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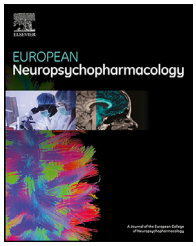

Reduced prefrontal cortex response to own vs. unknown emotional infant faces in mothers with bipolar disorder

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Abstract
Motherhood involves functional brain adaptations within a broad neural network purported to underlie sensitive caregiving behavior. Bipolar disorder (BD) is associated with aberrant brain response to emotional faces within a similar network, which may influence BD mothers' sensitivity to infant faces. This functional magnetic resonance imaging (fMRI) study aimed to investigate whether mothers with BD display aberrant neural responses to own infant faces compared to healthy mothers. Twenty-six mothers with BD in remission and 35 healthy mothers underwent

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fMRI during which they viewed happy and distressed still facial photographs of their own and of unknown infants. After the scan, mothers viewed the pictures again on a computer screen and rated the intensity of infants' facial emotions and their own emotional response to infant face images. Mothers with BD displayed lower left dorsolateral prefrontal cortex (dlPFC) response compared to healthy mothers to own vs. unknown infant faces specifically and abnormal positive functional connectivity between the left and right amygdala and prefrontal regions. BD mothers further displayed stronger deactivation of precuneus and occipital regions to all happy vs. distressed infant faces. After the scan, they rated their infants' distress and own response to their infants' distressed faces less negatively than healthy mothers. Blunted dlPFC response and aberrant fronto-limbic connectivity while viewing own infant faces and less negative ratings of own infants' distress in BD mothers may affect their responses to their own infants in real-life mother-infant interactions.
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1. Introduction

Children of parents with bipolar disorder (BD) are at increased risk of developing *any* mental illness (Rasic et al., 2014). Bipolar disorder is highly heritable and genetic factors have been estimated to account for approximately 65% of the risk (DeRubeis et al., 2016). While severe neglect and psychological trauma are well-known risk factors for mental illness, the effect of more subtle negative environmental influences is unknown. Emerging research has revealed psycho-social mechanisms, including parenting behavior, as mediating factors contributing to the transmission of risk from parents with BD to their children (Iacono et al., 2018). However, little is known about the influence of neurocognitive processing of emotional information in BD mothers on maternal sensitivity, early mother-infant interaction and child development.

1.1. The maternal brain

Mothers display faster attention allocation to and increase neural responsiveness to infant stimuli than non-mothers (Nishitani et al., 2011, 2014; Parsons et al., 2017; Seifritz et al., 2003; Thompson-Booth et al., 2014). This neurocognitive attunement to infant signals likely serves the evolutionary purpose of ensuring infant survival, is hard-wired into the brain and reflected by increased activation within a network of structures coined the "maternal neural network" (Bjertrup et al., 2019). The network supports instinctive emotion processing, tagging of personal relevance and saliency (e.g. amygdala, OFC and occipital areas) attention and higher order emotion processing (e.g. precuneus), empathy (e.g. insula), reward and motivation (e.g. OFC and striatum), automatic and voluntary emotion regulation and executive functions (e.g. anterior cingulate cortex (ACC) and dlPFC) (Bjertrup et al., 2019; Swain et al., 2014). Personal relevance has an effect on this, since mothers generally show increased activation in response own vs. unknown infant faces, irrespective of emotional valence (Bjertrup et al., 2019). Therefore, the maternal neural network likely supports maternal vigilance, sensitivity and affiliative behavior, particularly towards own infants. The structures in the maternal neural network most consistently reported to respond specifically to *own* vs. *unknown* emotional infant faces during functional magnetic resonance imaging (fMRI) are the amygdala (Bjertrup et al., 2019; Dudin et al., 2019; Wonch et al., 2016), dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), insula, striatum, fusiform gyri and precuneus (Bjertrup et al., 2019; Strathearn and Kim, 2013; Strathearn et al., 2008). Neural responses to own and unknown infant faces may be modulated by emotional valence. For example, studies have reported greater activation of the amygdala (Barrett et al., 2012; Strathearn and Kim, 2013; Wonch et al., 2016) and striatum (Strathearn et al., 2008) in response to own happy vs. unknown happy faces, while own distressed vs. unknown distressed infant faces activated ACC and STG (Barrett et al., 2012). However, findings are mixed, and it is therefore unclear precisely how and in which structures valence and personal relevance modulate neural response to infant faces.

1.2. Emotional neurocognition in bipolar disorder

Core features of BD are the trait-related abnormalities in emotion processing (both positive and negative biases) and difficulties with down-regulating emotions (Miskowiak et al., 2019; Miskowiak and Varo, 2021; Varo et al., 2021), which are accompanied by structural and functional abnormalities in a fronto-limbic network of regions that overlaps largely with the maternal neural network (Bjertrup et al., 2019; Swain et al., 2014). Specifically, during affective episodes and in remission patients with BD display amygdala *hyper*-activity to emotional stimuli, *hyper*-activity in the OFC, striatum and ventrolateral prefrontal cortex (vlPFC) during reward processing and *hypo*-activation of vlPFC during emotion regulation (Phillips and Swartz, 2014). Further, research has shown reduced activation of mirror-neuron-structures such as the insula in remitted patients with BD during Theory of Mind tasks (Kim et al., 2009). Neural processing of infant stimuli in mothers with BD has not previously been studied. However, mothers with postpartum depression (PPD) show blunted neural responses to infant stimuli within amygdala and in-

sula (Bjertrup et al., 2019) and aberrant functional connectivity (FC) between the amygdala and nucleus accumbens, dorsomedial PFC (Ho and Swain, 2017) and insula (Wonch et al., 2016). These neuronal changes may contribute to the attenuated imitation of their own infants' emotional expressions (Field, 2010) and negative bias in mother-infant interactions in dyads where the mother has PPD (Cohn et al., 1990). Based on these observations, it is possible that the general abnormalities in cognitive and neuronal response to emotional information in BD occurs in mothers with BD and has negative consequences for reciprocal interactions between these mothers and their infants.

1.3. Behavioural responses to infant emotions

The present report is based on a largely overlapping sample of BD and HC women to the larger sample of mothers with BD or MDD examined for psychophysiological and behavioural responses (Bjertrup et al., 2021), of whom only two (one BD and one HC) did not undergo fMRI due to claustrophobia. For this sample, we found that the remitted mothers with BD show less eye gazes towards and blunted psychophysiological response to infant stimuli (videos and pictures) than healthy mothers, which may indicate that they perceive them as less emotionally salient. They also displayed *misattuned* positive facial expressions while watching videos of infant cry vs. laughter and rated sounds of infant cry less negatively than healthy mothers. Importantly, the blunted visual attention toward infant stimuli was associated with less maternal sensitivity, while the misattuned positive facial expressions to infant distress were associated with less dyadic reciprocity in mother-infant interactions (Bjertrup et al., 2021). However, *neural correlates* of blunted attentional processing of and misattuned positive bias toward emotional infant stimuli in mothers with BD in remission remain unclear.

1.4. Aims and hypotheses

In this fMRI report based on the same sample of BD and healthy control mothers, we aimed to investigate the hypotheses that remitted mothers with BD show 1) blunted neural activity in the seven structures comprising the maternal neural network and aberrant FC between amygdala and prefrontal regions in response to all own vs. all unknown emotional infant faces, 2) different neural response to all (own and unknown) happy vs. distressed infant faces in the maternal neural network, in line with a more positive emotional bias and 3) amygdala hyperresponsiveness to the emotional content of the infant face images. Finally, we hypothesize that blunted neural activity in the maternal neural network across all mothers will correlate with less maternal sensitivity and dyadic reciprocity in real-life interactions with own infants. We also explored the effect of emotional valence on responses to own vs. unknown infant faces.

2. Experimental procedures

2.1. Participants

During pregnancy or shortly after birth, mothers with BD were recruited by their psychiatrist at psychiatric centers in the Capital and Northern Regions of Denmark. Healthy mothers were recruited at the Department of Obstetrics and Gynecology, Hvidovre Hospital. Mothers in both groups were also recruited via application through online adverts. General inclusion criteria were pregnancy or early motherhood ($\leq$8 months after birth) and age $\geq$18 years. For mothers with BD, the ICD-10 diagnosis had previously been made by a clinician and thus preceded inclusion in the study but was verified with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) conducted by a trained Ph.D. student. An additional inclusion criterion for mothers with BD was partial or full remission at the time of assessment defined by scores of $\leq$14 or $\leq$7, respectively, on the Hamilton Depression Rating Scale 17 items (Hamilton, 1967) and the Young Mania Rating Scale (Young et al., 1978). Inclusion criteria for healthy mothers were no personal history of mental illness as confirmed with MINI and no history of major psychiatric disorder among first-degree relatives. General exclusion criteria were magnetic resonance (MR) contra-indications (magnetic metal implants or severe claustrophobia), current alcohol or substance abuse (defined by ICD-10 F1X.1 [harmful use] or F1X.2 [dependence syndrome] criteria). Mother-infant pairs were excluded in case of infants born with Down syndrome, cerebral palsy or other severe neurological illnesses that would affect mother-infant interaction. All mothers and co-parents (as available) provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee in the Capital Region of Denmark (ID: H-17009045) and by the Danish Data Protection Agency Capital Region of Denmark (ID: RHP-2017-024; I-Suite: 05603).

2.2. Procedure

Home-visit were conducted approximately four months after birth and involved neurocognitive assessments of mothers (reported elsewhere (Bjertrup et al., 2021)) and evaluations of their interactions with their infants with the Coding Interactive Behavior (CIB) (Feldman, 1998). Mothers were instructed to 'be with' their infants as usual while the mother-infant interaction was video-filmed for five minutes and later coded with CIB (Feldman, 1998, 2012) by a trained rater, who was blind to the group status of mothers and infants (reported elsewhere (Bjertrup et al., 2021). Composite scores for maternal sensitivity and dyadic reciprocity in mother-infant interactions were used in correlation analyses in the current study.

Pictures of infants were taken and the images expressing the strongest positive, i.e., *Duchenne* smiles (Messinger and Fogel, 2007), and negative emotions were selected for the MR scan. Approximately one week after the home visit, mothers participated in an fMRI scanning session at Rigshospitalet, Copenhagen, Denmark where they watched the still photographs of their own infants and of an unknown in-

fant. In the MR-scanner, the mothers watched the images of their own infant's face among images of an unknown four-month-old Caucasian infant girl's face. Immediately after the scan, mothers were asked to rate the valence of infant images on two separate rating paper sheets assessing 1) how they thought the infant was feeling and 2) how they themselves were feeling when watching the infant images. They watched the images of own and unknown infants in a PowerPoint slide on a laptop and rated the infants'/their own feelings on a 9-point scale ranging from −4 (most distressed), 0 (neutral) to + 4 (most happy) by ticking one of nine boxes on the scale with a pen on a paper sheet.

2.3. fMRI paradigm

Infant images were edited using GNU Image Manipulation Program (GIMP) version 2.10.18 and standardized so that only the face (and hair) was visible and all faces had the same size, orientation, lighting and were displayed on a black background. For validation purposes, twelve independent individuals (researchers in the NEAD Group, Copenhagen University Hospital), who were blind to the group status of the infants, rated the emotional intensity of all the infant face images used during the scan on a scale with 5 possible scores: −4 (most distressed), −2 (medium distressed), 0 (neutral), +2 (medium happy) and +4 (most happy). Inter-rater reliability was calculated as Intra-Class Correlations (ICC) with 95% confidence intervals (CI) (Koo and Li, 2016). There was excellent agreement in the objective ratings of the images (average measure ICC=0.99, 95% CI 0.988–0.991) and no difference in the emotional intensity of infants of mothers with BD and infants of healthy mothers ($p \geq 0.13$). Infant stimuli were presented in an fMRI paradigm consisting of four blocks: 1) own happy, 2) own distressed, 3) unknown happy and 4) unknown distressed. The infant image paradigm was run in E-prime 2.0 and projected onto an opaque screen at the head-end of the MR bore, which mothers viewed through an angled mirror mounted on the head coil. Each block consisted of three images and was shown six times in a pseudorandomized order. Images were presented for 3750 ms and separated by 500 ms fixation crosses. Blocks were separated by 2500 ms fixation crosses. The total duration of the task was 6.3 min. Before the scan, mothers were informed that they were going to see images of their own infant among images of an unknown infant. They were instructed to simply watch the images to allow the most 'natural' and spontaneous maternal feelings and thoughts and to avoid cognitive and motor responses that would be elicited by performing a task with button presses.

2.4. MRI acquisition protocol

Neural responses to own and unknown infant emotional faces were investigated with blood oxygen-level dependent (BOLD) fMRI using a 3T Siemens MR scanner and a 64-channel head-neck coil. The total scanner sequence lasted for approximately 45 min and included: a localizer, a high-resolution T1-weighted structural images of the whole brain (T1 sequence: MPRAGE, echo time [TE]=2.58, repetition time [TR]=1900 ms, flip angle 9°, distance factor=50%, a 230 × 230 mm field of view [FOV] and slice-thickness=0.9 mm), a BOLD sensitive T2*-weighted gradient echo spiral echo-planar imaging sequence (with TE=30 ms, TR=2 s, and flip angle=90°). 193 total brain volumes were collected consisting of 32 slices and slice thickness of 3 mm with 25% gaps in between and FOV of 230 × 230 mm using a 64 × 64 grid. Finally, a standard B0 field map sequence (230 × 230 mm FOV; TR=400 ms; TE=7.38 ms; flip angle=60°) was obtained to correct the BOLD images for geometric distortions.

2.5. Statistical analysis of clinical variables, demographic data and ratings

Comparison between mothers with BD and healthy mothers on clinical and demographic variables were investigated by independent samples t-tests. For significant group differences in subsyndromal affective symptoms, mood symptoms were included as covariates in the fMRI analyses. Differences in ratings of infant stimuli were investigated with repeated measures analysis of variance (ANOVA) with infant emotion levels as within-subjects factor and group as between-subjects factor. Significant interaction effects were followed up by t-tests for normally distributed data and by Mann-Whitney U tests for non-normally distributed data. These analyses were conducted with the Statistical Package for the Social Sciences (SPSS) version 25 (Corp., 2017).

2.6. fMRI data analysis

Functional MRI data were analyzed with the FMRIB Expert Analysis Tool (FSL v. 6.00) (www.fmrib.ox.ac.uk/fsl). Preprocessing included removal of non-brain tissue using FSL brain extraction tool (BET) (Smith, 2002), motion correction with FSL MCFLIRT, registration to an MNI template, and spatial smoothing using a 5 mm full-width at half-maximum Gaussian kernel. For subjects with excessive head movement, defined by a relative inter-volume mean displacement >1 mm, respective volumes were discarded from first-level general linear model (GLM) using confounding regressors. The registration of the BOLD images to the MNI space was visually inspected and screened for artifacts and excessive movement for each participant.

Subject-level analyses were carried out in FSL FEAT using a GLM that included five conditions: 1) own happy, 2) own distress, 3) unknown happy, 4) unknown distress, and 5) intertrial intervals (fixation cross). The conditions were convolved with double-gamma hemodynamic response function and included spatial and temporal derivatives. The chosen contrasts were 1) own vs. unknown, 2) happy vs. distress (primary contrasts), and, for exploratory purposes, 3) own vs. unknown happy and 4) own vs. unknown distressed.

Group-level analysis were set up in FSL FEAT using a mixed-effects model (FLAME 1) with group (BD and healthy mothers), as the two explanatory variables (EVs). We investigated group differences for the four contrasts in a priori hypothesized *volumes of interest* (VOI): the OFC, insula, striatum, fusiform gyri, precuneus and the dlPFC structures middle frontal gyrus MFG and superior frontal gyrus. These are structures within the 'maternal neural

Table 1 Demographics, affective symptoms, medication status, infant characteristics, mother-infant interaction and post-scan ratings in mothers with BD compared with healthy mothers.

	BD mothers $N = 26$	Healthy $N = 35$	t/F/Chi-square	p-value*
Age, years, mean (SD)	31.2 (3.7)	30.9 (3.3)	0.33	0.74
Years of education, mean (SD)	15.9 (2.3)	16.5 (1.9)	1.22	0.23
Occupation				
Employed, n (%)	11 (42.3)	31 (88.6)	16.51	**≤ 0.001**
On sick leave, n (%)	3 (11.5)	0 (0)	4.20	**0.04**
Student, n (%)	8 (30.1)	4 (11.1)	3.53	0.06
Living with co-parent, n (%)	24 (92.3)	32 (91.4)	0.02	0.90
Right-handed, n (%)	25 (96.2)	33 (94.3)	1.11	0.74
HDRS-17, mean (SD)	5.4 (3.4)	2.1 (1.5)	4.68	**≤ 0.001**
YMRS, median (IR)	0.0 (2.0)	0.0 (1.0)	1.75	0.052
BD-I, n (%)	7 (26.9)	NA	..	..
BD-II, n (%)	18 (69.2)	NA	..	..
BD-unspecified, n (%)	1 (3.8)	NA	..	..
Partial remission, n (%)	4 (15.4)	NA	..	..
Remission, months, mean (SD)	33.8 (40.0)	NA	..	..
Psychotropic medication use, n (%)	24 (92.3)	0 (0)	41.23	**≤ 0.001**
Antidepressant medication, n (%)	5 (19.2)	0 (0)	7.33	**0.01**
Lithium, n (%)	5 (19.2)	0 (0)	7.33	**0.01**
Anticonvulsants, n (%)	17 (65.4)	0 (0)	33.60	**≤ 0.001**
Antipsychotics, n (%)	9 (34.6)	0 (0)	15.85	**≤ 0.001**
Breastfeeding, n (%)	13 (50.0)	31 (88.6)	10.0	**0.002**
Parity, median (R)	1 (1–3)	1 (1–4)	0.00	0.98
Infant female gender, n (%)	12 (46.2)	15 (42.9)	0.07	0.80
Infant age, months, median (IR)	4.1 (0.4)	4.0 (0.4)	1.84	0.07
GA, weeks, mean (SD)	39.9 (1.2)	39.9 (1.4)	0.04	0.97
Birth weight, gram, mean (SD)	3531.4 (499.8)	3479.9 (688.4)	0.32	0.75
CS, n (%)	4 (15.4)	4 (11.4)	0.21	0.65
Maternal sensitivity, mean (SD)	3.6 (0.8)	3.7 (0.5)	0.30	0.77
Dyadic reciprocity, mean (SD)	2.6 (1.1)	3.0 (0.7)	1.75	0.09
Post-scan rating, infants' feelings				
Own happy, mean (SD)	2.3 (1.0)	2.6 (0.9)	0.86	0.36
Own distressed, mean (SD)	−1.3 (1.6)	−1.9 (1.6)	2.20	0.14
Unknown happy, mean (SD)	2.0 (1.1)	2.8 (0.8)	9.29	**0.003**
Unknown distressed, mean (SD)	−2.8 (0.5)	−2.7 (1.1)	0.49	0.49
Post-scan rating, mothers' feelings				
Own happy, mean (SD)	2.9 (0.9)	3.2 (0.8)	1.00	0.32
Own distressed, mean (SD)	0.4 (2.1)	−1.4 (2.1)	11.5	**0.001**
Unknown happy, mean (SD)	1.7 (1.3)	2.4 (0.9)	4.62	**0.04**
Unknown distressed, mean (SD)	−1.6 (1.4)	−2.2 (1.2)	2.60	0.12

Abbreviations: BD, bipolar disorder; HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; GA, gestational age; CS: Cesarean section; NA: not applicable; Group differences were investigated with Chi-square tests for categorical data and t-tests or one-way ANOVA for numerical data with score as within-subjects factors and group comparison as between-subjects factor, *p -values for main effect of group. Values display means and standard deviations (SD) for normally distributed data and medians and full range (R) or interquartile range (IR) or number and percent for non-normally distributed data.

network' previously identified in our systematic review as specifically responsive to *own* vs. *unknown* emotional infant faces (Bjertrup et al., 2019). The VOI was created in FSLeyes on the MNI template and was based on probabilistic structures from the Harvard-Oxford cortical and subcortical structural atlases, thresholded at 25%. These structures were combined in one mask for small volume correction at group-level.

A region-of-interest (ROI) analysis was also performed by extracting mean percentage BOLD signal change to own and unknown infant happy and distressed faces from left and right amygdala. The amygdala ROIs were based on the Harvard-Oxford subcortical structural atlas, thresholded at 25%. The ROI analyses were performed with repeated measures ANOVA, with four levels (amygdala activation to own happy, own distressed, unknown happy and unknown distressed infant faces) for left and right amygdala separately in SPSS (level of alpha =0.05).

For exploratory purposes, we performed a whole brain analysis in FSL FEAT with the above contrasts. Finally, we

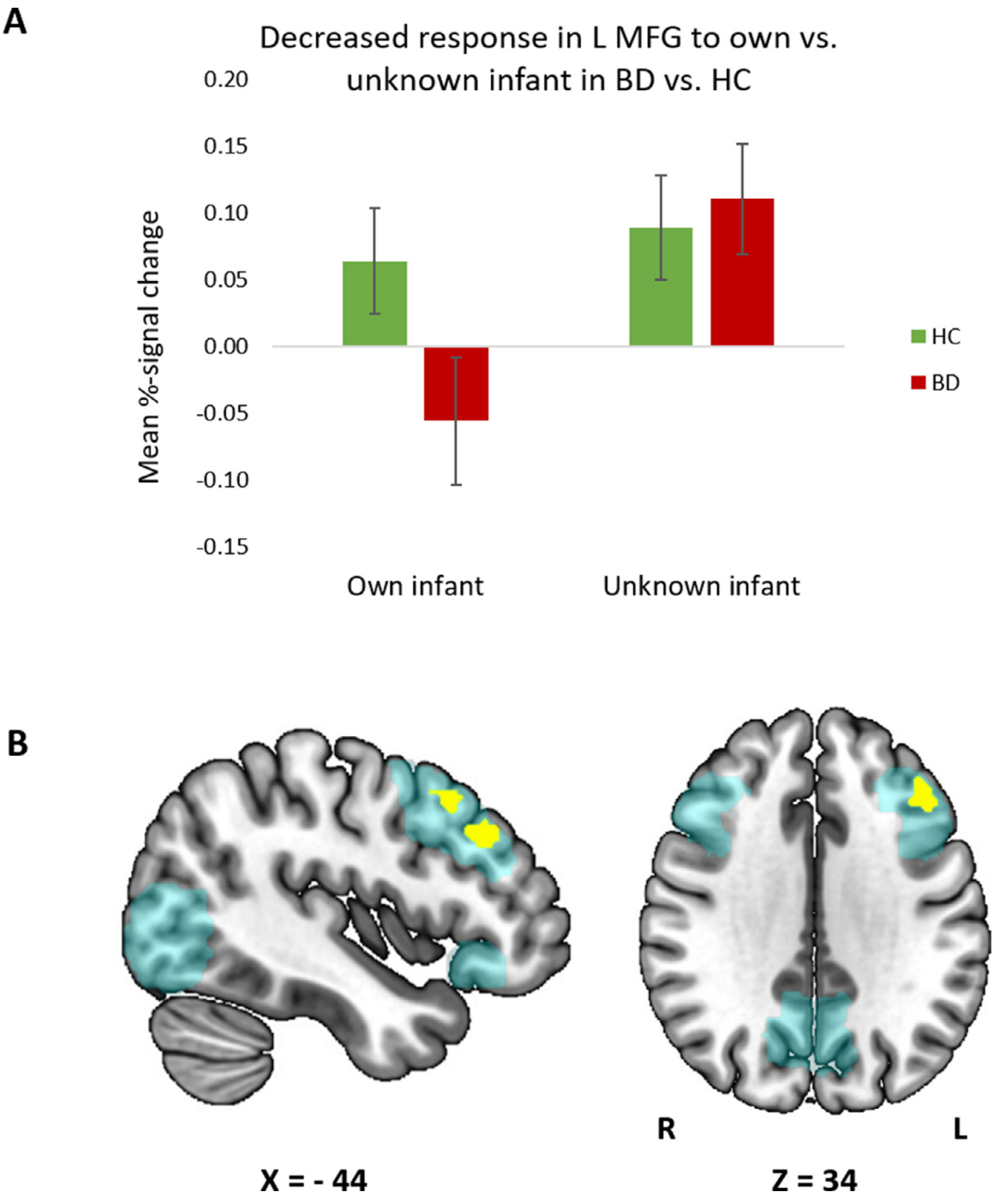

Fig. 1 Mothers with BD show decreased responses in left (L) dlPFC to their own vs. unknown infants' faces. **A)** The bars display mean percentage signal change in response to own and unknown infants. Errorbars display standard error of the mean. **B)** The brain illustrations show that the significant cluster with peak activation in L dlPFC (yellow) lies within the maternal neural network VOI (blue) Abbreviations: L, left; dlPFC, dorsolateral prefrontal cortex; BD: mothers with bipolar disorder; HC: healthy mothers.

conducted a psychophysiological interaction (PPI) analysis to identify regional brain activity that correlated with left and right amygdala activations when watching images of own vs. unknown infants and contrasted mothers with BD vs. healthy mothers. The left and right amygdala seed regions were based on the ROI analyses described above. Deconvolved time-series from the left and right amygdala were extracted for each participant and entered as the physiological regressors in FSL feat, along with the psychological regressor (i.e. the task regressor own vs. unknown infant face), other task regressors (own and unknown infant face, and fixation crosses) and the PPI regressor (own vs. unknown $\times$ time-series). These results were entered in the second level FEAT (BD vs. healthy mothers) and analyzed with mixed-effects analysis across the whole brain.

All group level analyses were conducted in FSL FEAT using a mixed-effects model (FLAME 1) and significance level for clusters was set to $p < 0.05$ corrected for mul-

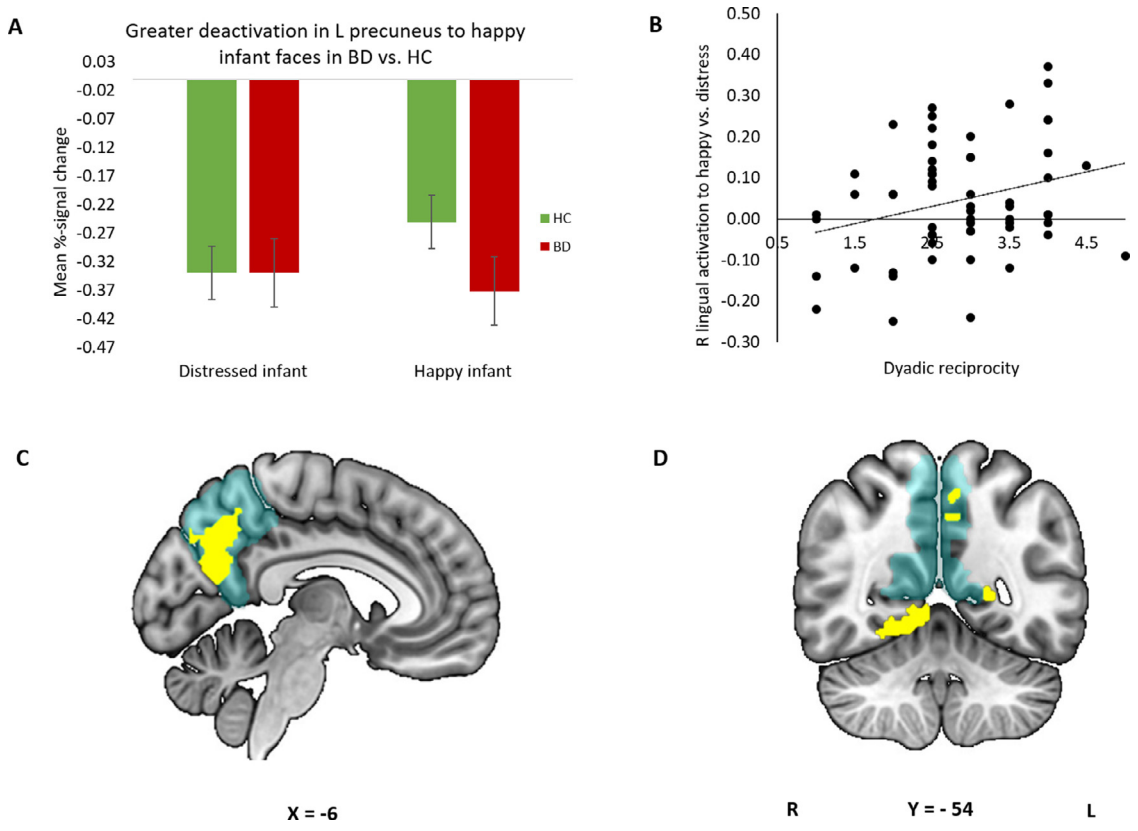

Fig. 2 A) Mothers with BD show greater deactivation to happy vs. distressed infant faces than healthy mothers in L precuneus within the maternal neural network. The bars display mean percentage signal change in L precuneus in response to happy and distressed infant faces. Error-bars display standard error of the mean. B) Mothers with BD show greater deactivation to happy vs. distressed infant faces than healthy mothers in R lingual gyruswhich correlated with lower dyadic reciproity in interactions with own infants. The brain illustrations show that the significant cluster with activation in C) L precuneus (yellow) lies within the maternal neural network VOI (blue) and that the significant cluster with activation in D) R lingual gyrus (yellow-red) lies outside the maternal neural network. Abbreviations: L, left; R: right, BD: mothers with bipolar disorder; HC, healthy mothers.

tiple comparisons using Gaussian Random Field theory following a cluster-forming threshold of $z = 2.57$ (uncorrected $p = 0.005$). Peak cluster foci were identified with Harvard-Oxford cortical and subcortical structural atlases in FSLeyes. Brodmann Areas were identified using the Talairach Atlas (Talairach, 1988). Mean percent BOLD signal-change from VOI and whole-brain analyses and average beta-coefficients from PPI analyses were extracted for each participant from clusters showing a significant effect of group using the FEATquery tool in FSL.

2.7. Correlation analyses

Mean percent signal change from clusters showing a significant effect of group in the main analysis and average beta-coefficients from clusters showing a significant effect of group in the PPI analysis were correlated with (I) mothers' post-scan ratings of own infant's feelings and (II) mothers' ratings of their own emotional response to watching their own infant's emotional faces, as well as (III) maternal sensitivity and (VI) dyadic reciprocity in mother-infant interactions. Correlation coefficients were reported as Pearson's r.

3. Results

3.1. Demographics

In total, 26 mothers with BD and 35 healthy mothers underwent an fMRI scan. There were no group differences in age or years of education (p-values≥0.23). However, mothers with BD experienced more subsyndromal depression symptoms ($p \leq 0.001$), were more often unemployed ($p \leq 0.001$), were more often taking psychotropic medication ($p \leq 0.001$) and breastfed less often ($p = 0.002$). Participant characteristics and demographics are described in Table 1.

3.2. Volumes of interest analysis

Compared with healthy mothers, mothers with BD showed lower BOLD response in the left dlPFC within the maternal neural network to images of own vs. unknown infant faces (Figure 1), greater *deactivation* of the left precuneus to images of happy vs. distressed infant faces (Figure 2). Table 2 presents the peak foci of clusters activated significantly differently in mothers with BD compared with healthy mothers by the contrasts own vs. unknown and happy vs. distressed infant faces. These findings prevailed in post hoc analyses adjusted for subsyndromal depression

Table 2 Peak cluster activation in VOI and whole-brain regions while watching own vs. unknown emotional infant faces and happy vs. distressed infant faces.

Condition	Region (BA)	R/L	Peak Z	X	Y	Z	P	Cluster size (voxels)
BD mothers < Healthy mothers								
VOI								
Own > unknown	Middle frontal gyrus (9)	L	2.16	−44	28	34	0.0070	249
Happy > distress	Precuneus (7)	L	3.86	−6	−62	38	< 0.0001	714
Whole brain								
Happy > distress	Lateral occipital cortex, superior division (19)	R	3.68	42	−84	12	0.0072	349
	Lateral occipital cortex, inferior division (37)	L	4.36	−54	−66	2	0.0097	332
	Lingual gyrus (19)	R	3.51	10	−56	−6	0.0328	265
	Lateral occipital cortex, superior division (19)	L	3.73	−34	−74	42	0.0354	261
Own happy > unknown happy	Supramarginal gyrus, posterior division (40)	R	4.02	62	−42	36	0.0123	329

Coordinates (x, y, z) based on Montreal Neurological Institute template refer to the localization of peak activation within a cluster for significant group differences where mothers with BD showed less neural activation compared to healthy mothers on the contrasts own vs. unknown emotional infant faces and distressed vs. happy infant faces. Significant clusters (corrected $p<0.05$) are presented with cluster size (voxels) and Z statistics for the peak voxel. We used Harvard-Oxford cortical and subcortical atlases in FSLeyes to identify structures and Talairach atlas to identify BA. Abbreviations: VOI, volumes of interest; BA, Brodmann Area; R, right; L, left.

symptoms (data not shown). There were no group differences in neural response to own vs. unknown happy or own vs. unknown distressed infant faces within the VOI structures. Among the BD mothers, there was no difference in BOLD response between those who were medicated and unmedicated (p-values>0.13) or between those in full or partial remission (p-values>0.41) in the regions showing differences between BD and HC mothers.

3.3. Whole-brain analysis

Mothers with BD displayed stronger *de*activation of the left and right lateral occipital cortex (superior division), left lateral occipital cortex (inferior division) (Figure 2& 3) and right lingual gyrus to images of happy vs. distressed infant faces compared with healthy mothers (Table 2). Mothers with BD showed reduced response to own vs. unknown happy infant faces in the right posterior supramarginal gyrus (Table 2). Post hoc analysis covaried for subsyndromal depression symptoms did not significantly change the result. The use of anticonvulsive (but no other) medication correlated with more deactivation to happy vs. distressed infant faces in left lateral occipital cortex within mothers with BD ($r=-0.48$, $p=0.01$). Post hoc t-tests comparing mean percent signal changes in occipital areas between mothers with BD in full remission and mothers with BD in partial remission found no significant differences between these groups (p-values≥0.55).

3.4. ROI analysis: amygdala

Across all mothers, viewing own and unknown infant face images significantly activated bilateral amygdala (own, right: $t=4.16$, df=60, $p\leq 0.001$; unknown, right: $t=3.23$, df=60, $p=0.002$; own, left: $t=3.56$, df=60, $p=0.001$; unknown, left: $t=2.57$, df=60, $p=0.01$). However, there were no differences between mothers with BD vs. healthy mothers in right or left amygdala responses to own or unknown happy or distressed infant faces (p-values≥0.25).

3.5. Functional connectivity

Compared to healthy mothers, mothers with BD showed a differential FC pattern between the left and right amygdala and widespread prefrontal regions while watching images of own vs. unknown infant faces: while the healthy mothers displayed a *negative* amygdala-frontal FC, mothers with BD displayed a *positive* amygdala-frontal FC (Figure 4 and Table 3).

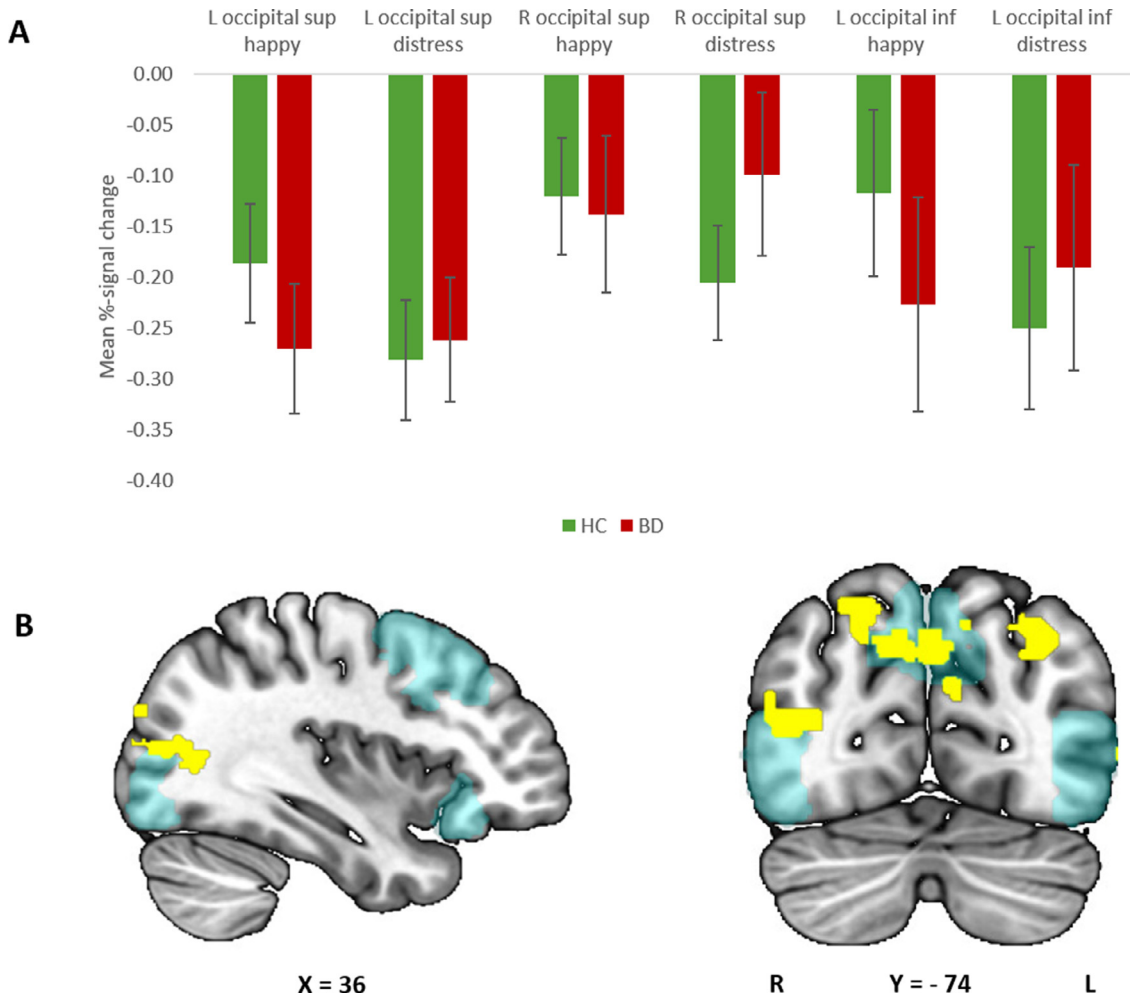

Fig. 3 Mothers with BD show greater deactivation to happy vs. distressed infant faces than healthy mothers in bilateral occipital areas. A) The bars display mean percentage signal change in bilateral occipital areas to happy and distressed infant faces. Error-bars display standard error of the mean. B) The brain illustrations show that the significant occipital clusters (yellow) extends into medial and posterior parietal regions but are located outside the maternal neural network VOI (blue). Abbreviations: L, left; R: right; sup: superior; inf: inferior; BD: mothers with bipolar disorder; HC, healthy mothers.

3.6. Ratings of infant images

Mothers with BD rated infants' emotions differently than healthy mothers ($F(2.31,133.89)=3.75$, $p = 0.02$, $\eta^2 = 0.6$). This was driven by *less positive* ratings of the unknown infant's happy faces in BD mothers ($U = 385.50$, $p = 0.01$, $r = -0.11$). This interaction effect remained significant after post hoc control for depression symptoms ($F(2.31,131.75)=4.56$, $p = 0.01$, $\eta^2 = 0.7$). Mothers with BD also rated their own emotional response while watching images of the infants' faces differently than healthy mothers ($F(2.38, 135.56)=9.40$, $p \leq 0.001$, $\eta^2 = 0.14$). This was driven by mothers with BD rating their emotional responses to own infant's distressed faces *less negatively* ($U = 633.00$, $p = 0.001$, $r = -0.12$) and their responses to the unknown infant's happy faces *less positively* ($U = 288.50$, $p = 0.04$, $r = 0.42$). This interaction effect remained significant after post hoc control for depression symptoms ($F(2.40,134.27)=9.42$, $p \leq 0.001$, $\eta^2 = 0.14$).

3.7. Associations between neural responses, subjective ratings and mother-infant interactions

Across all mothers, lower activity of the left dlPFC in response to own vs. unknown infant faces (as seen in BD mothers) was associated with *less negative ratings* of own infants' distressed faces and own emotional responses while watching their infants' *distressed* faces ($r = 0.30$, $p = 0.02$ and $r = 0.36$, $p = 0.01$, respectively). More deactivation of the right lingual gyrus in response to happy vs. distressed infant faces (as seen in BD mothers) correlated with *less dyadic reciprocity* in real-life mother-infant interactions ($r = 0.29$, $p = 0.03$). Across all mothers, more positive (or less negative) FC between the right and left amygdala and frontal areas (as seen in BD mothers) correlated with *less negative ratings* of own emotional responses while watching their own infants' distressed faces (right amygdala: $r = 0.29$, $p = 0.03$; left

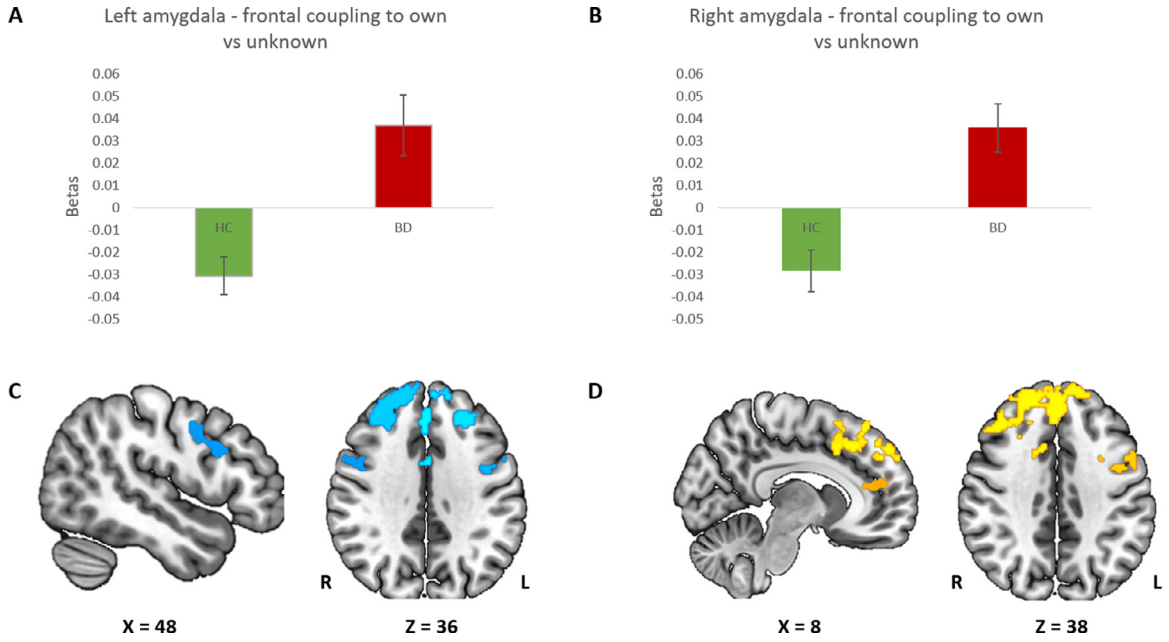

Fig. 4 Mothers with BD show positive, while healthy mothers show negative functional connectivity between A) left and B) right amygdala and frontal areas to own vs. unknown infant faces. A-B) The bars display average beta values. Error-bars display standard error of the mean. C-D) The brain illustrations display the frontal clusters showing positive and negative functional connectivity with the C) left amygdala (frontal clusters in blue) and D) right amygdala (frontal clusters in yellow) in mothers with BD and healthy mothers, respectively.

amygdala: $r = 0.31$, $p = 0.01$) and less positive rating of unknown infants' happy faces (right amygdala: $r = -3.71$, $p = 0.003$; left amygdala: $r = -3.3$, $p = 0.01$). For the identified clusters, in which BD and healthy mothers showed differential neural response, neural activity showed no associations with measures of maternal sensitivity (p-values$\geq$0.08).

4. Discussion

This is the first fMRI study of the neural underpinnings of aberrant neurocognitive response to emotional infant faces in mothers with BD in remission. We found that mothers with BD in remission displayed reduced activation to own (vs. unknown) infants' emotional faces within the left dlPFC and aberrant positive amygdala-frontal FC while watching own infants. They also showed more deactivation of occipital regions in response to happy infant faces regardless of familiarity. Mothers with BD also rated their own reaction to their infants' distressed faces less negatively than healthy mothers, while their ratings of unknown infants' happy faces - and their own reactions to these - were less positive. Lower left dlPFC activity and aberrant positive FC between the amygdala and frontal areas to own infant faces, specifically, correlated with *less negative ratings* of mothers' response to own infants' distressed faces. Further, more lingual deactivation to happy vs. distressed infant faces correlated with *less dyadic reciprocity* in real-life mother-infant interactions. Importantly, the differences between groups within the maternal network and occipital regions prevailed after post hoc control for differences between groups in subsyndromal depression symptoms. Moreover, the use of anticonvulsive (but no other) medication correlated with neural activation of one occipital cluster but none of the other five significant clusters in mothers with BD.

It is noteworthy that mothers with BD displayed attenuated left dlPFC activation and positive FC between amygdala and frontal regions while viewing own infant faces, specifically, and that this correlated with *less negative* evaluations of their infants' distress and of own negative feelings to their infants' distressed faces. These findings are in line with previous evidence that patients with BD show reduced regulation by frontal brain regions in response to emotional stimuli (Townsend and Altshuler, 2012) and reduced amygdala-frontal FC during emotion regulation (Townsend et al., 2013; Zhang et al., 2018). In contrast, healthy mothers show *increased* dlPFC response to own vs. unknown infants (Bjertrup et al., 2019) and greater dlPFC response to own vs. unknown infant faces has been associated with greater maternal "non-directiveness", which is a healthy accepting maternal behavior (Wan et al., 2014). The dlPFC may play a key role in the regulation of normal maternal responses towards own infants (Rilling and Sanfey, 2009) and efficient negative amygdala-frontal connectivity could be important for maternal responses that are both rapid, vigilant, regulated and attuned. However, mothers with BD in the current study may show inefficient top-down regulation in response to watching own infant faces. In fact, *positive* amygdala-frontal connectivity as seen in mothers with BD, may indicate either reduced top-down extinction of amygdala reactivity or amplification of emotional response. The less intense ratings of infant images by these mothers point to the former interpretation. Moreover, the positively biased ratings of own infant distress in mothers with BD

Table 3 Whole brain functional connectivity analysis seeding in left and right amygdala while viewing own vs. unknown emotional infant faces.

Condition	Region (BA)	R/L	Peak Z	X	Y	Z	P	Cluster size (voxels)
BD mothers > Healthy mothers								
Right amygdala								
	Paracingulate gyrus (9)	R	3.48	6	50	18	0.0327	205
	Precentral (9)	L	4.21	−54	8	30	< 0.0001	937
	Superior frontal gyrus (8)	R	4.42	2	40	38	< 0.0001	3003
Left amygdala								
	Precentral (6)	R	3.87	46	4	38	0.0064	255
	Inferior frontal gyrus (46)	L	3.6	−52	24	22	0.0007	347
	Frontal pole (8)	R	3.77	16	48	36	< 0.0001	684
	Frontal pole (10)	L	3.98	−26	48	18	< 0.0001	882
	Inferior frontal gyrus (6)	R	4.12	2	16	62	< 0.0001	1533
BD mothers (positive connectivity)								
Right amygdala								
	Middle frontal gyrus (9)	R	3.54	26	30	32	0.0468	191
	Precuneus (7)	L/R	3.46	0	−52	40	0.0344	203
	Precentral gyrus (9)	L	3.95	−54	10	28	0.018	229
	Superior frontal gyrus (6)	L/R	4.12	0	42	36	< 0.0001	2118
Left amygdala								
	Frontal pole (8)	L	3.32	−24	36	38	0.0342	191
Healthy mothers (negative connectivity)								
Left amygdala								
	Middle frontal gyrus (46)	R	3.68	42	22	22	0.0013	322

Coordinates (x, y, z) based on Montreal Neurological Institute template refer to the localization of peak activation within a cluster for significant group differences where mothers with BD showed positive connectivity or absence of negative functional connectivity with amygdala on the contrasts own vs. unknown emotional infant faces. Significant clusters (corrected $p<0.05$) are presented with cluster size (voxels) and Z statistics for the peak voxel. We used Harvard-Oxford cortical and subcortical atlases in FSLeyes to identify structures and Talairach atlas to identify BA. Abbreviations: BA, Brodmann Area.

could reflect less attuned responses to own infants' emotional states and that they have less need to downregulate negative emotions simply because they are not as negatively affected by watching own infant distress as healthy mothers are. Interestingly, we had observed that these mothers also displayed *misattuned* positive facial expressions during a video of a distressed infant, which correlated with less maternal sensitivity in the interaction with their own infant (reported elsewhere (Bjertrup et al., 2021)). Notably, the decreased dlPFC activity occurred in the absence of differences between mothers with BD and healthy mothers in amygdala response. This was unexpected given the blunted psychophysiological vigilance toward infant stimuli on behavioural measures, the evidence for blunted amygdala responses to own vs. unknown infant faces in mothers with PPD (Lenzi et al., 2016; Wonch et al., 2016) and the consistent evidence for limbic dysregulation in BD in general (Phillips and Swartz, 2014). Taken together, reduced dlPFC activation and positive amygdala-frontal connectivity at a neural level and overly positive responses to infants' emotional signals at a behavioral level may reflect less sensitive processing of infant signals, which could be associated with less sensitive and attuned behavior in reciprocal interactions with their infants in real life.

The greater deactivation in mothers with BD while viewing all happy vs. distressed infant faces within the left precuneus, the right lingual gyrus and bilateral occipital areas is noteworthy. Precuneus is considered part of the default mode network (DMN) (Raichle, 2015) that is active during self-referential, introspective processes and mind-wandering, whereas it *deactivates* when confronted with external attention-capturing stimuli (Fox et al., 2005; Raichle, 2015). Although not part of the DMN, occipital areas have been found to be more active during rest than when engaged in a task (Raichle et al., 2001). Therefore, more deactivation of the precuneus and occipital regions

to happy infant faces in mothers with BD is likely to reflect more attention capturing of happy infant faces specifically. The greater deactivation of these regions to happy expressions may support the observed *general positive* emotion processing bias in this cohort of mothers with BD (Bjertrup et al., 2021). More deactivation in right lingual gyrus to happy vs. distressed infant faces was also associated with less dyadic reciprocity in mothers' interactions with their own infants. Therefore, positive emotion processing bias may be related to difficulties "tuning in on" own infant's negative emotional expressions, which could hamper the synchrony of mother-infant interactions.

It was a limitation that mothers with BD experienced more subsyndromal depression symptoms than healthy mothers despite being in remission. However, the observed group differences in neuronal response to own and to happy infant faces prevailed in analyses adjusted for depressive symptoms. Although mothers with BD and healthy mothers were well matched for age and education, it was a limitation that almost all mothers with BD received psychotropic medication. This may have influenced their neural response to infant stimuli (Bilderbeck et al., 2016), but it was not possible to co-vary for this in the primary fMRI analyses because none of the healthy mothers received medication. However, activity within a left lateral occipital cluster correlated with anticonvulsive medication within the mothers with BD. Further, the results are only generalizable to mothers with BD in full or partial remission who receive psychotropic medication. However, mothers with BD are often in remission for long periods of time and commonly receive medication, which supports the generalizability of the findings. While the structures included in the VOI mask were selected based on a priori defined 'maternal neural network', it was a limitation that existing literature on brain responses to infant stimuli is characterized by great heterogeneity. More studies investigating FC of structures in the maternal neural network are needed to understand the neural underpinnings of modulation and coordination of emotional reactivity and regulation in mother-infant interaction. Lastly, the cross-sectional design cannot elucidate the long-term implication of mothers' aberrant neural and subjective emotional responses to their infants' signals of emotion.

In conclusion, this fMRI study found for the first time that mothers with BD in remission display attenuated dlPFC response and aberrant positive FC between amygdala and dlPFC to own infant faces, specifically, and more precuneus and occipital deactivation in response to happy infant faces in general. Importantly, these aberrant neural responses correlated with more misattuned positively biased ratings of own infants' distressed expressions (as seen in mothers with BD) and less dyadic reciprocity in their real-life interaction with their infants. If these findings are replicated in future studies, these insights into the associations between aberrant neural and cognitive responses to infant signals of emotion in BD mothers could provide a basis for an early prophylactic intervention for these mothers and their infants. Such mechanistically informed interventions targeting early, likely modifiable, neurocognitive risk factors for maternal caregiving could have long-term implications for prevention of mental illness in children of mothers with BD.

Contributors

Anne Bjertrup: Conceptualization, recruitment, project administration, data collection, data analyses and writing first draft of manuscript under supervision of Kamilla Miskowiak. **Julian Macoveanu:** setting up fMRI procedures, data analyses and manuscript writing. **Heidemarie Laurent:** fMRI paradigm design and revision of manuscript draft. **Mala Moszkowicz:** participant recruitment and revision of manuscript draft. **Megan Kate Finnegan:** fMRI analyses and revision of manuscript draft. **Ida Egmose:** Mother-infant observation coding and revision of manuscript draft. **Rene E Nielsen:** participant recruitment and revision of manuscript draft. **Patrick E Fischer:** setting up fMRI procedures and revision of manuscript draft. **Anne Katrine Pagsberg:** Conceptualization and revision of manuscript draft**. Lars V Kessing:** Conceptualization and revision of manuscript draft. **Mette Væver:** Conceptualization, supervision of Anne Bjertrup and revision of manuscript draft. **Kamilla Miskowiak:** First protocol draft, conceptualization, project leader, supervision of Anne Bjertrup

All authors contributed to and have approved the final manuscript.

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Conflicts of interests

Kamilla Miskowiak has received consultancy fees from Lundbeck and Janssen-Cilag in the past three years. Rene E Nielsen has received research grants from H. Lundbeck and Otsuka Pharmaceuticals for clinical trials, received speaking fees from Bristol-Myers Squibb, Astra Zeneca, Janssen & Cilag, Lundbeck, Servier, Otsuka Pharmaceuticals, Teva A/S, and Eli Lilly and has acted as advisor to Astra Zeneca, Eli Lilly, Lundbeck, Otsuka Pharmaceuticals, Takeda, and Medivir, and has acted as investigator for Janssen-Cilag, Lundbeck, Boehringer, Compass and Sage. Lars Vedel Kessing has within recent three years been a consultant for Lundbeck and Teva. Anne Bjertrup, Julian Macoveanu, Heidemarie Laurent, Mala Moszkowicz, Megan Kate Finnegan, Ida Egmose, Patrick MacDonald Fisher, Anne Katrine Pagsberg, and Mette Væver report no conflicts of interests.

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