



Pictures of preterm infants elicit increased affective responses and reduced reward-motivation or perspective taking in the maternal brain[☆]

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ABSTRACT

Preterm-birth increases the risk of several physical, cognitive, neuromotor, and psychosocial problems in children, and is also related to difficulties in the parent–child relationship. Research suggests that the development of early parent–child interactions in general is affected by deviations from typical infant facial characteristics, which may also be important in the case of small, preterm born infants. Therefore, we examined mothers' ($N = 22$, of whom 17 had no direct experience with preterm birth) neural responses to pictures of preterm and full-term infants using functional magnetic resonance imaging (fMRI). We also explored whether neural responses to preterm and full-term infants correlated with mothers' self-reported tendencies to be nurturing and protective with children, and with mothers' ratings of affection or aversion toward pictures of preterm infants. Results revealed that, compared to pictures of full-term infants, those of preterm infants elicited *more* activity in specific areas of the brain (dmPFC, right insula, left caudate, hippocampi, parahippocampi, and PAG), that have previously been associated with processing of negative emotions and with empathy. In addition, *less* activity was seen in one area of the brain (vmPFC) known to be associated with reward-motivation or mental state understanding and perspective-taking. Higher self-reported maternal nurturance was associated with increased activity to pictures of preterm infants vs full-term infants in the caudate, which might reflect approach- or reward-related processing. To conclude, neural responses to preterm infants are related to reward-motivation, mentalizing, negative emotions, and empathy. Future studies should examine whether such neural processing of preterm infant stimuli might underlie difficulties in the parent–child relationship of parents with a preterm child.

1. Introduction

Worldwide around 15 million children are born preterm (before 37 weeks gestation) each year [1]. Due to short gestation, preterm children may experience neonatal complications, such as breathing and feeding difficulties, infections, and brain hemorrhage [2,3]. Regarding long term development and compared to full-term peers, preterm children also show more physical, neuromotor, cognitive, social, emotional, and behavioral difficulties [4–8]. Preterm birth can also compromise the parent–child relationship, as evidenced by the increased risk preterm children have for developing insecure attachment relationships with their caregivers [9]. Further, when interacting with their children, parents of preterm children are more likely to show parenting practices that are associated with child behavior problems, such as firm control [10], overprotection [11], less sensitive responsivity [12], spoiling and

inconsistent discipline [13]. In order to improve understanding of parent–child relationships and associated behavioral problems in children after preterm birth, we need more information on the underlying mechanisms. Research has suggested that development of early parent–child interactions may be affected by deviations from typical infant facial characteristics [14]. Although it may be difficult to accept that vulnerable children who may need sensitive caregiving the most, deviations from typical infant facial characteristics may be present frequently in small, preterm born infants.

According to Lorenz [15] certain infant facial characteristics (large forehead, big eyes, chubby cheeks, small nose and mouth), which he referred to as baby schema, automatically trigger the “Kindschenschema”, an innate releasing mechanism for parenting behavior and affective orientation toward infants [16,17]. More specifically, the “Kindschenschema” can be considered as a biological mechanism,

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automatically generating caretaking and orienting responses to infants, with the evolutionary function of increasing survival chances of the infant [15,18,19]. Although all infants possess baby schematic facial features to a certain extent, there is individual variation in distinctiveness of baby schema. Mostly studied in this regard is cleft lip and palate, which changes typical baby schema. Consequently, non-parents rate infants with cleft lip as less cute than infants without cleft lip [20,21]. Infant faces with cleft lip or an abnormal alignment of the eyes (strabismus) are also rated less cute than infant faces with a small benign birth mark (hemangioma [22]). Relatedly, experimental manipulation of baby schema in infant faces has been associated with cuteness ratings and caregiving motivation in non-parents [18] as well as parents [23].

Less is known about how prematurity affects baby schema and perceived cuteness. Preterm infants often have very low birth weight (< 1500 grams), which is known to be associated with postnatal head molding, i.e., an elongation of the skull with flattening of both sides of the upper skull [24,25]. Despite handling of the infants to prevent this, such as frequent head turning in the incubators by nurses and parents, preterm infants often still have a high and narrow forehead, with eyes at the external edges of a long thin face, and a smaller mouth width [25,26], and a resumption of a more circular head shape may take up to three years [24]. Mothers rate preterm infants with such facial characteristics as less cute and are less sensitive to these infants [25]. Premature infants that were rated as more attractive by nurses showed better outcomes in terms of weight gain and length of hospital stay, possibly because they received more nurturing [27]. Full-term infants possess proportionally wider eyes and rounder heads than preterm infants, and non-parents rated these preterm infants as less likeable, attractive, and cute, less fun to be with, more irritating, poor functioning, and to have more eating problems than full-term infants [26]. In general, distinctive baby schema (i.e., cuteness) elicit fast orientation and attention toward infants, which sets the stage for slower and more complex parenting behaviors and attachment formation [28]. Thus, reduced distinctiveness of baby schema in preterm infants might negatively affect the parent-child relationship of parents with a preterm child.

Next to baby schema, other cues associated with preterm birth, such as low body weight, or need for incubator care or respiratory assistance, might also be associated with a reduced parental investment with preterm infants, because they provide cues of reduced health and survival chances [29]. Caring for a preterm infant might also be expected as different, perhaps less rewarding or even more aversive, than caring for a full-term infant. Premature infants are indeed described as less rewarding social partners [30], because they engage in interaction less frequently, show less positive and more negative affect, are less attentive, are easily over-aroused, and often avoid eye contact [31–33]. It is known that viewing baby faces with sad facial expressions and severe dermatological conditions evoked aversive emotional responses in nonmothers, compared to viewing happy, smiling baby faces [34]. Moreover, after preterm birth many mothers reported to experience negative feelings, such as fear, alienation, and distance, when first seeing their baby and during the first weeks at home when caring for their babies [35]. Furthermore, cries of preterm infants (when they are scheduled for discharge from the hospital), often at a higher pitch, are rated as more aversive than cries of full-term infants [36].

Neuroimaging studies can provide valuable information on the rapid, intuitive responses to infant cues [37]. There are no neuroimaging studies yet that have examined differences in neural responses to preterm versus full-term infants, but we can borrow from other neuroimaging studies on the baby schema effect or on negatively valenced baby stimuli. For example, Glocker et al. [18] showed that more distinctive baby schema in infant faces elicited increased activation in neural regions associated with the processing of rewards (i.e., nucleus accumbens, NAcc), compared to less distinctive baby schema or non-manipulated infant faces. In contrast, Bos et al. [38] found that low

baby-schematic infant faces elicited more activation in the amygdala compared to high baby-schematic infant faces. Another study using magnetoencephalography to assess neural responses to infants with cleft lip, demonstrated that early activity in the orbitofrontal cortex (OFC) is diminished when adults view infants with cleft lip compared to infants without cleft lip [39]. This suggests that the presence of structural abnormalities in infant faces disrupts normative processing of infant faces in areas involved in affective responding or the processing of rewards [39]. Moreover, negatively valenced baby faces with sad expressions and severe dermatological conditions elicited stronger bilateral amygdala activity than positively valenced baby faces [34]. Many other studies have consistently found activation in response to infant faces in several brain regions that are thought to be part of a reward-motivation network of parental care, supporting approach motivation, social orienting and seeking, goal-directed behavior, social learning, and the reward value of infant cues (for reviews see [28,40,41]). This network includes the amygdala, OFC, anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC), striatum (NAcc, caudate, putamen), and ventral tegmental area (VTA) [40].

Other brain areas might also be important when examining neural processing of preterm infants, because of the negative emotions experienced by parents after preterm-birth of their baby [35]. Meta-analytic work in humans demonstrated that passively viewing negatively valenced stimuli (i.e., aversive pictures, unpleasant auditory/tactile stimulation) consistently activates the ACC, dorsomedial prefrontal cortex (dmPFC), hippocampus, parahippocampus, and periaqueductal grey (PAG) [42,43]. These areas have been associated with aversion-related processing [43]. The insula is also important considering its role in social-emotional processing, specifically in the subjective experience of negative emotions (e.g., disgust, sadness, anxiety) and empathy for others in pain (for a review see [44]).

It is important to try to explain individual differences in neural processing of preterm-infant stimuli, because these might to some extent explain individual differences in infant caretaking. Therefore, we relate neural responses to preterm and full-term infants to individual variation in activation of the parental care system as well as to mothers' self-reported affect in response to pictures of preterm versus full-term infants. The parental care system can be viewed as a coordinated set of affective and cognitive mechanisms, motivating parents, as well as non-parents, to provide protection and nurturance for a child ([45,46]). Both negatively-valenced child stimuli (i.e., crying) and positively-valenced stimuli (i.e., smiles, baby schema) can activate the parental care system [45,46]. Recently, it was discovered that the parental care system consists of protection, which is the motivation to protect infants from harm, and nurturance, which is the tendency to view infants as affectively rewarding and respond to them in a supportive and nurturing way [47]. The parental care system is an approach-oriented motivational system [45,46]). Therefore, associations between protection and nurturance with increased neural responses to preterm versus full-term children could reflect an approach related response to preterm infants. On the other hand, associations between negative feelings, like aversion, when viewing preterm infants, with increased neural responses to preterm versus full-term children could reflect an avoidance related response to preterm infants.

In sum, in the current fMRI study we examined mothers' neural and affective responses to pictures of preterm and full-term infants. We also examined whether neural responses to preterm and full-term infant faces were associated with mothers' general tendencies to be nurturing and protective with children, or with mothers' affective responses toward preterm and full-term infants. We used a newly developed experimental paradigm with a block design in which mothers passively viewed alternating blocks of pictures of preterm infants (small newborns with low birth-weight in hospital incubators), full-term infants (big, healthy newborns in a crib), and scrambled visual controls. We hypothesized that pictures of full-term infants and pictures of preterm infants would elicit differential activity in brain areas specifically

associated with reward-motivation, empathy, and social-emotional processing (amygdala, ACC, VTA, vmPFC, OFC, striatum, dmPFC, hippocampus, parahippocampus, PAG, insula). Finally, we explored whether individual differences in neural responses to preterm- and full-term infants reflected variation in mothers' tendencies to be nurturing and protective with children, or mothers' affective responses toward preterm infants.

2. Materials and methods

2.1. Participants

A total number of 23 right-handed mothers with one or more children aged between 2 and 6 years old were recruited via the university website, parenting websites, and leaflets handed out in child-care centers. Participants had no history of psychiatric, neurological, or endocrine abnormalities. Participants were not pregnant and did not use psychotropic medication. Another inclusion criterion was that participants did not present (sub)clinical symptoms of psychopathology on the day of testing (mean score below 2 on the 5-point scale of the Brief Symptom Inventory 18; [48]), in order to reduce the confounding influence of (sub)clinical symptoms on the neural processing of infant stimuli. Almost 75% had no direct prematurity related experiences (i.e., have a preterm child, were born preterm themselves, or had a sibling who was born preterm). One mother did not want to complete the Prematurity Task (see below), because she had a preterm-born child herself and did not want to be confronted with pictures of preterm infants. This mother was therefore excluded from the final sample ($N = 22$). See Table 1 for the demographic characteristics of the participating mothers and children. Of the included mothers, one had a preterm-born child herself, two mothers were born preterm themselves, and two mothers had a sibling who was born preterm. Exclusion of the mother with a preterm infant did not change our results (results not shown).

2.2. Procedure

Scanning sessions were scheduled within 5–10 days following the start of menstruation to exclude noise related to hormonal changes

Table 1
Demographic characteristics of Sample ($N = 22$).

	<i>M</i> (<i>SD</i>)	Range
Mothers' age	36.95 (5.34)	27–45
% Highly educated ^a	91 %	
% Dutch-Caucasian ethnicity	96 %	
Marital status		
Married/registered partnership	62 %	
Cohabiting	19 %	
Single-mother	19 %	
Number of children		
1	23%	
2	73%	
3	4%	
Sibling gender composition		
Boys only	46%	
Girls only	18%	
Boy(s) and girl(s)	36%	
Age child 1	5.82 (2.08)	3–10
Age child 2	3.65 (1.97)	1–7
Age child 3	5	5
Percentage of mothers with a child aged		
0–1	5%	
2–3	36%	
4–5	77%	
> 5	41%	
Psychopathology symptoms ^b	0.23 (0.23)	0–0.89

^a Higher vocational or university level.

^b Assessed with the Brief Symptom Inventory (BSI-18) on 5-point scale (0–4).

within the cycle. Participants were informed not to drink alcohol or use drugs 24 hours prior to study participation. Before the scan session participants were screened for MRI contra-indications, and alcohol and drug use, and they were given brief explanations of the task. All participants gave written informed consent. Next, participants were screened using a metal detector, and they were instructed to position themselves on the scanner bed as comfortable as possible and to try to relax. Head movement was minimized by foam pads, which were placed between the radiofrequency (RF)-coil and participant's head. Instructions and task images were displayed on an MRI-compatible monitor positioned at the head end of the scanner visible via an angled mirror attached to the coil. Further instructions during the scan session were given by intercom. In the scanner, participants took part in the Prematurity Task (see below). After the scan session participants were asked to complete an online questionnaire via Limesurvey assessing maternal nurturance and protection, and mothers' affective responses when watching preterm- and full-term infants. Participants received financial compensation (€20) for their participation. The study protocol was approved by the ethics committee of the University Medical Centre Utrecht and in accordance with the latest declaration of Helsinki.

2.3. Measures

2.3.1. Prematurity task

Google Images was used to search for pictures of anonymous preterm and full-term newborns on general parenting, medical, and prematurity websites. Pictures of preterm born infants featured small newborns with low birth weight in hospital incubators. Pictures of full-term born infants featured big, healthy newborns in a crib. The pictures were selected by the first and last author, who are experts on infancy and/or prematurity, to be the most clear exemplars of each category. To avoid possible confounds between the pictures of preterm and full-term infants, the pictures in both categories had to be as similar as possible on the following aspects: 1) body position; 2) portion of the infant's body that was visible; 3) closed eyes; 4) no touching or holding of infants by adult. Pictures were converted into grayscale with similar resolution ($M = 183$ dpi) and luminance ($M = 177$) using Adobe Photoshop (histogram). To ensure the distinctiveness of the stimuli in each condition we asked an independent group of 44 university students to rate each picture on the following scales: 1) feelings of affection/aversion (9-point scale: 1 = strong affection, 4 = neutral/no feelings, 9 = strong aversion); 2) the cuteness of baby (10-point scale: 0 = not at all cute, 9 = very cute); 3) their willingness to take care of the baby (10-point scale: 0 = not at all willing to take care of this baby, 9 = very willing to take care of this baby). Pictures of preterm infants elicited significantly less affection than pictures of full-term infants ($t(46) = 4.76, p < .001$; preterm: $M = 3.73, SD = 0.42$; full-term: $M = 3.26, SD = 0.25$). Preterm infants were also rated as less cute than full-term infants ($t(46) = -10.37, p < .001$; preterm: $M = 4.50, SD = 0.51$; full-term: $M = 5.90, SD = 0.43$). However, students were more willing to take care of preterm infants compared to full-term infants ($t(46) = 3.36, p < .01$; preterm: $M = 5.51, SD = 0.27$; full-term: $M = 5.29, SD = 0.19$). To create the visual control stimuli, the selected pictures of preterm and full-term infants were pixelated with the Adobe Photoshop pixelate tool (cell size 30, resulting in 16 by 21.5 pixels) and rotated 180°. This transformation resulted in scrambled pictures with the same resolution ($M = 183$ dpi) and luminance ($M = 177$) as the test stimuli.

The prematurity task consisted of blocks of pictures of preterm and full-term infants (see Fig. 1). There were eight blocks of preterm infants, eight blocks of full-term infants, and eight blocks of visual control stimuli. Blocks were presented in a mirrored design avoiding covariation of task regressors with linear drift. The blocks had a duration of 24 s, during which 12 stimuli were randomly presented for 2 s. For each stimulus condition 24 unique stimuli were used, that were presented three times in total. The same stimuli were never presented twice in the

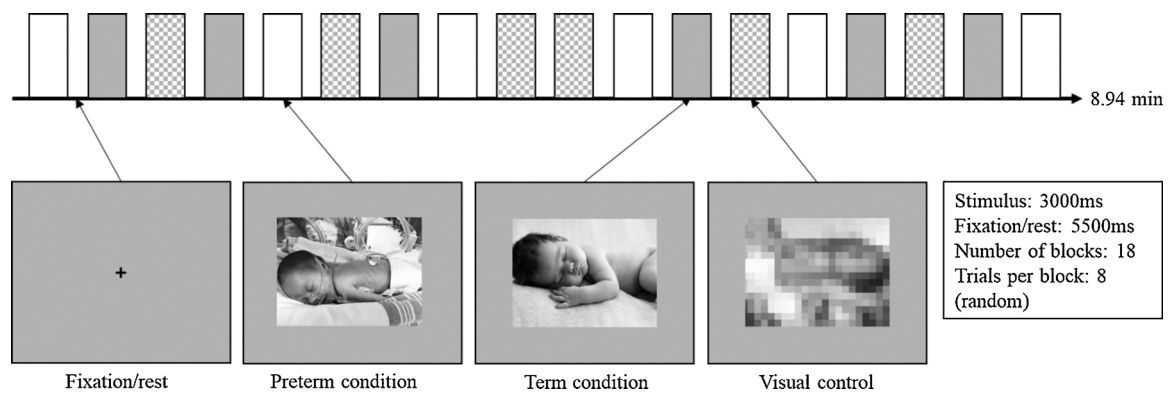


Fig. 1. Schematic representation of the fMRI block-paradigm for the prematurity task.

same block. The stimuli (size: 64 mm by 48 mm) were superimposed on a grey background (191;191;191) and were presented randomly across the blocks. Participants were instructed to pay attention to each picture, without the need for a specific response (i.e., passive viewing). When positioned in the scanner, and directly before the task started, participants received instructions. Stimulus presentation, timing, and measurement of behavioral response time and accuracy were controlled by E-Prime (v 2.0) software [49].

2.3.2. Maternal nurturance and protection

Participants completed the Parental Care and Tenderness (PCAT) questionnaire [45]. The PCAT measures parental care motivation [45] which consists of the conceptually separate constructs nurturance (PCAT-n, example item: “Babies melt my heart”) and protection (PCAT-p, example item: “I would hurt anyone who was a threat to a child”) [47]. The former uniquely predicts sensitivity for infant cuteness, whereas the latter predicts restrictive parenting practices and harsh moral judgments on moral transgressions [47]. In the validation study Cronbach’s α of the PCAT-n and PCAT-p was 0.88 and 0.90 respectively [47]. For the current sample we obtained Cronbach’s α ’s of 0.68 and 0.61 for respectively the PCAT-n and PCAT-p.

2.3.3. Ratings of affective responses to pictures of preterm and full-term infants

Mothers were presented with a random selection of pictures of 12 preterm infants and 12 full-term infants that were also presented to them in the Prematurity Task. Per picture, they were asked to rate on one scale how much affection or aversion they felt when looking at the picture (9-point scale: 1 = strong affection, 4 = neutral/no feelings, 9 = strong aversion). We explained that affection indicated feelings of tenderness and/or warmth, and that aversion indicated feelings of disgust and/or antipathy. Ratings were averaged separately for preterm infants and full-term infants, with mean scores > 4 reflecting aversion and scores < 4 reflecting affection.

2.4. Analyses

For the statistical analyses of the self-report data and the associations between self-report and imaging data, SPSS 23 (IBM analytics) was used with a significance level of $\alpha = 0.05$.

2.4.1. Self-report data

We performed a paired *t*-test to examine differences in mothers affective responses to preterm- and full-term infants. We also computed correlations between the self-report measures.

2.4.2. fMRI data

Scanning parameters are reported in the supplementary online material. Preprocessing and subsequent analyses were performed with

SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>). Functional scans were motion corrected after which the anatomical scan was then coregistered to the mean functional scan. Subsequently, using unified segmentation, the structural scan was segmented and normalization parameters were estimated. Using these normalization parameters, all volumes were normalized to a standard brain template (MNI) and were resliced at 2 mm isotropic voxel size. Smoothing with a 6 mm full width at half maximum Gaussian kernel was applied to the normalized functional volumes. Next, a general linear model (GLM) was applied to the data to investigate the effects of stimulus conditions (pictures of preterm and full-term infants). Neural responses to the different pictures were modeled using a 3 s boxcar function convolved with a hemodynamic response function (hrf) as implemented in the SPM12 software. To reduce unexplained variance in the data, realignment parameters and a discrete cosine transform high-pass filter with a cutoff of 128 s were added into the analyses as additional regressors of no interest.

The contrast maps of the two birth-status conditions (preterm, full-term) vs visual control were entered in a second-level factorial ANOVA, with birth-status condition as within-subjects factor. Comparative *t*-tests were performed to investigate the difference in (de)activations for the following stimulus contrasts: Preterm $>$ Full-term; Full-term $>$ Preterm. To control for multiple comparisons in the whole-brain analyses a voxel-wise threshold was set at $p < 0.05$ [family-wise error (FWE) corrected, $k = 0$ voxels]. For studies with small sample sizes ($N < 100$) it is recommended to specifically focus on a priori regions of interest, to reduce the risk of type II error [50]. Therefore, small volume corrections (SVC; $p < 0.05$ FWE) were applied for the predefined regions of interest (ROIs): amygdala, putamen, caudate, insula, ACC, hippocampus, and parahippocampus as based on the automated anatomical labeling (AAL) template [51]. The OFC was predefined based on the anatomy template [52]. The VTA, NAcc, vmPFC, dmPFC, and PAG are not included in these templates as separate masks and were therefore derived from previous empirical papers. The mask for the VTA was based on Groppe et al. [53] and consists of two spheres of 10 mm radius around MNI coordinates $\pm 9, -18, -18$. The bilateral mask for the NAcc was obtained from Bos et al. [38]. The mask for the vmPFC was based on Abraham et al. [54] and consisted of a 10 mm sphere around MNI coordinates $-1, 48, -1$. The mask for the dmPFC and PAG were based on meta-analyses by Hayes et al. [42] and consisted, respectively 10 mm spheres around MNI coordinates 0, 52, 32 (dmPFC), 6, $-34, -16$ (PAG). Contrast maps of the second-level analyses are publicly available in Neurovault (via the following link: <https://neurovault.org/collections/QXRVRRCN/>).

2.4.3. Associations between self-report data and fMRI data

We computed interactions between maternal care motivation data (nurturance, protection, affective responses) and mothers’ differential response to preterm- and full-term-born infants (contrasts: Full-term $>$ Preterm; Preterm $>$ Full-term) in separate factorial whole brain

Table 2
Descriptive statistics and correlations for self-report data.

	1.	2.	3.	4.	<i>M (SD)</i>
1. Affection/aversion; full-term					1.99 (0.72)
2. Affection/aversion; preterm	.76**				2.28 (0.87)
3. Prematurity sensitivity	-.10	.57**			0.29 (0.57)
4. Nurturance (PCAT-n)	-.15	-.24	-.18		4.16 (0.49)
5. Protection (PCAT-p)	-.31	-.27	-.03	.41	3.56 (0.71)

Note. Affection/aversion ratings were assessed outside the scanner on a 9-point scale: 1 = strong affection, 4 = neutral/no feelings, 9 = strong aversion. Maternal nurturance and protection were assessed with a self-report questionnaire (PCAT-n/PCAT-p).

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

analyses. For all the predefined anatomical ROIs that showed significant ($p < .10$), effects in these whole brain analyses, we extracted percent signal change using MarsBaR [55] to further specify and visualize the effects with correlational analyses.

3. Results

3.1. Self-report data

Table 2 shows descriptive statistics and correlations for the maternal self-report data. No outliers were detected and data approached normality. The mean scores around 2 on mothers' affective ratings indicated that, on average, mothers reported feelings of affection (and not aversion) when watching both preterm and full-term infants. Pictures of full-term infants elicited more mother-reported affection (mean closer to 1) than pictures of preterm infants, $t(21) = -2.41$, $p = .025$, $d = 0.36$. Therefore, we computed a prematurity sensitivity score, by subtracting the mean ratings that mothers gave to the preterm infants from the ratings they gave to the full-term infants. Higher scores indicated that prematurity had a greater effect on affection ratings.

Mothers' affection/aversion ratings of full-term infants were strongly and positively associated with her affection/aversion ratings of preterm infants. Prematurity sensitivity was specifically associated with higher aversion ratings of preterm infants. Neither maternal nurturance nor protection was associated with mothers' affection ratings.

3.2. Imaging data

Table 3 and Fig. 2 display the brain regions that became activated in response to pictures of preterm and full-term infants. Whole brain analyses on all participants showed significantly stronger activation in response to preterm infants vs full-term infants, in the following areas: bilateral visual cortices, cerebellum, bilateral inferior temporal cortices, left superior parietal lobe, and the orbital part of the right inferior frontal gyrus. In addition, the following ROIs showed significantly stronger activation levels in response to preterm infants vs full-term infants: dmPFC, right insula, left caudate, bilateral hippocampi, bilateral parahippocampi, and PAG. For the opposite contrast (Full-term > Preterm), greater activation in response to full-term infants vs preterm infants was found for the vmPFC. No differential activation in response to preterm and full-term infants was found in the amygdala, putamen, ACC, OFC, VTA, and NAcc.

3.3. Associations between self-report data and imaging data

We also examined interactions between maternal self-report data (i.e., prematurity sensitivity, nurturance (PCAT-n), protection (PCAT-p)) and differential neural activation in response to preterm infants vs full-term infants. Table 4 shows significantly ($p < .05$) activated voxels from analyses including interactions with PCAT-n and PCAT-p. These analyses revealed an interaction between increased left-caudate activity

to preterm infants vs full-term infants with mothers' self-reported nurturance. Mothers' self-reported protection was significantly associated with increased activity in the VTA in response to preterm infants vs full-term infants. Mothers' prematurity sensitivity did not interact with differential neural activation in response to preterm infants vs full-term infants.

To test the robustness of the associations with maternal nurturance (PCAT-n) and protection (PCAT-p), extracted values from the significant ROIs were entered in correlational analyses with the PCAT-n or PCAT-p, while controlling for 'direct prematurity experience' (whether mothers were born preterm themselves, or had a sibling who was born preterm). Higher maternal nurturance was associated with increased activity to preterm infants vs full-term infants in the caudate (left: $r = .46$, $p = .047$; right: $r = .48$, $p = .036$; see Fig. 3). The correlation coefficient was medium-sized. The correlations between maternal protection and differential VTA activity in response to preterm infants vs full-term infants was not significant (VTA: $r = .01$, $p = .961$). As mothers' age range was quite large, we checked whether inclusion of maternal age as a covariate changed our results. The correlations with maternal age as a covariate were nearly identical (caudate: $r = .51$, $p = .032$, VTA: $r = -.01$, $p = .959$).

4. Discussion

This fMRI study examined mothers' neural responses to pictures of preterm and full-term infants. Compared to full-term infants, preterm infants elicited *more* activity in the dmPFC, right insula, left caudate, hippocampi, parahippocampi, and PAG, but *less* activity in the vmPFC. Preterm and full-term infants did not elicit differential activation in the amygdala, putamen, ACC, OFC, VTA, and NAcc. We also explored whether individual differences in neural responses to preterm and full-term infants reflected variation in mothers' tendencies to be nurturing and protective with children or mothers' affective responses toward preterm infants. Higher self-reported maternal nurturance was associated with increased activity to preterm infants vs full-term infants in the caudate. There were no robust associations with protection or mothers affective responses, when controlling for mothers own experiences with prematurity.

In line with findings from recent meta-analyses [42,43] and reviews [44,56], viewing pictures of preterm infants elicited increased activity in several brain areas specifically associated with processing of negative emotions (dmPFC, hippocampus, parahippocampus, PAG, insula) and empathy for others in pain (insula). Yet, viewing preterm infants also reduced activity in one brain area: the vmPFC. This area is thought to be part of a reward-motivation network of parental care, supporting approach motivation, social orienting and seeking, goal-directed behavior, social learning, and the reward value of infant cues [40], or part of a mentalizing network, supporting mental-state understanding and perspective-taking [56]. Together with the lower levels of affection mothers reported in response to preterm infants, these findings might suggest that viewing preterm infants elicits more negative feelings or empathy and is associated with less reward motivation and perspective-taking than viewing full-term infants. This pattern of findings might be because caring for preterm infants is more demanding and less rewarding, due to poorer interactive and responsive behavior in preterm children as well as parents having to deal with possible developmental problems in their children [3]. Our results might also be because full-term infants possess more distinctive baby schema (wider eyes, rounder heads) than preterm infants [26]. Preterm infants often have a high and narrow forehead, with eyes at the external edges of a long thin face, and a smaller mouth width [25,26] which is associated with lower cuteness rating by mothers [25]. Full-term children possessing distinctive baby schema features have been rated as cuter [22], are more rewarding to look at [57,58], and elicit greater affection and playfulness [17]. Furthermore, other cues associated with prematurity in the stimuli we used, such as low body weight, or need for incubator care or respiratory

Table 3
Peak T- and F-values, p-values, cluster sizes, and MNI coordinates for significantly activated voxels in analysis without covariates.

Experimental effect	Peak voxel location			t/F-value	Cluster size voxels	p	
	Region	X	y				z
Full factorial							
T-test: preterm > term (+)							
Fusiform gyrus	L	-24	-64	-16	11.53	1312	0.000 ^a
Cerebellum (crus1)	L	-10	-84	-22	9.97	s.c.	0.000 ^a
Fusiform gyrus	L	-26	-52	-16	9.89	s.c.	0.000 ^a
	R	26	-52	-18	10.79	704	0.000 ^a
	R	26	-64	-14	10.05	s.c.	0.000 ^a
Cerebellum (crus1)	R	22	-80	-22	5.79	s.c.	0.022 ^a
Lingual gyrus	R	20	-88	-16	7.26	66	0.000 ^a
Fusiform gyrus	R	28	-84	-10	6.86	s.c.	0.001 ^a
Cerebellum (6)	R	12	-84	-16	6.46	s.c.	0.003 ^a
Middle occipital gyrus	L	-32	-84	2	7.17	159	0.000 ^a
Superior occipital gyrus	L	-24	-78	22	6.54	s.c.	0.003 ^a
Middle occipital gyrus	L	-32	-86	10	6.21	s.c.	0.007 ^a
	R	30	-82	6	6.65	75	0.002 ^a
	R	34	-78	12	5.59	s.c.	0.039 ^a
	R	32	-76	20	5.71	4	0.028 ^a
Superior parietal lobule	L	-20	-72	56	5.97	9	0.014 ^a
Pars orbitalis	R	44	30	-6	5.82	5	0.021 ^a
dmPFC	R	2	44	32	4.12	65	0.009 ^b
	R	8	48	28	4.03	s.c.	0.012 ^b
	R	2	48	40	3.35	s.c.	0.058 ^b
Insula	R	46	22	-6	5.32	51	0.003 ^b
	R	44	22	2	4.23	s.c.	0.051 ^b
Caudate	L	-10	6	10	4.13	22	0.035 ^b
Hippocampus	R	22	-30	-6	4.31	24	0.023 ^b
	R	18	-32	-4	4.16	s.c.	0.033 ^b
	L	-22	-32	-6	4.21	12	0.030 ^b
Parahippocampal area	L	-32	-26	-22	4.45	14	0.017 ^b
	L	-28	-28	-22	4.42	s.c.	0.019 ^b
	R	34	-40	-12	4.14	5	0.040 ^b
Periaqueductal grey	R	4	-32	-12	3.62	6	0.032 ^b
T-test: term > preterm (+)							
vmPFC	R	2	42	4	3.53	1	0.039 ^b

Note. R, right; L, left; s.c., same cluster as above.

^a Whole brain FWE corrected at cluster level.

^b Small volume FWE corrected at cluster level.

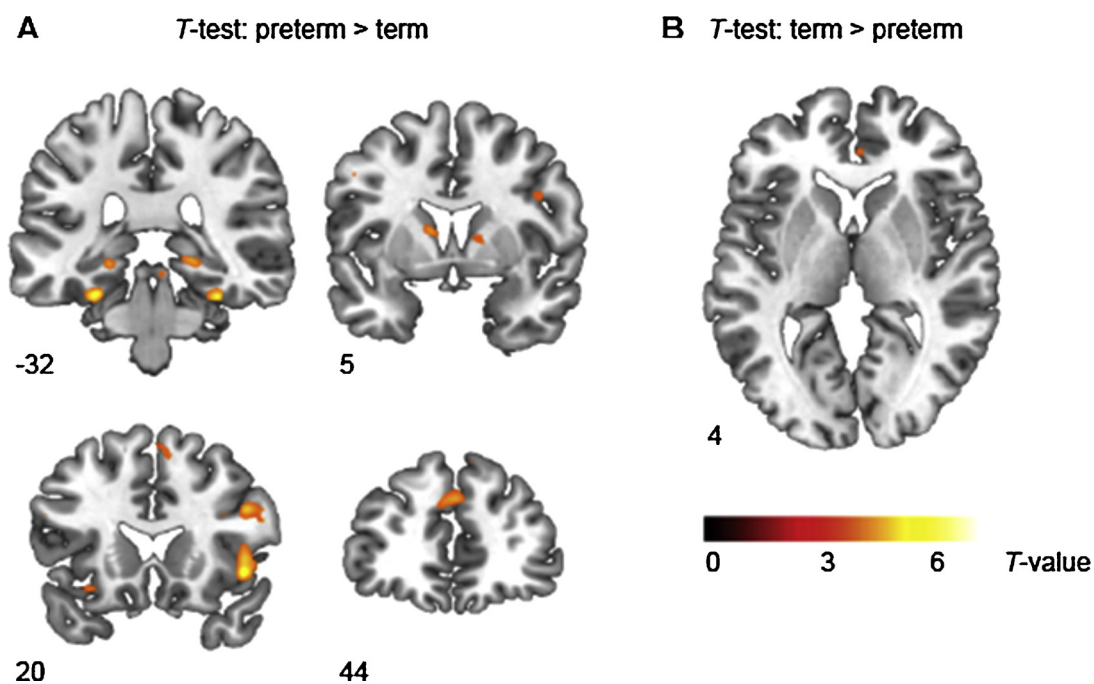


Fig. 2. (A) Coronal slices with corresponding Y-coordinates (MNI) from the T-map of neural activation of preterm infant pictures vs full-term infant pictures overlaid onto a standard anatomical template. (B) Axial slice with corresponding Z-coordinate (MNI) from the T-map of neural activation of full-term infant pictures vs preterm infant pictures on which activation of the vmPFC is visible.

Note. Accompanying statistics are described in the text. All statistical maps are thresholded at $p = 0.001$ uncorrected, for illustration purposes only.

Table 4
Peak T- and F-values, p-values, cluster sizes, and MNI coordinates for significantly activated voxels in analysis including interaction with PCAT-n and PCAT-p.

Experimental effect Region	Peak voxel location			t/F-value	Cluster size voxels	p	
	X	y	z				
Interaction contrast preterm > full-term x PCAT-n (+) ^a							
Caudate	L	-12	2	12	5.22	37	0.016 ^b
	R	22	26	2	4.46	11	0.065 ^b
	R	8	22	0	4.30	23	0.086 ^b
Interaction contrast preterm > full-term x PCAT-p (+) ^a							
VTA	R	6	-12	-12	4.66	3	0.011 ^b

Note. R, right; L, left.

^a The opposite contrast, PCAT (-), did not lead to significant activation in any of the ROIs.

^b Small volume FWE corrected at cluster level.

assistance, might also explain the lower reward value of and increased affective responses to preterm infants, because these cues are an indication of reduced health and survival chances [29].

Reduced reward motivation or perspective-taking and increased emotional processing when viewing preterm infant cues, might underlie possible problems in the parent-child relationship of parents with a preterm child. For example, experiencing increased negative feelings and reduced reward motivation or perspective-taking when looking at a preterm infant might be associated with reduced attention/orienting to infant cues (e.g. looking away; [59,60]). This in turn might hamper detection and interpretation of a child's signals, which is an essential prerequisite for sensitive parenting and a secure parent-child attachment relationship [61]. However, a stronger empathic response to preterm infants could benefit the parent-child relationship [62].

Interestingly, we found more consistent differential neural processing of preterm and full-term infants in brain areas associated with negative emotional processing or empathy than in brain areas

associated with reward motivation. This could indicate that preterm and full-term infants differ more in terms of empathic, negative, worrisome, or even aversive feelings than in rewarding feelings. These findings are in line with a broader line of neuroimaging research on effects of baby schema, indicating that infant faces in general elicit reward processing in the brain (for reviews see [28,41]). For parents it might be evolutionary adaptive to experience reward even when interacting with infants who possess less distinctive baby schema, because their own infant might not possess distinctive baby schema due to preterm birth or facial deformations. Another reason for the lack of differential reward processing of preterm and full-term infants by mothers might be that the current study examined maternal responses to *unfamiliar* infants, and not to mother's own children. Indeed for parents, unfamiliar infant stimuli have been found to elicit less neural rewarding processing than stimuli associated with their own child [63,64]. Additionally, it would be interesting for future research to examine with MEG or EEG whether the lack of difference in OFC activity in response to preterm and full-term infants could reflect that the fast and instinctive releasing mechanism for parental care triggered by baby schema is present for both preterm and full-term infants [65].

We also found an association between mothers' higher levels of self-reported nurturance and increased left caudate activity to preterm versus full-term infants, whereas no associations were found with mothers' affective ratings or protective tendencies. As our measure of nurturance taps the level of activation of the approach-oriented parental care system by infant stimuli [45], this provides some indication that the increased neural responses in the left-caudate to preterm infants might reflect reward-related processing. These findings are in line with the idea that negatively valenced child stimuli, such as crying, or preterm children in incubators, can activate the parental care system [45,46], and in particular the nurturance aspect of the parental care system [47]. Specifically for mothers with high nurturing tendencies, preterm infants might be more rewarding to care for than full-term children, possibly because these children need more support and nurturing. However, the caudate has also been implicated in processing

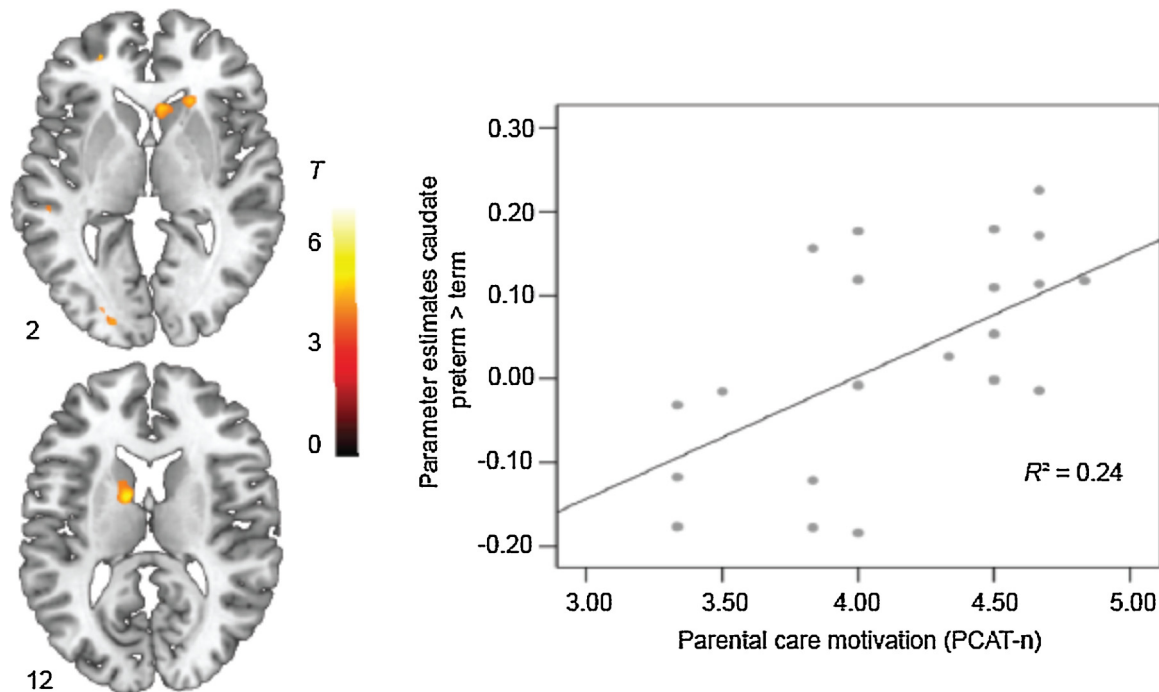


Fig. 3. Associations between maternal nurturance and neural activation toward preterm- versus full-term infants in the caudate.

Note. Figure depicts axial slices with corresponding Z-coordinates (MNI) from the T-map of neural activation in response to pictures of preterm vs full-term infants, associated with parental care motivation. Significant activation is found in the caudate. Accompanying statistics are described in the text. All statistical maps are thresholded at $p = 0.001$ uncorrected, for illustration purposes only.

information about positive and negative outcomes during decision making, especially in contexts with unpredictable outcomes [66,67]. Increased caudate activity to preterm infants might thus reflect the uncertainty associated with caring for a preterm infant.

These findings also provide important directions for future research with clinical implications, because increasing the perceived reward value of caring for a preterm infant might be able to improve the parent-child relationship of parents with a preterm child. Future research could for example study the usefulness of the 'baby-social-reward-task' for parents with preterm-children [68]. With this task that uses cute sounds and facial expressions, researchers demonstrated that the perceived reward value of infants (i.e., cuteness) is modifiable through experience, which is reflected by increased activity in a 'temperament learning network' including the OFC, amygdala, hippocampus, and parahippocampus [69]. It remains to be studied whether such a task could be transformed for effective use with parents of preterm infants. Another direction for future research is based on the idea that having realistic expectations might prevent disappointments and make parenting experiences more rewarding [70]. Future research could study whether parenting interventions that focus on creating realistic expectations about parenting and development of a preterm infant are associated with increased reward processing of preterm infant cues. Last, interventions could build upon a possible increased empathic responses to preterm infants, as well as on reducing the intense negative emotions experienced after preterm birth.

The following limitations of this study need to be addressed. First, almost our complete sample consisted of mothers with full-term children. Even though we statistically controlled for preterm birth of mothers themselves and preterm birth of one of their children or siblings, our findings might be different in mothers who have a preterm infant. For mothers of a preterm infant, viewing pictures of preterm infants might be even more difficult, considering their own experience with their newborn being admitted to the hospital. Indeed, one mother of a preterm born child did not want to participate in this study, because it would be too confronting. Yet, future research on neural processing of infant cues (with somewhat less confronting tasks) by parents with a preterm born child is essential to understand the importance of the first impressions of these parents, and this may also inform parenting interventions for this specific group. Such research could also examine whether increased neural processing of preterm infant cues in mothers with high nurturing tendencies might be associated with actual increased nurturing parenting practices with preterm infants. Moreover, studies examining links between parents' neural processing of stimuli associated with their own preterm infant and observations of actual parenting behavior with preterm children could further increase our understanding of the neural processes that underlie the parent-child relationship.

A second limitation concerns our measure of mothers' affective responses when viewing pictures of preterm infants which might not have reflected affection or aversion per se. As we assessed affection and aversion on a dimensional scale mothers' responses might therefore also represent a combination of affection and aversion. Mothers on average rated all infants, preterm and full-term, on the affection side of the dimension. Future studies could use more specific measures of affection or aversion, such as physiological measures (e.g., skin conductance; [71]), to further disentangle the neural responses to preterm infants. Relatedly, cuteness ratings of preterm and full-term infants could have provided more information about the reward-related processing of preterm infant stimuli.

A third limitation concerns our choice of stimuli which makes it difficult to disentangle whether differences in the processing of preterm and full-term infants are due to differences in baby schema, postnatal head molding, need for medical assistance, and/or health. However, our strategy to choose the most clear exemplars of both preterm- and full-term infants, in which health, baby schema, need for medical assistance, postnatal head molding, and prematurity status are likely to be

strongly related, may have limited the confounding effect on our results. Future research using stimuli of healthy and non-healthy preterm and full-term infants, with and without postnatal head molding, in- and outside hospital incubators, could further disentangle effects of prematurity status on parents' (neural) responses to these infants. Effects of health, postnatal head molding, and prematurity status might be similar as all three are related to reduced distinctiveness of baby schema and cuteness [26,29].

To conclude, viewing preterm infants elicited increased activity in several brain areas associated with processing of negative emotions and empathy, and reduced activity in one brain area associated with reward motivation or perspective taking. This might indicate that preterm and full-term infants differ more in terms of mothers' experienced negative affective or empathic responses than in their reward value for mothers. However, we also found that high nurturing maternal tendencies were associated with increased neural activity to preterm infants in the caudate, which might reflect approach- or reward-related processing. Thus, reduced reward-related processing and increased negative affective responses to infant cues might both underlie possible problems in the parent-child relationship of parents with a preterm child. Future research could study the effectiveness of interventions focusing on decreasing the negative affective responses to preterm infants, on increasing empathy or perspective-taking with preterm infants, or on increasing the reward motivation for parenting a preterm born child.

CRedit authorship contribution statement

Joyce J. Endendijk: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Peter A. Bos:** Conceptualization, Methodology, Formal analysis, Writing - review & editing. **Anne K. Smit:** Investigation, Writing - review & editing. **Anneloes L. van Baar:** Conceptualization, Methodology, Writing - review & editing.

Declaration of Competing Interest

None.

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