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Neural reactivity to infant emotion cues during pregnancy: Associations with peripartum anxiety and depressive symptoms

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ABSTRACT

Background: Pregnancy is marked by physiological and psychosocial changes for women, and event-related potentials (ERP) are comfortable and safe for examining brain function across pregnancy. The late positive potential (LPP) ERP, a measure of allocated attention to emotional stimuli, may provide insight into associations between internalizing symptoms and neural processing of infant emotion cues, which may be particularly salient in this life stage.

Methods: We developed a task to examine neural and behavioral responses to infant faces in pregnant women (N = 120, *M*age=31.09, *SD*=4.81), the impact of auditory infant cries on the LPP to faces, and associations between the LPP and anxiety and depressive symptoms. Participants matched distressed, happy, and neutral infant faces and shapes as a comparison condition with interspersed auditory conditions (infant cry sounds vs. white noise) while electroencephalogram data were collected. Participants also completed self-report measures of anxiety and depressive symptoms.

Results: Reaction time (RT) was faster for the infant cry vs. white noise condition and when matching shapes vs. infant faces. Depressive symptoms were associated with slower RTs to neutral infant faces. The LPP was enhanced overall to faces vs. shapes, but there was no main effect of auditory condition. Anxiety symptoms were associated with an enhanced LPP to infant distressed faces in the infant cry condition.

Conclusions: Results support these methods for measuring neural and behavioral responses to infant emotional cues in pregnancy and provide evidence that combinations of auditory and visual stimuli may be particularly useful for capturing emotional processes relevant to anxiety.

1. Introduction

Four million women give birth each year in the US (Martin et al., 2018). Although many demonstrate healthy adjustments to the physical and psychological changes associated with pregnancy and childbirth, the peripartum period is a high-risk time for anxiety and depression (Lebel et al., 2020; O'Connor et al., 2016). During pregnancy, the prevalence of anxiety diagnoses in women is approximately 20 % (Fawcett et al., 2019) and the prevalence of depression diagnoses is approximately 13 % (O'Connor et al., 2016). Anxiety and depression during pregnancy are further associated with a range of adverse outcomes for both women (e.g., miscarriage, preeclampsia, preterm delivery, postpartum depression) and offspring (e.g., preterm birth, low birth weight, reduced cognitive performance; Beck, 2001; Fawcett et al., 2019; Schaffir, 2018). Even subclinical levels of anxiety and depressive symptoms during pregnancy are associated with negative outcomes for women and offspring (Irwin et al., 2020; Kee et al., 2021). As such, there is an urgent need to identify underlying risk processes for internalizing symptoms during the peripartum period.

Anxiety and depression during pregnancy may be attributed in part to the many psychosocial and physiological changes that women undergo during this period (Cárdenas et al., 2020; Saxbe et al., 2018). In terms of psychosocial factors, many women experience pregnancy-specific stress during this period, such as fears and anxiety about childbirth (Alehagen et al., 2006). Further, the pending demands of caring for an infant can contribute to occupational stress and strains on relationships with romantic partners that may have consequences on anxiety and depression (Rosand et al., 2011; Saxbe et al., 2018). In terms

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of physiological changes, the peripartum period is associated with fluctuations in reproductive hormones (e.g., estrogen and progesterone) and changes in brain structure and function (e.g., reduction in gray matter volume, decreased activity in prefrontal areas during response inhibition tasks; for reviews, see Cárdenas et al., 2020; Kim et al. 2010). These physiological changes have been linked with anxiety and depressive symptoms in other developmental periods, such as adolescence, and may contribute to the emergence of psychopathology during pregnancy (Barba-Müller et al., 2018; Carmona et al., 2019). Yet, research on brain function in pregnancy is limited. Although magnetic resonance imaging [MRI] and functional magnetic resonance imaging [fMRI]) in pregnancy is considered acceptable for diagnostic purposes (Obstetrics Gynecology, 2017), there are concerns about the potential effects of tissue heating and the acoustic level on the fetus (Ray et al., 2016). Psychophysiological methods (e.g., EEG, ERP) can be implemented as alternative procedures. EEG/ERP can be used to measure neural activity related to sensory, cognitive, and affective processes (Hajcak et al., 2010; Luck et al., 2000) and may be particularly suitable for research across the peripartum period to reveal factors underlying depression and anxiety risk.

Women experience neural plasticity across pregnancy, but the impact of these changes on attentional processing and affective reactivity is not fully understood (Cárdenas et al., 2020). On the one hand, these changes are theorized to be evolutionarily adaptive as women transition to motherhood and caring for offspring (Gollan et al., 2014). For example, behavioral data indicate that women with young offspring, in comparison to women without offspring, demonstrate increased attention to infant faces (Thompson-Booth et al. 2014). Further, fMRI data indicate that mothers show activation of neural circuits related to reward and motivation in response to distressed infant faces (Landi et al., 2011). There is also evidence that variations in the attentional processing of infant distress during pregnancy prospectively relate to quality of the relationship between women and their offspring during the postpartum period (Pearson et al., 2011a). Affective attentional processes tend to be biased toward stimuli that support survival and reproduction, such as threat and sexual stimuli (Bernat et al., 2006; Sander et al., 2005). Thus, cues of infant distress may be particularly salient to women during pregnancy and the postpartum period, as they are social indicators that caregivers are motivated to fulfill to care for their infant.

A reliable measure for the allocation of attention to emotional stimuli is the late positive potential (LPP), a neurophysiological event-related potential (ERP) derived from electroencephalogram (EEG; Schupp et al. 2000). The LPP is modulated by motivational relevance (Schupp et al., 2000) and has been a critical tool in identifying patterns of emotional reactivity in anxiety and depression (Hill et al., 2010). Moreover, the LPP is economical, safe, and comfortable to assess, which is helpful for prospective clinical utility and critical to assessment during pregnancy. Research outside of the peripartum period indicates that anxiety is generally characterized by increased affective reactivity, as demonstrated by a potentiated LPP in response to negatively valanced, particularly threat-related, stimuli (MacNamara, 2018; MacNamara & Hajcak, 2010). Preliminary investigations examining associations between mothers' anxiety symptoms and attentional processing to infant distress yield conflicting findings. For example, one study found that the LPP in mothers was enhanced overall to distressed infant faces than neutral infant faces and that greater maternal state anxiety was associated with a potentiated LPP to infant neutral faces (Malak et al., 2015). In contrast, a recent study demonstrated that an enhanced LPP to positive infant images measured in pregnancy was prospectively associated with increased anxiety in the postpartum period (Mulligan et al. 2022).

In contrast to anxiety, depression is thought to be broadly characterized by dampened reactivity to emotional stimuli across valence (Bylsma, 2021). Consistent with this, pregnant women with depression, in comparison to those without, demonstrate decreased attentional biases for distressed infant faces as assessed by both a behavioral task (Pearson et al., 2010) and the P300 ERP component (Rutherford et al., 2016). These findings have implications for both women and offspring, as maternal sensitivity to distress, above and beyond sensitivity to other infant emotions, has a demonstrably larger impact on infant attachment security, social competence, behavioral adjustment, and affect regulation (Davidov & Grusec, 2006; Del Carmen et al., 1993; Leerkes, 2010; Leerkes et al., 2009).

In the context of pregnancy and the postpartum period, much of the LPP literature relies on responses to infant visual stimuli (Pearson et al., 2010; Laurent & Ablow, 2012, 2013). Yet, auditory cries are key signals of infant needs and likely particularly salient during pregnancy as women prepare for the demands of caregiving (Soltis, 2004). Several peripartum studies have measured ERPs in response to auditory infant cry (Kuzava & Bernard, 2018; Peoples et al. 2022; Rutherford et al., 2016). For example, there is evidence that new mothers exhibit an enhanced N100, an ERP thought to reflect attention and stimulus discrimination processes, to auditory cry stimuli compared to controls (Purhonen et al. 2001), suggesting an increase in arousal enabling greater alertness to infants' needs. Further, previous work suggests perception of infant auditory cry stimuli is supported by a multi-circuit neural network, including structures related to mothers' motor response, which could support caregiving responses to cries (Witteman et al. 2019). In addition, an ERP study found that infant auditory cries, in comparison to infant laughter, elicited a negative arousal bias (i.e., reduced attention to the task; smaller P200 component) that impacted performance on a Stroop task (inceased conflict processing; larger N450; Dudek et al., 2016). Response to infant auditory cry stimuli, like infant facial expressions, may serve as an adaptive function to draw attention away from other tasks and reorient parents to their infants' needs and secure offspring survival—a process that might emerge across the peripartum period and be disrupted in internalizing disorders.

The current literature on emotional reactivity to infant emotion cues focus on visual or auditory stimuli separately; however, humans rely on multiple types of sensory input to process emotions, especially when caring for infants. Indeed, auditory stimuli presented in conjunction with visual stimuli may impact the salience of various emotion cues for pregnant women and caregivers. To our knowledge, no study has investigated how infant auditory cry stimuli impact behavioral and neural responses to infant visual stimuli during pregnancy and the possible associations of these responses with anxiety or depression symptoms. That is, elucidating these associations may provide insight into underlying processes conferring risk for anxiety and depression symptoms during pregnancy. To address this gap in the literature, we developed a task to test the effects of interspersed auditory infant cry compared with auditory white noise on behavioral responses (i.e., reaction time [RT]) to and neural processing (i.e., LPP) of infant faces. We aimed to develop and validate this new task to elucidate how people process visual and auditory infant cues across the peripartum period, as well as associations with internalizing symptoms. In this initial proof-of-concept study, we present cross-sectional analyses of neural and behavioral responses to infant stimuli in a sample of women assessed in the 2nd trimester of pregnancy.

Given evidence that pregnant individuals show increased attention to threatening stimuli (e.g., distressed infant faces) in the peripartum period (Pearson et al., 2011b), we hypothesized RTs would be faster when matching infant distressed faces compared to other types of stimuli and faster in the auditory infant cry compared to white noise condition. Moreover, previous research has linked anxiety with enhanced emotional reactivity to threatening stimuli (MacNamara, 2018; Mulligan et al., 2022). Thus, we hypothesized that anxiety would be associated with faster RTs to infant distressed faces adjusting for response to shapes compared to other types of stimuli, particularly in the auditory infant cry condition, potentially reflecting faster processing of threatening stimuli. Finally, previous research has linked depression with blunted reactivity to emotional stimuli broadly (Bylsma, 2021; Rutherford et al., 2016) and with widespread alterations in emotional

face processing (Foti et al., 2010; Proudfit et al., 2015). Thus, we hypothesized that depression would be associated with RTs across emotional face types, particularly in the auditory infant cry condition. However, given mixed evidence of altered emotional reactivity measured in depression when measured behaviorally (McDermott & Ebmeier, 2009; Moran et al., 2013), we did not hypothesize a specific direction of associations.

For the LPP, we hypothesized that infant face stimuli, especially in the context of auditory infant cry stimuli, would evoke heightened neural responses in comparison to shapes. Further, previous research has linked anxiety with an enhanced LPP to threatening stimuli (MacNamara, 2018; Mulligan et al., 2022) and depression with a blunted LPP to emotional stimuli broadly (Bylsma, 2021; Rutherford et al., 2016). Thus, we hypothesized that anxiety would be associated with an enhanced LPP to infant distressed faces, particularly in the auditory infant cry condition. We also hypothesized that depression would be associated with a blunted LPP to both infant distressed and happy faces and that these patterns may be most apparent in the auditory infant cry condition. Given the possibly opposing effects of anxiety and depressive symptoms on neural emotional reactivity (i.e., hyper-reactivity in anxiety and hypo-reactivity in depression; Bauer & MacNamara, 2021; Kujawa et al., 2015; MacNamara et al., 2016; Weinberg et al., 2016), we conducted secondary analyses covarying anxiety symptoms in the depression model and depressive symptoms in the anxiety model.

2. Method

2.1. Participants

Participants were recruited through local obstetric clinics and the Vanderbilt University Medical Center, as well as social media advertisements. Eligibility criteria were that participants were currently pregnant, at least 18 years of age, and proficient in English. Exclusion criteria included being older than 40 years of age, having a previous diagnoses of mania/bipolar disorder, psychosis, or borderline personality disorder, and carrying multiples or a fetus with known congenital issues. We aimed to complete the initial assessments as close as possible to 20 weeks gestation to control for variability in gestational age. One hundred and twenty participants participated in the initial prenatal session (M=31.09 years, SD=4.81 years, gestational age M=20.05 weeks, SD=2.53, 78 % White, 10 % Black/African American, 8 % Multiracial/Other, 2 % Asian, 2 % missing data; and 9 % Hispanic/Latinx, 88 % non-Hispanic/Latinx, and 3 % missing data). Most participants were married or in a domestic partnership (83 % married or domestic partnership, 12% single and never married, and 3 % divorced, 2 % missing data) and employed for wages (83 % employed for wages, 5 % homemaker, 3 % out of work and looking for work, 3 % student, 2 % self-employed, 1 % other, 3 % missing data). In terms of annual household income, 1 % reported $0-$5,000, 3% $5,001-$15000, 4 % $15,001-$30,000, 17 % $30,001-$60,000, 22 % $60,001-$90,000, 28 % $90,001-$150,000 %, and 22 % greater than $150,000, 3 % missing data. Most participants were expecting their first child: 66 % reported no prior biological children, 27 % one child, 5 % two children, 1 % three children, and 1 % four children.

We oversampled for women at high risk for peripartum depression, and 54 % of the sample met criteria for a lifetime depressive disorder (i.e., major depressive disorder, persistent depressive disorder) assessed by the semi-structured Diagnostic Interview for Anxiety, Mood, and OCD and related Neuropsychiatric Disorders (DIAMOND; Tolin et al., 2018). Specifically, 51 % of our sample met criteria for a past depressive disorder (i.e., major depressive disorder and/or persistent depressive disorder), 4 % met criteria for a current depressive disorder, and 3 % met criteria for both a past and current depressive disorder. Current (but not past) anxiety diagnoses were also assessed, with 10 % of meeting diagnostic criteria. Specifically, 3 % of the sample met criteria for generalized anxiety disorder and 7 % for social anxiety disorder.

Of the 120 participants that consented to the study and completed the diagnostic interview, 117 completed questionnaires, and 114 completed the infant face matching task. Analyses were conducted on available data for all 120 participants. To account for missing data, we used restricted maximum likelihood (REML) for Analysis of Variance (ANOVA) analyses via the *lme4* package (Bates et al., 2015) and full information maximum likelihood (FIML) in correlation and regression analyses (Cham et al., 2017) via the *lavaan* package (Rosseel, 2012) in *R* (R Core Team, 2022).

Data used in the preparation of this manuscript are available on the National Institute of Mental Health (NIMH) Data Archive (NDA). NDA is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in mental health. Dataset identifier: https://dx.doi.org/10.15154/1528596).

2.2. Procedures

The Vanderbilt University Institutional Review Board approved the study. Potential participants first completed a phone screen to determine eligibility. At the beginning of the session, participant consent was obtained in accordance with the Declaration of Helsinki. Participants completed the diagnostic interview to assess past and current depressive episodes and current anxiety disorders through a videoconference meeting and self-report measures of depressive and anxiety symptoms through an electronic questionnaire. Next, participants visited the lab to complete a series of EEG assessments, including the infant face matching task with interspersed infant cry and white noise, completed in a counterbalanced order. Participants were compensated financially for their participation in the interview and EEG session.

2.3. Measures

2.3.1. Infant face matching task

The infant face matching task (see Fig. 1) was adapted from a well-established task designed to elicit amygdala activation to emotional faces; this task has previously been adapted for EEG/ERP using adult face stimuli (Hariri et al., 2002; Kujawa et al., 2015; MacNamara et al., 2013). On each trial, three faces or shapes were presented in a triangular configuration for 3000 ms and participants were instructed to press a mouse button to indicate which of the images at the bottom of the screen matched the image at the top of the screen. Next, a fixation (+) was presented for 4000 ms to allow time for interspersed auditory stimuli. The auditory stimulus was presented for the first 1000 ms, followed by a 3000 ms fixation with no auditory stimuli prior to the next visual stimulus presentation. All faces presented on the screen for each trial depict the same emotion, but two different infant faces were presented at the bottom (one that matches the infant at the top, one that does not). The task included 80 trials (i.e., 20 distressed faces, 20 happy faces, 20 neutral faces, and 20 shapes). Participants were provided four practice trials before the experiment began. The stimuli presentation for the first two practice trials (i.e., one neutral faces; one shapes) was not timed, which allowed the experimenter to explain the task to the participant. The second two practice trials (i.e., one neutral faces; one shapes) had the same presentation timing as the trials in the experiment blocks. No infant auditory stimuli were presented during the practice trials. Participants completed the infant face matching task twice in a counterbalanced order, once with an auditory cry stimulus presented between trials (i.e., infant cry condition) and once with white noise presented between trials matching the duration and intensity of auditory infant cry stimulus (i.e., white noise condition). Infant face stimuli were obtained from a previously validated stimulus set (Kringelbach et al., 2008). The infant cry auditory stimulus was obtained from a recording of a 6-month-old infant crying during the still-face procedure from a consenting mother from a previous research study (Humphreys et al., 2018). Each version of the task lasted approximately 9.5 min.

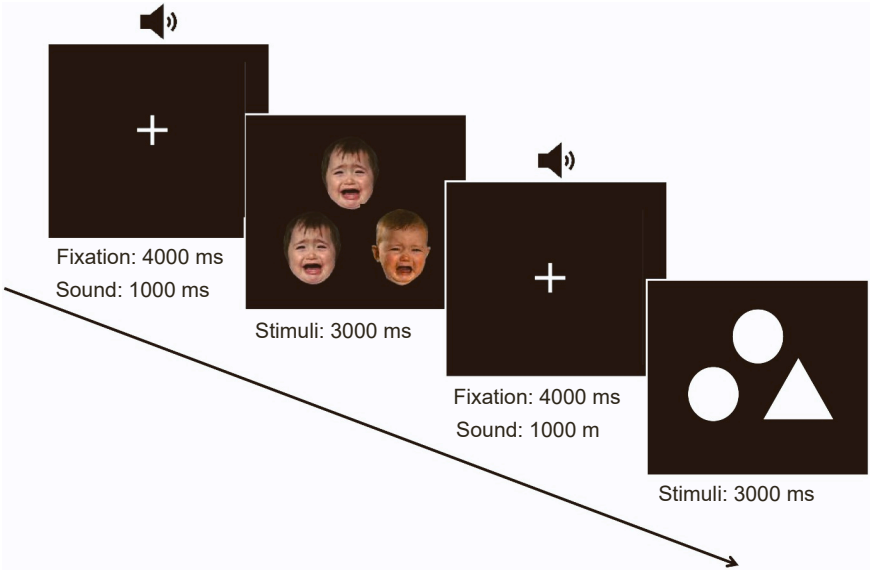

Fig. 1. Overview of the EEG infant face matching task. Participants were shown three faces or shapes in a triangular formation and asked to click the left or right mouse to indicate which of the two bottom images matched the image at the top of the screen. Between trials, participants were shown a fixation cross accompanied with auditory stimuli specific to the auditory condition (i.e., white noise or infant cry). Reaction time between stimulus presentation and participant response was recorded. The LPP was time-locked to stimulus presentation.

2.3.2. Depression symptoms

To measure depression symptoms, participants completed the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987). The EPDS is a validated and commonly used measure of depressive symptoms during pregnancy and postpartum (Cox et al., 1987). EPDS scores can range from 0 to 30. EPDS scores less than 8 suggest "depression not likely." Scores from 9 to 11 suggest "depression possible," scores from 12 to 13 suggest "fairly high possibility of depression," and scores greater than 14 suggest "probable depression." In this sample, 30 % met criteria for "depression possible". The mean was 6.72 (*SD*=4.32), and Cronbach's alpha was.86.

2.3.3. Anxiety symptoms

Anxiety was measured using the Generalized Anxiety Disorder Assessment (GAD-7; Spitzer et al., 2006). This is a 7-item self-report questionnaire used as a screening tool and a measure of the severity of generalized anxiety. The sum of the results can range from 0 to 21. Cut-off points of 5, 10, and 15 can be interpreted as mild, moderate, and severe levels of anxiety. In this sample, 35 % met criteria for at least mild severity of anxiety. The mean was 4.08 (*SD*=4.11), and Cronbach's alpha was.90.

2.4. EEG data collection and processing

EEG data were recorded with 32-electrodes using BrainProducts actiCHamp system (Munich, Germany) based on standard 10/20 layout. Of note, a 32-channel cap was used for all participants, but at the beginning of the study, we focused only on 16 channels in applying gel and lowering impedances in order to minimize time in close contact during the COVID-19 pandemic prior to availability of vaccines, consistent with recommendations (e.g., Simmons & Luck, 2020).

Impedances were reduced to below 30 kΩ. A sampling rate of 1000 Hz were used to digitize the recordings. BrainVision Analyzer software (Munich, Germany) was used to process the EEG data. Data were referenced to mastoid electrodes and band-pass filtered with 0.01 and 30 Hz as cutoffs. Data were segmented − 200 ms prior to and 3000 ms after stimuli presentation to capture the full window when stimuli were on the screen. Ocular correction was conducted with a modification of Gratton's algorithm (Gratton et al., 1983). Vertical (VEO) and horizontal (HEO) electrooculogram was measures from electrodes placed above and below the eyes and besides the outer canthus of eyes. Due to modified COVID protocols, we did not apply facial electrodes for the participants at the beginning of the study (i.e., those with 16 vs. 32 channels). For these participants, we used FP1 in lieu of VEO and FT9 and FT10 were used in lieu of HEO. Automatic artifact rejection criteria were a voltage step greater than 50.0 μV between sample points, the maximum voltage difference of 175 μV with trials, and minimum voltage difference of 0.5 μV within 100 ms intervals. After automatic artifact rejection, data were also inspected visually to reject any remaining artifacts. The LPP was averaged across stimulus type for each condition, and baseline corrected 200 ms prior to responses.

Prior research indicates that the LPP becomes stable after approximately 12 trials (Moran et al., 2013). One participant's behavioral and EEG data on the infant face matching task was excluded for poor behavioral data (i.e., pressed the same mouse button throughout the task). For the infant face matching task with interspersed infant cry condition, 16 participants had fewer than 12 artifact-free trials per condition and 2 participants were excluded because of technical problems (e.g., no markers codes, recording ended early). For the infant face matching with interspersed white noise, 11 participants were excluded because participant's task data were excluded for having fewer than 12 artifact-free trials per condition and 1 participant was excluded because of technical problems. In the auditory infant cry condition, there was available behavioral data for 113 participants and available EEG data for 95 participants. In the auditory white noise condition, there was available behavioral data for 113 participants and available EEG data for 101 participants.

In the auditory infant cry condition, following artifact rejection procedures, participants had on average 18.08–18.62 (range of *SD*=1.78–2.51) segments at Pz for stimuli in the auditory white noise and auditory infant cry conditions. To examine the LPP, data were extracted from 400 to 1000 ms pooled at occipitoparietal sites (i.e., CP1, CP2, Pz, Oz, O1, O2), consistent with prior research (Dickey et al., 2021) and where the LPP appeared maximal in the overall sample (see Figs. 3 and 4). All participants, regardless if they had 16 or 32 channels recorded at their visit, had data collected at sites CP1, CP2, Pz, Oz, O1, and O2. Although face stimuli were presented longer to allow for matching, we focused LPP analyses on the earlier LPP time window consistent with prior work (Decety et al., 2015; Kujawa et al., 2012), and given evidence that the LPP tends to be less reliable at later stages of processing (Hill et al. 2022; Macatee et al., 2021). LPP split-half reliability was acceptable for both the auditory infant cry condition (happy: r_{SB}=.82, neutral r_{SB}=.74, distressed r_{SB}=.77, shapes r_{SB}=.60) and auditory white noise condition (happy: r_{SB}=.85, neutral r_{SB}=.77, distressed r_{SB}=.84, shapes r_{SB}=.71).

Of the 114 participants who completed the EEG portion of the study, data from 55 participants were collected using 16 rather than 32 channels. Only electrodes included for all participants were analyzed in the current study, but this difference may affect data quality. We conducted independent samples *t*-tests to test differences in ERPs for participants with 16 vs. 32 channels for the stimulus types in each auditory condition. There was no significant differences in the LPP measured from 16 vs. 32 channel procedures across conditions and stimuli (all *ps*>.12). Further, in both auditory conditions, a similar percentage of participants with 16 channels and 32 channels were excluded. For the auditory infant cry condition, 16 % of participants with 16 channels were excluded and 15 % of participants with 32 channels were excluded. In the auditory white noise condition, 7 % of participants with 16 channels and 10 % with 32 channels were excluded.

2.5. Data analysis

2.5.1. Behavioral responses

We first computed a 2 (Auditory condition: auditory infant cry, auditory white noise) X 4 (Stimuli: happy, distressed, neutral, shapes) repeated measures ANOVA to test main effects of condition and stimulus and the auditory condition x stimulus interaction on RT. We then computed paired samples *t*-tests to further probe effects of auditory condition and stimulus on RT. Next, bivariate correlation analyses were conducted to examine associations between RT unstandardized residuals to infant faces (i.e., happy, distressed, or neutral controlling for response to shapes) in the auditory infant cry and auditory white noise conditions and clinical symptoms (i.e., depression, anxiety). To account for missing data, we used restricted maximum likelihood (REML). For these analyses, unstandardized residual scores were used to isolate behavioral responses to infant faces, adjusting for responses to shapes. Finally, four separate linear regression models were computed to examine associations between RT unstandardized residuals to infant faces in both the auditory infant cry and auditory white noise conditions and both depression and anxiety. Across models, RT to each stimulus type (adjusting for RT to shapes) was examined as simultaneous predictors to examine how each behavioral response uniquely relates to anxiety or depression symptoms and the cumulative association between RT observations and symptoms for each condition (i.e., R^2). To account for missing data, we used Full Information Maximum Likelihood (FIML) in regression analyses (Cham et al., 2017) via the *lavaan* package (Rosseel, 2012) in *R* (R Core Team, 2022). We also report effect sizes for each analysis.

2.5.2. LPP

We first computed a 2 (Auditory condition: auditory infant cry, auditory white noise) X 4 (Stimuli: happy, distressed, neutral, shapes) repeated measures ANOVA to test main effects of auditory condition and stimuli and the auditory condition x stimuli interaction on the LPP. We used REML to account for missing data. We computed paired samples *t*-tests to further probe effects of auditory condition and stimuli on the LPP. Next, bivariate correlation analyses were conducted to examine associations between the LPP unstandardized residuals to infant faces (i.e., happy, distressed, or neutral controlling for response to shapes) in the auditory infant cry and auditory white noise conditions and clinical symptoms (i.e., depression, anxiety). Unstandardized residual scores were computed to isolate the effects of emotional infant faces on the LPP, given evidence that this is a more rigorous scoring method than traditional subtraction-based difference scores (Meyer et al., 2017). Finally, four separate linear regression models were computed to examine associations between the LPP unstandardized residuals to infant faces in both the auditory infant cry and auditory white noise conditions and both depression and anxiety. Across models, LPP unstandardized residuals were entered as simultaneous predictors to examine unique associations of the LPP to each stimulus type with anxiety or depression symptoms. This was especially important when examining emotional reactivity, such that associations between the LPP to emotional infant faces and symptoms was examined while controlling for the LPP to neutral infant faces within the model. This model composition also allowed for the examination of the cumulative association between LPP observations across all infant face types and symptoms for each auditory condition (i.e., R^2). As with behavioral data analyses, we accounted for missing data via the use of FIML in regression analyses and we computed and reported relevant effect sizes for each analysis.

We conducted sensitivity analyses of required effects sizes for.80 power, which we report in the supplemental material. Additionally, although we were primarily interested in the LPP component, we also conducted supplementary analyses of the vertex positive potential (VPP), an ERP sensitive to face stimuli (MacNamara et al., 2013) and the P1, an early attentional or perceptual processing ERP component (Smith et al., 2013). See supplemental material.

2.5.3. Secondary analyses

Given the possibly opposing effects of anxiety and depressive symptoms on emotional reactivity (i.e., hyper-reactivity in anxiety and hypo-reactivity in depression; Bauer & MacNamara, 2021; Kujawa et al., 2015; MacNamara et al., 2016; Weinberg et al., 2016), we conducted secondary analyses covarying anxiety symptoms in the depression model and depressive symptoms in the anxiety model. We retested the regression models covarying anxiety symptoms when examining depressive symptoms as the outcome and covarying depressive symptoms when examining anxiety symptoms as the outcome.

3. Results

3.1. Behavioral analyses

Table 1 presents the mean RT for each condition and stimulus category. Results of the 2 (Auditory condition) X 4 (Stimuli) repeated measures ANOVA for RT revealed a significant effect of auditory condition [$F(1, 784)= 14.12, p < .001, \eta_p^2 = .018$] such that RTs were faster overall for the auditory infant cry vs. auditory white noise. There was also a significant main effect of stimuli [$F(3, 784)= 123.51, p < .001, \eta_p^2 = .321$] such that RTs were faster for shapes vs. infant faces. The interaction between auditory condition and stimuli was not significant [$F(3, 784)= 1.37, p = .250, \eta_p^2 = .005$] (see Fig. 2). Across conditions, RT was significantly faster for shapes compared to happy faces [$t(784) = 14.85, p < .001$, Cohen's $d= 0.97$], neutral faces, [$t(784) = 16.23, p < .001, d= 1.06$], and distressed faces, $t(784) = 15.94, p < .001, d= 1.03$. However, RT to specific faces did not significantly differ from each other: happy compared to neutral faces [$t(784) = -1.38, p = .514, d= 0.07$], happy compared to distressed faces [$t(784) = -1.10, p = .692, d= 0.06$], and neutral compared to distressed faces, $t(784) = 0.28, p = .992, d= 0.02$.

Next, bivariate correlation analyses were conducted to examine the

Table 1
Mean reaction time (ms) and LPP (μV) for each auditory condition and stimuli type.

Condition	Stimuli			
	Happy *M* (*SD*)	Neutral *M* (*SD*)	Distress *M* (*SD*)	Shapes *M* (*SD*)
Reaction time (ms)				
Infant cry	887.64 (239.74)	882.32 (262.59)	883.02 (244.90)	686.41 (159.78)
White noise	898.10 (283.70)	939.60 (263.73)	931.48 (264.56)	709.68 (186.62)
LPP (μV)				
Infant cry	6.02 (4.39)	6.03 (4.35)	6.22 (4.33)	2.53 (4.14)
White noise	5.86 (4.28)	5.51 (3.79)	5.91 (4.22)	2.20 (3.68)

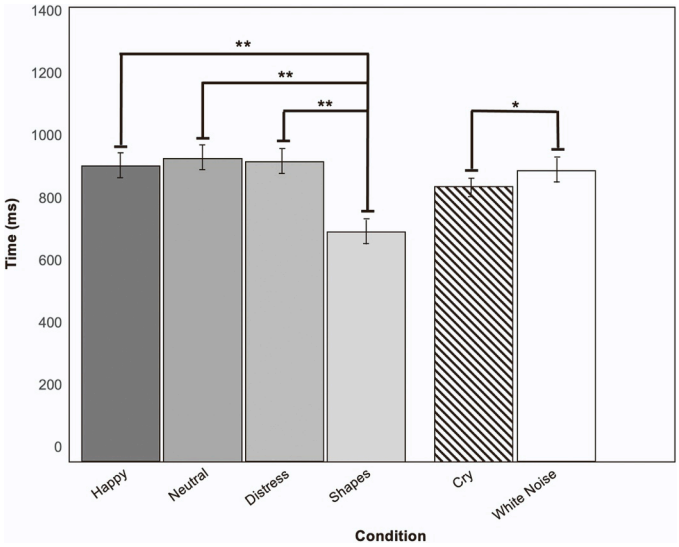

Fig. 2. RT means (and standard errors) across task conditions and stimuli. *Note*. *Difference was significant at the.05 level (2-tailed). * *Difference was significant at the.01 level (2 tailed).

associations between the RT unstandardized residuals to infant faces (i.e., happy, distress, or neutral adjusting for response to shapes) in the auditory infant cry and auditory white noise conditions and clinical symptoms (see Table 2). RTs across stimuli and auditory conditions were not associated with anxiety and depressive symptoms.

Finally, regression analyses were conducted to examine associations amongst the RT to infant faces and clinical symptoms of depression and anxiety. In the auditory infant cry and auditory white noise conditions, RT was not associated with anxiety symptoms (Table 3). Slower RT to neutral infant faces was associated with greater depressive symptoms with RT to happy and distressed faces in the model (Table 4). These associations were specific to RT in the context of auditory white noise and were not significant in the auditory infant cry condition.

3.2. LPP analyses

Table 1 presents the mean LPP for each condition and stimulus category. Figs. 3 and 4 present the grand-averaged waveforms and scalp topographies for the LPP elicited for each condition. Results of a 2 (Auditory condition) X 4 (Stimuli) repeated measures ANOVA for the LPP revealed a trend effect of auditory condition [$F(1, 680.88) = 3.48$, $p = .062$, $\eta_p^2 = .005$] such that LPP was enhanced overall in the auditory cry condition vs. white noise condition but did not reach significance. However, there was a significant main effect of stimuli, $F(1, 670.96) = 77.53$, $p < .001$, $\eta_p^2 = .104$. The interaction between auditory condition and stimuli was not significant, $F(3, 670.96) = 0.13$, $p = .942$, $\eta_p^2 < .001$. Across auditory conditions, the LPP was enhanced for happy faces [$t(671) = 12.48$, $p < .001$, $d = 0.98$], neutral faces, [$t(671) = 11.87$, $p < .001$, $d = 0.98$], and distressed faces [$t(671) = 12.92$, $p < .001$, $d = 1.03$] in comparison to shapes (see Fig. 5). There was no difference in the LPP amplitude to distressed compared to neutral faces, $t(671) = -1.05$, $p = .719$, $d = 0.08$, happy compared to neutral faces [$t(671) = 0.61$, $p = .930$, $d = 0.04$], or happy compared to distressed faces, $t(671) = -0.45$, $p = .971$, $d = 0.05$.

Table 3
Linear regression models between RT to infant faces and anxiety symptoms.

Variable	*b*	β	SE	*p*	95 % CI	
					LL	*UL*
Model 1						
Infant cry: RT to happy faces	-0.01	<0.01	0.12	.914	-0.26	0.23
Infant cry: RT to neutral faces	0.06	<0.01	0.12	.624	-0.18	0.30
Infant cry: RT to distressed faces	0.01	<0.01	0.10	.909	0.18	0.20
Model 2						
White noise: RT to happy faces	<0.01	-0.01	<0.01	.978	-0.01	0.01
White noise: RT to neutral faces	0.01	0.31	<0.01	.231	-0.01	0.01
White noise: RT to distressed faces	<-0.01	0.27	<0.01	.235	-0.01	<0.01

Note. RT = reaction time. *b* = unstandardized beta coefficient. *β* = standardized beta coefficient. RT are quantified as the unstandardized residual of the RT to infant faces (i.e., happy, distress, or neutral) controlling for the RT to shapes for each condition.

Table 4
Linear regression models between RT to infant faces and depressive symptoms.

Variable	*b*	β	SE	*p*	95 % CI	
					LL	*UL*
Model 1						
Infant cry: RT to happy faces	<-0.01	-0.12	<0.01	.316	-0.01	<0.01
Infant cry: RT to neutral faces	<0.01	0.17	<0.01	.148	<-0.01	0.01
Infant cry: RT to distressed faces	<-0.01	-0.09	<0.01	.347	-0.01	<0.01
Model 2						
White noise: RT to happy faces	<0.01	0.02	<0.01	.888	<-0.01	0.01
White noise: RT to neutral faces	**0.01**	**0.31**	**<0.01**	**.041**	**<0.01**	**0.02**
White noise: RT to distressed faces	-0.01	-0.23	<0.01	.096	-0.01	<0.01

Note. RT=reaction time. *b*=unstandardized beta coefficient. *β* = standardized beta coefficient. RT are quantified as the standardized residual of the RT to infant faces (i.e., happy, distress, or neutral) controlling for the RT to shapes for each condition. Statistically significant findings are bolded.

Table 2
Bivariate correlations between symptoms and RT.

Variable	1.	2.	3.	4.	5.	6.	7.	8.
1. Anxiety symptoms	-							
2. Depressive symptoms	.80**	-						
3. Infant cry: RT to happy faces	.03	-.04	-					
4. Infant cry: RT to neutral faces	.05	.08	.63**	-				
5. Infant cry: RT to distressed faces	.02	-.10	.24**	.14	-			
6. White noise: RT to happy faces	.05	.10	.37**	.19*	.10	-		
7. White noise: RT to neutral faces	.08	.15	.59**	.35**	.19*	.57**	-	
8. White noise: RT to distressed faces	-.01	.01	.51**	.34**	.39**	.43**	.76**	-

Note. * * Correlation was statistically significant at the.01 level (2-tailed). RT = reaction time. RT observations are quantified as the unstandardized residual of the RT to infant faces (i.e., happy, distress, or neutral) controlling for the RT to shapes for each condition. Anxiety symptoms are measured with the GAD-7. Depressive symptoms are measured with the EPDS.

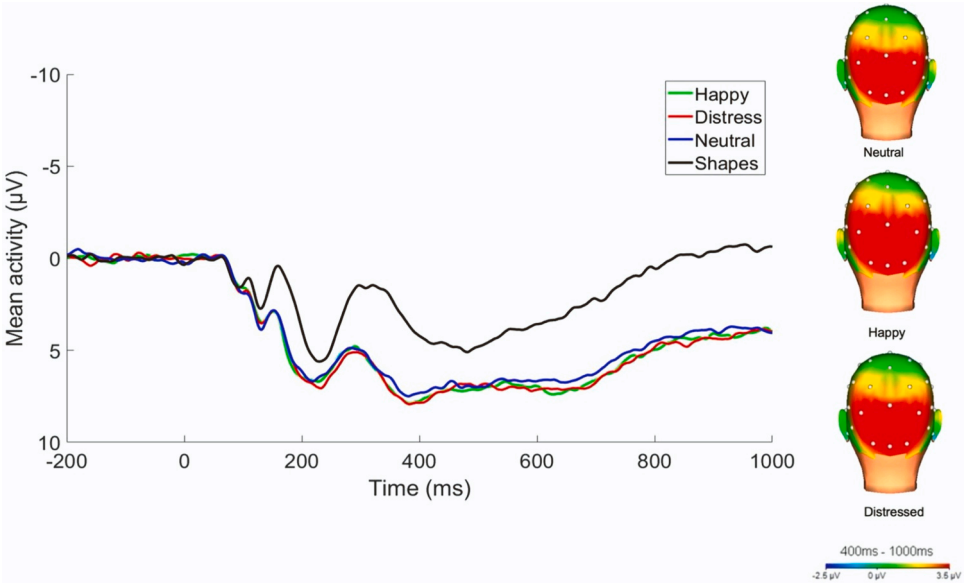

Fig. 3. Grand-averaged LPP waveforms in the auditory white noise condition for each stimulus type and scalp topographies for the LPP to infant faces minus shapes 400–1000 ms after stimulus onset. *Note*. The LPP was calculated as a pooling across electrode sites CP1, CP2, Pz, Oz, O1, O2.

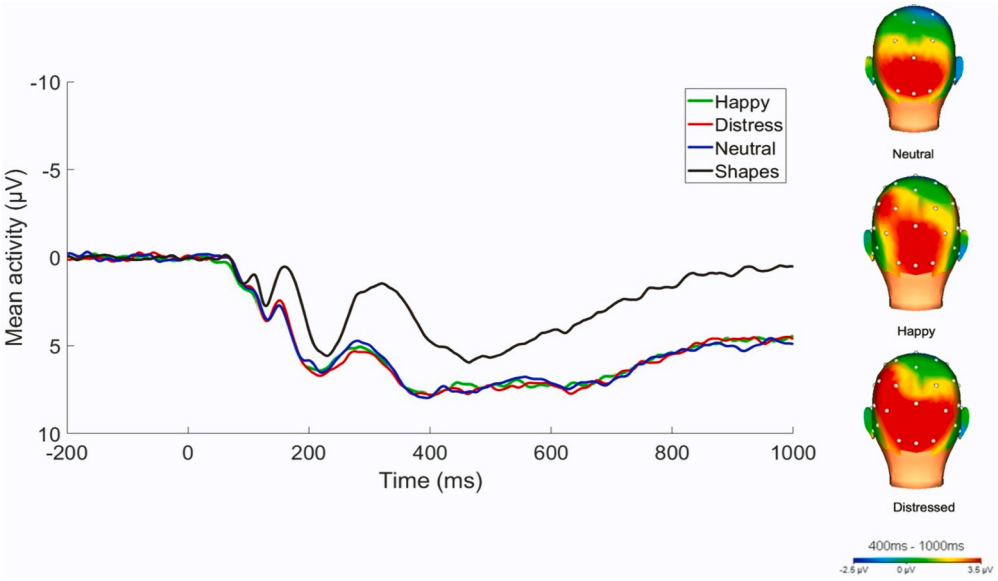

Fig. 4. Grand-averaged LPP waveforms in the auditory infant cry condition for each stimulus type and scalp topographies for the LPP to infant faces minus shapes 400–1000 ms. *Note*. The LPP was calculated as a pooling across electrode sites CP1, CP2, Pz, Oz, O1, O2.

To examine the impact of having another child on the LPP, we examined the repeated measures ANOVA for LPP with whether or not participants already had one or more biological children as the between subject factor. The main and interaction effects of a prior child were not significant.[1] In addition, we examined the repeated measures ANOVA for the LPP with a lifetime diagnosis of depression as the between subject factor.[2] The main and interaction effects of depression were not significant.

[1] There were no significant effects of Prior Biological Child Status [$F(1, 100.84) = 2.90$, $p = .092$, $\eta_p^2 = .028$], Condition x Prior Biological Child Status [$F(1, 679.67) = 1.62$, $p = .203$, $\eta_p^2 = .002$],Stimuli x Prior Biological Child Status [$F(3, 664.18) = 2.45$, $p = .063$, $\eta_p^2 = .011$], or Condition x Stimuli x Prior Biological Child Status [$F(3, 664.18) = 1.18$, $p = .318$, $\eta_p^2 = .005$].

[2] There were no significant effects of Lifetime Depression [$F(1, 99.85) = 0.72$, $p = .399$, $\eta_p^2 = .007$], Condition x Lifetime Depression [$F(1, 673.44) = 0.03$, $p = .853$, $\eta_p^2 < .001$], Stimuli x Lifetime Depression [$F(3, 664.04) = 0.70$, $p = .550$, $\eta_p^2 = .003$], or Condition x Stimuli x Lifetime Depression [$F(3, 664.04) = 0.80$, $p = .492$, $\eta_p^2 = .004$].

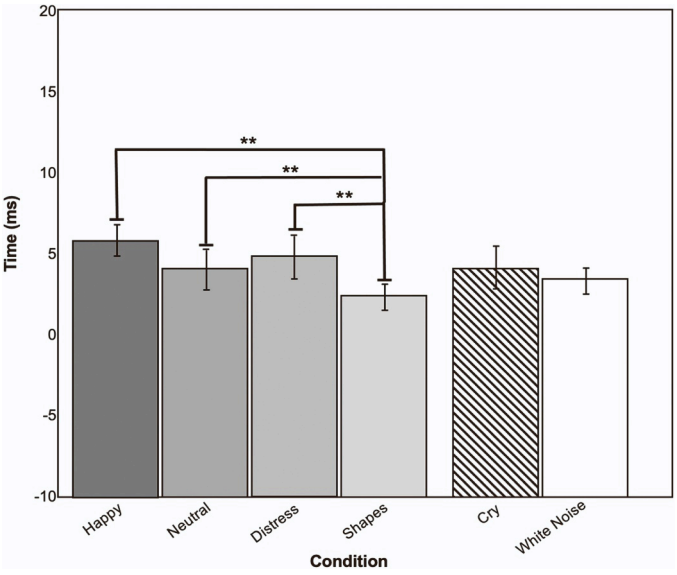

Fig. 5. LPP means (and standard errors) across stimuli and task conditions. *Note.* * *Difference was significant at the.01 level (2 tailed).

Next, bivariate correlation analyses were conducted to examine the associations amongst the LPP to infant faces in the auditory infant cry and auditory white noise conditions and clinical symptoms (see Table 5). As expected, LPPs across stimuli and conditions were positively correlated, as were symptoms of depression and anxiety, but no significant bivariate associations were observed between symptoms and LPP residuals to infant faces in the auditory infant cry or auditory white noise conditions.

Finally, linear regression analyses were conducted to examine associations amongst the LPP to infant faces and clinical symptoms of depression and anxiety. In the auditory infant cry condition, an enhanced LPP to distressed faces was associated with greater anxiety symptoms (Table 6), but not depressive symptoms (Table 7), when accounting for LPP to happy and neutral faces in the model. These associations appeared specific to the LPP to distressed infant faces in the context of interspersed auditory infant cry stimuli and were not statistically significant in the auditory white noise condition.

3.3. Secondary analyses

Given the possibility of anxiety and depression having opposing effects on the LPP, we also explored the regression models while covarying for anxiety symptoms in the depression model and depressive symptoms in the anxiety model. None of the LPP observations were significantly related to anxiety or depression in these models (*ps* >.201).

Table 6
Linear regression models between LPP observations to infant faces and anxiety symptoms.

Variable	*b*	*β*	SE	*p*	95 % CI	
					LL	*UL*
Model 1						
Infant cry: LPP to happy faces	-0.20	-0.19	0.16	.209	-0.51	0.11
Infant cry: LPP to neutral faces	-0.09	-0.08	0.16	.592	-0.41	0.23
Infant cry: LPP to distressed faces	**0.34**	**0.33**	**0.16**	**.031**	**0.03**	**0.64**
Model 2						
White noise: LPP to happy faces	-0.05	-0.05	0.18	.776	-0.40	0.30
White noise: LPP to neutral faces	0.06	0.05	0.16	.714	-0.25	0.36
White noise: LPP to distressed faces	0.06	0.06	0.20	.754	-0.33	0.46

Note. b = unstandardized beta coefficient. β = standardized beta coefficient. LPP observations were quantified as the unstandardized residual of the LPP to infant faces (i.e., happy, distress, or neutral) controlling for the LPP to shapes for each condition. Significant findings were bolded.

Table 7
Linear regression models between LPP observations to infant faces and depressive symptoms.

Variable	*b*	*β*	SE	*p*	95 % CI	
					LL	*UL*
Model 1						
Infant cry: LPP to happy faces	-0.29	-0.26	0.17	.088	-0.62	0.04
Infant cry: LPP to neutral faces	0.03	0.02	0.17	.878	-0.31	0.37
Infant cry: LPP to distressed faces	0.29	0.27	0.17	.085	-0.04	0.62
Model 2						
White noise: LPP to happy faces	-0.04	-0.04	0.19	.814	-0.41	0.33
White noise: LPP to neutral faces	0.11	0.10	0.16	.486	-0.21	0.43
White noise: LPP to distressed faces	0.05	0.04	0.21	.824	-0.37	0.46

Note. b=unstandardized beta coefficient.β = standardized beta coefficient. LPP=late positive potential. LPP observations were quantified as the unstandardized residual of the LPP to infant faces (i.e., happy, distress, or neutral) controlling for the LPP to shapes for each condition.

4. Discussion

We examined the effect of interspersed auditory infant cry stimuli compared with auditory white noise on behavioral (i.e., RT) and neural (i.e., LPP) responses to infant faces in women in their second trimester of pregnancy. We also examined whether behavioral and neural responses were associated with anxiety and depressive symptoms during this

Table 5
Bivariate correlations between symptoms and LPP.

Variable	1.	2.	3.	4.	5.	6.	7.	8.
1. Anxiety symptoms	-							
2. Depressive symptoms	.80**	-						
3. Infant cry: LPP to happy faces	<.01	-.06	-					
4. Infant cry: LPP to neutral faces	.05	.05	.68**	-				
5. Infant cry: LPP to distressed faces	.15	.10	.71**	.69**	-			
6. White noise: LPP to happy faces	.02	.07	.44**	.44**	.46**	-		
7. White noise: LPP to neutral faces	.03	.10	.49**	.46**	.60**	.61**	-	
8. White noise: LPP to distressed faces	.04	.07	.41**	.47**	.44**	.80**	.67**	-

Note. * * Correlation was significant at the.01 level (2-tailed). LPP observations were quantified as the unstandardized residual of the LPP to infant faces (i.e., happy, distress, or neutral) controlling for the LPP to shapes for each condition.

period. For behavioral measures, RTs were faster overall in the cry versus white noise conditions. In addition, RTs were faster in response to shape versus infant face stimuli. Further, slower RT to infant neutral faces in the white noise condition was positively associated with depressive symptoms when accounting for RT to shapes and happy and distressed faces. For neural measures, the LPP was enhanced for happy, neutral, and distressed infant faces compared to shapes, regardless of task auditory condition. Further, the LPP to distressed infant faces was significantly enhanced relative to the LPP to neutral infant faces. Moreover, an enhanced LPP to distressed infant faces in the context of auditory infant cry was associated with higher anxiety symptoms when accounting for the LPP to other face stimuli in the model. Surprisingly, there were no statistically significant associations amongst observations of the LPP to infant faces or shapes and depressive symptoms.

Taken together, these behavioral data suggest that infant cry may enhance efficiency in responding to task prompts in pregnant women, as reaction times were faster overall in the cry versus white noise condition. On the other hand, reaction time did not appear to differentiate responses to specific infant faces but was faster overall for shapes relative to faces, likely due to less complexity of the stimuli. Interestingly, regression analyses revealed that greater depressive symptoms were associated with slower responses specifically to neutral infant faces. Although preliminary, these results could indicate that pregnant women higher in depression symptoms have more difficulty disengaging from more ambiguous infant emotional expressions. Although a behavioral attention bias toward negative stimuli is commonly observed in depression (Peckham et al., 2010), increased attention processing for neutral stimuli has also been observed in depression (McCabe & Gotlib, 1995). Moreover, individuals with depression may be more likely to interpret neutral face stimuli as negatively valanced, which could then lead to increased processing and slowed behavioral responses (Leppänen et al., 2004).

We observed that potentiated neural emotional reactivity, measured via the LPP, was associated with anxiety symptoms, and this association was specific to infant distressed faces in the context of interspersed auditory infant cry. These results are consistent with the established literature on anxiety in association with potentiated LPP observations, particularly when negatively valanced and relating to threat (MacNamara, 2018; MacNamara & Hajcak, 2010; Mulligan et al., 2022). We did not observe associations between the LPP and depression, and these results are surprising given the previously demonstrated associations between attenuated LPP observations and depression (Foti et al., 2010; Hill et al., 2019; Proudfit et al., 2015; Rutherford et al., 2016; Weinberg et al., 2016). Further, these null associations are surprising given that over half of the present sample endorsed past or current depressive disorders assessed via a semi-structured interview. It may also be that the null associations observed are specific to the current study in that we examined LPP and depressive symptoms concurrently in the second trimester of pregnancy, a period known to be marked by biological and socioemotional change (Cárdenas et al., 2020; Roos et al., 2011; Saxbe et al., 2018). Longitudinal assessments across the perinatal period could provide additional insight into the progression of these associations. The present study advances the literature on emotional reactivity in relation to internalizing symptoms within the specific developmental period of pregnancy, wherein infant distressed cues are particularly salient to promote survival of the prospective offspring (Gollan et al., 2014).

There is a need for additional research probing associations between emotional reactivity and internalizing symptoms. These processes should be investigated longitudinally to examine prospective risk of internalizing in the postpartum period to support pregnant people at greatest risk. Further, it is important to note that the measure of depression used in the present study, the EPDS, includes anxiety items in the total score. There is likely heterogeneity in patterns of emotional reactivity across anxiety and depression, and potentially even within these diagnoses. Future work would benefit from examination of more narrowly defined measures of depressive symptomatology and associations with emotional reactivity. This line of research could inform how measures of emotional reactivity can be better used to address the needs of women at high risk for internalizing symptoms across the transition to parenthood. Additionally, the sample included both first-time pregnant women and women who were already parents, and we did not comprehensively measure individual differences in prior exposure to infants. Associations between the LPP and depressive symptoms could be masked in part due to the novelty of the stimuli for first-time parents, given that novelty is associated with an enhanced LPP and related ERP components (Bradley, 2009; Debener et al., 2005; Kutas & Hillyard, 1984; Määttä et al. 2005).

Contextualization of our current findings are an important step in understanding trajectories of risk for psychopathology. To date, there is a paucity of research examining neural markers of risk for peripartum anxiety and depression. Emerging literature on the LPP measured during pregnancy suggests that it may be a useful biological marker of internalizing symptoms, both cross-sectionally and prospectively. For example, a recent study found that the LPP measured during pregnancy predicted changes in anxiety symptoms from pregnancy to early postpartum (Mulligan et al., 2022). The present study, although cross-sectional, offers a novel task integrating auditory and visual infant cues for future use in the pursuit of understanding trajectories of internalizing symptoms, particularly anxiety, during pregnancy.

A few limitations of the present study should be considered when interpreting these results. First, the current study was cross-sectional. Thus, our findings are unable to indicate the degree to which symptoms of psychopathology are causally related to observed neural and behavioral patterns. For example, although the LPP to distressed faces residual was associated with greater anxiety symptoms, results should be replicated with longitudinal data collected across the peripartum period to examine potential links between LPP to distressed faces and trajectories of symptoms over the peripartum period. Second, although the photographs used for the infant face matching task were from a previously validated stimuli set (Kringelbach et al., 2008), the infants were limited in racial and ethnic diversity and may be limited in their ecological validity with the general population (Johnson & Lichter, 2010, 2016). Further, we did not include an adult face stimulus condition to discern if these results are related to threat cues more generally or specifically to infant cues. The current results indicate that infant distress cues are salient for pregnant people, potentially because these images reflect possible harm in the environment or shared negative affect; however, this social messaging is distinct from threat cues commonly studied in the literature. For example, Roos and colleagues (2012) found that women in pregnancy demonstrated greater attentional bias toward adult fearful faces. Notably, both increased responsivity to adult threat cues and infant distress cues is posited to be adaptive for the protection of offspring (De Carli et al. 2019; Pearson et al., 2011b; Roos et al. 2012), and future research could compare the LPP to both adult and infant faces across the peripartum period. Third, the study design focused on infant cry because of its salience. To minimize the number of blocks completed, we did not also include infant happy or neutral sounds. The congruency and incongruency between auditory cues and faces may have influenced our results. Future work could use a similar paradigm with interspersed infant laughter or babbling sounds to examine the impact of congruency between auditory and visual cues on ERPs. Given social reorientation during the peripartum period, pregnant individuals may become particularly sensitive to infant cues, and patterns of over or under-responsiveness may be associated with internalizing symptoms (Cárdenas et al., 2020). We did not include a comparison group of non-pregnant adults to determine whether responses to infant cues differ in pregnancy. Lastly, although the current results support the possible clinical utility of psychophysiology (e.g., the utility of ERP measurement in pregnancy to predict concurrent and prospective internalizing symptoms), a significant amount of research is necessary—examining incremental utility, individual versus normative effects, consideration of precision medicine approaches—before such

measures would be advisable for widespread implementation.

5. Conclusion

The present study is among the first to integrate multiple measures and examine emotional reactivity to infant faces in the context of auditory infant cues in pregnancy. We examined associations of neural and behavioral responses to infant emotional faces with anxiety and depressive symptoms in pregnant women, a period of high risk for anxiety and depression (Yim et al., 2015). RTs were faster in the infant cry vs. white noise auditory condition and when matching shapes vs. infant faces. Depressive symptoms were associated with slower RTs to neutral infant faces. LPP observations were enhanced overall to faces vs. shapes, and anxiety symptoms were associated with an enhanced LPP to infant distressed faces specifically in the infant cry auditory condition. The results highlight the potential utility of ERP measures of emotional reactivity for clarifying processes in the emergence internalizing symptoms in the peripartum period. This could be further clarified with longitudinal research probing the LPP to infant faces and distressed auditory cues across pregnancy and the postpartum period, as well as investigations of the possible differences across pregnant and non-pregnant people. Overall, this study sets the stage for examining to what extent measuring the LPP could aid in the early detection of internalizing symptoms for adults in the perinatal period.

Declaration of Competing Interest

The authors have no conflict of interest to disclose about the submitted findings. All authors declare that they have no conflicts of interest.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2023.108673.

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