Maternal Anxiety And Neural Responses To Infant Cues

Emily Vancor

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Maternal Anxiety and Neural Responses to Infant Cues

A Thesis Submitted to the Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Emily Vancor
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ABSTRACT

MATERNAL ANXIETY AND NEURAL RESPONSES TO INFANT CUES

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Maternal anxiety is highly prevalent during pregnancy and the postpartum period and is associated with disruptions to children’s socioemotional development. These long-term outcomes are thought to be mediated in part by anxiety’s effects on parenting and parental sensitivity to infant cues. Recent event-related potential (ERP) studies have found a positive association between generalized anxiety symptoms during the perinatal time and enhanced sustained processing of neutral infant faces. It has been suggested that for perinatal women with anxiety, the uncertainty of how an infant with a neutral expression may be feeling could be experienced as distressing, leading to enhanced sustained neural processing. While past studies employed measures of generalized anxiety, it has been suggested that measures of pregnancy-related anxiety may more specifically capture the worry domains and symptoms specific to maternal anxiety. In addition, little is known about the relationship between maternal anxiety and intolerance of uncertainty or about how maternal anxiety affects expectant mothers’ emotional responses to infant faces. In this study, 43 pregnant women in their third trimester were recruited from the community and viewed photographs of neutral and distress infant faces while undergoing continuous EEG recording. Participants rated their certainty of how each infant felt, their emotional response to each infant, and completed self-report measures of generalized anxiety, pregnancy-specific anxiety, intolerance of uncertainty, and depression. Findings suggest that while generalized anxiety symptoms are associated
with enhanced sustained neural processing of neutral infant faces in pregnant women, pregnancy-related anxiety is not. Further, an association approaching significance was found between increased generalized anxiety and decreased sustained neural processing of distress infant faces. No evidence was found that either intolerance of uncertainty or ratings of certainty for how neutral infants feel moderated maternal anxiety’s effects on enhanced sustained neural processing of neutral infant faces. Future work would benefit from a longitudinal approach to assess the progression of anxiety’s influence on infant cue perception throughout the transition to parenthood in both men and women. In addition, further studies should explore the neural processing of infant cues in maternal samples with clinical levels of anxiety.
Acknowledgements:

Many thanks to Dr. Helena Rutherford and the Before and After Baby Lab for sharing their guidance, expertise, and support. I am also grateful to the mothers and families who participated in our studies – thank you for sharing your time and stories with us and for making this work possible.

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INTRODUCTION

Women commonly experience anxiety during pregnancy and the postpartum period. While estimates vary widely, up to 30% of women are affected by clinically significant anxiety during the perinatal time, and many more experience subclinical symptoms (22). This suggests that anxiety is at least as common as depression during this period, which affects 15-20% of women perinatally (7, 9, 15, 23-28). Maternal anxiety has been associated with numerous adverse outcomes for both mothers and children, including long-term disruptions to socioemotional development and increased risk for later psychopathology in children (29-31). These long-term outcomes are thought to be mediated in part by the way that anxiety shapes parenting and the early childhood environment. Recent studies suggest that maternal anxiety specifically affects the way that mothers perceive and interpret infant cues at a neural level (32, 33). These disruptions to infant cue processing may have downstream effects on mother-child interactions that could help to explain the relationship between maternal anxiety and child outcomes. Gaining a better understanding of maternal anxiety’s role in neural processing may help to clarify the mechanisms underlying maternal anxiety’s effects on parenting and inform the development of interventions to prevent and treat the sequelae of maternal anxiety.

While maternal depression, particularly during the postpartum period, is widely discussed in both society and the research literature, maternal anxiety has received less attention. This relative disparity in awareness and attention is based in part on the way that perinatal anxiety and depression have historically been classified in clinical and research settings (11). Perinatal anxiety and depression are highly co-morbid (34) and
have been considered by some to be components of a broader pathology (11, 35, 36). Prenatal anxiety has been found to be a risk factor for the development of postpartum depression (19, 37), and some have argued that anxiety symptoms during pregnancy could represent the early stages in the development of maternal depression for some women (19, 38). This is similar to trends seen in the general population, where anxiety symptoms often precede the development of depression (39). In the clinical setting, the American College of Obstetricians and Gynecologists recommends screening women for depression and anxiety symptoms at least once during the perinatal period (40).

However, commonly used mental health screening measures such as the Edinburgh Postnatal Depression Scale (EPDS) have been shown to miss women with isolated anxiety symptoms, leading to underdetection of isolated anxiety disorders (41, 42). These complications have historically made it difficult to distinguish the differential courses and impacts of maternal anxiety and depression and have likely decreased the number of women with maternal anxiety who are clinically identified and treated.

While the literature has grown in recent years, studies have varied widely in their definitions and conceptualizations of maternal anxiety (43, 44). Some consider maternal anxiety to reflect an exacerbation of generalized anxiety symptoms during the perinatal time while others view maternal anxiety as a specific type of anxiety response (44). This specific response is often described as pregnancy-related anxiety, featuring cognitions and worries centered around pregnancy, delivery, and caregiving (45). Studies measuring and comparing both constructs suggest they reflect related, but distinct, entities. For example, several studies found low to moderate correlations between measures of general anxiety, depression, and pregnancy-related anxiety in pregnant women and found that
measures of general anxiety and depression only accounted for the variance in 8-10% of pregnancy-related anxiety (45, 46). Other studies have shown that some perinatal women with sufficient anxiety to lead to functional impairment may not meet DSM criteria for anxiety disorders due to the narrow range of their worries and anxiety cognitions centered around pregnancy or early parenting, suggesting that maternal anxiety may represent a specific anxiety disorder not encapsulated by generalized anxiety disorder (10, 43, 47, 48). As a result of varied definitions and understandings of maternal anxiety, the literature makes use of a wide variety of anxiety scales measuring overlapping, yet non-equivalent constructs (43). This likely contributes toward inconsistencies seen in the literature regarding the epidemiology, psychopathology, and effects of maternal anxiety and presents a further challenge toward effectively screening perinatal women for anxiety (43).

A further complication for the detection and study of maternal anxiety is the consideration that heightened anxiety levels may in some way be adaptive for new mothers as they take on new roles and responsibilities, and that this may be part of the normative transition into parenthood. In 1956, Winnicott described a stage of primary parental preoccupation from late pregnancy through the early postpartum period as “almost an illness” during which new parents tend to focus their energy and mental capacities on their new infant and creating a nurturing environment for them. Winnicott regarded this as not only normal, but necessary for the infant’s self-development (49 p. 302). Later studies on early parental preoccupation and behaviors have built on this idea and have described early parenthood as a time of increased sensitivity to emotional and environmental cues and increased focus on the new infant. For both mothers and fathers,
preoccupation with the new infant increases throughout pregnancy, peaking at the time of birth (50, 51). However, while some level of parental preoccupation is likely adaptive and helps to foster relationship-building and caregiving, an excess or persistence of preoccupation can become detrimental. Through the lens of preoccupation, many symptoms of anxiety, including excess worry or hypervigilance, may be perceived by both mothers and their healthcare providers as normal and even beneficial during pregnancy and postpartum, leading to less recognition of clinical symptoms and their significance.

In many longitudinal studies, maternal anxiety has been associated with adverse outcomes for both mothers and infants. During pregnancy, women with higher levels of anxiety experience more frequent nausea and vomiting (52), have decreased effective coping strategies (53), and have higher rates of eating disorders (54) and suicidality (55). After delivery, anxiety during pregnancy is a major risk factor for the development of postpartum depression and anxiety disorders (37, 56). For the developing fetus, high levels of anxiety during pregnancy have been linked to fetal growth restriction (57) and signs of delayed neurological development, including reduced fetal movement-fetal heart rate coupling (58). Prenatal anxiety has also been associated with higher rates of obstetrical complications including higher rates of pre-term labor and delivery (59). In infants, maternal anxiety has been linked to decreased birth weight (59) and birth length (60), higher rates of congenital malformations (61) and higher rates of admission to the neonatal intensive care unit (52).

Maternal anxiety has also been shown to negatively impact children’s long-term socioemotional development. Infants of mothers with perinatal anxiety have been shown
to be at an increased risk of attachment insecurity, with some studies reporting that up to 80% of infants of mothers with anxiety disorders form an insecure attachment (62). In particular, maternal anxiety has been associated with an insecure-ambivalent attachment style (63, 64), in which children experience separation anxiety when apart from their caretaker and are not reassured by their return (65). Children of mothers with maternal anxiety are more likely to have a behaviorally inhibited temperament, which is characterized by a tendency to withdraw from new or uncertain situations and is associated with higher risk for developing anxiety disorders (66, 67). Further, children of mothers with maternal anxiety have also been shown to have decreased social engagement, decreased maturity of regulatory behaviors at nine months of age (29), and increased risk of emotional and behavioral problems at four to seven years (30, 31). In adolescence, children of mothers who experienced anxiety during pregnancy have been found to have higher levels of internalizing problems (68).

The mechanisms through which maternal anxiety enacts its long-term effects on child development remain unclear. Likely, this process is multifactorial with contributions from genetics, epigenetics, hormonal alterations, the uterine environment, and the postnatal environment (69). A key area of interest has been maternal anxiety’s impact on parenting and the ways in which parenting style and behaviors may alter children’s developmental trajectories. In observed mother-infant interactions, mothers with higher levels of anxiety show decreased warm and positive interactions with their infants (70, 71) and are less likely to grant their infants the autonomy to explore (72). Maternal anxiety and increased levels of anxious and intrusive thoughts about infant wellbeing have also been associated with increased intrusive parenting behaviors (73-75)
and altered patterns of mother-infant synchrony and contingency (73, 76). Further, maternal anxiety has been associated with decreased parental sensitivity to infant cues (51, 77-80), which has been shown to mediate the relationship between anxiety and attachment insecurity (80).

While these early disruptions to parent-child interactions are well documented and have been shown to have lasting effects on children’s socioemotional development (62, 80), the mechanisms underlying anxiety’s influence on parenting remain poorly understood. In the general population, anxiety has been associated with cognitive biases wherein neutral or ambiguous information is interpreted as negative or threatening (81-84). These biases are thought to contribute to both the etiology and maintenance of anxiety disorders (82, 85, 86) and may reflect a target for intervention (87-90). Cognitive biases and are often content-specific for individual anxiety disorders. For example, while individuals with social anxiety are more likely to interpret ambiguous social vignettes as more threatening, their interpretation of ambiguous non-social vignettes is not affected (91). In the context of maternal anxiety, biases specific to the processing of infant and parenting cues may exist, leading mothers with maternal anxiety to more readily perceive threat toward their pregnancy or child (92). For example, an anxious mother may be more likely to perceive her child as being in danger in a relatively innocuous situation. This perception of threat to her child’s safety could lead her to intervene more readily in her child’s play or exploration, helping to explain the observed associations between maternal anxiety and decreased parental sensitivity and intrusive parenting behaviors.

It has been suggested that cognitive biases may play an essential role in the intergenerational transmission of anxiety (93). Anxiety disorders commonly run in
families (94, 95), and it is estimated that having a parent with an anxiety disorder increases one’s own risk of developing an anxiety disorder by up to seven times (96, 97). This increased risk may be explained in part by shared genetic vulnerability, but studies suggest that genetics alone cannot fully explain familial aggregation (98). Likely, genetic susceptibility interacts with shared environmental factors and social learning in the transmission of anxiety (99). Through example, parents may inadvertently introduce and reinforce the cognitive biases that fuel their own anxiety to their children, shaping the way that children learn to cope with uncertain or threatening situations (93, 100). Studies suggest that parental anxiety levels prospectively predict children’s level of attentional bias to threat (97), and that children with high levels of attentional bias are more likely to anticipate that their mother would also perceive an ambiguous situation as threatening (101). This suggests that cognitive biases associated with anxiety disorders may aggregate in families, as has previously been shown with cognitive vulnerability factors for depression (102). Further demonstrating the importance of parenting and the home environment, there is evidence that interventions for child anxiety that target parents alone can be highly effective (103, 104). For example, the Supportive Parenting for Anxious Childhood Emotions (SPACE) program, a parent-based treatment that focuses on reducing parental accommodation of children’s anxiety symptoms, has been shown to be as effective in decreasing children’s symptoms as individualized cognitive behavioral therapy for affected children (105).

Conceptual models of anxiety disorders emphasize the role that intolerance of uncertainty plays in shaping the cognitive biases and behaviors associated with anxiety (106-108). Intolerance of uncertainty describes one’s predisposition to perceive
uncertain situations as negative, unfair, or threatening and to actively minimize or avoid uncertainty (109-111). Intolerance of uncertainty has been strongly associated with worry, anxiety, depression, and neuroticism, and is thought to represent a transdiagnostic factor that is stable over time and may elevate the risk of developing an anxiety or mood disorder (109, 112, 113).

While intolerance of uncertainty has not been well studied in the context of maternal anxiety, it is thought to have important links to attachment and parenting (109, 114, 115). Infants who receive sensitive and predictable care are more likely to form secure attachments with their caregivers while those who experience less sensitive, consistent, or predictable care are at risk of forming insecure attachments (65). These early experiences with caregivers may shape the way that individuals learn to handle uncertainty and the unpredictable aspects of life. Children with insecure attachments have been shown to interpret neutral situations more negatively than children with secure attachments (116), and are more likely to have high intolerance of uncertainty as young adults (115). Further, studies suggest that intolerance of uncertainty may aggregate in families and play a role in the intergenerational transmission of anxiety. Of note, one study by Sanchez et al. showed an association between maternal intolerance of uncertainty and child intolerance of uncertainty at 7-13 years of age, which mediated the relationship between maternal and child anxiety levels (117). Gaining a better understanding of the cognitive vulnerabilities underlying maternal anxiety may prove useful not only for improving the detection and treatment of maternal anxiety, but also for preventing the development of anxiety in children.
Many past studies of cognitive biases have focused on the way that anxiety influences the perception and interpretation of emotional facial expressions. Facial expressions are highly salient social stimuli that convey important information about others’ emotional states and potential threats in the environment (118). Given the importance of non-verbal communication for socialization, biases that affect the perception and interpretation of facial expressions may have significant implications for social functioning (119). Interpretation biases have been especially well studied in social anxiety, which is characterized by excessive fear of social rejection and judgement (120) and wherein social cues are thought to be particularly salient (121). Individuals with high levels of social anxiety have a lower threshold for identifying negative facial expressions (122) and interpret neutral faces as more threatening (83, 123). In fMRI studies, individuals with high social anxiety have been shown to have increased amygdala activity in response to viewing neutral (124-126) and threatening (127-130) faces, suggesting increased attentional vigilance to threat (126, 131).

To date, the majority of studies exploring anxiety’s influence on emotional facial processing have focused on the interpretation of adult faces. In the context of maternal anxiety however, biases affecting infant face processing are of special interest. Mothers of infants must rely heavily on facial expressions to accurately and efficiently interpret how their child is feeling and to determine their needs (132). Visually, infant faces are structurally distinct from adult faces and feature a relatively large and round head, a wide forehead, and large eyes (133). This configuration of features, known as kindchenschema, is thought to activate the reward system and motivate caregiving behaviors in adults (133-135). While infant cues are highly salient for both parents and
non-parent adults alike (136, 137), studies suggest that expectant and new parents are particularly sensitive and attuned toward infant cues (138). Considering the high salience of infant cues to expectant and new mothers, and the tendency of cognitive biases to be content-specific for particular anxiety disorders, maternal anxiety may be characterized by biases specifically affecting infant face processing.

Given their excellent temporal resolution, electroencephalographic (EEG) methods, including event-related potentials (ERPs), are particularly useful for studying the influence of anxiety on cognitive processes, including the perception and interpretation of facial expressions (139). ERPs are measured by averaging EEG activity from selected electrodes at defined time points after the presentation of a stimulus. The amplitude and time course of ERPs can serve as neural markers for distinct cognitive processes including visual perception or attentional allocation (140). One commonly studied ERP is the late positive potential (LPP), a positive deflection measured 600-900 ms after stimulus presentation, which has been employed as an index of sustained processing of motivationally-relevant visual and auditory stimuli (141, 142). In past studies, the LPP has been used as a measure of motivated attention toward visual stimuli and is affected by both automatic and top-down cognitive processing (143, 144). For example, many studies have demonstrated that the LPP amplitude is greater when participants view emotionally-charged images compared to neutral images. Similarly, in studies of maternal populations, the LPP amplitude evoked by distress infant faces is greater than the LPP amplitude evoked by neutral infant faces, reflective of the high emotional salience of a distressed infant (32, 33, 145).
A small number of studies have begun to use ERP methods to examine maternal anxiety’s impact on the neural processing of infant facial expressions. In sample of postpartum women, Malak et al. compared the LPP amplitude in response to viewing neutral and distress infant faces. A positive correlation was found between state anxiety and LPP amplitude in response to neutral, but not distress, infant faces. In other words, postpartum women with higher levels of anxiety showed enhanced sustained neural processing specifically of neutral infant faces (33). In 2017, Rutherford et al. extended this finding in a sample of pregnant women. In this study, both infant and adult faces were included, as well as photographs of houses as a non-social visual stimulus. Higher anxiety was again found to be associated with a greater LPP amplitude in response to neutral infant faces, with weak associations between anxiety and neutral adult faces, as well as distressed infant and adult faces. No associations were found between anxiety and LPP amplitude in response to houses. Given the high co-morbidity of anxiety and depression symptomatology, this study also controlled for level of depression and the results held. These findings suggest that in pregnant women, anxiety specifically enhances sustained neural processing of neutral infant faces, even when controlling for depression (32). Of note, a study of undergraduate and community non-parent adults showed no association between anxiety level and LPP amplitude in response to neutral infant faces, suggesting that anxiety’s effect on neural processing of neutral infant faces is specific to the maternal population (146).

Taken together, these studies suggest that for perinatal women with anxiety, neutral infant faces have increased emotional and motivational salience. However, the cognitive processes underlying these ERP findings remain unclear. Given anxiety’s close
relationship with intolerance of uncertainty, one possible explanation is that for pregnant and postpartum women with anxiety, the ambiguity of a neutral infant face and the uncertainty of how the infant may be feeling could be experienced as stressful or distressing, resulting in increased emotional salience and a greater LPP amplitude. However, as past studies have not assessed participants’ subjective experiences viewing infant faces, this model remains speculative.

Of note, while the literature suggests that generalized anxiety during pregnancy and pregnancy-related anxiety are related yet distinct constructs (44), past ERP studies of maternal anxiety have only measured generalized anxiety symptoms (32, 33). As measures of pregnancy-related anxiety may better capture the worries most closely related to pregnancy and parenting (45), it is possible that the specific cognitive biases associated with maternal anxiety may be more closely linked with measures of pregnancy-related anxiety rather than with generalized anxiety. In addition, as some studies suggest that pregnancy-related anxiety may be a better predictor for child outcomes than generalized anxiety symptoms (147), pregnancy-related anxiety may be a more relevant construct for studying the effects of maternal anxiety on parenting. It is possible then, that the relationship between maternal anxiety and enhanced sustained neural processing of neutral infant faces may be more pronounced when pregnancy-related anxiety is measured rather than generalized anxiety. No studies to date have examined the neural correlates of pregnancy-specific anxiety or compared the effects of generalized anxiety and pregnancy-specific anxiety on the neural processing of infant cues, reflecting an important gap in the literature.
To assess the validity of the potential model for the link between maternal anxiety, uncertainty, and the enhanced sustained processing of neutral infant faces, it will be important to understand perinatal women’s emotional responses to neutral infant faces and their certainty of how neutral infants feel. Based on the proposed model, perinatal women with increased anxiety would feel less certain of how neutral infant faces felt and thus, would have a more negative emotional response to viewing these ambiguous faces and show an increased LPP amplitude. As in the case for measuring maternal anxiety, it may be beneficial to consider both general and specific measures of uncertainty. To assess how perinatal women handle uncertainty more generally, measures of dispositional intolerance of uncertainty like the Intolerance of Uncertainty Scale (IUS-12) (148) can be used. During the perinatal time, uncertainty related to parenting and caregiving may be particularly salient. To better examine the specific impact of uncertainty on perinatal women’s responses to infant cues, women’s subjective experiences viewing neutral infant faces and their self-reported certainty of how infants feel could be explored. Together, these measures of uncertainty may help to explain the connection between maternal anxiety and increased LPP in response to neutral infant faces. More broadly, despite the relevance of uncertainty to both anxiety and the attachment system, little is known about its role in maternal anxiety and in parenting. By studying the association between maternal anxiety and the intolerance of uncertainty and by examining uncertainty’s effects on the neural processing of infant cues, we hope to better understand this relationship and its potential importance for the prevention and treatment of maternal anxiety’s outcomes for both mothers and children.
Statement of Purpose and Specific Aims

Past ERP studies have demonstrated a clear link between maternal anxiety and an increased LPP amplitude in response to neutral, but not distress, infant faces (32, 33, 149). As the LPP amplitude is as a marker of attentional allocation toward emotionally-relevant stimuli (142, 150), this finding suggests that neutral infant faces hold enhanced saliency for women with maternal anxiety. The relationship between maternal anxiety and LPP response to neutral infant faces may reflect a disruption to typical neural processing of infant cues which could have downstream consequences on early parent-child interactions. Given maternal anxiety’s known associations with decreased parental sensitivity to infant cues (78) and disrupted attachment formation (62), understanding the neural mechanisms underlying maternal anxiety’s effects on infant cue processing may have important implications for parenting and child development.

We sought to further characterize the relationship between maternal anxiety and sustained neural processing of neutral infant faces by considering the role of pregnancy-related anxiety and uncertainty. In the current study, expectant mothers viewed a series of photographs of neutral and distress infant faces while EEG was recorded. Each face was then re-presented and participants were asked to rate their certainty for how the infant felt and their emotional response to the infant. The LPP amplitude in response to neutral and distress infant faces was assessed in relation to measures of generalized anxiety, pregnancy-related anxiety, intolerance of uncertainty, ratings of emotional response to infant faces, and ratings of certainty for infants’ emotional states.

Of note, we chose to include expectant mothers rather than postpartum women so that generalized anxiety and pregnancy-related anxiety measures could be directly
compared. While maternal anxiety is common in postpartum women (151), pregnancy-related anxiety as a construct examines worries and fears specific to pregnancy and delivery that may no longer be relevant for postpartum mothers. In addition, as both pregnancy-related anxiety and generalized anxiety symptoms have been shown to vary over the course of pregnancy (44, 152), all participants were run during their third trimester of pregnancy to limit the potential of gestational age to act as a confounding factor. Given the high co-morbidity of anxiety and depression, both generally and during the perinatal time, we also controlled for depression symptoms in our analysis.

Our aims in this study were two-fold. First, we asked whether pregnancy-related anxiety was associated with increased LPP amplitude in response to neutral infant faces. Second, we examined the role that uncertainty plays in the relationship between maternal anxiety and LPP response to neutral infant faces both generally and specifically.

**Aim 1: Is pregnancy-related anxiety associated with sustained neural processing of neutral infant faces?**

While past ERP studies of maternal anxiety have employed measures of generalized anxiety symptoms, the literature suggests that pregnancy-related anxiety may be a better predictor for some outcomes of maternal anxiety (147). We hypothesized that generalized anxiety and pregnancy-related anxiety would be positively correlated with each other and that each anxiety measure would be positively correlated with LPP amplitude in response to neutral, but not distress, infant faces. Further, we hypothesized that pregnancy-related anxiety would show a stronger association with the LPP amplitude in response to neutral infant faces than generalized anxiety.
Aim 2: Does uncertainty moderate the relationship between maternal anxiety and increased LPP amplitude in response to neutral infant faces?

While past ERP studies show evidence of a relationship between maternal anxiety and increased LPP response to neutral infant faces, the cognitive processes underlying this process remain unclear. It has been proposed that for women with maternal anxiety, the uncertainty of how an infant with a neutral facial expression feels could be experienced as stressful or distressing. This negative emotional response would then be reflected by an increased LPP amplitude. To assess the validity of this model, we examined whether general or specific measures of uncertainty moderated the relationship between maternal anxiety and LPP response to neutral infant faces. To measure intolerance of uncertainty more generally, we employed the IUS-12 (148). To measure the role of uncertainty in the context of processing infant faces, we asked participants to rate their subjective certainty for how each infant in the EEG task felt and their emotional response to each infant.

Given the close interrelationship between anxiety and uncertainty, we hypothesized that intolerance of uncertainty would be positively correlated with generalized anxiety, pregnancy-related anxiety, and LPP amplitude in response to neutral infant faces. With regard to participants’ ratings of certainty and emotional response, we predicted that participants with greater anxiety (as measured by both generalized anxiety and pregnancy-related anxiety) would report lower certainty for how neutral infants felt and would report a more negative emotional response to neutral infants and that these responses would be associated with increased LPP amplitude in response to neutral infant faces. Further, we predicted that both general and specific measures of uncertainty would
moderate the relationship between maternal anxiety and LPP response to neutral infant faces in indirect pathway analysis.

METHODS

Participants

Forty-three women in their third trimester of pregnancy (\(M=29.58\) years, \(SD=5.40\) years, range=18-39 years) were recruited through flyers posted in the community and were compensated for their participation. Demographic characteristics of participants are summarized in Table 1. All participants reported normal or corrected-to-normal vision. The Human Investigations Committee at the Yale School of Medicine approved all procedures prior to recruitment and all participants provided written informed consent.
<table>
<thead>
<tr>
<th>Demographic Characteristics of Participants</th>
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<tr>
<td>Age (years)</td>
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<td>Gestational Age (weeks)</td>
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<td>30-35 weeks</td>
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<td>35-40 weeks</td>
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<td>Native Hawaiian/Pacific Islander</td>
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<td>Marital Status</td>
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<td>Separated</td>
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<td>Parity</td>
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<td>Diploma</td>
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<tr>
<td>Graduate Degree</td>
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Apparatus and stimuli

For continuous EEG monitoring, participants were seated in a sound-attenuated room with low ambient light. 128 Hydrocel Ag/AgCl electrode sensor nets (153) were used to record EEG and were allowed to soak in a warm solution of potassium chloride and shampoo before being placed on participants’ heads. Nets were then adjusted so that the electrodes symmetrically covered the scalp. Electrodes were referenced to Cz and electrolyte solution was used to ensure that all electrode resistances were less than or equal to 40 kΩ at the start of the task. Net Station 4.2.1 software was used with a sampling rate of 250 Hz and Net Amps 200 high impedance amplifiers with a high pass of 0.1 Hz and a low pass of 100 Hz.

During continuous EEG recording, a series of greyscale infant face photographs adapted from Proverbio et al. (1) were presented to participants using E-Prime 1.2 software at a distance of 61 cm. The series of photographs included 25 unique neutral infant faces and 25 unique distress infant faces of 18.3 cm by 11.5 cm. Each infant was about 15 months of age, Caucasian, and unfamiliar to participants. In each photograph, the infant face was centered in the foreground and rotated no more than 45° from a frontal or inclined position. These face stimuli have previously been validated for emotional valence using the Self-Assessment Manikin (33, 154). Representative infant face stimuli are shown in Figure 1.
Measures

To measure generalized anxiety level, we employed the Beck Anxiety Inventory (BAI) (155), which has high internal consistency and reliability (155) and has been widely used in both pregnant (156) and non-pregnant (157) samples. The BAI includes 21 items and uses a 4-point Likert scale to ask participants how much they have been bothered by anxiety symptoms over the past week, with “0” meaning “Not at all” and “3” meaning “Severely – I could barely stand it”. In our sample, the mean score was 11.26 (SD=7.66, range=0-31), with 20 participants scoring above the cut-off score of 11, suggestive of subthreshold anxiety (158).

To measure pregnancy-related anxiety, we used the Pregnancy-Related Anxiety Questionnaire-Revised 2 (PRAQ-R2) (159). The PRAQ-R2 consists of 10 items that form 3 subscales: Fear of giving birth (3 items), Worries about bearing a physically or mentally handicapped child (4 items), and Concern about own appearance (3 items). For each item, participants used a 5-point Likert scale with “1” meaning “Absolutely not
relevant” and “5” meaning “Very relevant” to describe the relevance of statements expressing pregnancy-specific anxiety to their own experience. The PRAQ-R2 has predictive validity for birth and childhood outcomes independent of general anxiety measures, has good internal consistency and convergent validity, and been validated for both nulliparous and parous women (159). One participant did not complete this measure and was excluded from subsequent analysis involving the PRAQ-R2. The mean PRAQ-R2 score in our sample was 26.50 ($SD=6.87$, $range=14-47$).

To measure intolerance of uncertainty, we employed the Intolerance of Uncertainty Scale (IUS-12) (148). The IUS-12 features 12 items and assesses participants’ responses to uncertain or ambiguous situations. The IUS-12 asks participants to use a 5-point Likert scale with “1” meaning “Not at all characteristic of me” and “5” meaning “ Entirely characteristic of me” to describe to what extent they agree with statements expressing discomfort with uncertain circumstances. The IUS-12 has a two-factor structure and features two subscales, Prospective and Inhibitory Intolerance of Uncertainty, which represent different styles of responding to uncertainty. While the IUS-Prospective measures attitudes and behaviors that seek to gain information to reduce apparent uncertainty, the IUS-Inhibitory measures responses reflective of avoiding uncertainty (160). The IUS-12 has been shown to have high internal consistency and validity (148). One participant did not complete this measure and was excluded from subsequent analysis involving the IUS-12. The mean IUS-12 total score in our sample was 28.38 ($SD=10.77$, $range=12-57$), the mean IUS-Prospective score was 18.17 ($SD=6.34$, $range=7-32$), and the mean IUS-Inhibitory score was 10.12 ($SD=4.98$, $range=5-25$).
To assess for depression, the Beck Depression Inventory-II (BDI-II) (161) was included. The BDI-II consists of 21 items describing symptoms of depression. Participants used a 4-point Likert scale to indicate how much they had been bothered by depression symptoms over the past 2 weeks, with “0” meaning “Not at all” and “3” meaning “Severely – I could barely stand it”. This self-report measure has been widely used in pregnant (162, 163) and non-pregnant samples (164) and has high reliability and validity (164). A high score on the BDI-II is correlated with higher levels of depression symptomatology with 0-13 representing minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression (161). Mean depression score in our sample was 13.67 (SD=8.01, range=2-38), with 33 participants reporting minimal-mild depression and 10 participants reporting moderate-severe depression. Depression was included as a covariate in analyses assessing anxiety effects.

**Procedure**

Participants first completed the ERP paradigm followed by the questionnaire measures. In the first portion of the ERP paradigm, participants passively viewed a series of 50 infant faces (25 neutral and 25 distress) presented by E-Prime 1.2 software in a random order. Each trial sequence included a central fixation cross (2000 ms), a blank screen (jittered between 500-700 ms), the infant face (1500 ms), and a blank screen. Each face was presented only once. Participants were asked to sit as still as possible during the task and to attend to the stimuli.

During the second portion of the ERP paradigm, each infant face was re-presented and participants were asked to respond to two questions displayed on the computer screen with a mouse. First, participants were asked to rate how certain they were of how each
infant felt using a 7-point Likert scale with “1” meaning “Not at all certain” and “7” meaning “Very certain” by clicking on the appropriate number. Participants were then asked how each infant face made them feel using a 7-point Likert scale with “1” meaning “Sad”, “4” meaning “Neutral”, and “7” meaning “Happy”. In total, the ERP paradigm lasted about 20 minutes with some variability due to participant response time.

**Data analysis**

Net Station 4.5.7 was used to filter, segment, and remove artifacts from the raw EEG data. A 30 Hz low-pass filter was applied to the data, followed by segmentation into 1 second epochs (100 ms before stimulus presentation to 900 ms after stimulus presentation). Spine interpolation was used to replace electrode channels containing artifacts in >50% of trials. Ocular Artifact Removal (OAR) was applied with a blink scope threshold of 14 μV/ms (165) and blink and movement thresholds of 150 mV.

Next, spine interpolation was again used to replace electrode channels containing artifacts in >40% of trials. EEG data were then re-referenced to the average reference of all electrodes and baseline-corrected. In each condition, segments from each of the 25 trials were averaged. Due to technical malfunctions during data collection, EEG data from three participants could not be pre-processed correctly and these participants were excluded from further analysis. Across the remaining participants (N=40), an average of 18.85 trials were completed in the neutral infant condition and an average of 18.49 trials were completed in the distress infant condition.

Based on past studies of emotional infant face processing using dense-array EEG (33, 141, 145), nine electrodes (61, 62, 67, 71, 72, 75, 76, 77, 78) in the centro-parietal region were chosen to assess the LPP. The LPP electrode array is shown in Figure 2B.
The grand averaged data from these nine electrodes was visually inspected to select the 600-900 ms time window for the mean LPP. This time window was then confirmed individually for each participant. To assess for extreme outliers, boxplots were used to inspect the distribution of the ERP data. At this stage, two participants were excluded from subsequent LPP analysis (N=38).

For data from questionnaire measures and the rating measures, boxplots were used to inspect for extreme outliers. As neutral infant face processing was the main focus of this study, only ratings of certainty and emotional response for neutral infant faces were included in subsequent analysis. For both the IUS-12 and the PRAQ-R, one participant did not complete the questionnaire and was excluded from subsequent analysis of the respective measure (N=39). For the rating measures, one participant was excluded from analysis due to inappropriate completion of the task (N=39). The Kolmogorov–Smirnov test was used to examine the normality of each variable. The distribution of data for each variable was further examined through the kurtosis and skewness values. Variables with non-normal distributions, including ratings of certainty for how neutral infant faces felt and the IUS-Inhibitory score, were log-transformed for subsequent analysis requiring parametric distribution. Although the BDI-II measure of depression was not found to have a normal distribution, it was not log-transformed when assessing effects of anxiety given that it was only employed as a covariate.

Correlations were performed to assess for relationships between questionnaire measures, LPP amplitude, and rating measures. Pearson’s correlations were employed for variables with parametric distributions whereas Spearman’s rank order correlations were employed for those with non-parametric distributions. One-tailed correlations were
used when directional hypotheses were made regarding the relationships between variables, and two-tailed correlations were used and when there were no *a priori* hypotheses made concerning the relationship between variables. Partial correlations were used to control for depression symptomatology when assessing effects of anxiety. Repeated measures ANOVAs were used to assess for interaction effects between questionnaire measures of anxiety or intolerance of uncertainty and infant emotional expression on the LPP amplitude. To examine for indirect effects of uncertainty on LPP amplitude, Model 4 in the PROCESS macro (166) for SPSS v.24 was employed and bootstrapping was completed with 5000 samples.

**Author contributions**

H.J.V.R. conceptualized and developed this study. E.V. recruited participants and collected data for about 50% of participants. With the guidance and support of H.J.V.R., E.V. pre-processed EEG data, performed statistical analysis, and wrote this manuscript.

**RESULTS**

Forty participants were included in data analysis (*M*= 29.95 years, *SD*= 5.28 years, *range*= 18-39 years). To explore the relationships between questionnaire measures, ratings of certainty and emotional response for neutral infant faces, and LPP amplitude evoked by infant faces, a series of correlations were performed and are summarized in Table 2. As depression was found to be significantly positively correlated with both generalized and pregnancy-related anxiety, anxiety effects were controlled for depression to minimize confounding effects in subsequent analysis.
Table 2

**Means, Standard Deviations, and Correlations**

<table>
<thead>
<tr>
<th>Variables</th>
<th>M</th>
<th>SD</th>
<th>n</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Generalized Anxiety (BAI)</td>
<td>11.15</td>
<td>7.87</td>
<td>40</td>
<td></td>
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<tr>
<td>2. Pregnancy-Related Anxiety (PRAQ-R)</td>
<td>26.21</td>
<td>7.04</td>
<td>39</td>
<td>.680*</td>
<td></td>
<td>.287*</td>
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<td></td>
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<tr>
<td>3. Depression (BDI-II)</td>
<td>13.25</td>
<td>8.07</td>
<td>40</td>
<td></td>
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<tr>
<td>4. Intolerance of Uncertainty - Total Score (IUS-T)</td>
<td>27.38</td>
<td>11.62</td>
<td>39</td>
<td>.247</td>
<td>.161</td>
<td>.347*</td>
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</tr>
<tr>
<td>5. Intolerance of Uncertainty - Prospective Score (IUS-P)</td>
<td>17.68</td>
<td>6.99</td>
<td>39</td>
<td>.209</td>
<td>.223</td>
<td>.348*</td>
<td>.967*</td>
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<td>6. Intolerance of Uncertainty - Inhibitory Score (IUS-I)</td>
<td>9.70</td>
<td>5.18</td>
<td>39</td>
<td>.324*</td>
<td>.023</td>
<td>.323*</td>
<td>.909*</td>
<td>.786*</td>
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<tr>
<td>7. LPP Amplitude Evoked by Neutral Infant Faces</td>
<td>-.33</td>
<td>2.72</td>
<td>38</td>
<td>.258</td>
<td>.055</td>
<td>.136</td>
<td>.147</td>
<td>.117</td>
<td>.215</td>
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<td>8. LPP Amplitude Evoked by Distress Infant Faces</td>
<td>-.36</td>
<td>3.03</td>
<td>38</td>
<td>-.282</td>
<td>-.150</td>
<td>-.139</td>
<td>-.115</td>
<td>-.137</td>
<td>-.216</td>
<td>-.340*</td>
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<tr>
<td>9. Certainty Rating of Neutral Infant Faces</td>
<td>4.79</td>
<td>1.19</td>
<td>39</td>
<td>-.098</td>
<td>-.388*</td>
<td>-.218</td>
<td>-.231</td>
<td>-.201</td>
<td>-.262</td>
<td>.083</td>
<td>.017</td>
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<td></td>
</tr>
<tr>
<td>10. Emotional Response to Neutral Infant Faces</td>
<td>4.89</td>
<td>.65</td>
<td>39</td>
<td>.034</td>
<td>-.285*</td>
<td>-.175</td>
<td>.262</td>
<td>.230</td>
<td>.264</td>
<td>-.197</td>
<td>-.005</td>
<td>.189</td>
<td></td>
</tr>
</tbody>
</table>

Note. *M*=mean; *SD*=standard deviation; *BAI*=Beck Anxiety Inventory; *PRAQ-R*=Pregnancy-Related Anxiety-Revised; *BDI-II*=Beck Depression Inventory-II; *IUS*=Intolerance of Uncertainty; *LPP*=Late positive potential

Variability in reported sample size is due to missing data and extreme outliers

* indicates two-tailed correlation with *p*<0.05, + indicates one-tailed correlation with *p*<.05.
Generalized anxiety, pregnancy-related anxiety, and LPP amplitude in response to infant faces

Grand averaged LPP waveforms as a function of infant emotional expression and the electrode array used to capture LPP are shown in Figure 2. To assess the effect of generalized anxiety on the relationship between infant emotional expression and LPP amplitude, a one-way repeated measures ANCOVA was used including both generalized anxiety and depression as covariates. No significant main effect of infant emotional expression, $F(1,35)=2.296, p=.139$, generalized anxiety, $F<1$, or depression, $F<1$, was found. The interaction effect between infant emotional expression and generalized anxiety was found to be statistically significant, $F(1,35)=4.660, p=.038$, while no significant interaction effect was found between infant emotional expression and depression, $F<1$.

![A](image1.png)  ![B](image2.png)

Figure 2: (A) Grand averaged waveforms of the late positive potential (LPP) in response to distress (solid line) and neutral (dashed line) infant faces. ERP is averaged across nine centro-parietal electrodes (61, 62, 67, 71, 72, 75, 76, 77, 78) and measured using a 128 Hydrocel Ag/AgCl electrode sensor net. The time window of the LPP is 600-900 ms. (B) Schematic of the 128 Hydrocel Ag/AgCl electrode sensor net. Electrodes used in analysis of the late positive potential (LPP) are shaded in gray. Reference electrode Cz is shaded in white. R: right side of head. L: left side of head.
Generalized anxiety and LPP amplitude in response to neutral infant faces were found to be significantly positively correlated through a one-tailed partial correlation controlling for depression, $r(35)=.289$, $p=.042$. A negative trend approaching significance was found between generalized anxiety and LPP amplitude in response to distress infant faces with a one-tailed partial correlation controlling for depression, $r(35)=-.272$, $p=.051$. Plots showing the relationships between generalized anxiety and the LPP amplitude in response to neutral and distress infant faces are shown in Figure 3.

![Figure 3: Plots demonstrating a positive correlation between generalized anxiety and LPP amplitude in response to neutral infant faces (left) and a negative trending association between generalized anxiety and LPP amplitude in response to distress infant faces (right). Of note, these plots represent trends that are not controlled for depression level. Partial correlations controlling for depression showed a significant association between greater generalized anxiety and increased LPP amplitude evoked by neutral infant faces, $r(35)=.289$, $p=.042$ and an association trending toward significance between greater generalized anxiety and decreased LPP amplitude, $r(35)=-.272$, $p=.051$.](image)

To assess whether pregnancy-related anxiety also interacted with the main effect of infant emotional expression on LPP amplitude, a one-way repeated measures
ANCOVA was performed including both pregnancy-related anxiety and depression as covariates. No significant main effect was found for infant emotional expression, $F<1$, pregnancy-related anxiety, $F<1$, or depression, $F<1$. In addition, no significant interaction effect was found between infant emotional expression, and pregnancy-related anxiety, $F<1$, or between infant emotional expression and depression, $F<1$.

**Anxiety, uncertainty, and LPP response to neutral infant faces**

While a significant one-tailed correlation was found between generalized anxiety and the IUS-Inhibitory score, this relationship was found to no longer be significant when controlling for depression, $r(34)=.166 \ p=.166$. Indirect pathway analysis was used to assess whether IUS-Inhibitory score moderated the effect of generalized anxiety on LPP amplitude in response to neutral infant faces. While generalized anxiety was found to be significantly positively associated with IUS-Inhibitory score, $R^2=.108$, $B=.018$, $SE=.009$, $p=.047$, IUS-Inhibitory score was not found to be significantly associated with LPP amplitude evoked by neutral infant faces, $R^2=.090$, $B=.885$, $SE=1.052$, $p=.406$.

Generalized anxiety was not found to have a significant direct effect on LPP amplitude response to neutral infant faces, $R^2=.090$, $B=.071$, $SE=.059$, $p=.233$, or to have a significant indirect effect on LPP amplitude response to neutral infant faces through IUS-Inhibitory score, $R^2=.090$, $B=.014$, $SE=.025$, *Confidence Intervals* $=-.029-.072$. A model of this relationship is shown in Figure 4. To further explore this relationship, a one-tailed partial correlation controlling for IUS-Inhibitory score and depression, showing a non-significant positive association between generalized anxiety and LPP amplitude in response to neutral infant faces, $r(33)=.273$, $p=.057$. As shown in Table 2, no significant associations were found between participant ratings of certainty for how neutral infants
felt or ratings of emotional response to neutral infant faces and LPP response to neutral infant faces.

**DISCUSSION**

![Figure 4: Model representing the direct and indirect effects of generalized anxiety and Intolerance of Uncertainty-Inhibitory Score on LPP amplitude response to neutral infant faces.](image)

**Indirect effect: B=0.016, 95% Confidence Intervals=-0.029 to 0.072**

**Figure 4:** Model representing the direct and indirect effects of generalized anxiety and Intolerance of Uncertainty-Inhibitory Score on LPP amplitude response to neutral infant faces.

Taken together, our results show that while generalized anxiety was associated with an increased LPP amplitude in response to neutral infant faces, pregnancy-related anxiety was not. Generalized anxiety was also found to show a negative association approaching statistical significance with LPP amplitude in response to distress infant faces. In addition, while generalized anxiety and IUS-Inhibitory were positively correlated, no relationship was found between LPP amplitude in response to neutral infant faces and any measure of uncertainty. Further, through indirect pathway analysis, the IUS-Inhibitory was not found to moderate the relationship between generalized anxiety and LPP amplitude in response to neutral infant faces.
Despite its high prevalence and known associations with negative outcomes for both mothers and children (4), maternal anxiety and the mechanisms underlying its effects on parenting remain poorly understood. Importantly, maternal anxiety has been associated with decreased parental sensitivity to infant cues, which is thought to mediate its adverse effects on attachment formation (64, 78). Thus, a key area of interest has been in unraveling how maternal anxiety may disrupt the way that mothers perceive, interpret, and respond to cues from infants. Given their millisecond temporal resolution, ERP methods are particularly well suited to studying these rapid processes as they enable the examination of discrete cognitive processes (139).

Recent ERP studies suggest that increased anxiety in pregnant and postpartum women is associated with enhanced sustained neural processing of neutral, but not distress, infant faces (32, 33). These results suggest that for anxious perinatal women, neutral infant faces have increased emotional and motivational salience. To help explain this finding, it has been proposed that for mothers with anxiety, the ambiguity of neutral infant faces and the uncertainty of how they feel could be experienced as stressful or negative, leading to the observed increase in LPP amplitude (32, 33). However, this idea remains untested.

In the current study, we further examined the cognitive processes underlying the observed association between maternal anxiety and increased LPP amplitude in response to neutral infant faces. To do so, we focused on understanding the roles of pregnancy-related anxiety and uncertainty. While past ERP studies of maternal anxiety have employed measures of generalized anxiety, there is evidence that pregnancy-related anxiety represents a related, but distinct concept that may serve as a more specific
measure of maternal anxiety symptoms (45). In Aim 1, we asked whether a measure of pregnancy-related anxiety would show a similar association with increased LPP amplitude in response to neutral infant faces as seen with generalized anxiety measures have shown in past ERP studies. In Aim 2, we explored the role of uncertainty and asked whether anxiety’s effect on sustained neural processing of neutral infant faces was moderated by uncertainty. In addition to a general measure of dispositional intolerance of uncertainty, we asked participants to rate their certainty for how infants felt and their emotional response to viewing infant faces in order to more specifically gauge uncertainty in the context of infant cues.

In line with findings from past studies of maternal samples (32, 33), increased generalized anxiety was found to be associated with an increased LPP amplitude in response to neutral infant faces when controlling for depressive symptoms. As the LPP reflects attentional allocation toward motivationally-relevant stimuli (142, 150), this suggests that neutral infant faces have increased salience for expectant mothers with anxiety. Of note, this relationship between anxiety and increased LPP amplitude in response to neutral infant faces has been demonstrated in pregnant (32) and postpartum (33) samples, but not in samples of non-parent adults (146). Replication of this effect in an independent pregnant sample further supports that the association between generalized anxiety and enhanced sustained neural processing of neutral infant faces reflects a neural correlate of maternal anxiety.

In addition, we observed an association approaching statistical significance between generalized anxiety and decreased LPP amplitude in response to distress infant faces when controlling for depression. In other words, we found that while expectant
mothers with greater generalized anxiety showed increased attentional allocation toward neutral infant faces, they showed decreased attentional allocation toward distress infant faces. This suggests that distress infant faces hold less emotional salience for expectant women with greater generalized anxiety than for those with lower generalized anxiety. Of note, this finding is inconsistent with past ERP studies of maternal anxiety which have shown no significant association between anxiety level and LPP response to distress infant faces (32, 33). It is possible that our sample of pregnant women differed in meaningful ways from past maternal samples. Of note, our sample had a higher mean depression score than measured by Rutherford et al. in another sample of pregnant women in their third trimester recruited from the community (mean BDI-II scores of 13.25 and 10 respectively (32)). Although each individual study controlled for depression level in data analysis, it is possible that variation in depression burden between the sampled populations could help to explain this discrepancy. Maternal depression has previously been associated with blunted attentional and affective responses toward emotional infant cues (167-169). For our sample of expectant mothers experiencing an increased burden of depressive symptoms, the observed association between generalized anxiety and decreased LPP in response to distress infant faces may reflect a blunted and avoidant response. Additional factors that were not measured but may play a role in distinguishing between the two samples could include variations in income level, social support, and previous negative experiences related to pregnancy or delivery such as miscarriage or medical complications.

Importantly, the direction of the observed relationship between anxiety and decreased LPP response to distress infant faces also runs counter to findings from past
studies of anxiety’s influence on adult face processing. In community adults, high levels of anxiety have been associated with an increased LPP response to negative adult faces (170, 171). As anxiety has consistently been associated with an attentional bias toward threatening stimuli (172), it seems intuitive that individuals with greater anxiety would allocate more attention toward negative or threatening faces, resulting in an increased LPP amplitude. However, this pattern has not been observed in ERP studies employing infant face stimuli, with past studies showing no association between anxiety level and LPP response to distress infant faces in maternal (32, 33) and non-parent adult samples (146) and the current study showing a trend toward an association between greater anxiety and decreased LPP response to distress infant faces in expectant mothers. This may suggest that although distress infant faces are clearly negatively valenced, they are not perceived as more threatening for individuals with high anxiety and thus are not preferentially attended to. In part, this may be due to the unambiguous nature of distress infant faces. In contrast to neutral infant faces, distress infant faces clearly communicate their discomfort and need for caregiving. As a result, less cognitive energy and problem-solving may be required for a parent to address a clearly upset infant’s needs. This clear-cut situation may be perceived as less stressful or threatening than the experience of trying to determine what an infant with more ambiguous non-verbal communication may need. Due to the inconsistent findings regarding the relationship between anxiety and LPP response to distress infant faces, further replication and investigation is warranted.

Given our relatively small sample size, it is possible that the current study is underpowered to show the true effect of anxiety on LPP response to distress face and that this relationship could be clarified in future work by increasing the number of
participants. Further, the correlations reported in our results are not corrected for multiple comparisons, which may lead to the overestimation of associations. Therefore, it is important to be cautious with this finding and associated interpretations given these factors.

As measures of pregnancy-related anxiety are thought to more specifically capture the worries and cognitions of maternal anxiety (45) and have been shown in some studies to serve as better predictors of child developmental outcomes of maternal anxiety than measures of generalized anxiety (173, 174), we had hypothesized that pregnancy-related anxiety would be more strongly associated with enhanced sustained neural processing of neutral infant faces than generalized anxiety. However, pregnancy-related anxiety was not found to be significantly associated with LPP amplitude in response to neutral or distress infant faces, and was not found to interact with the main effect of infant emotional expression on LPP amplitude. In addition, pregnancy-related anxiety and generalized anxiety were not found to be significantly correlated. These findings emphasize that measures of generalized anxiety symptoms during pregnancy and measures of pregnancy-related anxiety are not equivalent and likely assess distinct constructs. Further, the finding that generalized anxiety symptoms are more closely associated with enhanced sustained neural processing of neutral infant cues than pregnancy-related anxiety suggests that women with higher trait anxiety may be more vulnerable to disruptions in infant cue processing than those whose anxiety symptoms are more narrowly focused on pregnancy. However, the literature addressing the neural correlates of pregnancy-related anxiety is sparse, and further study of the role of
pregnancy-related anxiety on both early and late stages of infant cue processing will be needed before any conclusions can be made.

Considering the importance of intolerance of uncertainty in the etiology and maintenance of anxiety and the ambiguity of neutral infant faces, we hypothesized that uncertainty would moderate the association between greater generalized anxiety and increased LPP amplitude in response to neutral infant faces. As the IUS-Inhibitory subscore was found to be positively associated with generalized anxiety, we performed indirect pathway analysis to assess whether generalized anxiety had an indirect effect on LPP amplitude in response to neutral infant faces and no significant moderation was found. Further, neither of our specific measures of uncertainty in the context of infant face processing (ratings of certainty for how neutral infants feel and rating of emotional response to neutral infants) showed a significant association with LPP response to neutral infants. Taken together, this suggests that uncertainty does not fully explain the mechanism underlying generalized anxiety’s association with enhanced sustained neural processing of neutral infant faces in expectant and postpartum mothers. Of note, our self-report measures of certainty and emotional response are likely prone to response bias. For example, participants with high intolerance of uncertainty may report higher certainty for how neutral infants feel than they truly experienced due to their discomfort with uncertainty or because they felt social pressure to appear more certain and decisive than they felt. In future analysis, it may be insightful to analyze participants’ response times to these questions as a more objective and behavioral measure of certainty. Hypothetically, participants who feel less certain of how neutral infants feel may take longer to rate their certainty and emotional responses to neutral infants. This behavioral
measure may be less susceptible to bias as participants would not be aware that their responses were being timed. Additional behavioral tasks measuring uncertainty, such as the HiLo game (175), could also be incorporated into future work to further explore the role of uncertainty more objectively.

As our results suggest that uncertainty does not explain the mechanism underlying maternal anxiety’s association with increased LPP amplitude in response to neutral infant faces, future work should consider the role of alternative aspects of maternal anxiety. For example, trait worry is highly associated with anxiety and has been shown to affect both emotional processing and attentional allocation (176). In a cued image paradigm, trait worry has been associated with decreased differentiation between LPP response to threatening and neutral stimuli, which has been hypothesized to be due to disrupted attentional control and increased sensitivity to threat (177). It is possible that for expectant and postpartum mothers with high trait worry, ambiguous infant faces may initiate patterns of negative and repetitive thinking regarding the infant’s needs leading to enhanced attentional allocation and increased LPP amplitude.

In addition, the role of social anxiety on maternal processing of infant faces should be further examined. Social anxiety is characterized by excessive fear of social rejection and increased self-focused attention and has been consistently associated with emotional face processing biases wherein neutral adult faces are interpreted as threatening (83, 122, 123). In the context of the perinatal period, social anxiety has been found to be a predictor of pregnancy-related anxiety and to be positively associated with fear of childbirth, child-related worries, and concerns about change in appearance (178). It is thought that social anxiety symptoms may worsen during the perinatal time due to
increased social attention and perceived appraisal around this life transition (178, 179). However, despite its associations with altered adult face processing and relevance to the perinatal time, little is known about the role of social anxiety in the neural processing of infant faces or in early parenting. It is possible that expectant and postpartum mothers with increased social anxiety may be more likely to interpret neutral infant faces more negatively, resulting in an increased LPP amplitude. As increased self-focused attention in social anxiety has been associated with altered attentional allocation (180), it is also possible that the ambiguity of what a neutral infant may need could trigger fears of negative evaluation of parenting ability in pregnant or postpartum women with high social anxiety, disrupting typical attentional allocation toward infant cues.

In order to further generate hypotheses regarding the link between maternal anxiety and increased LPP amplitude in response to neutral infant faces, a qualitative approach may prove beneficial. We are currently piloting a brief task in which participants are shown a photo of a neutral or distress infant face and are asked to share their initial reaction to the infant and to write a brief story about what might be going through the infant’s mind. This open-ended task may provide insight into women’s subjective experiences while viewing ambiguous or distress infant faces and could be impactful in steering future research questions.

To better understand maternal anxiety’s effects on the neural processing of infant faces, it will be important to include positive infant face stimuli in subsequent studies. In a past study using a morphed face paradigm, women with postnatal generalized anxiety disorder identified happy infant faces at a lower intensity than postnatal women without anxiety, and it has been suggested that this positive interpretation bias may reflect a
strategy for minimizing perceived uncertainty and for seeking reassurance for mothers with high anxiety (181). As past maternal anxiety ERP studies have included only neutral and negative infant faces, it is possible that the observed increase in LPP amplitude in response to neutral infant faces reflects the comparatively positive valence of the neutral infant faces rather than their ambiguity (33). According to the emotionality hypothesis, individuals with high levels of anxiety may show attentional biases toward emotional stimuli versus neutral stimuli, regardless of valence (182). In addition, evidence suggests that neural processing of neutral stimuli may be dependent upon the affective context in which they are viewed and that this effect may be modulated by anxiety level. In one illustrative study, individuals with high social anxiety showed an increased LPP amplitude in response to ambiguous adult faces preceded by negative self-referential statements rather than neutral or positive statements. This pattern was not shown for participants with low social anxiety, who showed enhanced LPP response to neutral faces preceded by positive statements (183). Together, these points emphasize the importance of including a range of stimuli with positive, neutral, and negative facial expressions in future work to more holistically understand maternal anxiety’s influence on infant face processing.

In future studies of maternal anxiety’s role in infant emotional face processing, it may be beneficial to take a longitudinal approach. As past ERP studies of maternal anxiety have focused solely on women in late pregnancy or in the postpartum period, little is known about when anxiety’s effects on sustained neural processing of neutral infant faces emerge. It is possible that this neural correlate of maternal anxiety precedes conception or the development of clinical symptoms and may serve as an early biomarker
of vulnerability to maternal anxiety. Alternatively, this change in facial processing may develop after the onset of anxiety symptoms and could be caused or maintained by clinical symptoms. In addition, little is known about the stability of anxiety’s influence on infant facial processing over time in individual women and whether altered facial perception can be reversed with treatment of anxiety. It would also be of interest to study whether these changes in infant facial perception are maintained as a mother with maternal anxiety’s infant grows older and whether these neural correlates of anxiety are associated with child health and development outcomes.

In addition, it will be important to study anxiety’s role in infant emotional face processing in fathers and partners of expectant and new mothers. As the parenting literature has largely focused on pregnant women and mothers, little is known about the transition to parenthood for partners and how anxiety may influence their interpretation of infant cues. This would further our understanding of the normative and psychopathologic processes occurring in parents during this stage of life and may help to clarify the links between parental factors and children’s socioemotional development. In addition, studying the neurobiological changes that occur during fatherhood would likely provide further context to our understanding of the transition to motherhood. Comparisons of these parallel transitions may provide insight into the varying contributions of social, biological, and psychologic factors toward this process.

To date, all ERP studies of maternal anxiety’s role in infant face processing have used self-report anxiety measures in non-clinical populations. In future studies, it may be beneficial to incorporate a clinical diagnostic measure of anxiety and to include participants with clinical levels of anxiety. Currently, little is known about the effect of
clinical anxiety disorders on infant cue processing and on differential effects of specific diagnoses. Likewise, it may also be of interest to compare the effects of anxiety on infant cue processing in women with a history of anxiety prior to pregnancy versus those with onset of anxiety during the perinatal period.

In this study, we examined the influence of pregnancy-related anxiety and uncertainty on the neural processing of infant facial expressions in a non-clinical sample of pregnant women. Our findings suggest that while generalized anxiety symptoms during pregnancy are associated with enhanced sustained neural processing of neutral infant faces, pregnancy-related anxiety symptoms are not. In addition, no evidence was found for intolerance of uncertainty’s proposed role as a moderator of maternal anxiety’s effect on LPP amplitude in response to neutral infant faces. This study is the first to assess the role of pregnancy-related anxiety and intolerance of uncertainty on the neural processing of infant cues. In future research, it will be beneficial to take a longitudinal approach toward understanding anxiety’s impact on infant face processing throughout the transition to parenthood in both mothers and their partners.
References


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