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Children prenatally exposed to maternal anxiety devote more attentional resources to neutral pictures

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Abstract

Maternal anxiety during pregnancy can negatively affect fetal neurodevelopment, predisposing the offspring to a higher risk of behavioral and emotional problems later in life. The current study investigates the association between maternal anxiety during pregnancy and child affective picture processing using event-related brain potentials (ERPs). Mothers reported anxiety during the second trimester using the anxiety subscale of the Symptom Checklist (SCL-90). At age 4 years, child affective picture processing (N = 86) was measured by recording ERPs during viewing of neutral, pleasant, and unpleasant pictures selected from the International Affective Pictures System. The late positive potential (LPP)—an ERP component reflecting individual differences in affective processing—was used as child outcome. The expected positive association between maternal anxiety and LPP amplitude for unpleasant pictures was not found. Nevertheless, we found a positive association between maternal anxiety during pregnancy and LPP amplitudes for neutral pictures in the middle and late time window at anterior locations (all $p < .05$). These associations remained significant after adjusting for maternal postnatal anxiety and gestational age at birth and after FDR correction for multiple comparisons. Our study provides neurophysiological evidence that children prenatally exposed to higher maternal anxiety devote more attentional resources to neutral pictures, but not to unpleasant pictures. Possibly, these children show enhanced vigilance for threat when viewing neutral pictures. Although useful in dangerous environments, this enhanced vigilance may predispose children prenatally exposed to higher maternal anxiety to developing behavioral and/or emotional problems later in life. A video abstract of this article can be viewed at: https://www.youtube.com/watch?v=kEzYi6IS2HA

RESEARCH HIGHLIGHTS

- The current study investigated the association between maternal anxiety during pregnancy and child affective picture processing using event-related brain potentials (ERPs).
- Child affective picture processing was measured by recording ERPs during viewing of neutral, pleasant, and unpleasant pictures.
- Positive associations were found between maternal anxiety during pregnancy and the late positive potential (LPP) amplitudes for neutral pictures, but not for unpleasant pictures.
- The associations in the late LPP time window remained significant after adjusting for maternal postnatal anxiety and gestational age at birth and after FDR correction for multiple comparisons.
- Possibly, children prenatally exposed to higher levels of maternal anxiety show enhanced vigilance for threat when viewing neutral pictures.

1 | INTRODUCTION

Accumulating evidence shows that children prenatally exposed to maternal anxiety (PREMA) have a higher risk of developing behavioral and emotional problems later in life (Bock, Rether, Gröger, Xie, & Braun, 2014; Bolten et al., 2013; Van den Bergh, 2011). Experimental animal studies and natural experiments in humans suggest that prenatal exposure to maternal anxiety can elicit modulation

of "*developmental programming*" in the offspring (Bock, Wainstock, Braun, & Segal, 2015; Daskalakis, Bagot, Parker, Vinkers, & de Kloet, 2013; de Kloet, Joels, & Holsboer, 2005; Laplante, Brunet, Schmitz, Ciampi, & King, 2008). Although potentially underlying mechanisms are not fully understood, it has frequently been proposed that maternal anxiety leads to increased production of maternal stress hormones (e.g., cortisol, noradrenaline) and down-regulation of the placental 11β-HSD2 enzyme that metabolizes maternal cortisol into inactive cortisone (O'Donnell et al., 2012; Rakers et al., 2015). This may result in increased levels of cortisol in the fetal circulation, which together with other processes such as inflammation (Christian, 2014) and neuro-inflammation (Hanamsagar & Bilbo, 2016; Labouesse, Langhans, & Meyer, 2015) may elicit long-term changes in structure and function of the developing brain via epigenetic pathways (Bock et al., 2015; Monk, Spicer, & Champagne, 2012; Van den Bergh, 2011).

In this way, cues in the intrauterine environment (e.g., elevated cortisol levels or pro-inflammatory cytokines) may guide adaptation of the offspring phenotype to the expected postnatal environment in order to increase subsequent chances of survival ("*developmental plasticity*") (Del Giudice, 2014; Godfrey, Lillycrop, Burdge, Gluckman, & Hanson, 2007). However, a "mismatch" with the postnatal environment can occur when the postnatal environmental conditions turn out not to resemble the prenatally received cues or when the postnatal environment changes quickly. As a consequence a maladaptive phenotype can predispose the child for later onset of behavioral and emotional problems ("*mismatch hypothesis*") (Frankenhuis & Del Giudice, 2012; Gluckman & Hanson, 2006).

The fetal brain may be particularly sensitive to environmental influences, since it develops very rapidly during pregnancy (Bock et al., 2015; Fox, Levitt, & Nelson, 2010; Knudsen, 2004). Animal research has clearly demonstrated that prenatal exposure to maternal stress affects the offspring's brain, with most prominent effects shown in the limbic system (e.g., hippocampus, amygdala, corpus callosum, and hypothalamus) and prefrontal cortex (for a review, see Bowers & Yehuda, 2016; Charil, Laplante, Vaillancourt, & King, 2010). Recently, structural alterations in the brain of human offspring prenatally exposed to higher levels of maternal cortisol and/or anxiety have also been examined (Buss, Davis, Muftuler, Head, & Sandman, 2010; Buss et al., 2012). In line with animal studies, these studies showed that maternal anxiety during pregnancy was associated with alterations in limbic structures related to emotional reactions and stress responsivity (e.g., amygdala, hippocampus, and rostral anterior cingulate cortex). Recently, diffusion tensor imaging (DTI) studies have shown that maternal anxiety during pregnancy was related to changes in infants' microstructure in brain pathways that are important for emotional functioning (Qiu, Tuan, et al., 2015; Rifkin-Graboi et al., 2015).

In the context of developmental plasticity, these alterations in brain structure can be seen as adaptations to prepare the offspring for the predicted threatening environment (Del Giudice, 2014; Glover, 2011; Gluckman & Hanson, 2007). Changes in the function and structure of the limbic system may, for instance, lead to increased attention allocation to threatening/fearful stimuli in order to facilitate faster fight or flight response of the child, increasing its survival in dangerous environments. Studies demonstrating increased behavioral and physiological reactivity in PREMA children seem in line with this notion (Braeken et al., 2013; de Weerth, Buitelaar, & Beijers, 2013; Henrichs et al., 2009; Monk et al., 2004). Studies that have directly examined processing of threatening/fearful stimuli in PREMA children are very scarce, however.

To our knowledge, only one paper has investigated this hypothesis (Otte, Donkers, Braeken, & Van den Bergh, 2015). For this purpose, infants' processing of emotional (fearful and happy) face/voice compounds was measured in an event-related potential (ERP) study at 9 months of age. The results showed that maternal anxiety during pregnancy was associated with altered infants' brain responses to fearful vocalizations, irrespective of the emotion in the visual prime (fearful or happy). In line with the theory of increased allocation to threatening/fearful stimuli, these results suggest that PREMA infants process threat-related (fearful) auditory stimuli more extensively. Nevertheless, Otte et al. (2015) found no association between maternal anxiety during pregnancy and infants' brain responses to fearful *visual* stimuli, indicating that PREMA infants may not display more threat-related responses when observing visual stimuli than infants not exposed to higher maternal anxiety. Possibly, visual effects may only be found in older children since the visual cortex matures more slowly during early development than the auditory cortex (Anderson & Thomason, 2013). In addition, it is unclear whether more extensive processing of threatening/fearful stimuli in association with PREMA is also present in early childhood. In the current study, we therefore investigated the response to affective stimuli in the visual domain in PREMA children at the age of 4.

To examine affective processing in these children we adapted the paradigm described by Solomon, DeCicco, and Dennis (2012), focusing on the late positive potential (LPP)—a commonly used event-related potential (ERP) component to study affective processing of visual stimuli (Moran, Jendrusina, & Moser, 2013). The LPP is a slow positive waveform that develops approximately 300–400 ms post-stimulus and increases in amplitude in response to more salient pictures, such as emotional pictures (Kujawa, Klein, & Proudfit, 2013). Recent studies show that the LPP has a good internal consistency (Moran et al., 2013) and is stable over development in 8–13-year-olds (Kujawa et al., 2013). In addition, Solomon et al. (2012) found that larger LPP amplitude differences between unpleasant and neutral stimuli were associated with greater observed fear in 5–7-year-old children. Although a study by Hua et al. (2014) showed that there is evidence that the LPP is detectable in children as young as 4 years of age, the results were based on a relatively small sample (N = 20) with children that were 5 years on average (i.e., 61 months [range: 51–71 months]). This makes it uncertain whether children as young as 48 months are indeed able to detect differences between neutral and affective pictures. The current study therefore tested a large group (N = 68) of children around their fourth birthday.

The current study has two main aims: (1) to investigate whether 4-year-olds are able to differentiate between neutral and affective

(i.e., pleasant and unpleasant) pictures, and (2) to examine the association between prenatal exposure to maternal anxiety and child affective picture processing using event-related brain potentials in 4-year-olds. Based on earlier work by Hajcak and Dennis (2009), Solomon et al. (2012), and Hua et al. (2014) and previous PREMA research (Braeken et al., 2013; de Weerth et al., 2013; Henrichs et al., 2009; Monk et al., 2004), we hypothesized that: (1) 4-year-olds show a larger LPP amplitude in response to pleasant and unpleasant pictures compared to neutral pictures, and (2) prenatal exposure to higher levels of maternal anxiety would be associated with higher LPP amplitude differences between unpleasant pictures and neutral pictures, while no such effect would be observed for pleasant pictures.

2 | METHODS AND MATERIALS

2.1 | Participants and study design

The present study was a follow-up study of the PELS study—a prospective cohort study conducted at Tilburg University, the Netherlands, examining the effect of maternal stress during pregnancy on child development, following pregnant women and their children from the first trimester of pregnancy onward. All participating mothers and partners provided informed consent. The study was approved by the medical ethical committee of the St Elisabeth Hospital, Tilburg, the Netherlands, and was conducted in full compliance with the Helsinki Declaration.

We recruited a total of 190 pregnant women during early to mid-pregnancy from four midwife practices and a general hospital. For the current study, we analyzed the data of those mother-child dyads that had complete maternal questionnaire data during mid-pregnancy and child ERP data during the follow-up measurement at age 4 years. From the 103 children aged 4 years that underwent the EEG-measurement, 17 children were excluded due to either: missing maternal questionnaire data (n = 4), technical problems (n = 4), fussiness/tiredness/boredom (n = 5), low number of artifact free trials (<20 trials) (n = 3), and due to cortical visual impairment (n = 1). No significant differences were found between children that were included in the study and children excluded from the study (e.g., drop-out, no reliable/useful EEG data) regarding maternal anxiety when the child was 4 years of age (Included: M = 13.26, SD = 4.66; Excluded: M = 12.67, SD = 2.39, t = −.952, p = .343) and gestational age at birth (Included: M = 39.4 weeks, SD = 1.42; Excluded: M = 39.66 weeks, SD = 1.72, t = .078, p = .938). However, we did find that mothers of excluded children reported higher anxiety scores during pregnancy (M = 14.14, SD = 4.83) than mothers of children included in the study (M = 12.60, SD = 2.83, t = 2.510, p = .012).

The 86 children (44 girls) included in the current study had a mean age of 48.0 ± 0.8 months. On average, their mothers were aged 31.9 years ± 3.7 when the assessment during pregnancy took place. Table 1 shows descriptives of the characteristics of mothers and children included in the current study.

2.2 | Measures

2.2.1 | Maternal anxiety

Maternal anxiety was measured at 21.1 ± 1.9 weeks of pregnancy and at age 4 years using the Dutch version of the anxiety subscale of the Symptom Checklist (SCL-90; Arrindell & Ettema, 2003)—a self-report measure of anxiety symptoms, consisting of 10 items with 5-point Likert scales ranging from 0 (*not at all*) to 4 (*extremely*). Higher sum scores indicate higher anxiety. The scale has good convergent and divergent validity and has good internal consistency (α = .88 for the anxiety subscale; Arrindell & Ettema, 2003). In the current study, the internal consistency also proved to be good (during pregnancy: α = .73; at age 4 years: α = .92).

2.2.2 | Affective picture processing

At age 4 years, child affective processing was measured by recording ERPs during viewing of affective pictures. Stimulus selection and procedure were based on the study of Solomon et al. (2012) with a few alterations due to the younger age of the current sample.[1] The stimuli consisted of 90 developmentally appropriate pictures all taken from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008): 30 neutral pictures[2] depicting household objects or nature scenes, 30 pleasant pictures[3] depicting candy and happy scenes, and 30 unpleasant pictures[4] depicting accidents and scary animals.

The affective processing task was administered using E-Prime software version 2.0.8.74 (Psychology Software Tools, Pittsburgh, PA). The pictures were all presented full screen (1280 by 1024 display

TABLE 1 Characteristics of the participating mother-child dyad sample

Children (N = 86)	***N***	**%**	***M* ± *SD***
Age at EEG-measurement (months)	86		48.0 ± 0.8
Gender			
Girl	44	51.2	
Boy	42	48.8	
Mothers (N = 85)	***N***	**%**	***M* ± *SD***
Age (years)	86		31.9 ± 3.7
SCL-90 Anxiety—Prenatal	86		12.6 ± 2.8[b]
SCL-90 Anxiety—Postnatal	82[a]		13.3 ± 4.7[b]

Notes. SCL-90 = Symptom Checklist; [a] N = 4 mothers included in the study did not complete the postnatal questionnaire; [b] In a Dutch population sample, scores between 12 and 14 are considered "mean anxiety", scores between 15 and 22 are considered "above average and high anxiety" and scores of 22 and higher as "extremely high anxiety" (Arrindell & Ettema, 2003).

resolution) in color on a 19 inch (48.26 cm) CRT monitor. The assessment of this task was embedded in a 2-hour follow-up assessment at age 4 years (including a break and electrode placement) that took place in a dimly lit and sound-attenuated room in the Developmental Laboratory at Tilburg University, the Netherlands. Children were seated approximately 75 cm from the computer screen and were motivated to participate by being given a sticker after each completed measure and a small toy of choice after the experiment was over. During the affective processing task the experimenter was always sitting next to the child. The pictures were randomly selected and presented on the screen for 2000 ms with a 500 ms inter-stimulus interval. The experiment was videotaped with two cameras (one in front and one behind the child). The videos were used to score whether the child was looking at the pictures and was attentive (e.g., not fussy, bored or too tired). Trained research assistants scored the videos afterwards.

2.3 | ERP measurement and data processing

EEG was recorded with BioSemi ActiveTwo amplifiers (www.biosemi.com) with a sampling rate of 512 Hz. We used 64-electrode caps placed according to the extended International 10–20 system. The standard BioSemi reference (CMS-DRL) was used for online recording (see www.biosemi.com/faq/cms&drl.htm for details) and two additional electrodes were placed on the left and right mastoids, respectively, and mathematically combined off-line to produce an average mastoids reference derivation. Electrooculogram (EOG) was recorded using four electrodes: horizontal EOG was recorded from one electrode placed ±1 cm next to the left and another next to the right eye. Vertical EOG was recorded from one electrode placed ±1 cm above and one below the left eye. BrainVision Analyzer 2 (Brain Products, Munich, Germany) and MATLAB (version R2012b, The Mathworks, Inc.) based EEGLAB (version 13.0.1; Delorme & Makeig, 2004) software packages were used to analyze the EEG data. Data were processed in accordance with Solomon et al. (2012) except for artifact rejection criteria—due to our younger sample we used more liberal settings for artifact rejection.[5] In addition, due to extensive artifacts in our EOG data (i.e., many 4-year-olds touched the EOG electrodes or even pulled them off during recording), the EEG signal was corrected for blinks and eye movements using independent component analysis (ICA) as implemented in EEGLAB. The data were filtered off-line with a zero-phase Butterworth bandpass 0.1–30 Hz (slope 24 dB) filter. Subsequently, the data were segmented into epochs of 2400 ms duration including a 400 ms pre-stimulus period. Epochs with a voltage change exceeding 200 μV within a sliding time window of 200 ms duration, with changes exceeding the speed of 75 μV/ms or with activity lower than 0.2 μV per 100 ms were excluded from analysis. Children with less than 20 artifact free trials were excluded from analysis. The average number of remaining trials included in the analyses for the three stimulus types were as follows: neutral: 25; pleasant: 26; unpleasant: 25.

ERPs were constructed by averaging the signal for each stimulus type (neutral, pleasant, unpleasant) and baseline-corrected to the average voltage in the 400 ms pre-stimulus period. Subsequently, mean LPP amplitudes were exported to SPSS for three time windows (cf. Solomon et al., 2012): early (300–700 ms), middle (700–1200 ms) and late (1200–2000 ms). We averaged the LPP over three regions: posterior (PO4, PO8, O2, Oz, POz, PO3, PO7, and O1), central (C4, C6, CP6, Cz, CPz, C3, C5, and CP5), and anterior (FC4, F4, F6, Fpz, AFz, FC3, F3, and F5).

2.4 | Statistical analysis

With regard to the first aim we examined whether we could confirm and extend LPP results obtained in previous studies using an almost identical child affective processing paradigm (Hajcak & Dennis, 2009; Hua et al., 2014; Solomon et al., 2012). More specifically, we examined whether the LPP amplitude for affective pictures (pleasant and unpleasant) was larger than the LPP for neutral pictures in a large group of 4-year-old children. In correspondence with Solomon et al. (2012), analyses were conducted separately for each region using a 3 (picture type: unpleasant, pleasant, neutral) × 3 (window: early, middle, late) × 2 (gender) repeated measures ANOVA. Greenhouse-Geisser correction was applied where appropriate (ε correction factors reported). Post-hoc tests of main effects were adjusted for multiple testing using Bonferroni correction.

To examine our second aim, that is, the association of maternal anxiety during pregnancy with child LPP amplitude differences (unpleasant-neutral and pleasant-neutral), we first intended to test whether the LPP response to neutral pictures was affected by our predictor (maternal anxiety during pregnancy). If the LPP to neutral pictures was not affected by our predictor, we planned to conduct Pearson's correlations between the LPP difference scores (unpleasant-neutral and pleasant-neutral) and our predictors. If, however, the LPP amplitude to neutral pictures proved to be affected by our predictor, no difference scores would be computed. In this case, we planned to compute correlations between the LPP amplitudes and our predictors separately for the two types of affective stimuli (i.e., neutral and unpleasant). This approach was taken because a neutral stimulus may not necessarily be perceived as "neutral" (i.e., Schneider, Veenstra, Van Harreveld, Schwarz, & Koole, 2016) and if ERPs to a baseline stimulus differ between two groups or are affected by a predictor, computing difference waves may hinder interpretation of the findings. A similar analytic approach was used by van den Heuvel, Donkers, Winkler, Otte, and Van den Bergh (2015).

To test the association between maternal anxiety during pregnancy and affective stimuli processing, we conducted multiple regression analyses that were controlled for gestational age and maternal anxiety at age 4 years. Gestational age at birth was also entered as a covariate, because previous studies have shown effects of gestational age at birth on cognitive functioning (Espel, Glynn, Sandman, & Davis, 2014; van den Heuvel, Otte et al., 2015) and brain development (Davis et al., 2011) in young children. Moreover, previous research has demonstrated that maternal postnatal anxiety is an important confounder in the association of maternal anxiety during pregnancy with child neurodevelopmental outcome (van Batenburg-Eddes et al., 2013). In addition, we controlled for multiple testing by using the False Discovery Rate correction (FDR; Benjamini & Hochberg, 1995). FDR correction was preformed to correct for running 9 regressions, 3 time windows (early, middle, late) × 3 brain regions (posterior, central, anterior), that

were conducted per hypothesis. Corrected *p*-levels were reported if appropriate.

The LPP and maternal reported anxiety ratings were statistically evaluated using IBM SPSS 19.0 for Windows. All significant results are reported together with the partial η^2 effect size values; $\alpha = .05$.

3 | RESULTS

3.1 | Affective processing in 4-year-olds

Our first aim was to investigate whether 4-year-olds are able to differentiate between neutral and affective (i.e., pleasant and unpleasant) pictures, which would be reflected in larger LPP amplitudes for unpleasant and pleasant compared to neutral pictures. Figure 1 presents the stimulus-locked ERPs in response to the three types of pictures at posterior, central and anterior recording sites. Note that for the anterior and central regions the LPP is mirrored, resulting in negative-going waveforms for the LPP. Higher LPP amplitudes for these areas are defined as more negative values. Results are reported separately for posterior and anterior/central regions.

3.1.1 | Posterior region

For the posterior electrodes sites, the LPP varied by window, $F(2, 168) = 95.153$, $p = .001$ $\eta^2 = .531$, $\varepsilon = .662$, and picture type, $F(2, 168) = 23.581$, $p = .001$ $\eta^2 = .219$. Interactions were found between window and picture type, $F(4, 336) = 6.868$, $p = .001$ $\eta^2 = .076$, $\varepsilon = .738$, and between window and gender, $F(2, 168) = 3.861$, $p = .040$, $\eta^2 = .044$, $\varepsilon = .662$. Post-hoc tests for the main effect of window showed that the LPP amplitude was smaller (i.e., less positive) in the late window than in the middle and early windows and smaller in the middle than in the early window, early>middle>late, all $p < .001$, correction for multiple testing. Post-hoc tests for the main effect of picture type revealed that both emotional pictures elicited higher LPP amplitudes than the neutral pictures, both $p < .001$, correction for multiple testing. No significant difference in LPP amplitude was found between the pleasant and unpleasant pictures. Post-hoc analysis for the interaction between window and picture type showed that in the early window the LPP elicited by pleasant pictures was significantly larger than for neutral pictures ($p = .041$), while this was not the case for the middle and late windows. However, after correction for multiple testing the difference was no longer significant. Post-hoc tests for the interaction effect between window and gender did not reveal any gender differences for the LPP amplitude as a function of time window. This might indicate that the interaction effect is merely a false positive (Type I error). No significant main effect of gender was found.

3.1.2 | Central and anterior region

For the central and anterior electrode sites, the LPP amplitude varied by window, central: $F(2, 168) = 635.601$, $p = .001$ $\eta^2 = .882$, $\varepsilon = .727$;

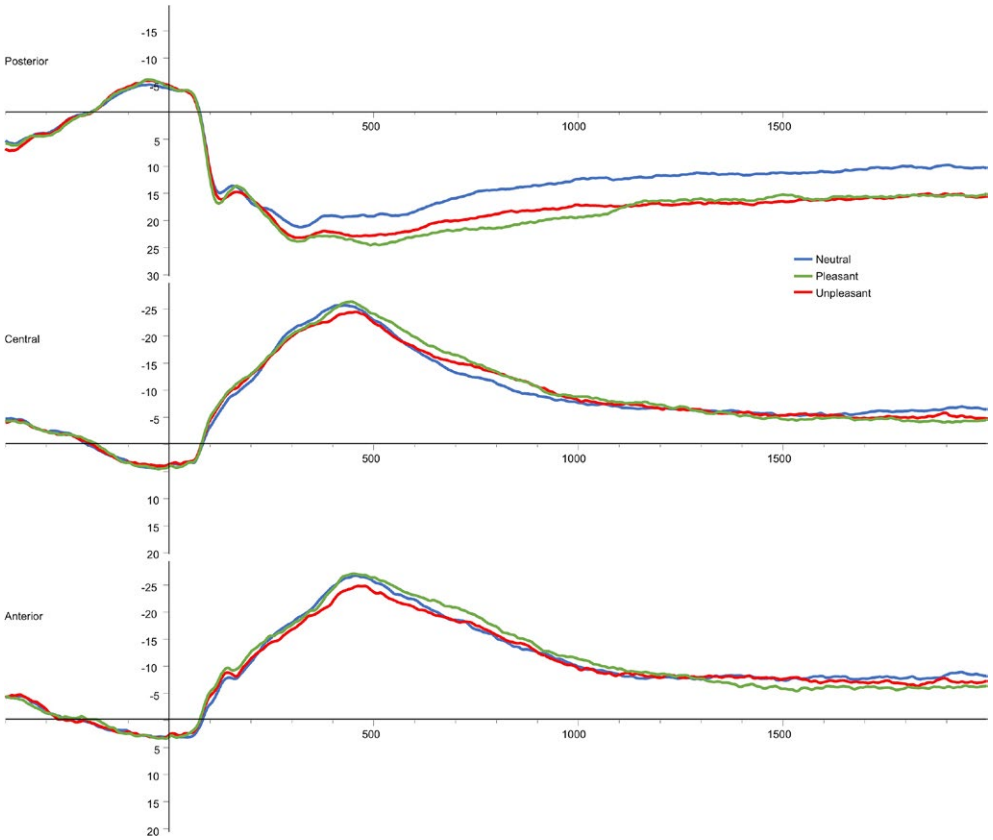

FIGURE 1 Group-average ($N = 86$) LPP amplitudes elicited by pleasant (green line), unpleasant (red line) and neutral (blue line) pictures

anterior: $F(2, 168) = 408.663$, $p = .001$ $\eta^2 = .829$, $\varepsilon = .717$. We also found a significant interaction between window and picture type for both central and anterior electrode sites, central: $F(4, 336) = 5.747$, $p = .001$, $\eta^2 = .064$, $\varepsilon = .737$; anterior: $F(4, 336) = 5.352$, $p = .001$, $\eta^2 = .060$, $\varepsilon = .828$. Post-hoc tests for the main effect of window for both regions showed that the LPP amplitude was smaller (i.e., less negative) in the late window than in the middle and early windows and smaller in the middle than in the early window, early>middle>late, all $p < .001$, correction for multiple testing. Post-hoc tests for the interaction between window and picture type for the central regions showed that in the middle window the LPP amplitude elicited by pleasant pictures was significantly larger than for neutral pictures ($p = .034$). However, after correction for multiple testing the difference was no longer significant. Post-hoc tests for the interaction between window and picture type for the anterior region showed that in the early window the LPP elicited by pleasant pictures was larger than for unpleasant pictures on a trend level, $p = .071$. For the anterior region the interaction between window and gender also reached significance, $F(2, 168) = 5.308$, $p = .013$, $\eta^2 = .059$, $\varepsilon = .717$. Post-hoc analysis for the interaction effect of window and gender revealed that in the early window girls showed a higher LPP amplitude to pleasant pictures than to neutral, $p = .024$, and unpleasant, $p = .011$, pictures. After correction for multiple testing only the higher LPP amplitude for girls to pleasant versus unpleasant pictures remained significant ($p = .033$). No significant main effects of picture type and gender were found.

3.2 | Associations between maternal anxiety during pregnancy and child LPP amplitudes

The second research aim was to examine the association between prenatal exposure to maternal anxiety and child affective picture processing. Since we did observe significant correlations between the LPP amplitudes in response to the neutral stimuli and maternal anxiety (see below) we conducted our main analysis with the LPP amplitudes separately for the three types of stimuli (i.e., neutral, negative, and pleasant), instead of using difference scores. To provide a complete picture of the results of our study, we also conducted analyses using difference scores as outcomes (see footnotes). The correlations of maternal anxiety during pregnancy and child LPP amplitudes for the three types of stimuli in the posterior, central and anterior region are presented in Table 2.

To ease interpretation, the results are reported separately for each region.

3.2.1 | Posterior region

Maternal anxiety during pregnancy was not associated with child LPP amplitudes to neutral, pleasant or unpleasant pictures in the posterior region (all $p > .05$).[6]

3.2.2 | Central region

Maternal anxiety during pregnancy was not associated with child LPP amplitudes in response to unpleasant pictures in the central region, Early: $r = -.092$, $p = .399$; Middle: $r = -.086$, $p = .431$; Late: $r = -.002$, $p = .984$, or pleasant pictures, Early: $r = -.206$, $p = .057$; Middle: $r = -.193$, $p = .075$; Late: $r = -.062$, $p = .568$.[7] We found an inverse association between maternal anxiety during pregnancy and the LPP elicited by the neutral pictures in the middle and late time window, Middle: $r = -.242$, $p = .025$; Late: $r = -.272$, $p = .011$, indicating that higher maternal anxiety during pregnancy was associated with higher LPP amplitudes (i.e., more negative) to neutral stimuli. The association remained significant after controlling for gestational age and maternal anxiety at age 4 years. After FDR correction, the association in the middle time window became marginally significant ($p = .056$) while the one in the late window remained significant ($p = .049$). A graphical representation of the correlations is presented in Figure 2a. To illustrate the difference in child LPP amplitude elicited by the neutral pictures for high and low maternal anxiety, we used a cut-off score for high maternal anxiety (sum score = 15), taken from the average of the normal Dutch population (Arrindell & Ettema, 2003). A total of 17 women were considered as "highly anxious" by this criterion.

3.2.3 | Anterior region

Maternal anxiety during pregnancy was not associated with child LPP amplitudes in response to unpleasant pictures in the anterior region,

TABLE 2 Pearson's correlations between LPP for posterior, central, and anterior region and prenatal maternal anxiety

		Prenatal maternal anxiety		
Picture type	Window	Posterior region	Central region	Anterior region
Pleasant	Early	−.076	−.206	−.127
	Middle	−.023	−.193	−.108
	Late	.014	−.062	.042
Unpleasant	Early	−.034	−.092	−.066
	Middle	.034	−.086	−.117
	Late	.004	−.002	.040
Neutral	Early	−.005	−.084	−.064
	Middle	−.044	−.242*[a]	−.243*[a]
	Late	−.103	−.272*	−.272*

Notes. *$p < .05$; [a]No longer significant after FDR correction for multiple testing.

Early: $r = -.066$, $p = .548$; Middle: $r = -.117$, $p = .285$; Late: $r = .040$, $p = .717$, or pleasant pictures, Early: $r = -.109$, $p = .318$; Middle: $r = -.108$, $p = .323$; Late: $r = -.042$, $p = .702$.[8] Similar to the results in the central region, we observed inverse associations between maternal anxiety during pregnancy and the LPP amplitude elicited by the neutral pictures in the middle and late time window, Middle: $r = -.243$, $p = .025$; Late: $r = -.272$, $p = .011$. These associations indicate that higher maternal anxiety during pregnancy was associated with higher LPP amplitudes (i.e., more negative) for the neutral pictures. Both associations remained significant after controlling for gestational and maternal anxiety at age 4 years. However, similar to the central region, the association in the middle time window became marginally significant while the one in the late window remained significant (middle: $p = .056$; late: $p = .049$) after FDR correction. A graphical representation of the correlations is presented in Figure 2b.

4 | DISCUSSION

The current study investigated affective picture processing in 4-year-olds and the association between maternal anxiety during pregnancy and affective picture processing using event-related brain potentials (ERPs) during exposure to visual stimuli. Remarkably, in contrast to what we expected with regard to our second research aim, maternal anxiety during pregnancy was not associated with LPP amplitudes to unpleasant pictures. We did find significant associations between maternal anxiety and LPP amplitudes in response to the neutral pictures, however. Specifically, we found that higher maternal anxiety during pregnancy was associated with higher LPP amplitudes to neutral pictures in the middle and late time windows at the central and anterior electrode locations. Importantly, the results remained significant after controlling for gestational age at birth and maternal anxiety when the child was 4 years old. However, only the late effects of the late LPP window survived FDR correction for multiple testing. Taken together, our study provides neurophysiological evidence that children prenatally exposed to maternal anxiety may devote more attentional resources to neutral pictures.

In addition, results with regard to our first aim showed that 4-year-olds responded with higher LPP amplitudes to affective (pleasant and unpleasant) pictures compared to neutral stimuli at posterior electrode sites, indicating that children of this age are capable

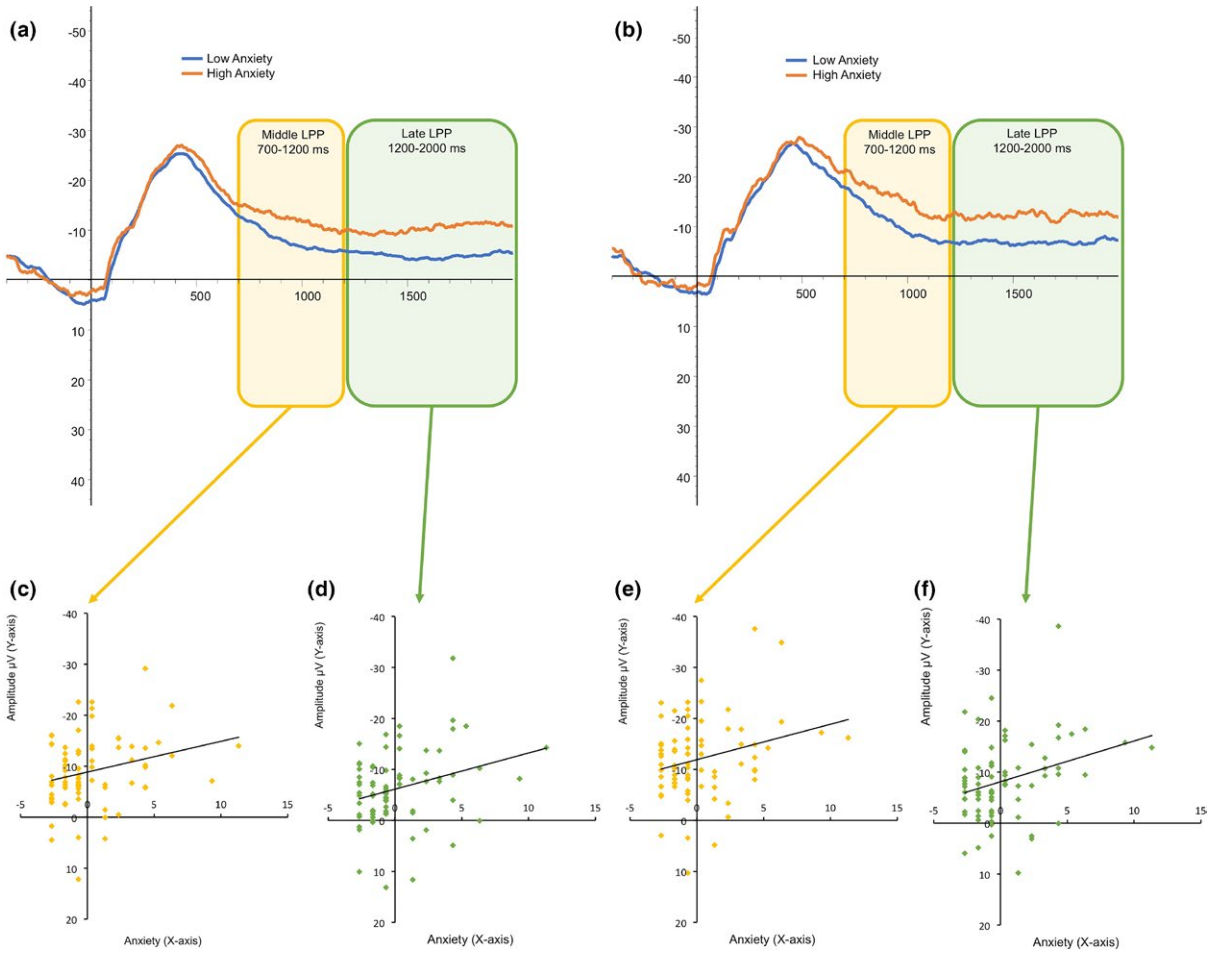

FIGURE 2 Group-average ($N = 86$) LPP amplitudes to the neutral pictures of children exposed to low (blue line; $N = 69$) and high (orange line; $N = 17$) anxiety, for the central electrode sites (a) and the anterior electrode sites (b). The scatterplots shows the correlation between maternal anxiety and the LPP amplitudes for the middle and late windows, for the central electrode sites (c and d, respectively) and the anterior electrode sites (e and f, respectively). *Notes*: The statistical analyses were performed with anxiety as continuous predictor (c, d, e and f). Panels a and b are for illustration purposes, only

of detecting differences between neutral and affective pictures. Our results confirmed the results of previous studies (Hajcak & Dennis, 2009; Hua et al., 2014; Solomon et al., 2012) and extended these by showing that children as young as 48 months already show electrophysiological evidence of the ability to differentiate between neutral and affective pictures.

Our findings with regard to our second aim are in line with previous studies, showing that PREMA infants aged 9 months display a higher ERP response to neutral sounds in an oddball paradigm (van den Heuvel, Donkers et al., 2015) and reporting no association between maternal anxiety during pregnancy and infant ERP amplitude to unpleasant pictures (fearful faces) in infants (Otte et al., 2015). In addition, our results are in line with other studies that report an attention bias to neutral stimuli instead of a bias to negative stimuli. For example, Malak, Crowley, Mayes, and Rutherford (2015) examined the effect of maternal state anxiety on the LPP response to neutral and distressed infant faces and found that the degree of LPP amplitude elicited by neutral infant faces was positively correlated with maternal state anxiety, while there were no associations between anxiety and the LPP elicited by distressed infant faces. Moreover, studies have reported attention bias to neutral instead of negative stimuli in anxious patients (Brunetti et al., 2010; Olatunji, Ciesielski, Armstrong, Zhao, & Zald, 2011) and adult participants exposed to stress (Preuß & Wolf, 2009).

Nevertheless, Otte et al. (2015) also reported associations between prenatal exposure to higher levels of maternal anxiety in infants and higher ERP responses to fearful sounds. An explanation for the fact that we do not find an association between maternal anxiety during pregnancy and LPP for unpleasant pictures might be that the differences in threat level of the stimuli used in previous studies (van den Heuvel, Donkers et al., 2015; Otte et al., 2015) resulted in different outcomes. Previous research on threat processing has demonstrated that when threat exceeds a certain threshold, it captures attention in everyone regardless of anxiety level of the participant (Mogg & Bradley, 1998; Wilson & MacLeod, 2003). Probably the unpleasant pictures used in the current study and the fearful faces used by Otte et al. (2015) exceeded the threshold for threat and therefore captured high attention in all infants/children, while the fearful sounds used in Otte et al. (2015) did not exceed this threshold and hence were experienced as only mildly threatening. However, future studies using mild versus high threat stimuli are needed to test this hypothesis.

Taking previous findings in the literature and our current findings together, it may be the case that the enhanced reactivity reported in PREMA offspring (Braeken et al., 2013; de Weerth et al., 2013; Henrichs et al., 2009; Otte et al., 2015; Monk et al., 2004; Van den Bergh, 1990; van den Heuvel, Donkers et al., 2015) does not result in more attention allocation to threatening visual stimuli, as was first expected, but instead, may result in more attention allocation to neutral visual stimuli. A possible explanation for this might be that children prenatally exposed to maternal anxiety may view neutral pictures as more threatening because these pictures are more ambiguous for them. This could be due to PREMA offspring being more vigilant than offspring not prenatally exposed to maternal anxiety, resulting in a lower threshold for (unconscious) threat appraisal when viewing "neutral" (or ambiguous) pictures (Kimble et al., 2014; Weymar, Keil, & Hamm, 2014). Interestingly, the brain regions identified as key structures for (hyper)vigilance and threat perception, that is, the amygdala, hippocampus, and prefrontal cortex (Dejean et al., 2015; Fox, Oler, Tromp, Fudge, & Kalin, 2015; Lipka, Miltner, & Straube, 2011; Whalen, 1998) are also reported to be affected by prenatal exposure to maternal anxiety (Rifkin-Graboi et al., 2015), maternal depression (Posner et al., 2016; Qiu, Anh et al., 2015; Rifkin-Graboi et al., 2013), and early life stress (Grant et al., 2015; Malter Cohen et al., 2014). In addition, previous papers about the effects of prenatal (Glover, 2011; Propper & Holochwost, 2013) and early postnatal (Propper & Holochwost, 2013) stress exposure have discussed the existence of adaptive increased vigilance in the offspring. In a dangerous environment, the benefits of detecting real threat in a seemingly neutral situation may outweigh the costs of misinterpreting a neutral situation as threatening. Although potentially beneficial in certain environments, enhanced vigilance may ultimately lead to higher risk for developing behavioral and emotional disorders later in life, especially when the postnatal environment does not match the expected one (Del Giudice, 2014; Frankenhuis & Del Giudice, 2012; Glover, 2011; Loman & Gunnan, 2010). Interestingly, previous research has found that vulnerability to anxiety disorders primarily stems from a lower threshold for appraising threat (i.e., showing a threat response to neutral and harmless stimuli), rather than an attention bias to threatening stimuli (Egeland, Zunszain, & Pariante, 2015; Mogg et al., 2000; Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012; Thayer & Friendman, 2002). Building on this, it is tempting to speculate that evaluating relatively innocuous stimuli as having higher subjective threat may place PREMA children at a higher risk for developing internalizing problems later in life, including anxiety (e.g., Van den Bergh & Marcoen, 2004) and depressive symptoms (e.g., Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2007). However, more research needs to be conducted to validate this theory and to rule out the possibility that our findings are false positives.

4.1 | Strengths and limitations

The choice of our stimuli, pictures of scenes, constitutes both strengths and limitations for the current study. An important strength is the inclusion of neutral pictures, as previous work focusing on neurophysiological markers of affective processing in PREMA offspring only included fearful and happy stimuli (Otte et al., 2015). The results of our study emphasize the importance of the inclusion of neutral stimuli as target stimuli in future research and emphasize the need for discretion when using neutral stimuli as a baseline condition in developmental research. In line with the latter, other research groups have recently argued that the use of neutral stimuli as a baseline condition should be discouraged in developmental research (Marusak, Zundel, Brown, Rabinak, & Thomason, 2017). A possible drawback of the choice for unpleasant scenes as "fearful stimuli" might be the diversity of the scenes depicted; some show scary animals while others show sad, angry or scared children. Some of the pictures may not elicit a bias to threatening stimuli. Furthermore, the design of the current

study does not completely allow ruling out whether avoidance of threat instead of enhanced vigilance to threat may be an alternative explanation for our results. Indeed, avoidance of threat could also be related to higher LPP amplitude for neutral pictures. Nevertheless, a recent study examined attentional biases in children with and without anxiety using eye-tracking and found that cognitive biases in children were related to hypervigilance rather than avoidance (Seefeldt, Krämer, Tuschen-Caffier, & Heinrichs, 2014). Future studies could include eye-tracking to examine whether children prenatally exposed to higher levels of maternal anxiety either spend more time looking at neutral pictures (enhanced vigilance) or less time (avoidance) than a control group of children. Lastly, although previous studies have validated the emotional and neutral pictures used in this study in terms of valence and arousal levels (Hajcak & Dennis, 2009), the lack of information on valence and arousal ratings from the current cohort is a limitation. This information would have allowed us to test whether, for example, PREMA children reported higher arousal for neutral pictures than non-PREMA children, and whether reporting of higher arousal is related to higher LPP amplitudes for neutral pictures.

In addition, we cannot completely rule out that selective non-response influenced our findings since data were more complete in mothers with lower levels of prenatal anxiety. This can lead to an underestimation of the association of maternal anxiety during pregnancy with child LPP amplitudes for neutral pictures but not to spurious associations. Nevertheless, selective non-response may have affected our ability to detect associations between PREMA and ERP responses to non-neutral stimuli.

It is possible that shared genetic factors may partly explain the association between maternal anxiety during pregnancy and child neurophysiological responses to neutral pictures. Yet, human studies evaluating the consequences of stressful life events on development, such as natural disasters, suggest that the effects of prenatal stress cannot be explained by genetic predispositions alone (Laplante et al., 2004). Although we did control for postnatal maternal anxiety, other postnatal factors (e.g., impaired parent–child interactions) may also account for the association between maternal anxiety during pregnancy and child outcome. Future randomized controlled trials testing the efficacy of stress-reduction interventions on maternal well-being and child outcome are needed to show whether maternal anxiety during pregnancy indeed exerts intrauterine effects on offspring development independent of postnatal environmental factors and genetic influences.

4.2 | Conclusion

Our study provides neurophysiological evidence that suggests that children prenatally exposed to higher maternal anxiety may devote more attentional resources to neutral pictures. Interestingly, the same result was not found for unpleasant pictures, as was initially expected. These results provide new insights into the functional alterations in PREMA children. Moreover, they emphasize the need to include neutral stimuli as target stimuli, in addition to negative/fearful stimuli, in the study of the effects of prenatal programming on offspring (neuro)behavioral outcome and discourage the use of "neutral" stimuli as a baseline condition in developmental research. Our results may indicate that PREMA children display enhanced vigilance, possibly resulting in a lower threshold for appraising threat in seemingly neutral stimuli. Since effect sizes of our findings were small to medium, future research using different stimuli (i.e., ambiguous versus neutral, mild versus high threat, auditory versus visual) should validate this tentative conclusion. Although useful in dangerous environments, enhanced vigilance may predispose PREMA children to higher risk for developing behavioral and/or emotional problems later in life.

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FINANCIAL DISCLOSURES

The authors report no biomedical financial interests or potential conflicts of interest.

ENDNOTES

[1] The following changes to the selection of pictures of Solomon et al. (2012) were made: we replaced picture #5970 (a tornado) with picture #9600 (sinking boat), because Dutch children are not as familiar with tornados as American children are, and picture #9490 (burned corpse) with picture #8485 (fire accident, without corpse), because the corpse was not deemed age-appropriate for our younger sample.

[2] The IAPS numbers for neutral pictures were 5220, 5711, 5740, 5750, 5800, 5820, 7000, 7002, 7004, 7006, 7009, 7010, 7025, 7031, 7035, 7041, 7050, 7080, 7090, 7100, 7140, 7150, 7175, 7190, 7224, 7233, 7235, 7236, 7595 and 7950.

[3] The IAPS numbers for pleasant pictures were 1460, 1463, 1601, 1610, 1710, 1750, 1811, 1920, 1999, 2070, 2091, 2165, 2224, 2311, 2340, 2345, 2791, 4603, 5831, 7325, 7330, 7400, 7502, 8031, 8330, 8380, 8461, 8490, 8496, and 8620.

[4] The IAPS numbers for unpleasant pictures were 1050, 1120, 1201, 1300, 1321, 1930, 2120, 2130, 2688, 2780, 2810, 2900, 3022, 3230, 3280, 5970, 6190, 6300, 6370, 7380, 9050, 9250, 9421, 9470, 9480, 9490, 9582, 9594, 9600, and 9611.

[5] Compared to Solomon et al. (2012) we did not apply an "amplitude differences greater than ±120 uV within a segment" as an additional criterion for artifact rejection.

[6] When analyses were computed with difference scores (unpleasant-neutral and pleasant-neutral), results remained non-significant (unpleasant-neutral:

Early: r = −.156, p = .151; Middle: r = .069, p = .527; Late: r = 0.41, p = .705; pleasant-neutral: Early: r = −.143, p = .190; Middle: r = .048, p = .660; Late: r = .116, p = .286).

[7] When analyses were computed with difference scores (unpleasant-neutral and pleasant-neutral), results remained non-significant (unpleasant-neutral: Early: r = .048, p = .663; Middle: r = .020, p = .857; Late: r = −.074, p = .501; pleasant-neutral: Early: r = .118, p = .281; Middle: r = .094, p = .391; Late: r = −.030, p = .786).

[8] When analyses were computed with difference scores (unpleasant-neutral and pleasant-neutral), results remained non-significant (unpleasant-neutral: Early: r = .033, p = .762; Middle: r = .047, p = .668; Late: r = −.099, p = .363; pleasant-neutral: Early: r = .061, p = .579; Middle: r = .039, p = .724; Late: r = −.105, p = .335).

REFERENCES

Anderson, A.L., & Thomason, M.E. (2013). Functional plasticity before the cradle: A review of neural functional imaging in the human fetus. *Neuroscience and Biobehavioral Reviews*, *37*, 2220–2232.

Arrindell, W.A., & Ettema, J.H.M. (2003). *SCL-90. Symptom Checklist. Handleiding bij een multidimensionele psychopathologie-indicator*. Lisse: Swets Test Publishers.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing, *Journal of the Royal Statistical Society. Series B (Methodological)*, *57*, 289–300.

Bock, J., Rether, K., Gröger, N., Xie, L., & Braun, K. (2014). Perinatal programming of emotional brain circuits: An integrative view from systems to molecules. *Frontiers in Neuroscience*, *8*, 11.

Bock, J., Wainstock, T., Braun, K., & Segal, M. (2015). Stress in utero: Prenatal programming of brain plasticity and cognition. *Biological Psychiatry*, *78*, 315–326.

Bolten, M., Nast, I., Skrundz, M., Stadler, C., Hellhammer, D.H., & Meinlschmidt, G. (2013). Prenatal programming of emotion regulation: Neonatal reactivity as a differential susceptibility factor moderating the outcome of prenatal cortisol levels. *Journal of Psychosomatic Research*, *75*, 351–357.

Bowers, M.E., & Yehuda, R. (2016). Intergenerational transmission of stress in humans. *Neuropsychopharmacology*, *41*, 232–244.

Braeken, M.A.K.A., Kemp, A.H., Outhred, T., Otte, R.A., Monsieur, G.J.Y.J., Jones, A., & Van den Bergh, B.R.H. (2013). Pregnant mothers with resolved anxiety disorders and their offspring have reduced heart rate variability: Implications for the health of children. *PLoS ONE*, *8*, e83186.

Brunetti, M., Sepede, G., Mingoia, G., Catani, C., Ferretti, A., Merla, A., … Babilone, C. (2010). Elevated response of human amygdala to neutral stimuli in mild post traumatic stress disorder: neural correlates of generalized emotional response. *Neuroscience*, *168*, 670–679.

Buss, C., Davis, E.P., Muftuler, L.T., Head, K., & Sandman, C.A. (2010). High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6–9-year-old children. *Psychoneuroendocrinology*, *35*, 141–153.

Buss, C., Davis, E.P., Shahbaba, B., Pruessner, J.C., Head, K., & Sandman, C.A. (2012). Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. *Proceedings of the National Academy of Sciences, USA*, *109*, E1312–E1319.

Charil, A., Laplante, D.P., Vaillancourt, C., & King, S. (2010). Prenatal stress and brain development. *Brain Research Reviews*, *65*, 56–79.

Christian, L.M. (2014). Effects of stress and depression on inflammatory immune parameters in pregnancy. *American Journal of Obstetrics and Gynecology*, *211*, 275–277.

Daskalakis, N.P., Bagot, R.C., Parker, K.J., Vinkers, C.H., & de Kloet, E.R. (2013). The three-hit concept of vulnerability and resilience: Toward understanding adaptation to early-life adversity outcome. *Psychoneuroendocrinology*, *38*, 1858–1873.

Davis, E.P., Buss, C., Muftuler, L.T., Head, K., Hasso, A., Wing, D.A., … Sandman, C.A. (2011). Children's brain development benefits from longer gestation. *Frontiers in Psychology*, *2*, 1.

Dejean, C., Courtin, J., Rozeske, R.R., Bonnet, M.C., Dousset, V., Michelet, T., & Herry, C. (2015). Neuronal circuits for fear expression and recovery: Recent advances and potential therapeutic strategies. *Biological Psychiatry*, *78*, 298–306.

de Kloet, E.R., Joels, M., & Holsboer, F. (2005). Stress and the brain: From adaptation to disease. *Nature Reviews Neuroscience*, *6*, 463–475.

Del Giudice, M. (2014). Early stress and human behavioral development: Emerging evolutionary perspectives. *Journal of Developmental Origins of Health and Disease*, *5*, 270–280.

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*, 9–21.

de Weerth, C., Buitelaar, J.K., & Beijers, R. (2013). Infant cortisol and behavioral habituation to weekly maternal separations: Links with maternal prenatal cortisol and psychosocial stress. *Psychoneuroendocrinology*, *38*, 2863–2874.

Egeland, M., Zunszain, P.A., & Pariante, C.M. (2015). Molecular mechanisms in the regulation of adult neurogenesis during stress. *Nature Reviews Neuroscience*, *16*, 189–200.

Espel, E.V., Glynn, L.M., Sandman, C.A., & Davis, E.P. (2014). Longer gestation among children born full term influences cognitive and motor development. *PLoS ONE*, *9*, e113758.

Fox, A.S., Oler, J.A., Tromp, D.P.M., Fudge, J.L., & Kalin, N.H. (2015). Extending the amygdala in theories of threat processing. *Trends in Neurosciences*, *38*, 319–329.

Fox, S.E., Levitt, P., & Nelson, C.A., 3rd (2010). How the timing and quality of early experiences influence the development of brain architecture. *Child Development*, *81*, 28–40.

Frankenhuis, W.E., & Del Giudice, M. (2012). When do adaptive developmental mechanisms yield maladaptive outcomes? *Developmental Psychology*, *48*, 628–642.

Glover, V. (2011). Annual research review: Prenatal stress and the origins of psychopathology: An evolutionary perspective. *Journal of Child Psychology and Psychiatry*, *52*, 356–367.

Gluckman, P.D., & Hanson, M.A. (2006). *Mismatch: How our world no longer fits our bodies*. Oxford: Oxford University Press.

Gluckman, P.D., & Hanson, M.A. (2007). Developmental plasticity and human disease: Research directions. *Journal of Internal Medicine*, *261*, 461–471.

Godfrey, K.M., Lillycrop, K.A., Burdge, G.C., Gluckman, P.D., & Hanson, M.A. (2007). Epigenetic mechanisms and the mismatch concept of the developmental origins of health and disease. *Pediatric Research*, *61*, 5R–10R.

Grant, M.M., Wood, K., Sreenivasan, K., Wheelock, M., White, D., Thomas, J., … Deshpande, G. (2015). Influence of early life stress on intra- and extra-amygdaloid causal connectivity. *Neuropsychopharmacology*, *40*, 1782–1793.

Hajcak, G., & Dennis, T.A. (2009). Brain potentials during affective picture processing in children. *Biological Psychology*, *80*, 333–338.

Hanamsagar, R., & Bilbo, S.D. (2016). Sex differences in neurodevelopmental and neurodegenerative disorders: Focus on microglial function and neuroinflammation during development. *Journal of Steroid Biochemistry and Molecular Biology*, *160*, 127–133.

Henrichs, J., Schenk, J.J., Schmidt, H.G., Velders, F.P., Hofman, A., Jaddoe, V.W.V., … Tiemeier, H. (2009). Maternal pre- and postnatal anxiety and infant temperament. The generation R study. *Infant and Child Development*, *18*, 556–572.

Hua, M., Han, Z.R., Chen, S., Yang, M., Zhou, R., & Hu, S. (2014). Late positive potential (LPP) modulation during affective picture processing in preschoolers. *Biological Psychology*, *101*, 77–81.

Kimble, M., Boxwala, M., Bean, W., Maletsky, K., Halper, J., Spollen, K., & Fleming, K. (2014). The impact of hypervigilance: Evidence for a forward feedback loop. *Journal of Anxiety Disorders*, *28*, 241–245.

Knudsen, E.I. (2004). Sensitive periods in the development of the brain and behavior. *Journal of Cognitive Neuroscience*, *16*, 1412–1425.

Kujawa, A., Klein, D.N., & Proudfit, G.H. (2013). Two-year stability of the late positive potential across middle childhood and adolescence. *Biological Psychology*, *94*, 290–296.

Labouesse, M.A., Langhans, W., & Meyer, U. (2015). Long-term pathological consequences of prenatal infection: Beyond brain disorders. *American Journal of Physiology*. *Regulatory, Integrative and Comparative Physiology*, *309*, R1–R12.

Lang, P.J., Bradley, M.M., & Cuthbert, B.N. (2008). *International Affective Picture System (IAPS): Affective ratings of pictures and instruction manual*. Technical Report A-8. Gainesville, FL: University of Florida.

Laplante, D.P., Barr, R.G., Brunet, A., Galbaud du Fort, G., Meaney, M.L., Saucier, J.F., … King, S. (2004). Stress during pregnancy affects general intellectual and language functioning in human toddlers. *Pediatric Research*, *56*, 400–410.

Laplante, D.P., Brunet, A., Schmitz, N., Ciampi, A., & King, S. (2008). Project Ice Storm: Prenatal maternal stress affects cognitive and linguistic functioning in 5½-year-old children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*, 1063–1072.

Lipka, J., Miltner, W.H.R., & Straube, T. (2011). Vigilance for threat interacts with amygdala responses to subliminal threat cues in specific phobia. *Biological Psychiatry*, *70*, 472–478.

Loman, M.M., & Gunnar, M.R. (2010). Early experience and the development of stress reactivity and regulation in children. *Neuroscience and Biobehavioral Reviews*, *34*, 867–876.

Malak, S.M., Crowley, M.J., Mayes, L.C., & Rutherford, J.J.V. (2015). Maternal anxiety and neural responses to infant faces. *Journal of Affective Disorders*, *172*, 324–330.

Malter Cohen, M., Jing, D., Yang, R.R., Tottenham, N., Lee, F.S., & Casey, B.J. (2014). Early-life stress has persistent effects on amygdala function and development in mice and humans. *Proceedings of the National Academy of Sciences*, *USA*, *110*, 18274–18278.

Marusak, H.A., Zundel, C.G., Brown, S., Rabinak, C.A., & Thomason, M.E. (2017). Convergent behavioral and corticolimbic connectivity evidence of a negativity bias in children and adolescents. *Social Cognitive and Affective Neuroscience*, *12*, 517–525.

Mogg, K., & Bradley, B.P. (1998). A cognitive-motivational analysis of anxiety. *Behaviour Research and Therapy*, *36*, 809–848.

Mogg, K., McNamara, J., Powys, M., Rawlinson, H., Seiffer, A., & Bradley, B.P. (2000). Selective attention to threat: A test of two cognitive models of anxiety. *Cognition and Emotion*, *14*, 375–399.

Monk, C., Sloan, R.P., Myers, M.M., Ellman, L., Werner, E., Jeon, J., … Fifer, W.P. (2004). Fetal heart rate reactivity differs by women's psychiatric status: An early marker for developmental risk? *Journal of the American Academy of Child and Adolescent Psychiatry*, *43*, 283–290.

Monk, C., Spicer, J., & Champagne, F.A. (2012). Linking prenatal maternal adversity to developmental outcomes in infants: The role of epigenetic pathways. *Development and Psychopathology*, *24*, 1361–1376.

Moran, T.P., Jendrusina, A.A., & Moser, J.S. (2013). The psychometric properties of the late positive potential during emotion processing and regulation. *Brain Research*, *1516*, 66–75.

O'Donnell, K.J., Bugge Jensen, A., Freeman, L., Khalife, N., O'Connor, T.G., & Glover, V. (2012). Maternal prenatal anxiety and downregulation of placental 11beta-HSD2. *Psychoneuroendocrinology*, *37*, 818–826.

Olatunji, B.O., Ciesielski, B.G., Armstrong, T., Zhao, M., & Zald, D.H. (2011). Making something out of nothing: Neutral content modulates attention in generalized anxiety disorder. *Depression and Anxiety*, *28*, 427–434.

Otte, R.A., Donkers, F.C.L., Braeken, M.A.K.A., & Van den Bergh, B.R.H. (2015). Multimodal processing of emotional information in 9-month-old infants II: Prenatal exposure to maternal anxiety. *Brain and Cognition*, *95*, 107–117.

Posner, J., Cha, J., Roy, A.K., Peterson, B.S., Bansal, R., Gustafsson, H.C., & Monk, C. (2016). Alterations in amygdala-prefrontal circuits in infants exposed to prenatal maternal depression. *Translational Psychiatry*, *6*, e935.

Preuß, D., & Wolf, O.T. (2009). Post-learning psychosocial stress enhances consolidation of neutral stimuli. *Neurobiology of Learning and Memory*, *92*, 318–326.

Propper, C.B., & Holochwost, S.J. (2013). The influence of proximal risk on the early development of the autonomic nervous system. *Developmental Review*, *33*, 151–167.

Qiu, A., Anh, T.T., Li, Y., Chen, H., Rifkin-Graboi, A., Broekman, B.F., … Meaney, M.J. (2015). Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. *Translational Psychiatry*, *5*, e508.

Qiu, A., Tuan, T.A., Ong, M.L., Li, Y., Chen, H., Rifkin-Graboi, A., … Meaney, M.J. (2015). COMT haplotypes modulate associations of antenatal maternal anxiety and neonatal cortical morphology. *American Journal of Psychiatry*, *172*, 163–172.

Rakers, F., Bischoff, S., Schiffner, R., Haase, M., Rupprecht, S., & Kiehntopf, M., … Schwab, M. (2015). Role of catecholamines in maternal-fetal stress transfer in sheep. *American Journal of Obstetrics and Gynecology*, *213*, 684.e1–684.e9.

Rifkin-Graboi, A., Bai, J., Chen, H., Hameed, W.B., Sim, L.W., Tint, M.T., … Qiu, A. (2013). Prenatal maternal depression associates with microstructure of right amygdala in neonates at birth. *Biological Psychiatry*, *74*, 837–844.

Rifkin-Graboi, A., Meaney, M.J., Chen, H., Bai, J., Hameed, W.B., Tint, M.T., … Qiu, A. (2015). Antenatal maternal anxiety predicts variations in neural structures implicated in anxiety disorders in newborns. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54* (313–321), e2.

Schneider, I.K., Veenstra, L., van Harreveld, F., Schwarz, N., & Koole, S.L. (2016). Let's not be indifferent about neutrality: Neutral ratings in the International Affective Picture System (IAPS) mask mixed affective responses. *Emotion*, *16*, 426–430.

Seefeldt, W.L., Krämer, M., Tuschen-Caffier, B., & Heinrichs, N. (2014). Hypervigilance and avoidance in visual attention in children with social phobia. *Journal of Behavior Therapy and Experimental Psychiatry*, *45*, 105–112.

Solomon, B., DeCicco, J.M., & Dennis, T.A. (2012). Emotional picture processing in children: An ERP study. *Developmental Cognitive Neuroscience*, *2*, 110–119.

Thayer, J.F., Åhs, F., Fredrikson, M., Sollers, J.J., & Wager, T.D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience and Biobehavioral Reviews*, *36*, 747–756.

Thayer, J.F., & Friedman, B.H. (2002). Stop that! Inhibition, sensitization, and their neurovisceral concomitants. *Scandinavian Journal of Psychology*, *43*, 123–130.

Van Batenburg-Eddes, T., Brion, M.J., Henrichs, J., Jaddoe, V.W.V., Hofman, A., Verhulst, F.C., … Tiemeier, H. (2013). Parental depressive and anxiety symptoms during pregnancy and attention problems in children: A cross-cohort consistency study. *Journal of Child Psychology and Psychiatry*, *54*, 591–600.

Van den Bergh, B.R.H. (1990). The influence of maternal emotions during pregnancy on fetal and neonatal behavior. *Journal of Prenatal and Perinatal Psychology and Health*, *5*, 119–130.

Van den Bergh, B.R.H. (2011). Developmental programming of early brain and behaviour development and mental health: A conceptual framework. *Developmental Medicine and Child Neurology*, *53*, 19–23.

Van den Bergh, B.R.H., & Marcoen, A. (2004). High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. *Child Development*, *75*, 1085–1097.

Van den Bergh, B.R.H., Van Calster, B., Smits, T., Van Huffel, S., & Lagae, L. (2007). Antenatal maternal anxiety is related to HPA-axis dysregulation

and self-reported depressive symptoms in adolescence: A prospective study on the fetal origins of depressed mood. *Neuropsychopharmacology*, *33*, 536–545.

van den Heuvel, M.I., Donkers, F.C., Winkler, I., Otte, R.A., & Van den Bergh, B.R. (2015). Maternal mindfulness and anxiety during pregnancy affect infants' neural responses to sounds. *Social Cognitive and Affective Neuroscience*, *10*, 453–460.

van den Heuvel, M.I., Otte, R.A., Braeken, M.A., Winkler, I., Kushnerenko, E., & Van den Bergh, B.R. (2015). Differences between human auditory event-related potentials (AERPs) measured at 2 and 4months after birth. *International Journal of Psychophysiology*, *97*, 75–83.

Weymar, M., Keil, A., & Hamm, A.O. (2014). Timing the fearful brain: Unspecific hypervigilance and spatial attention in early visual perception. *Social Cognitive and Affective Neuroscience*, *9*, 723–729.

Whalen, P.J. (1998). Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala. *Current Directions in Psychological Science*, *7*, 177–188.

Wilson, E., & MacLeod, C. (2003). Contrasting two accounts of anxiety-linked attentional bias: Selective attention to varying levels of stimulus threat intensity. *Journal of Abnormal Psychology*, *112*, 212–218.

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