS in early, mid or late pregnancy have been linked to amygdala development in offspring (Acosta, Kantojärvi, et al., 2020; Acosta, Tuulari, et al., 2020; Rifkin-Graboi et al., 2013). Amygdala development begins early in the embryonic period, and all the main amygdala subdivisions become evident around the first month of pregnancy (Humphrey, 1968; Müller & O'Rahilly, 2006). Amygdala neuronal migration, differentiation, axonal outgrowth and synaptogenesis continue throughout the second and third trimesters (Acosta, Tuulari, et al., 2020; Humphrey, 1968; Müller & O'Rahilly, 2006; Ulfig et al., 2006). As a result, PMDS at different stages of pregnancy may have different effects on amygdala development.

PMDS exposures have been observed to associate with the amygdala in a sex-specific manner (Acosta, Kantojärvi, et al., 2020; Acosta, Tuulari, et al., 2020; Lehtola et al., 2020; Wen et al., 2017). PMDS have been found to be associated with the amygdala in girls more than boys at the macro- and microstructural levels (Wen et al., 2017), whereas in other studies, PMDS have been found to be significantly associated with amygdala volumes in boys more than girls (Acosta, Kantojärvi, et al., 2020; Acosta, Tuulari, et al., 2020; Lehtola et al., 2020). Although investigating sex differences would allow a better assessment of the potential effects of PMDS, to the best of our knowledge, the sex-specific effects of PMDS measured in the amygdala microstructure at different pregnancy time points have not been investigated.

In the current study, we explored the effects of PMDS, measured by the Edinburgh Postnatal Depression Scale (EPDS), during gestational weeks (GW) 14, 24 and 34 on the amygdala MD metrics in infants aged 11–54 days. We explored the sexually dimorphic associations of PMDS with amygdala MD metrics. The nature of this work was exploratory, and no specific hypotheses were established.

2 | MATERIALS AND METHODS

2.1 | Participants

Participants were mother–infant dyads from the FinnBrain Birth Cohort Study (www.finnbrain.fi) (Karlsson et al., 2018). All mothers were Caucasian and Finnish. Background information was assessed via the mothers' self-report questionnaires at GW 14 and/or 34. Obstetric data were gathered from the Finnish Medical Birth Register of the National Institute for Health and Welfare (http://www.thl.fi). In all, 189 infants underwent MRI scans between the ages of 11 and 54 days after birth. Inclusion criteria were birth weights > 2500 g and gestational ages ≥ 36 weeks. Exclusion criteria were previously diagnosed congenital abnormalities of the central nervous system (CNS) and abnormal findings in a prior magnetic resonance imaging (MRI) scan. Of the 189 infants, 64 were excluded due to motion artifacts in the MR images, and five were excluded due to missing EPDS questionnaires. In the final sample, DTI images with 60 diffusion directions from 84 infants were included. In our sample, 11 infants had a record of mild asphyxia, and three had CPR and respirator treatment. All parent(s) provided written informed consent. This study was conducted following the Declaration of Helsinki and was approved by the Ethics Committee of

the Hospital District of Southwest Finland (ETMK:31/180/2011).

2.2 | Maternal prenatal depressive symptoms

PMDS were measured at GW 14, 24 and 34 using the EPDS questionnaire (Cox et al., 1987). The EPDS is a self-rated 10-item questionnaire validated for the evaluation of the previous 7 days of depressive symptoms (Adouard et al., 2005; Cox et al., 1987). Each item is scored on a 4-point scale with a total score range from 0 to 30 (Cox et al., 1987).

2.3 | Diffusion-weighted imaging data acquisition and processing

MRI scans were performed using the Siemens Magnetom Verio 3T scanner (Siemens Medical Solutions, Erlangen, Germany) as described before (Lehtola et al., 2019). A 96-direction diffusion-weighted imaging (DWI) protocol was divided into three parts (composed of 31, 32 and 33 non-identical diffusion encoding directions). The diffusion encoding directions were evenly distributed across the 3D space in the full 96-direction protocol in each part (each with a duration of approximately 6 min). For this study, 60 diffusion directions using $b = 1000$ s/mm^2 in addition to three $b = 0$ s/mm^2 images were selected. The sequences were acquired using the Spin Echo-Echo Planar Imaging sequence at 2-mm^3 isotropic resolution [field of view (FOV) 208 mm; 64 slices; repetition time (TR) 8500 ms; echo time (TE) 90 ms]. DWI data were processed as previously described (Merisaari et al., 2019). In each of the three DWI segments, the good-quality b0 volumes were aligned, averaged and moved to the front of the four-dimensional (4D) series. A brain mask was then created from the selected b0 volume using FSL (FMRIB Software Library v 5.0.9) (Jenkinson et al., 2012) and FSL's Brain Extraction Tool (Smith, 2002). The qualities of each diffusion data sets were evaluated using the DTIprep software version 1.2.4 (Oguz et al., 2014). The three DWI segments that now contained only quality-controlled data were combined by co-registering and averaging the B0 volumes of each segment and applying the transforms to the corresponding DWI data while adjusting the *b*-matrix correspondingly for the rotational component of the transforms. These fusion data sets contained a variable number of diffusion encoding directions (>60 directions). Directions in excess of 60 were removed while maximizing the angular resolution (Merisaari et al., 2019) and maintaining an even distribution of encoding directions (Roalf et al., 2016). The motion and eddy currents were corrected with FSL tools (Andersson & Sotiropoulos, 2016). The correlation to minor residual motion (after DTIprep and motion correction) was deemed small (Merisaari et al., 2019). Finally, to yield MD metrics, we processed the 4D diffusion dataset with FSL's dtifit, using the brain mask to limit the modelling exclusively to brain tissue.

2.4 | Labelling the structures

The left and right amygdala were identified in each subject using label-fusion-based methods. These methods depend on achieving good registrations between the entries using library templates, based on each study subject. We constructed a population-specific base template based on the methods described in Fonov et al. (2011), warped that template to the 21 subjects that best represented the morphological variation in the sample and manually labelled the amygdala on each template as previously described (Hashempour et al., 2019) (Figure 1). We then unwrapped these 21 manual segmentations, created consensus segmentation labels on the base template via a voxel-wise majority vote and constructed a library of warped versions of the labelled template that represented the morphological variation in the sample for those structures. This library was then used to label the individual brains via label-fusion-based labelling methods. A detailed description of the methods can be found in Lewis et al. (2019) and in Acosta, Tuulari, et al. (2020).

2.5 | Extracting diffusion metrics

The diffusion data were registered with the T1-weighted data, and the DTI metrics were extracted for the structures of interest as follows: (1) The B0 volume that contains raw T2 signal with no diffusion weighting was extracted from the diffusion datasets and registered with the nonuniformity-corrected T1-weighted data in native space; (2) the resultant transform was then concatenated with the transform from native to stereotaxic group average template space, and the result was applied to each of the DTI maps to overlay them on the T1-weighted data in stereotaxic space. For each DTI map, the mean values within the amygdala were calculated, taking into account the partial volume effects on the borders of each structure. The resolution of the diffusion data was 2 mm isotropic; thus, complete elimination of partial volume effects would have discarded a large portion of the measurements within small structures such as the amygdala. To eliminate most of the partial volume effects, while

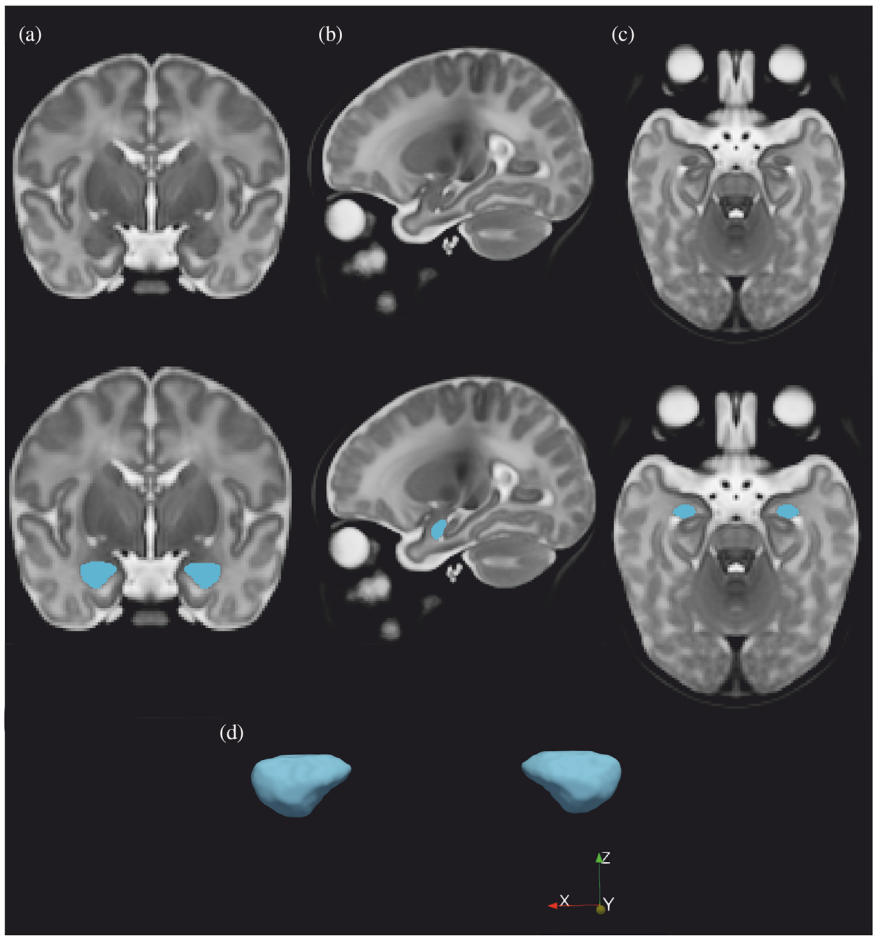


FIGURE 1 An example of manual segmentation of the amygdala on one of the templates that was used for the majority vote segmentation of the structural MRI data. The amygdala manual segmentation in (a) coronal (b) sagittal and (c) axial planes. (d) Three-dimensional segmentation of the amygdala.

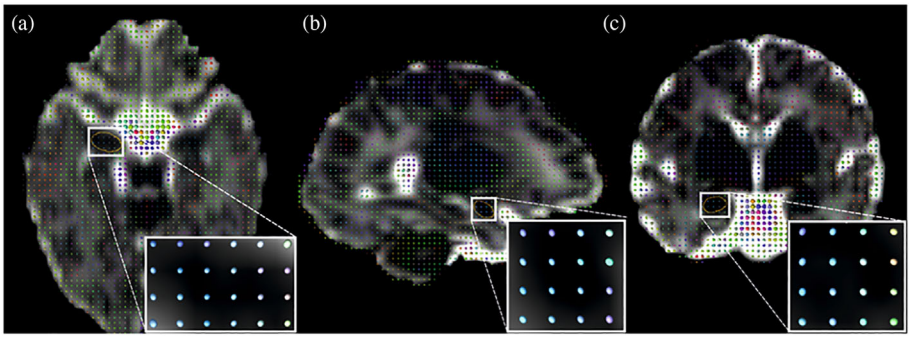


FIGURE 2 Example of the amygdala ellipsoids obtained from one of the participants in the study. The subject was a boy, exposed to a high level of prenatal maternal depressive symptoms. The amygdala ellipsoids on the (a) axial, (b) sagittal and (c) coronal planes. The MD map is the background in the figure.

also retaining a sufficient set of DTI measures for the statistical analysis, we eroded the amygdala labels by 1.5 mm before using the eroded labels as masks for the calculation of the mean of the remaining measures in each of the DTI maps. The DTI directions showing amygdala diffusion ellipsoids are shown in Figure 2.

2.6 | Statistical analyses

Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY) and R version 3.6.3 (http://www.r-project.org/). Figures were created using ParaView, ITK-SNAP and FSLeyes software (Ayachit, 2015; Jenkinson et al., 2012; Yushkevich et al., 2006).

The MD metrics were evaluated for the normality of their distributions across subjects and were not found to deviate statistically significantly from normal distributions ($p > .05$). To report associations of maternal and infant demographics with each other and with EPDS and MD metrics, bivariate Pearson correlations between measurement variables, one-way ANOVA and two-sample *t*-test between nominal and measurement variables were

performed. Covariates were tested with both EPDS and MD, and they were selected for further analyses if they had a significant association with either EPDS scores or MD metrics. Prenatal and postnatal factors considered for inclusion in the models were maternal use of selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), other CNS affecting medications, maternal age at the due date, economic situation based on parent(s) perspective obtained through questionnaires, maternal pre-pregnancy body mass index (BMI), infant 5-min Apgar score and infant weight at birth. In all the analyses, infant age at scan time, infant GW at birth and infant sex were included in the models.

The associations between the right and left amygdala MD metrics and EPDS scores were analysed using multiple linear regression models. Sex-specific associations between EPDS scores and the amygdala MD metrics were investigated using models that included an interaction between sex and an EPDS score. The *p*-values were corrected for multiple comparisons using the false-discovery rate (FDR) method (Benjamini & Hochberg, 1995). FDR corrections were performed separately over the six main effects analyses (from the models: MD ~ EPDS + covariates), and over the six sex interactions analyses (the interactions in the models: MD ~ EPDS*sex + covariate). In all analyses, the level of statistical significance was set at .05 (for both non-corrected and corrected *p*-values) (Table 1).

For the statistically significant outcomes, sensitivity analyses were carried out by repeating the multiple linear regression tests by adding and removing each of the included covariates (maternal use of SSRIs, SNRIs and CNS affecting medications, maternal age at the due date, economic situation, maternal pre-pregnancy BMI, infant 5-min Apgar score, infant weight at birth, infant age at scan time, infant GW at birth and infant sex) in the model, in a leave-one-out fashion. In the sensitivity analysis, we did not apply multiple comparison corrections. An overview of the performed sensitivity analyses is shown in Table 1.

3 | RESULTS

3.1 | Maternal and infants demographics

Table 2 shows the associations between the EPDS scores and the MD metrics with the demographics. The monthly income of the mothers is reported for the purposes of describing the sample's characteristics. However, only the mother's subjective assessment of their economic situation has been used in the analyses as it had significant associations with the EPDS scores. It has been shown that traditional objective social status does not completely represent perceived rankings of social hierarchy (Shaked et al., 2016). Additionally, research has demonstrated that a person's subjective assessment of their economic standing is more closely related to psychological outcomes like depressive symptoms than their absolute financial income (Shaked et al., 2016). Mothers with lower EPDS scores reported a better economic situation than mothers with higher EPDS scores during GW 24 and 34 ($r = -.261$, $p = .004$). Moreover, there was a negative association between EPDS scores during GW 14 and maternal age ($r = -.286$, $p = .002$). In infants, a negative correlation between maternal EPDS scores at GW 34 and infants' 5-min Apgar scores was observed ($r = -.201$, $p = .030$). Furthermore, higher MD metrics of the left amygdala were positively associated with infant age from birth at scan time ($r = -.399$, $p = .0004$). Maternal and infant demographic characteristics are presented in Tables 3 and 4, respectively.

3.2 | The main effect of PMDS on the amygdala MD metrics

The multiple linear regression analyses showed no main effects of any EPDS scores (GW 14, 24 and 34) on the MD of either the left or right amygdala when controlling for prenatal and postnatal factors (Table 5).

3.3 | Sex-specific associations of PMDS with the amygdala MD metrics

The analyses revealed a significant sex interaction effect of the EPDS GW 14 scores on MD of the left amygdala (EPDS GW 14-MD*sex B = −.005, $p = .006$, FDR-corrected, $p = .036$) (Table 6). The EPDS GW 14 were more positively associated with MD of the left amygdala in boys compared with girls after controlling for prenatal and postnatal factors (maternal use of SSRIs, SNRIs and CNS affecting medications, maternal age at the due date, economic situation, maternal pre-pregnancy BMI, infant 5-min Apgar score, infant weight at birth, infant age at scan time, infant GW at birth and infant sex). In boys, there was a positive association between EPDS GW 14 and MD of the left amygdala (EPDS GW 14-MD B = .005, $p = .007$, FDR-corrected, $p = .036$) (Figure 3). After all the sensitivity analyses, the sex interaction effect of EPDS GW 14 on the MD of the left amygdala remained significant ($p < .050$).

TABLE 1 Overview of the performed statistical analyses.

Statistical analysis steps	
1. Data normality for descriptive variables, DTI and EPDS measures were checked by visual inspection and the Shapiro–Wilk test.	
2. We performed descriptive statistics across the demographics.	
3. If covariates were associated with EPDS or MD metrics, they were selected for further analysis.	
4. We then perform multiple regression models controlling for the covariates and FDR correction.	
5. For the statistically significant outcomes, sensitivity analyses were carried out.	
a. Dependent variable: MD left and right amygdala	
b. Independent variables of interest: EPDS GW 14, 24 and 34.	
c. Identified potential covariates: maternal use of SSRIs, SNRIs and CNS affecting medications, maternal age at the due date, maternal economic situation based on parent(s) perspective obtained through questionnaire, maternal pre-pregnancy BMI, infant 5-min Apgar score and infant weight at birth. Infant age at scan, infant GW at birth and infant sex were included in all models.	
d. The level of statistical significance in all analyses was set at .05 (non-corrected and corrected *p*-values).	
Main effects analyses	
Left amygdala	**Right amygdala**
Model 1: MD LA ~ EPDS GW 14 + Covariates	Model 4: MD RA ~ EPDS GW 14 + Covariates
Model 2: MD LA ~ EPDS GW 24 + Covariates	Model 5: MD RA ~ EPDS GW 24 + Covariates
Model 3: MD LA ~ EPDS GW 34 + Covariates	Model 6: MD RA ~ EPDS GW 34 + Covariates
FDR correction over the six models	
Sex interaction analyses	
Model 1: MD LA ~ EPDS GW 14* infant sex + Covariates	Model 4: MD RA ~ EPDS GW 14* infant sex + Covariates
Model 2: MD LA ~ EPDS GW 24* infant sex + Covariates	Model 5: MD RA ~ EPDS GW 24* infant sex + Covariates
Model 3: MD LA ~ EPDS GW 34* infant sex + Covariates	Model 6: MD RA ~ EPDS GW 34* infant sex + Covariates
FDR correction over the six models	
Sensitivity analyses for statistically significant outcomes	
Model 1: MD LA ~ EPDS GW 14* infant sex + infant age at scan	
Model 2: MD LA ~ EPDS GW 14* infant sex + infant GW at birth	
Model 3: MD LA ~ EPDS GW 14* infant sex + infant 5-min Apgar score	
Model 4: MD LA ~ EPDS GW 14* infant sex + infant weight at birth	
Model 5: MD LA ~ EPDS GW 14* infant sex + maternal age at the due date	
Model 6: MD LA ~ EPDS GW 14* infant sex + maternal pre-pregnancy BMI	
Model 7: MD LA ~ EPDS GW 14* infant sex + maternal use of SSRIs/SNRIs	
Model 8: MD LA ~ EPDS GW 14* infant sex + maternal use of CNS affecting medications	
Model 9: MD LA ~ EPDS GW 14* infant sex + maternal economic situation	
Model 10: MD LA ~ EPDS GW 14* infant sex + infant age at scan + infant GW at birth	
Model 11: MD LA ~ EPDS GW 14* infant sex + infant age at scan + infant GW at birth + infant GW at birth	
Model 12: MD LA ~ EPDS GW 14* infant sex + infant age at scan + infant GW at birth + infant GW at birth + infant 5-min Apgar score	
Model 13: MD LA ~ EPDS GW 14* infant sex + infant age at scan + infant GW at birth + infant GW at birth + infant 5-min Apgar score + infant weight at birth	
Model 14: MD LA ~ EPDS GW 14* infant sex + infant age at scan + infant GW at birth + infant GW at birth + infant 5-min Apgar score + infant weight at birth + maternal age at the due date	
Model 15: MD LA ~ EPDS GW 14* infant sex + infant age at scan + infant GW at birth + infant GW at birth + infant 5-min Apgar score + infant weight at birth + maternal age at the due date + maternal pre-pregnancy BMI	
Model 16: MD LA ~ EPDS GW 14* infant sex + infant age at scan + infant GW at birth + infant GW at birth + infant 5-min Apgar score + infant weight at birth + maternal age at the due date + maternal pre-pregnancy BMI + maternal use of SSRIs/SNRIs	
Model 17: MD LA ~ EPDS GW 14* infant sex + infant age at scan + infant GW at birth + infant GW at birth + infant 5-min Apgar score + infant weight at birth + maternal age at the due date + maternal pre-pregnancy BMI + maternal use of SSRIs/SNRIs + maternal use of CNS affecting medications	
Model 18: MD LA ~ EPDS GW 14* infant sex + infant age at scan + infant GW at birth + infant GW at birth + infant 5-min Apgar score + infant weight at birth + maternal age at the due date + maternal pre-pregnancy BMI + maternal use of SSRIs/SNRIs + maternal use of CNS affecting medications + maternal economic situation	

TABLE 2 Associations between the EPDS scores, the amygdala mean diffusivity (MD) and the demographics.

Variables	EPDS GW 14	EPDS GW 24	EPDS GW 34	MD LA	MD RA
Maternal pre-pregnancy BMI, *r*	−.06	−.00	−.07	.94	.19
Mother's age at due date (years), *r*	−.32**	−.23*	−.19	−.12	.01
Infant gestational age at birth (week), *r*	−.01	.05	.05	.15	−.14
Infant age at the scan date (days), *r*	.03	.02	.00	−.42**	−.05
Birth weight (g), *r*	−.07	.01	.06	.01	−.06
Apgar, 5 min, *r*	−.08	−.12	−.14	−.12	.02
Infant head circumference (cm), *r*	−.04	.02	−.07	.10	.12
Birth complications					
Asphyxia, *p*	.63	.46	.58	.36	.91
Yes, mean (SD)	4.5 (4.5)	5.7 (5.5)	6.0 (5.6)	1.03 (.02)	1.05 (.02)
No, mean (SD)	6.0 (5.5)	6.0 (5.6)	5.7 (5.3)	1.04 (.04)	1.05 (.04)
Respirator treatment after birth, *p*	$p = .97$	$p = .96$	$p = .92$	$p = .55$	$p = .94$
Yes, mean (SD)	3.7 (3.2)	3.3 (2.1)	5.3 (2.5)	1.02 (.01)	1.05 (.02)
No, mean (SD)	5.9 (5.5)	6.0 (5.6)	5.8 (5.4)	1.04 (.04)	1.05 (.03)
Pregnancy complications					
Anemia, *p*	.43	.93	.97	.84	.96
Yes, mean (SD)	6.2 (6.3)	3.8 (4.3)	4.8 (4.9)	1.03 (.02)	1.05 (.04)
No, mean (SD)	5.9 (5.4)	6.1 (5.7)	5.8 (5.4)	1.04 (.04)	1.05 (.03)
Hypertension, *p*	.83	.44	.84	.24	.17
Yes, mean (SD)	4.3 (4.2)	8.0 (5.3)	7.0 (1.0)	1.04 (.04)	1.05 (.03)
No, mean (SD)	5.9 (5.5)	5.9 (5.6)	5.7 (5.4)	1.07 (.01)	1.08 (.06)
Diabetes, *p*	.920	.065	.106	.77	.81
Yes, mean (SD)	4.0 (3.0)	4.9 (5.1)	4.6 (3.9)	1.04 (.04)	1.05 (.04)
No, mean (SD)	6.1 (5.6)	6.1 (5.6)	5.9 (5.4)	1.04 (.03)	1.05 (.03)
Parent's relationship status, *p*	.20	.18	.67	.80	.89
Married, mean (SD)	5.8 (5.4)	5.8 (5.5)	5.6 (5.4)	1.04 (.03)	1.05 (.04)
In a relationship, mean (SD)	8.0 (5.5)	9.2 (6.0)	7.2 (4.2)	1.05 (.03)	1.03 (.02)
No relationship, mean (SD)	.0 (NA)	.0 (NA)	5.0 (NA)	1.03 (NA)	1.06 (NA)
Economic situation, *p*	.01	.04	.03	.80	.33
Very good, mean (SD)	3.5 (3.4)	2.0 (1.7)	3.2 (2.6)	1.05 (.04)	1.05 (.02)
Fairly good, mean (SD)	5.1 (5.5)	5.2 (5.4)	4.6 (5.1)	1.04 (.04)	1.04 (.04)
Not good, mean (SD)	6.2 (5.0)	6.2 (5.0)	6.1 (4.8)	1.04 (.04)	1.05 (.03)
Fairly bad, mean (SD)	9.9 (6.0)	9.9 (6.0)	12.0 (4.4)	1.04 (.04)	1.07 (.04)
Very bad, mean (SD)	.0 (NA)	.0 (NA)	.0 (NA)	.0 (NA)	.0 (NA)
Prenatal alcohol consumption, *p*	.49	.41	.12	.51	.38
Yes, mean (SD)	3.7 (3.5)	1.7 (1.6)	4.2 (2.5)	1.04 (.04)	1.05 (.01)
No, mean (SD)	5.4 (4.8)	5.6 (4.9)	5.5 (5.1)	1.05 (.03)	1.06 (.03)
Prenatal medication use of selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, *p*	.02	.38	.31	.13	.90
Yes, mean (SD)	8.2 (6.1)	8.2 (5.6)	8.8 (7.4)	1.07 (.08)	8.2 (5.6)
No, mean (SD)	5.4 (5.1)	5.4 (5.1)	5.4 (5.0)	1.04 (.03)	1.05 (.03)

TABLE 2 (Continued)

Variables	EPDS GW 14	EPDS GW 24	EPDS GW 34	MD LA	MD RA
Prenatal education level, *p*	.15	.47	.652	.32	.27
Low (high school or lower)	6.1 (5.7)	5.7 (4.9)	6.3 (5.7)	1.05 (.05)	1.06 (.04)
Middle (vocational degree)	5.1 (5.0)	5.3 (5.6)	4.6 (4.8)	1.04 (.05)	1.04 (.03)
High (master's degree or higher)	6.1 (5.6)	6.5 (6.1)	6.1 (5.4)	1.03 (.02)	1.04 (.03)

* $p < .05$
** $p < .01$

TABLE 3 Maternal demographics.

Variables	Entire sample $N = 84$	Girls $N = 42$	Boys $N = 42$	Difference in *p*-value between girls and boys
EPDS (GW 14), Mean (SD)	5.9 (5.5)	5.8 (6.0)	6.0 (5.1)	.6
EPDS (GW 24), Mean (SD)	6.0 (5.6)	6.1 (6.2)	5.9 (5.0)	.8
EPDS (GW 34), Mean (SD)	5.9 (5.3)	5.7 (5.5)	6.0 (5.1)	.9
Maternal pre-pregnancy BMI, Mean (SD)	24.6 (4.2)	24.0 (3.8)	25.2 (4.5)	.8
Mother's age at due date (years), Mean (SD)	30.0 (4.6)	29.7 (4.6)	30.3 (4.6)	.3
Pregnancy complications, %				
Anemia	6%	2.4%	9.5%	.3
Hypertension	3.6%	7.1%	0%	.2
Diabetes (none of the mothers had diabetes prior to pregnancy)	10.7%	11.9%	9.5%	1
Parent's relationship status, %				
Married/in a relationship	96.5%	92.9%	100%	.5
Maternal monthly income in euros				1.6
<1000	20.1%	19.6%	18.2%	
1000–2000	55.6%	56.8%	54.6. %	
2000–3000	22.5%	21.6%	21.2%	
>3000	1.8%	2%	6%	
Maternal economic subjective rating, %				.1
Very good	7.1%	2.4%	11.9%	
Fairly good	52.4%	59.5%	45.25%	
Not good	29.8%	31%	28.6%	
Fairly bad	9.5%	4.8%	14.3%	
Very bad	0%	0%	0%	
Prenatal alcohol, % yes	8.7%	4.8%	7.1%	.6
Nicotine consumption, % yes	0%	0%	0%	0
Illicit drug consumption, % yes	0%	0%	0%	0
Prenatal medication use of selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, % yes	6%	4.8%	7.1%	1
Prenatal use of CNS affecting medication, % yes	.9%	0%	1.5%	.1
Prenatal education level %				.7
Low (high school or lower)	28.6%	23.8%	33.3%	
Middle (vocational degree)	34.5%	33.3%	35.7%	
High (master's degree or higher)	35.7%	40.5%	31%	

TABLE 4 Infants demographics.

Variables	Entire sample $N = 84$	Girls $N = 42$	Boys $N = 42$	Difference p-value between girls and boys
Infant gestational age at birth (week), Mean (SD)	39.9 (1.1)	39.75 (1.1)	40.06 (1.1)	.2
Infant age at the scan date (days), Mean (SD)	25.43 (7.8)	25.76 (7.4)	25.1 (8.3)	.8
Birth weight (gram), Mean (SD)	3491.9 (464.2)	3368.1 (387.3)	3621 (508)	.02
Apgar, 5 min	8.93 (1.0)	9.2 (.5)	8.6 (1.3)	.1
Infant head circumference (cm), Mean (SD)	34.9 (1.2)	34.6 (1.2)	35.3 (1.2)	.01
Birth complications % yes	0%	0%	0%	0
Asphyxia	13.1%	19.%	7.1.%	.1
Respirator treatment after birth	3.6%	2.4%	4.8%	1

TABLE 5 The main effect of the Edinburgh Postnatal Depression Scale (EPDS) after controlling for maternal use of SSRIs/SNRIs, other CNS affecting medications, maternal age at the due date, the maternal economic situation, maternal pre-pregnancy BMI, infant 5-min Apgar score, infant weight at birth, maternal age at the due date, infant age at scan, infant GW at birth and infant sex on amygdala MD metrics are shown.

	Left amygdala				Right amygdala			
Multiple linear regression model	B	SE	P	P (FDR)	B	SE	P	P (FDR)
EPDS GW 14 + control variables	.001	.001	.420	.885	−.001	.001	.564	.885
EPDS GW 24 + control variables	−.0002	.001	.820	.885	−.001	.001	.438	.885
EPDS GW 34 + control variables	.0001	.001	.885	.885	−.0004	.001	.664	.885

Note: B, estimates; SE, standard error; P, uncorrected p-values; P (FDR), FDR-corrected p-values.

TABLE 6 The interaction effect of the Edinburgh Postnatal Depression Scale (EPDS) and sex after controlling for maternal use of SSRIs/SNRIs, other CNS affecting medications, maternal age at the due date, economic situation, maternal pre-pregnancy BMI, infant 5-min Apgar score, infant weight at birth, maternal age at the due date, infant age at scan, infant GW at birth, and infant sex on amygdala MD metrics are shown.

	Left amygdala				Right amygdala			
Multiple linear regression model	B	SE	P	P (FDR)	B	SE	P	P (FDR)
Sex * EPDS GW 14 + control variables	−.005	.002	.006*	.036*	−.002	.002	.283	.351
Sex * EPDS GW 24 + control variables	−.002	.002	.351	.351	−.003	.002	.224	.351
Sex * EPDS GW 34 + control variables	−.002	.002	.344	.351	−.003	.002	.147	.351

Note: B, estimates; SE, standard error; P, uncorrected p-values; P (FDR), FDR-corrected p-values.
*Significant results ($p < .05$).

4 | DISCUSSION

In this study, we investigated for the first time the influences of PMDS measured during GW 14, 24 and 34 on the amygdala MD of infants. Our study may have overcome some of the limitations of the existing literature by using a longitudinal strategy to assess PMDS at different time points to determine its prevalence throughout the pregnancy. Furthermore, we analysed sex as an interacting factor, to explore sex differences. Our analyses revealed no main effects of any EPDS scores on the amygdala MD. However, greater PMDS measured at the GW 14 were associated with a normal distribution higher MD of the left amygdala in boys compared with girls. These findings that survived the multiple comparison analyses may suggest that the amygdala microstructure is sensitive to PMDS and that sensitivity differs between sexes.

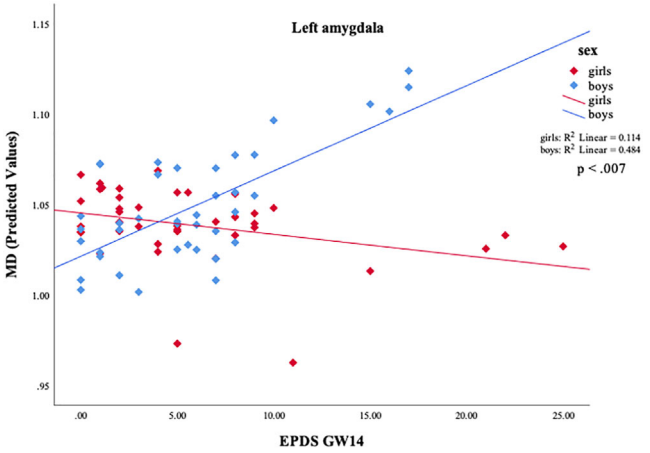


FIGURE 3 The interaction between Edinburg Postnatal Depression Scale (EPDS) gestational week (GW) 14 and infant sex on the mean diffusivity (MD) of the infant left amygdala is presented (predicted values, controlling for maternal use of selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, other CNS affecting medications, maternal age at the due date, economic situation, maternal pre-pregnancy body mass index, infant 5-min Apgar score, weight at birth, infant age at scan, infant GW at birth and infant sex).

4.1 | Sex differences in the effects of PMDS

The underlying mechanisms causing the different effects of PMDS on fetal development in boys and girls remain unclear. The sustainability of boys to PMDS observed in our findings may be attributed to different reasons. One potential explanation is the different placental responses to glucocorticoids in boy and girl pregnancies (Clifton, 2010). Elevated maternal cortisol can modulate placental gene expression and protein synthesis and reduces growth in girls to increase survival (Clifton, 2010). In contrast, there are fewer changes in placental function in boy pregnancies, ensuring growth even in the presence of negative environmental factors but likely increasing vulnerability to other risk factors (Clifton, 2010). Moreover, shortly after birth, boys' brains have 10.2% more cortical GM, 6.4% more WM and 7.8% more subcortical GM than girls' at birth (Gilmore et al., 2007). These differences most likely occur during prenatal brain development (Gilmore et al., 2007). Consequently, boy brains form a greater number of connections, myelin and synapses (Alonso-Nanclares et al., 2008). This may make them more susceptible to the negative effects of PMDS, leading to an increased likelihood of neurodevelopmental disorders. For instance, studies have found that boys who were exposed to high levels of PMDS during infancy displayed symptoms such as heightened anxiety, poorer motor skills and increased sleep disturbances (Gerardin et al., 2011; Hay et al., 2019). Whether girls or boys are more vulnerable to PMDS depends on the type, severity, timing of PMDS exposures and age of the offspring at the time of investigation (Bale et al., 2015; Glover et al., 2010).

4.2 | Timing of prenatal depressive symptoms exposures

Increased maternal cortisol levels can cross the placenta and permanently alter the fetal HPA axis, affecting cognitive and behavioural functions later in life (Glover et al., 2010; Rakers et al., 2016). 11Beta hydroxysteroid dehydrogenase 2 (11-HSD2) enzyme regulates placental glucocorticoid metabolism (Murphy & Clifton, 2003), and it converts the glucocorticoids cortisol into its inactive form (Benediktsson et al., 1997). Although the 11β–HSD2 enzyme inactivates approximately 80%–90% of the maternal cortisol, the foetus is less protected from maternal cortisol during early pregnancy, when placental 11β-HSD2 levels are lower or are not yet activated (Rakers et al., 2016). The results of the current study suggest that the negative effects of PMDS may be more significant when exposure occurs during early pregnancy, as opposed to later stages. Exposure to cortisol during early pregnancy can be linked not to fetal susceptibility but to maternal susceptibility, as the fetal HPA axis cannot produce cortisol until late gestation (Magyar et al., 1980; Rakers et al., 2016). PMDS measured at different pregnancy time points allows for a more accurate assessment of potentially vulnerable prenatal periods.

4.3 | Prenatal depressive symptoms and the left amygdala vulnerability

The analyses in this study revealed that the left amygdala MD is associated with PMDS. The vulnerability of the left amygdala to PMDS can be attributed to the fact that the left hemisphere grows faster during the prenatal period (Andescavage et al., 2017). In infants, the left-hemisphere GM is approximately 5% larger than the right-hemisphere GM (Gilmore et al., 2007). Furthermore, in patients with major depressive disorder, top-down responses may involve only the left amygdala (Ramasubbu et al., 2014). Moreover, positive associations between PMDS and the connectivity of the left amygdala with other brain regions have been observed (Qiu et al., 2015). Additionally, higher pregnancy-specific anxiety has been linked to smaller left amygdala volumes in offspring (Acosta

et al., 2019). However, further research is needed to fully understand the underlying mechanisms of the left amygdala's vulnerability to PMDS.

4.4 | Prenatal depressive symptoms and the amygdala diffusivity

Our findings support prior research that has established an association between PMDS and amygdala microstructural changes in infants (Rifkin-Graboi et al., 2013). Rifkin-Graboi et al. (2013) reported that higher PMDS during GW 26 was associated with lower right and left amygdala FA as well as lower right amygdala AD metrics. Although FA and AD are commonly used DTI metrics, they are not always reliable markers to be evaluated in GM structures such as the amygdala (Gillespie et al., 2017; Jeurissen et al., 2013). This can be attributed to the isotropic nature of diffusion in GM, implying that changes in diffusion are similar in all three directions (Gillespie et al., 2017; Jeurissen et al., 2013; Sexton et al., 2010; Yrondi et al., 2019). However, we additionally compared the associations of PMDS (GW 14, 24 and 34) and amygdala FA and AD metrics in our sample with those reported by Rifkin-Graboi et al. (Rifkin-Graboi et al., 2013). As expected, after controlling for the prenatal and postnatal factors, no alterations in the amygdala FA or AD metrics in either the main effect or sex-specific association analyses were observed. The amygdala does not contain much white matter (WM) (Jeurissen et al., 2013; Yrondi et al., 2019), FA commonly measures the fibre orientation and integrity of WM structures (Bao et al., 2018; Yrondi et al., 2019) and AD may largely reflect MD in regions with little WM such as the amygdala. Although there is evidence for the presence of WM pathways to the amygdala nuclei (McFadyen et al., 2019), FA and AD metrics in the amygdala should be interpreted with caution. Thus, measurement of the MD metrics may be more appropriate to provide information on the microstructure of the amygdala and other GM structures. Another interpretation for the unchanged amygdala FA and AD may be attributed to our improved labelling procedure for the amygdala and the 1.5 mm erosion, which may have reduced the partial volume effect on the data (see Section 2). Additionally, other factors might have contributed to the disparity in these findings, such as ethnicity and cultural differences in the rate and type of prenatal maternal stressors. Moreover, differences in the applied DTI methodology, such as the different number of diffusion directions [60 in our dataset and 19 in Rifkin-Graboi et al. (2013) dataset] and different *b*-values [1000 s/mm^2 in our dataset and 600 s/mm^2 in Rifkin-Graboi et al. (2013) dataset], could also have contributed to these discrepancies. There has been controversy over the use of the optimal number of diffusion directions (Jones, 2004; Pervolaraki et al., 2018). However, in cases and where feasible, utilizing a greater number of diffusion directions enables a more robust tensor model fitting and enhances the accuracy of the outcomes (Tian et al., 2020). This can be particularly useful in the imaging of infant brains, due to the lower image resolution (Gousias et al., 2012) and the presence of artifacts due to movement during the scan (Weisenfeld et al., 2006).

The underlying mechanisms behind the observed changes in the amygdala MD in our study are not clear. MD is generally expected to decrease in children and young adolescents (Lebel et al., 2010; Moura et al., 2016; Pohl et al., 2016; Taki et al., 2013), as well as in neonates, due to preliminary myelination (Aeby et al., 2009; Dubois et al., 2008; Mukherjee et al., 2002; Partridge et al., 2004). Reduced MD metrics throughout childhood and adolescence are generally indicative of brain maturation (Tamnes et al., 2010; Yoshida et al., 2013). MD alterations can occur from a shift in the concentration of water within the intracellular and extracellular compartments (Gillespie et al., 2017). Elevated MD metrics have been associated with a reduction in neuron size and synapse loss, along with alterations in the cytoarchitecture that lead to neurofibrillary changes and an increase in the extracellular space (Cherubini et al., 2010; De Gennaro et al., 2011; Gillespie et al., 2017; Kantarci et al., 2005). These changes in tissue structure can result in faster water diffusion and are observed in instances of both immature brain development and tissue degeneration (Cherubini et al., 2010; De Gennaro et al., 2011; Gillespie et al., 2017; Kantarci et al., 2005). Additionally, it has been reported that increased MD metrics in the left amygdala are associated with reduced microstructure integrity in subjects with lower emotional load scores, shorter dreams (De Gennaro et al., 2011) and anxiety in patients with traumatic brain injury (Juranek et al., 2012). Higher amygdala MD has been linked to cognitive impairment, Alzheimer's disease (Cherubini et al., 2010) and excessive alcohol use (Sasaki et al., 2009). However, it has also been correlated with improved empathizing ability, cooperativeness and cognitive function (Takeuchi et al., 2019). Interestingly, a decrease in the left amygdala MD has been observed after electroconvulsive therapy in patients with treatment-resistant depression, indicating possible normalization of microstructural integrity (Yrondi et al., 2019).

Increased cortisol exposure in utero due to higher levels of PMDS may have negative effects on fetal brain development. This may result in greater MD metrics in the amygdala possibly due to several physiological

mechanisms such as increased water diffusivity, neuron shrinkage and altered tissue maturation. However, it remains uncertain which mechanisms are responsible for the higher MD metrics in the amygdala or why these alterations occur in response to PMDS. Furthermore, alterations in the amygdala MD metrics may be linked to psychiatric disorders and adverse emotional outcomes in the offspring. Nonetheless, these alterations may be important aspects of normal brain development, and optimal mental health and brain development are not necessarily contingent on a greater number of neural components in healthy individuals. These hypotheses are purely speculative, and further research is needed to investigate them thoroughly.

4.5 | Limitations

Several of the limitations in this study should be considered in future works. DTI analysis of GM is currently constrained because of the small size of GM in some brain regions, which might fall below the resolution of DTI acquisition parameters (Salat, 2013). Alternatively, limitations in the current DTI methodologies prove the potential of DTI to map GM microstructural properties and the need for further improvement of DTI techniques (Salat, 2013). Furthermore, biophysical tissue modelling, such as neurite orientation and dispersion density imaging, may be more suitable in GM studies for inferring tissue microstructure (Stoye et al., 2020). In addition, although our data had an improved amygdala delineation on higher resolution template MR images (.5 mm), our region-of-interest (ROI) delineations were limited to the amygdala as a whole, without segmenting the amygdala nuclei separately. This emphasizes the importance of considering sub-regions of the amygdala when possible, as PMDS could alter the development of the amygdala nuclei differentially. However, this is particularly difficult in infants because of the small brain size and lower resolution of the infants' brain MR and DTI images (Hashempour et al., 2019). In addition, the sample size of our study was rather small, which might have reduced the power of our study results. The findings therefore need replication with a larger sample size. Furthermore, the PMDS in this study were not clinically confirmed and were based on the mother's report of her own depressive symptoms. Moreover, measuring the activity of 11β-HSD2 might provide a more accurate measure of regulation of the placental barrier for cortisol (Acosta et al., 2019). Additionally, our results were based on only PMDS, and the effects may be different from other psychological symptoms such as pregnancy-specific anxiety and general anxiety (Satu J. Lehtola et al., 2020). Furthermore, the assessment of PMDS in a high-income country with relatively high social support could affect our results. Therefore, the results could differ on a worldwide scale. Finally, investigating the emotional, cognitive and behavioural impacts of altered brain DTI metrics may be a valuable tool to predict the vulnerability of offspring to psychological and psychiatric disorders later in childhood, adolescence and adulthood.

5 | CONCLUSIONS

In conclusion, our findings provide new insights into the associations between PMDS and fetal amygdala development. Our study was the first to report associations between PMDS measured at three different pregnancy time points and amygdala diffusion properties in infants. We observed that greater PMDS during early pregnancy was associated with higher MD metrics in the left amygdala of boys but not of girls. Future studies are needed to determine the underlying mechanism of the observed changes and how changes in the diffusion properties of the amygdala in response to PMDS may impact the behavioural and mental health of offspring.

AUTHORS' CONTRIBUTION

Niloofar Hashempour: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing–Original Draft, Writing–Review and Editing, Visualization. **Jetro J. Tuulari:** Conceptualization, Software, Formal analysis, Investigation, Data Curation, Writing–Review and Editing, Supervision. **Harri Merissari:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing–Review and Editing. **Henriette Acosta & Juho Pelto**: Methodology, Formal analysis, Writing–Review and Editing. **John D. Lewis:** Conceptualization, Methodology, Software, Data Curation, Formal analysis, Writing–Review and Editing. **Noora M. Scheinin:** Conceptualization, Investigation, Writing–Review and Editing. **D. Louis Collins:** Project administration, Funding acquisition, Writing–Review and Editing. **Vladimir S. Fonov:** Methodology, Software, Writing–Review and Editing. **Satu J. Lehtola:** Investigation, Writing–Review and Editing. **Jani Saunavaara, Tuire Lähdesmäki & Riitta Parkkola:** Investigation, Writing–Review and Editing. **Linnea Karlsson:** Resources, Project administration, Funding acquisition, Writing–Review and Editing. **Hasse Karlsson:** Conceptualization, Resources, Supervision, Project administration, Funding acquisition, Writing–Review and Editing.

ACKNOWLEDGEMENTS

This work was funded by the University of Turku Graduate School (NH); the Orion Research Foundation (NH, JJT); the Sigrid Juselius Foundation (JJT); the Emil Aaltonen Foundation (JJT); the Juho Vainio Foundation (JJT and SJL); the Hospital District of Southwest Finland State Research Grants [NH, HM, SJL, grant number P3006 (JJT), grant number P3003 (NMS), grant number P3498 (HK), grant number P3654 (LK) and K3562 (RP)]; the Jane and Aatos Erkko Foundation (HA and HK); the Maire Taponen Foundation (SJL); the Azrieli Neurodevelopmental Research Program [grant number ANRP-MIRI13–3388 (JDL)]; the Canadian Institutes of Health Research (VSF and DLC); the Natural Sciences and Engineering Research Council of Canada (DLC); the NARSAD Brain and Behavior Research Foundation [grant number 1956 (LK)]; the Signe and Ane Gyllenberg Foundation (LK and HK); the Academy of Finland [grant number 26080983 (HM), grant number 308176 (LK), grant numbers 264363, 253270 and 134950 (HK)]. Finally, we thank Teemu Kemppainen, Krisse Kuvaja and assisting personnel that helped with participant recruitment, as well as all FinnBrain families that took part in the imaging studies.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The datasets for this study will not be made publicly available because of Finnish data protection legislation. Requests to access the datasets should be directed to the principal investigator of the FinnBrain Birth Cohort study (Hasse Karlsson; hasseka@utu.fi).

ORCID

Niloofar Hashempour https://orcid.org/0000-0002-5855-8969
Harri Merisaari https://orcid.org/0000-0002-8515-5399

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.15989.

REFERENCES

Acosta, H., Kantojärvi, K., Hashempour, N., Pelto, J., Scheinin, N. M., Lehtola, S. J., Lewis, J. D., Fonov, V. S., Collins, D. L., Evans, A., Parkkola, R., Lähdesmäki, T., Saunavaara, J., Karlsson, L., Merisaari, H., Paunio, T., Karlsson, H., & Tuulari, J. J. (2020). Partial support for an interaction between a polygenic risk score for major depressive disorder and prenatal maternal depressive symptoms on infant right amygdalar volumes. *Cerebral Cortex*, *1–14*, 6121–6134. https://doi.org/10.1093/cercor/bhaa158

Acosta, H., Tuulari, J. J., Scheinin, N. M., Hashempour, N., Rajasilta, O., Lavonius, T. I., Pelto, J., Saunavaara, V., Parkkola, R., Lähdesmäki, T., Karlsson, L., & Karlsson, H. (2019). Maternal pregnancy-related anxiety is associated with sexually dimorphic alterations in amygdala volume in 4-year-old children. *Frontiers in Behavioral Neuroscience*, *13*(August), 1–16. https://doi.org/10.3389/fnbeh.2019.00175

Acosta, H., Tuulari, J., Scheinin, N., Hashempour, N., Rajasilta, O., Lavonius, T., Pelto, J., Saunavaara, V., Parkkola, R., Lähdesmäki, T., Karlsson, L., & Karlsson, H. (2020). Prenatal maternal depressive symptoms are associated with smaller amygdalar volumes of four-year-old children. *Psychiatry Research: Neuroimaging*, *304*(July), 111153. https://doi.org/10.1016/j.pscychresns.2020.111153

Adouard, F., Glangeaud-Freudenthal, N. M. C., & Golse, B. (2005). Validation of the Edinburgh postnatal depression scale (EPDS) in a sample of women with high-risk pregnancies in France. *Archives of Women's Mental Health*, *8*(2), 89–95. https://doi.org/10.1007/s00737-005-0077-9

Aeby, A., Liu, Y., De Tiège, X., Denolin, V., David, P., Balériaux, D., Kavec, M., Metens, T., & Van Bogaert, P. (2009). Maturation of thalamic radiations between 34 and 41 weeks' gestation: A combined voxel-based study and probabilistic tractography with diffusion tensor imaging. *American Journal of Neuroradiology*, *30*(9), 1780–1786. https://doi.org/10.3174/ajnr.A1660

Alonso-Nanclares, L., Gonzalez-Soriano, J., Rodriguez, J. R., & DeFelipe, J. (2008). Gender differences in human cortical synaptic density. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(38), 14615–14619. https://doi.org/10.1073/pnas.0803652105

Andersson, J., & Sotiropoulos, S. N. (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *NeuroImage*, *125*, 1063–1078. https://doi.org/10.1016/j.neuroimage.2015.10.019

Andescavage, N. N., du Plessis, A., McCarter, R., Serag, A., Evangelou, I., Vezina, G., Robertson, R., & Limperopoulos, C. (2017). Complex trajectories of brain development in the healthy human fetus. *Cerebral Cortex (New York, N.Y.: 1991)*, *27*, 5274–5283. https://doi.org/10.1093/cercor/bhw306

Ayachit, U. (2015). *The paraview guide: A parallel visualization application* (p. 2015). Kitware, Inc.

Bale, T. L., Neill Epperson, C., & Neurosci, N. (2015). Sex differences and stress across the lifespan HHS public access author manuscript. *Nature Neuroscience*, *18*(10), 1413–1420. https://doi.org/10.1038/nn.4112

Bao, Y., He, R., Zeng, Q., Zhu, P., Zheng, R., & Xu, H. (2018). Investigation of microstructural abnormalities in white and gray matter around hippocampus with diffusion tensor imaging (DTI) in temporal lobe epilepsy (TLE). *Epilepsy and Behavior*, *83*, 44–49. https://doi.org/10.1016/j.yebeh.2017.12.002

Benediktsson, R., Calder, A. A., Edwards, C. R. W., & Seckl, J. R. (1997). Placental 11β-hydroxysteroid dehydrogenase: A key regulator of fetal glucocorticoid exposure. *Clinical Endocrinology*, *46*(2), 161–166. https://doi.org/10.1046/j.1365-2265.1997.1230939.x

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing.

Journal of the Royal Statistical Society: Series B: Methodological, *57*(1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Bennett, H. A., Einarson, A., Taddio, A., Koren, G., & Einarson, T. R. (2004). Prevalence of depression during pregnancy: Systematic review. *Obstetrics and Gynecology*, *103*(4), 698–709. https://doi.org/10.1097/01.AOG.0000116689.75396.5f

Bonari, L., Pinto, N., Ahn, E., Einarson, A., Steiner, M., & Koren, G. (2004). Perinatal risks of untreated depression during pregnancy. *Canadian Journal of Psychiatry*, *49*(11), 726–735. https://doi.org/10.1177/070674370404901103

Cherubini, A., Péran, P., Spoletini, I., Di Paola, M., Di Iulio, F., Hagberg, G. E., Sancesario, G., Gianni, W., Bossù, P., Caltagirone, C., Sabatini, U., & Spalletta, G. (2010). Combined volumetry and DTI in subcortical structures of mild cognitive impairment and Alzheimer's disease patients. *Journal of Alzheimer's Disease*, *19*(4), 1273–1282. https://doi.org/10.3233/JAD-2010-091186

Clark, K. A., Nuechterlein, K. H., Asarnow, R. F., Hamilton, L. S., Phillips, O. R., Hageman, N. S., Woods, R. P., Alger, J. R., Toga, A. W., & Narr, K. L. (2011). Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia. *Psychiatry Research*, *23*(1), 1–7. https://doi.org/10.1161/CIRCULATIONAHA.110.956839

Clifton, V. L. (2010). Review: Sex and the human placenta: Mediating differential strategies of fetal growth and survival. *Placenta*, *31*(SUPPL), S33–S39. https://doi.org/10.1016/j.placenta.2009.11.010

Cox, J. L., Holden, J. M., & Sagovsky, R. (1987). Detection of postnatal depression: Development of the 10-item Edinburgh postnatal depression scale. *British Journal of Psychiatry*, *150*(JUNE), 782–786. https://doi.org/10.1192/bjp.150.6.782

Davalos, D. B., Yadon, C. A., & Tregellas, H. C. (2012). Untreated prenatal maternal depression and the potential risks to offspring: A review. *Archives of Women's Mental Health*, *15*(1), 1–14. https://doi.org/10.1007/s00737-011-0251-1

De Gennaro, L., Cipolli, C., Cherubini, A., Assogna, F., Cacciari, C., Marzano, C., Curcio, G., Ferrara, M., Caltagirone, C., & Spalletta, G. (2011). Amygdala and hippocampus volumetry and diffusivity in relation to dreaming. *Human Brain Mapping*, *32*(9), 1458–1470. https://doi.org/10.1002/hbm.21120

Diego, M. A., Field, T., Hernandez-Reif, M., Schanberg, S., Kuhn, C., & Gonzalez-Quintero, V. H. (2009). Prenatal depression restricts fetal growth. *Early Human Development*, *85*(1), 65–70. https://doi.org/10.1016/j.earlhumdev.2008.07.002

Douros, K., Moustaki, M., Tsabouri, S., Papadopoulou, A., Papadopoulos, M., & Priftis, K. N. (2017). Prenatal maternal stress and the risk of asthma in children. *Frontiers in Pediatrics*, *5*(September), 1, 202–9. https://doi.org/10.3389/fped.2017.00202

Dubois, J., Dehaene-Lambertz, G., Perrin, M., Mangin, J. F., Cointepas, Y., Duchesnay, E., Le Bihan, D., & Hertz-Pannier, L. (2008). Asynchrony of the early maturation of white matter bundles in healthy infants: Quantitative landmarks revealed noninvasively by diffusion tensor imaging. *Human Brain Mapping*, *29*(1), 14–27. https://doi.org/10.1002/hbm.20363

Favaro, A., Tenconi, E., Degortes, D., Manara, R., & Santonastaso, P. (2015). Neural correlates of prenatal stress in young women. *Psychological Medicine*, *45*(12), 2533–2543. https://doi.org/10.1017/S003329171500046X

Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., & Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. *NeuroImage*, *54*(1), 313–327. https://doi.org/10.1016/j.neuroimage.2010.07.033

Gerardin, P., Wendland, J., Bodeau, N., Galin, A., Bialobos, S., Tordjman, S., Mazet, P., Darbois, Y., Nizard, J., Dommergues, M., & Cohen, D. (2011). Depression during pregnancy: Is the developmental impact earlier in boys? A prospective case-control study. *Journal of Clinical Psychiatry*, *72*(3), 378–387. https://doi.org/10.4088/JCP.09m05724blu

Gillespie, N. A., Neale, M. C., Hagler, D. J., Eyler, L. T., Fennema-Notestine, C., Franz, C. E., Lyons, M. J., McEvoy, L. K., Dale, A. M., Panizzon, M. S., & Kremen, W. S. (2017). Genetic and environmental influences on mean diffusivity and volume in subcortical brain regions. *Human Brain Mapping*, *38*(5), 2589–2598. https://doi.org/10.1002/hbm.23544

Gilmore, J. H., Lin, W., Prastawa, M. W., Looney, C. B., Vetsa, Y. S. K., Knickmeyer, R. C., Evans, D. D., Smith, J. K., Hamer, R. M., Lieberman, J. A., & Gerig, G. (2007). Regional gray matter growth, sexual dimorphism, and cerebral asymmetry in the neonatal brain. *Journal of Neuroscience*, *27*(6), 1255–1260. https://doi.org/10.1523/JNEUROSCI.3339-06.2007

Glover, V., O'Connor, T. G., & O'Donnell, K. (2010). Prenatal stress and the programming of the HPA axis. *Neuroscience and Biobehavioral Reviews*, *35*(1), 17–22. https://doi.org/10.1016/j.neubiorev.2009.11.008

Goodman, S. H., Rouse, M. H., Connell, A. M., Broth, M. R., Hall, C. M., & Heyward, D. (2011). Maternal depression and child psychopathology: A meta-analytic review. *Clinical Child and Family Psychology Review*, *14*(1), 1–27. https://doi.org/10.1007/s10567-010-0080-1

Gousias, I. S., Edwards, A. D., Rutherford, M. A., Counsell, S. J., Hajnal, J. V., Rueckert, D., & Hammers, A. (2012). Magnetic resonance imaging of the newborn brain: Manual segmentation of labelled atlases in term-born and preterm infants. *NeuroImage*, *62*(3), 1499–1509. https://doi.org/10.1016/j.neuroimage.2012.05.083

Hashempour, N., Tuulari, J. J., Merisaari, H., Lidauer, K., Luukkonen, I., Saunavaara, J., Parkkola, R., Lähdesmäki, T., Lehtola, S. J., Keskinen, M., Lewis, J. D., Scheinin, N. M., Karlsson, L., & Karlsson, H. (2019). A novel approach for manual segmentation of the amygdala and hippocampus in neonate MRI. *Frontiers in Neuroscience*, *13*(September), 1, 1025–15. https://doi.org/10.3389/fnins.2019.01025

Hay, R. E., Letourneau, N., Dewey, D., & Lebel, C. (2019). Examining the relationship between prenatal depression, amygdala-prefrontal structural connectivity and behaviour in preschool children. *BioRxiv*, *403*.

Humphrey, T. (1968). The development of the human amygdala during early embryonic life. *Journal of Comparative Neurology*, *132*(1), 135–165. https://doi.org/10.1002/cne.901320108

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Jeurissen, B., Leemans, A., Tournier, J. D., Jones, D. K., & Sijbers, J. (2013). Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Human Brain Mapping*, *34*(11), 2747–2766. https://doi.org/10.1002/hbm.22099

Jones, D. K. (2004). The effect of gradient sampling schemes on measures derived from diffusion tensor MRI: A Monte Carlo study. *Magnetic Resonance in Medicine*, *815*, 807–815. https://doi.org/10.1002/mrm.20033

Juranek, J., Johnson, C. P., Prasad, M. R., Kramer, L. A., Saunders, A., Filipek, P. A., Swank, P. R., Cox, C. S., & Ewing-Cobbs, L. (2012). Mean diffusivity in the amygdala correlates with anxiety in pediatric TBI. *Brain Imaging and Behavior*, *6*(1), 36–48. https://doi.org/10.1007/s11682-011-9140-5

Kantarci, K., Petersen, R. C., Boeve, B. F., Knopman, D. S., Weigand, S. D., O'Brien, P. C., Shiung, M. M., Smith, G. E., Ivnik, R. J., Tangalos, E. G., & Jack, C. R. (2005). DWI predicts future progression to Alzheimer disease in amnestic mild cognitive impairment. *Neurology*, *64*(5), 902–904. https://doi.org/10.1212/01.WNL.0000153076.46126.E9

Karlsson, L., Tolvanen, M., Scheinin, N. M., Uusitupa, H. M., Korja, R., Ekholm, E., Tuulari, J. J., Pajulo, M., Huotilainen, M., Paunio, T., & Karlsson, H. (2018). Cohort profile: The FinnBrain Birth Cohort Study (FinnBrain). *International Journal of Epidemiology*, *47*(1), 15–16j. https://doi.org/10.1093/ije/dyx173

Kinney, D. K., Munir, K. M., Crowley, D. J., & Miller, A. M. (2008). Prenatal stress and risk for autism. *Neuroscience and Biobehavioral Reviews*, *32*(8), 1519–1532. https://doi.org/10.1016/j.neubiorev.2008.06.004

Klawiter, E. C., Schmidt, R. E., Trinkaus, K., Liang, H. F., Budde, M. D., Naismith, R. T., Song, S. K., Cross, A. H., & Benzinger, T. L. (2011). Radial diffusivity predicts demyelination in ex vivo multiple sclerosis spinal cords. *NeuroImage*, *55*(4), 1454–1460. https://doi.org/10.1016/j.neuroimage.2011.01.007

Lebel, C., Caverhill-Godkewitsch, S., & Beaulieu, C. (2010). Age-related regional variations of the corpus callosum identified by diffusion tensor tractography. *NeuroImage*, *52*(1), 20–31. https://doi.org/10.1016/j.neuroimage.2010.03.072

Lehtola, S. J., Tuulari, J. J., Karlsson, L., Parkkola, R., Merisaari, H., Saunavaara, J., Lähdesmäki, T., Scheinin, N. M., & Karlsson, H. (2019). Associations of age and sex with brain volumes and asymmetry in 2–5-week-old infants. *Brain Structure and Function*, *224*(1), 501–513. https://doi.org/10.1007/s00429-018-1787-x

Lehtola, S. J., Tuulari, J. J., Scheinin, N. M., Karlsson, L., Parkkola, R., Merisaari, H., Lewis, J. D., Fonov, V. S., Louis Collins, D., Evans, A., Saunavaara, J., Hashempour, N., Lähdesmäki, T., Acosta, H., & Karlsson, H. (2020). Newborn amygdalar volumes are associated with maternal prenatal psychological distress in a sex-dependent way. *NeuroImage: Clinical*, *28*(May), 102380. https://doi.org/10.1016/j.nicl.2020.102380

Lewis, J. D., Fonov, V. S., Collins, D. L., Evans, A. C., & Tohka, J. (2019). Cortical and subcortical T1 white/gray contrast, chronological age, and cognitive performance. *NeuroImage*, *196*-(April), 276–288. https://doi.org/10.1016/j.neuroimage.2019.04.022

Lugo-Candelas, C., Cha, J., Hong, S., Bastidas, V., Weissman, M., Fifer, W. P., Myers, M., Talati, A., Bansal, R., Peterson, B. S., Monk, C., Gingrich, J. A., & Posner, J. (2018). Associations between brain structure and connectivity in infants and exposure to selective serotonin reuptake inhibitors during pregnancy. *JAMA Pediatrics*, *172*(6), 525–533. https://doi.org/10.1001/jamapediatrics.2017.5227

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434–445. https://doi.org/10.1038/nrn2639

Magyar, D. M., Fridshal, D., Elsner, C. W., Glatz, T., Eliot, J., Klein, A. H., Lowe, K. C., Buster, J. E., & Nathanielsz, P. W. (1980). Time-trend analysis of plasma cortisol concentrations in the fetal sheep in relation to parturition. *Endocrinology*, *107*(1), 155–159. https://doi.org/10.1210/endo-107-1-155

Markham, J. A., & Koenig, J. I. (2011). Prenatal stress: Role in psychotic and depressive diseases. *Psychopharmacology*, *214*(1), 89–106. https://doi.org/10.1007/s00213-010-2035-0

McFadyen, J., Mattingley, J. B., & Garrido, M. I. (2019). An afferent white matter pathway from the pulvinar to the amygdala facilitates fear recognition. *eLife*, *8*, 1–51. https://doi.org/10.7554/eLife.40766

Merisaari, H., Tuulari, J. J., Karlsson, L., Scheinin, N. M., Parkkola, R., Saunavaara, J., Lähdesmäki, T., Lehtola, S. J., Keskinen, M., Lewis, J. D., Evans, A. C., & Karlsson, H. (2019). Test-retest reliability of diffusion tensor imaging metrics in neonates. *NeuroImage*, *197*, 598–607. https://doi.org/10.1016/j.neuroimage.2019.04.067

Moura, L. M., Kempton, M., Barker, G., Salum, G., Gadelha, A., Pan, P. M., Hoexter, M., Del Aquilla, M. A. G., Picon, F. A., Anés, M., Otaduy, M. C. G., Amaro, E., Rohde, L. A., McGuire, P., Bressan, R. A., Sato, J. R., & Jackowski, A. P. (2016). Age-effects in white matter using associated diffusion tensor imaging and magnetization transfer ratio during late childhood and early adolescence. *Magnetic Resonance Imaging*, *34*(4), 529–534. https://doi.org/10.1016/j.mri.2015.12.021

Mukherjee, P., Miller, J. H., Shimony, J. S., Philip, J. V., Nehra, D., Snyder, A. Z., Conturo, T. E., Neil, J. J., & McKinstry, R. C. (2002). Diffusion-tensor MR imaging of gray and white matter development during normal human brain maturation. *American Journal of Neuroradiology*, *23*(9), 1445–1456.

Müller, F., & O'Rahilly, R. (2006). The amygdaloid complex and the medial and lateral ventricular eminences in staged human embryos. *Journal of Anatomy*, *208*(5), 547–564. https://doi.org/10.1111/j.1469-7580.2006.00553.x

Murphy, V. E., & Clifton, V. L. (2003). Alterations in human placental 11β=hydroxysteroid dehydrogenase type 1 and 2 with gestational age and labour. *Placenta*, *24*(7), 739–744. https://doi.org/10.1016/S0143-4004(03)00103-6

Nazzari, S., Fearon, P., Rice, F., Dottori, N., Ciceri, F., Molteni, M., & Frigerio, A. (2019). Beyond the HPA-axis: Exploring maternal prenatal influences on birth outcomes and stress reactivity. *Psychoneuroendocrinology*, *101*(April 2018), 253–262. https://doi.org/10.1016/j.psyneuen.2018.11.018

Nolvi, S., Karlsson, L., Bridgett, D. J., Korja, R., Huizink, A. C., Kataja, E. L., & Karlsson, H. (2016). Maternal prenatal stress and infant emotional reactivity six months postpartum.

Journal of Affective Disorders, *199*, 163–170. https://doi.org/10.1016/j.jad.2016.04.020

O'Connor, T. G., Glover, V., Heron, J., Golding, J., Beveridge, M., & Glover, V. (2002). Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. *British Journal of Psychiatry*, *180*(06), 502–508. https://doi.org/10.1192/bjp.180.6.502

Oguz, I., Farzinfar, M., Matsui, J., Budin, F., Liu, Z., Gerig, G., Johnson, H. J., & Styner, M. (2014). DTIPrep: Quality control of diffusion-weighted images. *Frontiers in Neuroinformatics*, *8*-(January), 1, 4–11. https://doi.org/10.3389/fninf.2014.00004

Partridge, S. C., Mukherjee, P., Henry, R. G., Miller, S. P., Berman, J. I., Jin, H., Lu, Y., Glenn, O. A., Ferriero, D. M., Barkovich, A. J., & Vigneron, D. B. (2004). Diffusion tensor imaging: Serial quantitation of white matter tract maturity in premature newborns. *NeuroImage*, *22*(3), 1302–1314. https://doi.org/10.1016/j.neuroimage.2004.02.038

Pervolaraki, E., Tyson, A. L., Pibiri, F., Poulter, S. L., Reichelt, A. C., Rodgers, R. J., Clapcote, S. J., Lever, C., Andreae, L. C., & Dachtler, J. (2018). The within-subject application of diffusion tensor MRI and CLARITY reveals brain structural changes in Nrxn2 deletion mice. *BioRxiv*, *1–13*. https://doi.org/10.1101/300806

Pohl, K. M., Sullivan, E. V., Rohlfing, T., Chu, W., Kwon, D., Nichols, B. N., Zhang, Y., Brown, S. A., Tapert, S. F., Cummins, K., Thompson, W. K., Brumback, T., Colrain, I. M., Baker, F. C., Prouty, D., De Bellis, M. D., Voyvodic, J. T., Clark, D. B., Schirda, C., … Pfefferbaum, A. (2016). Harmonizing DTI measurements across scanners to examine the development of white matter microstructure in 803 adolescents of the NCANDA study. *NeuroImage*, *130*, 194–213. https://doi.org/10.1016/j.neuroimage.2016.01.061

Qiu, A., Anh, T. T., Li, Y., Chen, H., Rifkin-Graboi, A., Broekman, B. F. P., Kwek, K., Saw, S. M., Chong, Y. S., Gluckman, P. D., Fortier, M. V., & Meaney, M. J. (2015). Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. *Translational Psychiatry*, *5*(2), e508. https://doi.org/10.1038/tp.2015.3

Rakers, F., Rupprecht, S., Dreiling, M., Bergmeier, C., Witte, O. W., & Schwab, M. (2016). Transfer of maternal psychosocial stress to the fetus. *Neuroscience and Biobehavioral Reviews*, *117*, 185–197. https://doi.org/10.1016/j.neubiorev.2017.02.019

Ramasubbu, R., Konduru, N., Cortese, F., Bray, S., Gaxiola-Valdez, I., & Goodyear, B. (2014). Reduced intrinsic connectivity of amygdala in adults with major depressive disorder. *Frontiers in Psychiatry*, *5*(FEB), 1, 17–11. https://doi.org/10.3389/fpsyt.2014.00017

Rifkin-Graboi, A., Bai, J., Chen, H., Hameed, W. B. R., Sim, L. W., Tint, M. T., Leutscher-Broekman, B., Chong, Y. S., Gluckman, P. D., Fortier, M. V., Meaney, M. J., & Qiu, A. (2013). Prenatal maternal depression associates with microstructure of right amygdala in neonates at birth. *Biological Psychiatry*, *74*(11), 837–844. https://doi.org/10.1016/j.biopsych.2013.06.019

Roalf, D. R., Quarmley, M., Elliott, M. A., Satterthwaite, T. D., Vandekar, S. N., Ruparel, K., Gennatas, E. D., Calkins, M. E., Moore, T. M., Hopson, R., Prabhakaran, K., Jackson, C. T., Verma, R., Hakonarson, H., Gur, R. C., & Gur, R. E. (2016). The impact of quality assurance assessment on diffusion tensor imaging outcomes in a large-scale population-based cohort. *NeuroImage*, *125*, 903–919. https://doi.org/10.1016/j.neuroimage.2015.10.068

Ronald, A., Pennell, C. E., & Whitehouse, A. J. O. (2011). Prenatal maternal stress associated with ADHD and autistic traits in early childhood. *Frontiers in Psychology*, *1*(JAN), 1, 223–8. https://doi.org/10.3389/fpsyg.2010.00223

Rosso, I. M., Cintron, C. M., Steingard, R. J., Renshaw, P. F., Young, A. D., & Yurgelun-Todd, D. A. (2005). Amygdala and hippocampus volumes in pediatric major depression. *Biological Psychiatry*, *57*(1), 21–26. https://doi.org/10.1016/j.biopsych.2004.10.027

Salat, D. H. (2013). Diffusion tensor imaging in the study of aging and age-associated neural disease. In *Diffusion MRI: From quantitative measurement to in vivo neuroanatomy* (Second Edi ed.). Elsevier. https://doi.org/10.1016/B978-0-12-396460-1.00012-3

Salo, R. A., Belevich, I., Manninen, E., Jokitalo, E., Gröhn, O., & Sierra, A. (2018). Quantification of anisotropy and orientation in 3D electron microscopy and diffusion tensor imaging in injured rat brain. *NeuroImage*, *172*(January), 404–414. https://doi.org/10.1016/j.neuroimage.2018.01.087

Sandman, C. A., Wadhwa, P. D., Dunkel-Schetter, C., Chicz-DeMet, A., Belman, J., Porto, M., Murata, Y., Garite, T. J., & Crinella, F. M. (1994). Psychobiological influences of stress and HPA regulation on the human fetus and infant birth outcomes. *Annals of the New York Academy of Sciences*, *739*(1), 198–210. https://doi.org/10.1111/j.1749-6632.1994.tb19822.x

Sasaki, H., Abe, O., Yamasue, H., Fukuda, R., Yamada, H., Takei, K., Suga, M., Takao, H., Kasai, K., Aoki, S., & Ohtomo, K. (2009). Structural and diffusional brain abnormality related to relatively low level alcohol consumption. *NeuroImage*, *46*(2), 505–510. https://doi.org/10.1016/j.neuroimage.2009.02.007

Sexton, C. E., Mackay, C. E., Lonie, J. A., Bastin, M. E., Terrière, E., O'Carroll, R. E., & Ebmeier, K. P. (2010). MRI correlates of episodic memory in Alzheimer's disease, mild cognitive impairment, and healthy aging. *Psychiatry Research: Neuroimaging*, *184*(1), 57–62. https://doi.org/10.1016/j.pscychresns.2010.07.005

Shaked, D., Williams, M., Evans, M. K., & Zonderman, A. B. (2016). Indicators of subjective social status: Differential associations across race and sex. *SSM - Population Health*, *2*(May), 700–707. https://doi.org/10.1016/j.ssmph.2016.09.009

Sidebottom, A., Vacquier, M., LaRusso, E., Erickson, D., & Hardeman, R. (2021). Perinatal depression screening practices in a large health system: identifying current state and assessing opportunities to provide more equitable care. *Archives of Women's Mental Health*, *24*(1), 133–144. https://doi.org/10.1007/s00737-020-01035-x

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1002/hbm.10062

Stebbins, G. T. (2010). Diffusion tensor imaging in Parkinson's disease. *Encyclopedia of Movement Disorders*, *109*, 308–310. https://doi.org/10.1016/B978-0-12-374105-9.00020-4

Stoye, D. Q., Blesa, M., Sullivan, G., Galdi, P., Lamb, G. J., Black, G. S., Quigley, A. J., Thrippleton, M. J., Bastin, M. E.,

Reynolds, R. M., & Boardman, J. P. (2020). Maternal hair cortisol is associated with neonatal amygdala microstructure and connectivity in a sexually dimorphic manner. *BioRxiv*, *1–18*. https://doi.org/10.1101/2020.06.16.154922

Straub, J., Metzger, C. D., Plener, P. L., Koelch, M. G., Groen, G., & Abler, B. (2017). Successful group psychotherapy of depression in adolescents alters fronto-limbic resting-state connectivity. *Journal of Affective Disorders*, *209*, 135–139. https://doi.org/10.1016/j.jad.2016.11.024

Takeuchi, H., Taki, Y., Nouchi, R., Yokoyama, R., Kotozaki, Y., Nakagawa, S., Sekiguchi, A., Iizuka, K., Yamamoto, Y., Hanawa, S., Araki, T., Miyauchi, C. M., Sakaki, K., Sassa, Y., Nozawa, T., Ikeda, S., Yokota, S., Daniele, M., & Kawashima, R. (2019). Empathizing associates with mean diffusivity. *Scientific Reports*, *9*(1), 1, 8856–13. https://doi.org/10.1038/s41598-019-45106-1

Taki, Y., Thyreau, B., Hashizume, H., Sassa, Y., Takeuchi, H., Wu, K., Kotozaki, Y., Nouchi, R., Asano, M., Asano, K., Fukuda, H., & Kawashima, R. (2013). Linear and curvilinear correlations of brain white matter volume, fractional anisotropy, and mean diffusivity with age using voxel-based and region-of-interest analyses in 246 healthy children. *Human Brain Mapping*, *34*(8), 1842–1856. https://doi.org/10.1002/hbm.22027

Tamnes, C. K., Østby, Y., Fjell, A. M., Westlye, T., Due-tønnessen, P., & Walhovd, K. B. (2010). Brain maturation in adolescence and young adulthood: Regional age-related changes in cortical thickness and white matter volume and microstructure. *Cerebral Cortex*, *20*(3), 534–548. https://doi.org/10.1093/cercor/bhp118

Tao, J., Wang, X., Zhong, Z., Han, H., Liu, S., Wen, S., Guan, N., & Li, L. (2017). Alterations of white matter fractional anisotropy in unmedicated obsessive-compulsive disorder. *Neuropsychiatric Disease and Treatment*, *13*, 69–76. https://doi.org/10.2147/NDT.S123669

Tian, Q., Bilgic, B., Fan, Q., Liao, C., & Ngamsombat, C. (2020). NeuroImage DeepDTI: High-fidelity six-direction diffusion tensor imaging using deep learning. *NeuroImage*, *219*(June), 117017. https://doi.org/10.1016/j.neuroimage.2020.117017

Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M., & Nishijo, H. (2012). Developmental trajectories of amygdala and hippocampus from infancy to early adulthood in healthy individuals. *PLoS ONE*, *7*(10), e46970. https://doi.org/10.1371/journal.pone.0046970

Ulfig, N., Setzer, M., & Bohl, J. (2006). PDFlib PLOP: PDF linearization, optimization, protection page inserted by evaluation version genomics update. *Annals of the New York Academy of Sciences*, *985*(1), 22–33. https://doi.org/10.1111/j.1749-6632.2003.tb07068.x

Weisenfeld, N. I., Mewes, A. U. J., & Warfield, S. K. (2006). Highly accurate segmentation of brain tissue and subcortical gray matter from newborn MRI. In R. Larsen, M. Nielsen, & J. Sporring (Eds), *Medical Image Computing and Computer-Assisted Intervention – MICCAI 2006*. MICCAI 2006. Lecture Notes in Computer Science (Vol. 4190). Springer. https://doi.org/10.1007/11866565_25

Wen, D. J., Poh, J. S., Ni, S. N., Chong, Y. S., Chen, H., Kwek, K., Shek, L. P., Gluckman, P. D., Fortier, M. V., Meaney, M. J., & Qiu, A. (2017). Influences of prenatal and postnatal maternal depression on amygdala volume and microstructure in young children. *Translational Psychiatry*, *7*(4), e1103. https://doi.org/10.1038/tp.2017.74

Yoshida, S., Oishi, K., Faria, A. V., & Mori, S. (2013). Diffusion tensor imaging of normal brain development. *Pediatric Radiology*, *43*(1), 15–27. https://doi.org/10.1007/s00247-012-2496-x

Yrondi, A., Nemmi, F., Billoux, S., Giron, A., Sporer, M., Taib, S., Salles, J., Pierre, D., Thalamas, C., Schmitt, L., Péran, P., & Arbus, C. (2019). Significant decrease in hippocampus and amygdala mean diffusivity in treatment-resistant depression patients who respond to electroconvulsive therapy. *Frontiers in Psychiatry*, *10*(SEP), 1, 694–8. https://doi.org/10.3389/fpsyt.2019.00694

Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R. G., Ho, S., Gee, J. C., & Gerig, G. (2006). User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *NeuroImage*, *31*(3), 1116–1128. https://doi.org/10.1016/j.neuroimage.2006.01.015

How to cite this article: Hashempour, N., Tuulari, J. J., Merisaari, H., Acosta, H., Lewis, J. D., Pelto, J., Scheinin, N. M., Fonov, V. S., Collins, D. L., Lehtola, S. J., Saunavaara, J., Lähdesmäki, T., Parkkola, R., Karlsson, L., & Karlsson, H. (2023). Prenatal maternal depressive symptoms are associated with neonatal left amygdala microstructure in a sex-dependent way. *European Journal of Neuroscience*, *57*(10), 1671–1688. https://doi.org/10.1111/ejn.15989