

The early postpartum period – differences between women with and without a history of depression

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Abstract

Depression is a highly recurrent disorder. When in remission, it affords an important opportunity to understand the state-independent neurobiological alterations, as well as the socio-demographic characteristics, that likely contribute to the recurrence of major depressive disorder (MDD). The present study examined 110 euthymic women in their early postpartum period. A comparison was made between participants with ($n = 20$) and without ($n = 90$) a history of MDD by means of a multimodal approach including an fMRI experiment, assessment of hair cortisol concentration (HCC) and a clinical anamnestic interview. Women with a personal history of MDD were found to have decreased resting-state functional connectivity (RSFC) between the lateral parietal cortex (LPC) and the posterior cingulate cortex (PCC), and their Edinburgh Postnatal Depression Scale (EPDS) scores were significantly higher shortly after childbirth. More often than not, these women also had a family history of MDD. While women with no history of depression showed a negative association between hair cortisol concentration (HCC) and gray matter volume (GMV) in the medial orbitofrontal cortex (mOFC), the opposite trend was seen in women with a history of depression. This implies that women with remitted depression show distinctive neural phenotypes and show subclinical residual symptoms, potentially predisposing them to later depressive episodes.

Keywords: Postpartum depression, multimodal neuroimaging, default mode network, hair cortisol concentration, stressful life events, hypothalamic-pituitary adrenal axis

Introduction

Depression is a recurrent disorder with about 50-85% of remitted patients remaining vulnerable to further depressive episodes in their lifetime (Mueller et al., 1999). With a sex ratio of 2:1, depression is found to be more common in females than in males (Kuehner, 2017), with the former being exposed to an increased risk of relapse (Kuehner, 2003). The risk of recurrence has been associated with the number of previous episodes and the experience of residual symptoms (Hardeveld et al., 2010). Depressive episodes in women occur more frequently at particular stages of their reproductive life, e.g. following the onset of puberty or during and after pregnancy (Harald and Gordon, 2012; Noble, 2005).

Previous studies have shown altered brain structure and connectivity patterns in individuals with major depressive disorder (MDD). More specifically, altered resting-state functional connectivity (RSFC) in the default mode network (DMN) has been reported in individuals with high risk of depression compared to their low-risk counterparts (Posner et al., 2016) as well as in those with manifest (for a review, see Mulders et al., 2015) and remitted (Wu et al., 2013) depression. The DMN, which includes the posterior cingulate cortex (PCC), the medial prefrontal cortex (MPFC), and the left and right lateral parietal cortices (LPC) (Buckner et al., 2008), is involved in self-generated cognition, emotion regulation and self-referential processing as well as in memory processing and consciousness (Andrews-Hanna et al., 2010; Li et al., 2014), and has been linked to depressive rumination (Hamilton et al., 2015). Further, the functional connections in the DMN are among the most discriminating networks that classify individuals with MDD compared to healthy controls (Zeng et al., 2012). With regard to brain structure, earlier findings in individuals with MDD have shown that gray matter volume is reduced in the insula, the hippocampus (Stratmann et al., 2014), the amygdala (Sacher et al., 2012), the anterior cingulate cortex (Lai, 2013), and the mOFC (Lacerda et al., 2004).

MDD has been associated not only with alterations in brain structure and function, but also with disruptions in neurobiological stress response systems including the hypothalamic-pituitary adrenal (HPA) axis (Barden, 2004; Nestler et al., 2002). The HPA axis responds to stressful stimuli by releasing the glucocorticoid hormone cortisol and thereby helping maintain homeostasis in response to stressors (Juruena et al., 2018). Hair cortisol concentration (HCC), a biomarker of long-term cortisol secretion, can be used as a measure to reflect cumulative cortisol release over a period of several months (Stalder and Kirschbaum, 2012). According to our previous results, HCC reveals links between the long-term effects of stress and activation of brain regions (e.g. ACC) (Stickel et al., 2019) relevant to the regulation of stress response (Chattarji et al., 2015). Further, exposure to stress over a longer period of time is known to

cause structural as well as functional changes in brain regions involved in the stress response (e.g. hippocampus, amygdala; Chattarji et al., 2015; Nestler et al., 2002). Elevated stress levels result in hypercortisolemia, which in turn leads to neural changes in brain regions regulating the HPA axis, among them the hippocampus, the amygdala and the prefrontal cortex (Chattarji et al., 2015). These brain regions have also been shown to undergo changes in individuals with MDD (Lorenzetti et al., 2009), supporting the notion of MDD being a stress-related disorder (Chattarji et al., 2015).

A personal history of depression has been found to be one of the most crucial risk factors for the development of a new depressive episode later in life (Buckman et al., 2018) as well as postpartum depression (PPD; Verkerk et al., 2003). Therefore, the overarching goal of our study, which is part of a longitudinal project (Risk of Postpartum Depression - RiPoD) related to early recognition of PPD, was to explore whether differences between currently euthymic women with and without a history of depression are identifiable based on socio-demographic, clinical-anamnestic, hormonal (hair cortisol) and neuroimaging data. And we posit that the differences found in the currently euthymic women with, compared to those without, prior experience of depression would represent trait characteristics of depression, likely predisposing affected women to further recurrence. Different neuroimaging modalities (involving brain function at rest as well as brain structure) were used to make the group comparison. By integrating HCC into our neuroimaging analysis, we sought to determine potential links between cumulative cortisol exposure and brain structure (voxel-based morphometry) and function (resting-state imaging). The hypotheses targeted by our study were the following:

Hypothesis 1: Based on the literature (Deligiannidis et al., 2019; Stickel et al., 2019), we expected to find group differences between women with and without a history of depression in the default mode network activity and structure.

Hypothesis 2: Further, we expected to find a detectable link between cumulative cortisol exposure during the last trimester of pregnancy (HCC at T0) and the structure and function of brain regions that modulate stress response (e.g. the hippocampus, the insula, and the prefrontal and orbitofrontal cortices).

Hypothesis 3: Women with a history of depression would differ from their counterparts without prior experience of depression based on socio-demographic and clinical-anamnestic characteristics.

Methods

Study participants

The present study included 110 postpartum women taking part in the functional magnetic resonance imaging (fMRI) experiment. The inclusion criteria were no depression (according to the clinical interview) at the time of recruitment, being between 18 and 45 years of age, being in an early postpartum period (1 to 6 days following childbirth), and being eligible for the MRI. Severe birth- and pregnancy-related complications (e.g. eclampsia, HELLP), use of glucocorticoids during pregnancy, alcoholic or psychotropic substance dependency or use during pregnancy, antidepressant or antipsychotic medication during pregnancy, and lack of sufficient command of German or English were the exclusion criteria. The exclusion criteria based on the child's condition comprised very premature birth (less than 26 weeks of gestation), very low weight (less than 1000g), genetic defects (e.g. trisomy), pathological neurological assessment on the basis of the German Child Health Test (U2), which takes place within the first 3 to 10 days of life, or other developmental anomalies.

The participants were split into two groups based on their history of depression (Group D, $n = 20$ individuals with a previous depressive episode; group ND, $n = 90$ individuals with no previous depressive episode) as such a history is one of the main risk factors of PPD (Silverman et al., 2017; Verkerk et al., 2003). The history of depression was assessed by means of an anamnestic questionnaire and clinical interview conducted by an experienced psychiatrist (NC), and the participants were required to indicate whether they had experienced a depressive episode, its time of occurrence, and whether they received any form of treatment. It must be noted that none of the participants had any current clinical manifestations of depression, nor had they received antidepressant therapy during their most recent pregnancy.

Table 1: Description of the study population

	Group D ($n = 20$)	Group ND ($n = 90$)		p
	Mean (SD)	Mean (SD)	Range	
Age	31.1 (5.3)	31.7 (4.72)	20-42	.608
Depression score EPDS	10.45 (5.02)	4.04 (2.87)	0-25	.001
HCC (in pg/mg)	8.53 (7.51)	10.22 (15.28)	0.7-91.55	.468
Length of pregnancy in days	269.95 (17.45)	272.29 (15.41)	211-294	.605
Child's birth weight (in gram)	3226.00 (747.20)	3455.48 (725.99)	1430-5350	.190
	n (%)	n (%)		
Family Status				.196
Married	11 (55.0%)	63 (70.0%)		
Unmarried	9 (45.0%)	27 (30.0%)		

Number of children				.518
1	8 (40.0%)	48 (53.3%)		
2	9 (45.0%)	32 (35.6%)		
3	3 (15.0%)	6 (6.7%)		
4	-	3 (3.3%)		
5	-	1 (1.1%)		
Highest education				.444
No school graduation	1 (5.0%)	1 (1.1%)		
Secondary school degree	2 (10.0%)	3 (3.3%)		
Junior high school degree	3 (15.0%)	11 (12.2%)		
University entrance	9 (45.0%)	4 (46.7%)		
Diploma				
College degree	5 (25.0%)	25.6 (26.1%)		
Doctoral degree	-	8.9 (8.0%)		
Birth mode				.427
Spontaneous	12 (60.0%)	60 (66.7%)		
Ventouse	1 (5.0%)	5 (5.6%)		
Section	3 (15.0%)	18(20.0%)		
Emergency section	4 (20.0%)	7 (7.8%)		
Breast feeding at T0 (yes)	16 (80.0%)	74 (82.2%)		.816
Psychological or physical birth trauma (yes)	5 (31.3%)	7 (8.1%)		.008
Family psychiatric history (yes)	14 (70.0%)	18 (20.0%)		< .001
Baby blues (yes)	10 (62.5%)	34 (39.5%)		.089
Stressful life events (SLESQ) (yes)	16 (80.0%)	38 (42.2%)		.002
	Mean (SD)	Mean (SD)	Range	
Number of stressful life events (SLESQ)	2.25 (2.12)	0.73 (1.12)	0-7	.003

Notes: SLESQ = Stressful Life Events Screening Questionnaire; EPDS = Edinburgh Postnatal

Depression Scale, HCC = hair cortisol concentration

Procedure

The study, approved by the Ethics Committee of the University Hospital RWTH Aachen, conformed to the ethical standards of the Helsinki declaration. Healthy postpartum women were approached 1 to 6 days after childbirth at the Department of Gynecology and Obstetrics, RWTH University Hospital Aachen. Following receipt of the participants' informed consent, a clinical anamnestic interview was executed by an experienced psychiatrist (NC) to obtain anamnestic and pregnancy-related information, e.g. family history of psychiatric conditions, previous psychiatric history, income, marital status, complications during pregnancy,

experience of baby blues symptoms, or birth mode. Subsequently, the participants filled in several questionnaires, of which two will be detailed below (see 'Questionnaires'). A hair sample of 3 cm was taken from the posterior vertex of the head close to the scalp to reflect cortisol exposure over the last three months of pregnancy (Stalder and Kirschbaum, 2012). Afterwards, the women took part in an fMRI measurement and received a compensation for their participation.

Questionnaires

The Edinburgh Postnatal Depression Scale (EPDS), which is a self-report measure, was used to assess depressive symptomatology in the postpartum period (Cox et al., 1987). In addition, we used the Stressful Life Events Screening Questionnaire (SLESQ), a self-report screening measure consisting of 13 items, which assesses exposure to various traumatic events over the life course of an individual (Goodman et al., 1998).

Hair sample preparation

Hair samples were stored in aluminum foil and analyzed with the automated online SPE LC-MS method described in Quinete et al., 2015. Specifically, 50 mg of hair was weighed out in a polypropylene tube and subsequently washed with isopropanol for 2 minutes. After drying the hair at room temperature overnight, the internal standards cortisone-d and cortisol-d were added, and the samples were incubated in methanol for 24 hours. Finally, the samples were analyzed with liquid chromatography triple quadrupole mass spectrometry by the use of an ion trap (Agilent Technologies 1200 infinity series -QTRAP 5500 ABSciex). The limits of quantification for the analysis were 0.05 ng/mL or 2 pg/mg hair, respectively. Cortisol data showed skewed distribution and, therefore, a log-transformation was applied to reduce the skewness statistic.

Behavioral data analysis

The groups were compared with regard to baby blues, family psychiatric history, EPDS score, and number of stressful life events, as assessed with the SLESQ. For each of the continuous measures, independent sample t-tests were conducted, with history of depressive episodes (yes vs. no) as independent variable. For categorical measures, chi square tests were conducted. For all measures, the bootstrapping method was chosen to control for the different group sizes, and all behavioral results were based on 1000 bootstrap samples. The analysis was conducted using IBM Statistics 25 (SPSS, Chicago, IL).

fMRI procedure

Participants went to the MR scanner while nurses took care of their children. The MRI scanning was conducted using a 3 Tesla Prisma MR Scanner (Siemens Medical Systems, Erlangen,

Germany) located in the Medical Faculty of RWTH Aachen University. Functional images were acquired for an 11-minute resting-state sequence with an echo-planar imaging (EPI) T2*-weighted contrast sequence sensitive to blood-oxygen-level dependent (BOLD) contrast (34 slices, TR = 2.2 s, TE = 28 ms, FoV = 192×192 mm², flip angle = 90°, voxel resolution = $3.0 \times 3.0 \times 3.0$ mm³). T1-weighted structural images were acquired by means of a three-dimensional magnetization-prepared rapid acquisition gradient echo imaging (MPRAGE) sequence (4.12 minutes; 176 slices, TR = 2.3 s, TE = 1.99 ms, TI = 900 ms, FoV = 256×256 mm², flip angle = 9°, voxel resolution = $1 \times 1 \times 1$ mm³).

Resting-state functional connectivity (RSFC)

For preprocessing, the Statistical Parametric 12 (SPM12) software was used (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>), implemented in Matlab 2015b (MathWorks, Inc., Natick, MA). Six motion parameters were estimated and used to realign the functional images to their mean, with the differences in image acquisition time between slices being corrected. The resulting images were then co-registered to the structural image that was segmented into tissue components (gray and white matter, and cerebrospinal fluid), and normalized to the standard brain template from the Montreal Neurological Institute (MNI). The functional images were further smoothed using an 8mm full width at half-maximum (FWHM) Gaussian kernel.

The functional connectivity analysis was performed using the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) which computes Fisher-transformed correlation coefficient (z) between a pair of predefined ROIs. The functional images were denoised, following the default strategy implemented in the CONN toolbox. Images of the whole recording session were band-pass filtered at 0.008 – 0.1Hz and were convolved with a canonical hemodynamic response function implemented in SPM12. BOLD signal from the white matter and cerebrospinal fluid as well as the functional outlier and motion parameters were taken as regressors of no interest. The connectivity strengths (z) across a priori-defined four regions of DMN was calculated (the network atlas of the DMN implemented by Yeo et al., 2014): the MPFC, the PCC, and the right and left lateral parietal cortices (rLPC, ILPC). The mean connectivity strengths across all four ROIs were then computed for analysis in SPSS 25 (SPSS, Chicago, IL).

Subsequently, we performed a seed-based connectivity analysis using the CONN toolbox to examine the functional coupling of a ROI with every voxel in the brain. The four ROIs of the DMN, defined above, were separately subjected to a seed-based analysis. The correlations between the mean BOLD time-series of the one of four ROIs and the time-series of each voxel throughout the whole brain were computed for each subject. The resulting correlation maps were subsequently used for group-level analysis with a two-sample t-test to

investigate the difference between groups. This seed-based approach allowed us to examine the functional coupling of DMN regions with all other voxels in the brain, while the connection strength changes between groups. The significance of the group effect was thresholded using a voxel-level uncorrected $p < 0.001$ and cluster-level FWE-corrected at $p < 0.05$.

Voxel-based morphometry

The anatomical imaging data were preprocessed using the Computational Anatomy Toolbox (CAT12) and SPM12 toolbox implemented in Matlab 2015b (MathWorks, Inc., Natick, MA). At first, the 3D T1-weighted MRI scans were manually reoriented to the intercommissural plane. Next, the default settings of CAT12 were applied for spatial registration, segmentation and normalization. We used Diffeomorphic Anatomic Registration Through Exponentiated Linear algebra algorithm (DARTEL) for normalization (Klein et al., 2009) as DARTEL affords a more precise spatial normalization to the template than the conventional algorithm (Ashburner, 2007). The images were segmented into gray matter, white matter, and cerebrospinal fluid, and modulated with Jacobian determinants. A homogeneity check identified no outliers, thus the gray matter volumes (GMV) of all participants were included in subsequent analyses. Finally, the modulated GMV were smoothed with an 8 mm FWHM Gaussian kernel.

The VBM ROI gray matter analyses were performed on eight a priori-defined regions: the left and the right insula, the left and the right amygdala, the left and the right hippocampus, the ACC and the mOFC. The ROIs (created using the WFU Pickatlas toolbox, Wake Forest School of Medicine, Winston Salem) were chosen based on the literature examining GMV changes in individuals with MDD, indicating decreased GMV in the mOFC, the hippocampus, the ACC, and the insula (Bora et al., 2012; Chattarji et al., 2015). GMV reductions have also been reported in the amygdala (for a meta-analysis, see Hamilton et al., 2008). These regions have also been implicated in the stress response system and show alterations if exposed to heightened long-term cortisol secretion (Nestler et al., 2002). The mean parameter estimates of each ROI were then extracted using MarsBaR (<http://marsbar.sourceforge.net/>) for analysis in SPSS 25 (SPSS, Chicago, IL), during which the total intracranial volume (TIV) and age were used as covariates.

Results

Behavioral results

The results of an independent samples t-test indicate a significant group difference in depressive symptoms as measured by EPDS scores, ($t(108) = 7.732, p = .001, 95\% \text{ CI } [4.21,$

8.85], with a higher EPDS score in the group D ($M = 10.45$, $SD = 5.02$) compared to group ND ($M = 4.04$, $SD = 2.87$). Further, significantly more women in group D experienced stressful life events ($N = 16$, 80%) compared to those in the group ND ($N = 38$, 42.2%), $\chi^2(1, 110) = 9.345$, $p = .002$. Among the women with stressful life events, the ones in group D tended to have experienced higher numbers of stressful life events ($M = 2.25$, $SD = 2.12$) compared to their counterparts in group ND ($M = 0.73$, $SD = 1.12$), $t(108) = 4.539$, $p = .003$, 95% CI [-0.61, 2.52]). More women in group D ($N = 5$, 31.3%) reported to have experienced the birth as traumatic compared to women in group ND ($N = 7$, 8.1%), $\chi^2(1, 102) = 6.941$, $p = .008$. A significantly higher number of women in group D ($N = 14$, 70%) had close relatives with a psychiatric history compared to the ones in group ND ($N = 18$, 20%), $\chi^2(1, 110) = 19.832$, $p < .001$. In addition, more women in group D experienced baby blues ($N = 10$, 62.5%) compared to those in group ND (39.5%), although this result did not reach statistical significance, $\chi^2(1, 102) = 2.901$, $p = .089$. The groups did not differ significantly in terms of other demographical and anamnestic variables (see Table 1).

Resting-state functional connectivity (RSFC) results

The mean RSFC across the default mode network showed a significantly decreased connectivity strength ($M = .70$, $SD = .13$) in the women in group D compared to those in group ND ($M = .79$, $SD = .16$), $t(108) = 2.21$, $p = .012$, 95% CI [0.019, 0.144] (for ROIs, see Figure 1). While examining the group differences for each of the six possible connections across the four ROIs (although all of them showed decreased connectivity strength in group D), none of the results survived after correcting for multiple comparisons (independent samples t-tests uncorrected p-values $> .032$). Further, there was a significant negative correlation between level of HCC and mean RSFC (controlled for age) in group ND ($r = -.235$, $p = .034$). In group D, the same pattern was seen, although it did not reach statistical significance ($r = -.201$, $p = .439$). After applying Fisher's z-transformation and calculating a z-score of the differences between the correlations, no significant difference was found in the correlation coefficients between groups ($z = -.135$, $p = .446$).

The seed-based analysis of the group effect further supports the decreased functional connectivity of the DMN. The functional connectivity between the seed left LPC ROI and a voxel cluster within the PCC was significantly decreased in group D (Figure 1). It should be noted that the significant voxels were clustered within the PCC ROI of the DMN, but not in other brain regions. Seed-based analyses subjecting other ROIs as a seed did not show any significant voxel cluster.

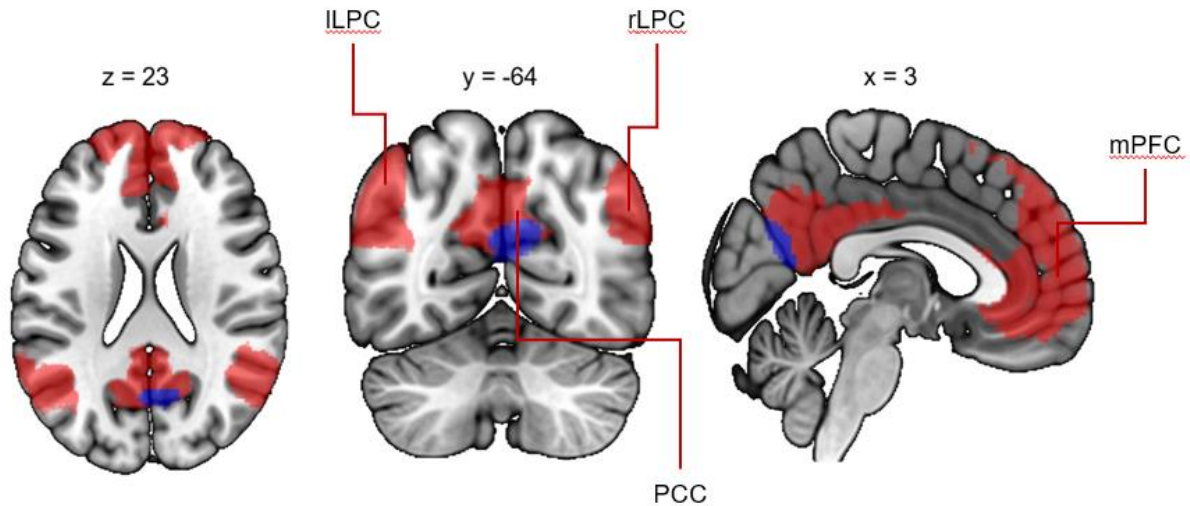


Figure 1. Seed-to-voxel analysis: overlap (blue part) indicates the PCC, showing significantly decreased RSFC with the seed region left LPC. The red parts reflect the ROIs: PCC, MPFC, left and right LPC.

VBM results

No group differences were found in the VBM analysis. In the ND group, there were significant negative correlations between HCC during the last three months of pregnancy and GMV in the mOFC, the right insula, and the left hippocampus (see Figure 2 and Table 2). The same analyses were conducted while controlling for length of pregnancy, showing no differences in the results. Therefore, the uncorrected results are reported.

While the ND group showed a significant negative correlation between GMV in the mOFC and HCC ($r = -.286$, $p = .004$), the opposite trend was seen in group D ($r = .264$, $p = .322$). After applying Fisher's z-transformation and calculating a z-score of the differences between the correlations, the comparison of correlation coefficients between groups D and ND revealed a significant difference between the two groups ($z = -2.129$, $p = .017$; Figure 3).

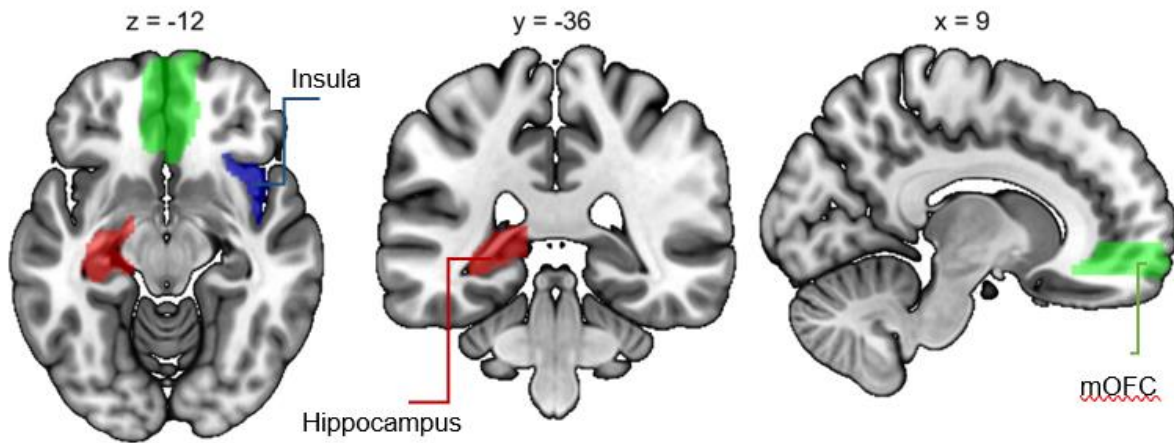


Figure 2. Group ND: significant negative correlations between HCC and GMV in mOFC, right insula and left hippocampus

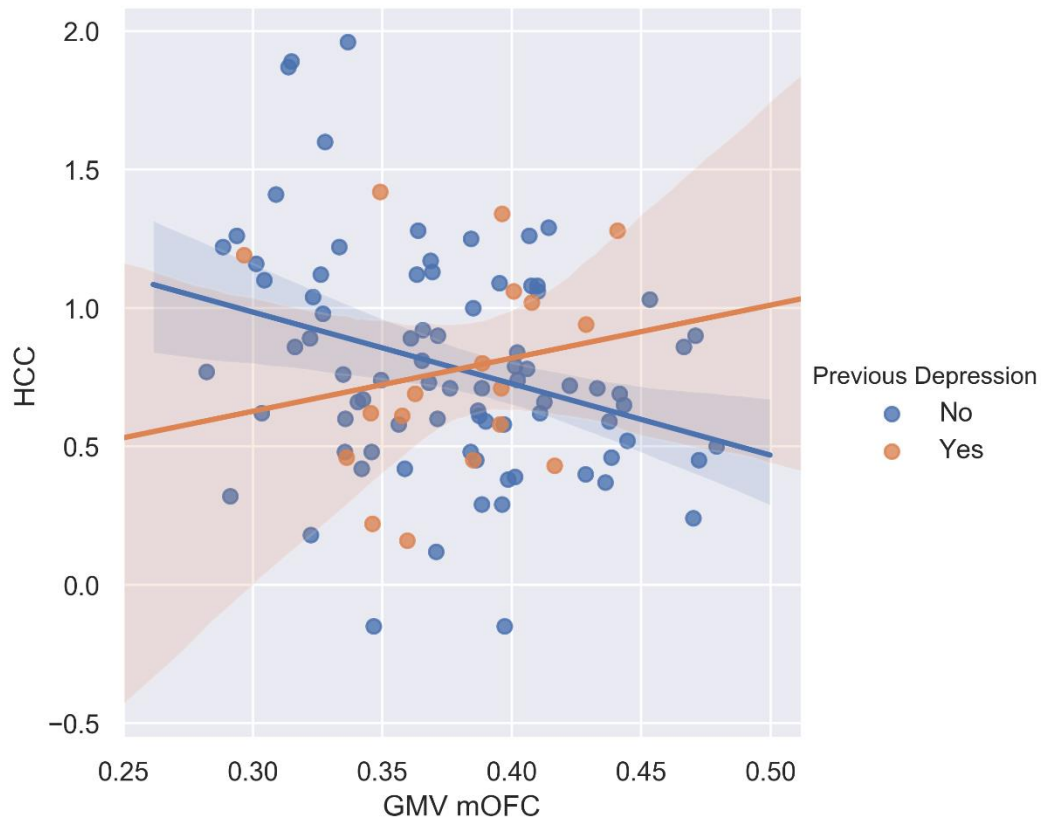


Figure 3. Correlation between gray matter volume in the medial orbitofrontal cortex (mOFC) and cumulative hair cortisol concentration (HCC) in the last three months of pregnancy, per group.

Table 2. Partial correlations (controlling for age and total intracranial volume, TIV) between level of HCC and gray matter volume (GMV) in the two groups

	Group ND	Group D	Comparison of correlation coefficients
			<i>z</i>
mOFC	-.281*	.264	2.109*
L Insula	-.204	-.042	.622
R Insula	-.294*	.127	1.624
L Amygdala	-.077	-.175	-.376
R Amygdala	-.067	-.224	-.606
L Hippocampus	-.236*	-.049	.722
R Hippocampus	-.146	.151	1.128
ACC	-.199	.135	1.273

Note. ACC = anterior cingulate cortex, mOFC = medial orbitofrontal cortex, L = left, R = right, D = history of depression, ND = no history of depression

* $p < .05$

Discussion

State- or trait-independent neurobiological alterations, as well as factors such as socio-demographic characteristics and life stressors, may contribute to the likelihood of recurrence of major depressive disorder (MDD). The aim of the present study, therefore, was to determine whether euthymic women with a history of depression are different from those without any experience of depression based on the socio-demographic, clinical-anamnestic, hormonal (hair cortisol) and neuroimaging data. According to the evaluation made during the participants' inclusion in the study, which was within 1 to 6 days of childbirth, none suffered from clinical depression.

We found that the average RSFC in the DMN was decreased in women with a history of depression, with the disturbed RSFC pattern seen between the left LPC and the PCC. In line with our observation, the LPC has been found to show reduced RSFC to the PCC in unmedicated depressed individuals compared to healthy controls (Li et al., 2014). Furthermore, on the basis of a meta-analysis involving 32 studies (N= 848 patients), Yan et al. (2019) reported decreased dorsal medial PFC/posterior DMN RSFC in depressed individuals with recurrent depression. Being among the central parts of the DMN, the LPC and the PCC have been implicated in internally directed attention and thoughts (Leech et al., 2011), which are self-referential processes, as well as in memory retrieval (Sestieri et al., 2011). Previously, disruptions in self-referential processes like self-criticism (Hartlage et al., 1998) as well as altered functional connectivity between regions of the DMN were thought to be trait-independent of current depression.

We also noticed links between the neurobiological stress response systems and brain structure and function. In the present study, women with no history of depression showed a negative association between hair cortisol concentration (HCC) and gray matter volume (GMV) in the medial orbitofrontal cortex (mOFC), whereas the opposite trend was seen in women with a history of depression. Again, only in individuals without a history of depression, there was a negative association between HCC and the mean RSFC in the DMN. A previous study of our workgroup showed a negative association between HCC in the last three months of pregnancy and OFC activation during the presentation of anxious faces (Stickel et al., 2019), indicating a link between higher stress levels in pregnancy and stronger response to anxious faces shortly after childbirth. Repeated stress exposure or high levels of cortisol are known to cause structural changes in brain regions such as the mOFC as these regions are involved in stress regulation (Chattarji et al., 2015). Also, a decreased coupling of regions within the DMN has been shown to depend on the cortisol level (more cortisol resulting in less coping), implying a role of the DMN in an individual's stress responsiveness (Zhang et al., 2019). Collectively, these observations demonstrate that increased levels of stress may be an additional risk factor given that more stress (higher HCC level) is associated with less brain volume and an

increased connectivity pattern in the DMN. However, because this relationship was seen only in women without a history of depression, the observation may be without any significance. The opposite pattern, on the other hand, may indicate an altered stress response in women with a history of depression. During pregnancy, cortisol levels rise steadily and peak during the last trimester of pregnancy, which is thought to be an adaptive process and aid fetal development (for a review, see Dickens and Pawluski, 2018). The maternal brain has been found to undergo major and lasting changes during pregnancy, including reductions in GMV in the insula, the hippocampus, and the mOFC (Hoekzema et al., 2017). Changes in GMV in the limbic system may, therefore, serve an adaptive purpose and prepare women for their new role, enhancing emotion and face recognition (Anderson and Rutherford, 2012; Pearson et al., 2009) and further facilitating the recognition of the child's needs (Hoekzema et al., 2017). The altered patterns of adaptation to stress during pregnancy in women with a history of depression therefore may be linked to diminished mother-child attachment.

We observed group differences also with respect to socio-demographic and clinical-anamnestic characteristics. In particular, in line with previous research (for a meta-analysis, see Sullivan et al., 2000), women with a history of depression were found (significantly more often) to have close relatives who had also suffered from depression (70%) compared to their counterparts with no history of depression (20%). This group of women had significantly higher EPDS scores shortly after childbirth and were found to have experienced more stressful life events, which is not surprising given that there is a link between stressful life experiences and the subsequent development of depression (Saleh et al., 2017; Kendler and Gardner, 2016). To date, several studies have revealed that many patients continue to experience persistent subclinical symptoms following remission, which may increase the likelihood of recurrence (e.g. Kanai et al., 2003; Karp et al., 2004). Also, the cumulative effect of risk factors such as stressful life events, a personal and family history of depression and persistent subclinical symptoms increases the risk of a depressive relapse. For instance, Zimmermann et al. (2008) found that stressful life events are associated with increased incidence of depressive episodes in individuals with a history of depression; the same, however, did not hold true for individuals without a history of depression.

To summarize, women with a history of depression suffer from a range of vulnerability factors that increase the risk of further depressive episodes. These women are also at a 20-fold higher risk of developing postpartum depression, a severe obstetric complication affecting 10-15% of women (O'Hara and McCabe, 2013). El-Hachem et al. (2014) reported a strong link between an above-nine EPDS score as well as a history of depression and a subsequent diagnosis of PPD. These vulnerabilities can be traced back to genetic factors as well as stressful life events, and the vulnerabilities are augmented by differential brain structure and function in the early postpartum period. Further, the postpartum period is in itself a sensitive

period in a woman's life due to hormonal changes and adjustments in personal life. Therefore, women with risk factors may benefit from closer follow-ups during this period. In addition, a comprehensive understanding of the PPD risk factors may help improve prevention strategies and the development of effective prediction methods.

The study is not without limitations. For instance, the observed differences between the two groups might very well be trait differences, which do not in all cases have clinical relevance. Observations over a longer period of time, starting at the beginning of pregnancy, will help determine the precise causal links. Not all women with a history of depression will necessarily develop postpartum depression. By helping identify those individuals who will not develop PPD, despite having the same risk factors, a longitudinal approach can shed valuable light on additional factors that trigger clinical manifestations of PPD and make a prediction possible. It also needs to be noted, that although MDD and PPD share clinical symptoms, there are studies indicating the involvement of different underlying neuronal networks in both disorders (Pawluski et al., 2017; Stickel et al., 2019). As fMRI studies on PPD are still scarce, further neuroimaging research is needed to disentangle the similarities and differences in the underlying neurobiology between MDD and PPD.

Nevertheless, the study benefits from a homogenous sample of healthy unmedicated postpartum women, the use of structured clinical interviews and the multimodal approach. Although earlier studies reported a history of depression to be one of the main risk factors for postpartum depression, this is the first study to compare women based on this risk factor in the early postpartum period. The results presented here combine findings from anamnestic, hormonal, and neuroimaging data acquired within the first week after childbirth.

In summary, the results of the current study indicate that women with a history of depression can be differentiated from those without a history of depression already shortly after birth by means of a multimodal approach and that a history of depression needs to be considered a significant risk factor for future depressive episodes.

Declarations of interest

None

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