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The Influence of Maternal Anxiety and Depression Symptoms on fNIRS Brain Responses to Emotional Faces in 5- and 7-Month-Old Infants

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Declarations of interest

None.

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Highlights

- fNIRS asymmetry of facial emotional processing was investigated in infants.
- fNIRS responses to emotional faces were not lateralized in 5- and 7-month-olds.
- Maternal anxiety and depression were not associated with infants' fNIRS asymmetry.
- Infants of mothers with higher depression symptoms had greater oxyHb in the left IFG.
- Maternal depression and early experiences may influence infants' emotion processing.

Abstract

Greater relative right (versus left) frontal cortical activation to emotional faces as measured with alpha power in the electroencephalogram (EEG), has been considered a promising neural marker of increased vulnerability to psychopathology and emotional disorders. We set out to explore multichannel fNIRS as a tool to investigate infants' frontal asymmetry responses (hypothesizing greater right versus left frontal cortex activation) to emotional faces as influenced by maternal anxiety and depression symptoms during the postnatal period. We also explored activation differences in fronto-temporal regions associated with facial emotion processing. Ninety-one typically developing 5- and 7-month-old infants were shown photographs of women portraying happy, fearful and angry expressions. Hemodynamic brain responses were analyzed over two frontopolar and seven bilateral cortical regions subdivided into frontal, temporal and parietal areas, defined by age-appropriate MRI templates. Infants of mothers reporting higher negative affect had greater oxyhemoglobin (oxyHb) activation across all emotions over the left inferior frontal gyrus, a region implicated in emotional communication. Follow-up analyses indicated that associations were driven by maternal depression, but not anxiety symptoms. Overall, we found no support for greater right versus left frontal cortex activation in association with maternal negative affect. Findings point to the potential utility of fNIRS as a method for identifying altered neural substrates associated with exposure to maternal depression in infancy.

Keywords: fNIRS, maternal depression, emotion processing, infants, cortical activation

The effects of maternal anxiety and depression symptoms on fNIRS cortical hemodynamic responses to emotional faces in 5- and 7-month-old infants

Offspring of anxious and depressed mothers are at increased risk for developing behavioral and emotional problems in infancy (Feldman et al., 2009), which may later develop into clinically significant internalizing disorders (Keenan, 2006). Infants' exposure to maternal anxiety and depression may contribute to experience-dependent fine-tuning of emotional brain systems in the first years of life (Leppänen, 2011; Leppänen & Nelson, 2009). Evidence for neurodevelopmental embedding of maternal depression and anxiety is therefore a growing area of inquiry (Aktar & Bögels, 2017; Porto, Nunes, & Nelson, 2016), that may elucidate mechanisms linking parental risk with maladaptive outcomes in children, and offer unique biomarkers that can aid in early detection and intervention. To contribute to this line of work, we explored connections between maternal depression and anxiety symptoms and infants' neural responses to emotional facial expressions using functional near infrared spectroscopy (fNIRS). Based on substantive literature demonstrating associations between maternal depression and infants' EEG-based frontal asymmetry patterns, we specifically tested whether patterns of frontal asymmetry would be associated with exposure to maternal depression and anxiety. We also explored connections between maternal depression and anxiety and activation in key frontal and temporal regions of interest, previously implicated in facial and emotion processing. Thus, the present study aimed to contribute to the current body of knowledge about by considering the influence of maternal depression and anxiety exposure on neurodevelopmental underpinnings of emotional face processing in infancy.

Substantive work has demonstrated links between maternal depression and anxiety and altered neural function in infants. Most studies to date have used EEG, which is non-invasive, and given tolerance for motion, is well suited to assess neural function in infants. Prior work in children and adults has demonstrated greater relative right versus left frontal EEG activation, as indicated by greater left versus right alpha power, referred to as frontal asymmetry, in association with depression exposure (Davidson, 1988). Greater relative right versus left frontal cortex activation is theorized to underlie greater tendencies to show negative emotion, negative affect and avoidance (Fox, 1991), which may increase susceptibility to clinically significant mood and anxiety disorders. Relative to infants of non-depressed mothers, infants of depressed mothers have shown greater relative right versus left frontal alpha asymmetry at rest in numerous studies (see Field & Diego, 2008, for a review). Effects are shown to appear as early as the first month of life, and persist until at least early childhood (Diego, Jones, & Field, 2010; Field et al., 2004; Thibodeau, Jorgensen, & Kim, 2006).

Most work has investigated frontal alpha asymmetry in the context of a "resting state" measure, in which EEG is recorded while children are not explicitly engaged in a cognitive task. A limited number of studies have also tested for frontal alpha asymmetry while infants view salient emotional stimuli, such as to emotional facial expressions. Building off work in resting EEG studies, it has been theorized that individual differences in frontal asymmetry to emotional faces may signal individual differences in emotion processing. Specifically, greater right versus

left activation to facial expressions may indicate greater avoidance or negative affect experienced during its processing, which may serve as a neural marker for later affective risk. As a means for potentially identifying intergeneration pathways to risk for affective problems, a number of studies have examined associations between maternal depression exposure and frontal asymmetry patterns when infants view salient or emotional facial expressions. In one study, infants of depressed mothers with high levels of intrusive behavior have shown greater relative right frontal asymmetry when viewing sad versus happy expressions to strangers' facial expressions (Diego et al., 2002). Greater relative right versus left frontal activation has also been observed when infants of depressed mothers view images of their mothers face showing various emotional expressions (Diego et al., 2004) or engage in playful interactions with their mothers (Jones, Field, Fox, Davalos, & Gomez, 2001).

Although EEG provides excellent temporal resolution, spatial precision is limited due to volume conduction of electrophysiology activity throughout the brain, surrounding tissue, and skull. In recent years there is growing usage of fNIRS in infant samples, given its greater tolerance of motion (as compared with fMRI), and greater spatial specificity (as compared with EEG), such that neural activation patterns can be localized to specific cortical regions (Vanderwert & Nelson, 2014). fNIRS is an optical imaging technique that measures changes in concentrations of oxygenated, deoxygenated, and total hemoglobin (oxyHb, deoxyHb, and totalHb) in cortical areas, providing an indirect measurement of neural activity (Gervain et al., 2011).

A growing number of studies have applied fNIRS to understand the development of circuitries supporting facial emotion processing (see Maria et al., 2018, for a review). Some have examined infants' cortical activation patterns in response to mother's versus stranger faces. One study involving 6- to 9-month-old infants, demonstrated significant right frontal and temporal activation when infants viewed their own mother's face versus that of an unfamiliar woman (Carlsson, Lagercrantz, Olson, Printz, & Bartocci, 2008). Another study of 7- to 8-month-old infants showed bilateral temporal activation in response to mothers' faces versus a baseline non-face condition (Nakato, Otsuka, Kanazawa, Yamaguchi, Honda, et al., 2011).

A separate set of studies have examined cortical activation when infants view positive and negative facial emotion expressions. The results on the extent of fNIRS based frontal activation patterns to emotional facial images are mixed. In one study, 7-month-old infants indicated greater right frontal activation when infants were viewing videos of their mothers' smiling facial expressions in contrast to their mothers' neutral faces (Fox, Wagner, Shrock, Tager-Flusberg, & Nelson, 2013), In another study, 7-month-olds characterized as having a low negative emotionality temperament showed increased left prefrontal cortex activation in response to happy faces versus a neutral baseline video (Ravicz, Perdue, Westerlund, Vanderwert, & Nelson, 2015). In a separate study, 9- to 13-month-old infants showed greater medial prefrontal activation when viewing video clips of the own mother versus an unfamiliar woman smiling (Minagawa-Kawai et al., 2009).

A related question concerns the involvement of key temporal regions in infants' processing of facial emotions. Data on temporal lobe involvement is also mixed. For example, infants between 7 and 8 months of age showed greater left temporal superior temporal sulcus (STS) activation in response to happy faces and right STS activation in response to angry faces versus a non-face condition (Nakato, Otsuka, Kanazawa, Yamaguchi, & Kakigi, 2011). However, in another study of younger, 5-month-old infants, only weak activation for temporal regions was

found, with much stronger activation over occipital cortical regions (Di Lorenzo et al., 2019). This suggests that specialization of key temporal circuitries associated with face processing of positive and negative facial emotions may develop over the first year of life.

Therefore, data thus far suggests that fNIRS is a promising tool for understanding the neurodevelopmental processes underlying emotion processing in infants. However, there are outstanding questions on whether similar frontal asymmetry described in EEG work (greater right versus left frontal cortex activation to negative versus positive emotions) are also registered with fNIRS. Given enhanced spatial localization to frontal brain regions, fNIRS based patterns of frontal asymmetry would bolster theory that right versus left frontal activation varies according to early social input (maternal emotion exposure) and may also signal affective risk.

An additional outstanding question concerns the involvement of key temporal cortical regions when infants process emotional faces. Data thus far indicate mixed results, and significant variation across age. Part of the problem may be the lack of consideration of early environmental risk factors that may contribute to individual differences in activation. Indeed, the majority of work has focused on identifying normative neurodevelopmental patterns elicited with fNIRS.

Our goal was to use fNIRS to further address these questions, to better understand how maternal negative affect, including depression and anxiety symptoms, influence neural correlates of facial emotion processing during infancy. We specifically tested for influence on frontal asymmetry patterns, and in activation patterns of key frontal and temporal cortical regions of interest known to subserve salient emotional and facial input. We had several specific hypotheses. First, we expected that infants of mothers who reported higher levels of negative affect would show greater right versus left frontal activation, especially in ventral (more orbitofrontal) regions. Following findings from EEG work, we expected that frontal asymmetry would be most pronounced when infants viewed negative versus positive facial emotional expressions. Next, we expected that there would be significant associations between maternal depression and anxiety and key temporal regions known to subserve facial and emotional processing.

Depression and anxiety symptoms are highly comorbid (Pawluski, Lonstein, & Fleming, 2017). Therefore, we focused on the influence of maternal negative affect in our primary hypotheses. However, on an exploratory basis, we questioned whether there may be differential effects in the influence of maternal depression and anxiety on infants' neural responses to facial emotions. This was motivated by prior work showing mothers with depression versus anxiety exhibited variations in their emotional expression to infants. For example, maternal depression has been associated with lower positive affect, greater emotional withdrawal and/or higher levels of anger than non-depressed mothers (Aktar, Colonnesi, de Vente, Majdandžić, & Bögels, 2017; Beck, 1998; Murray, Halligan, & Cooper, 2010; Stanley, Murray, & Stein, 2004), whereas maternal anxiety has been associated with greater displays of fear but not necessary reduced positive affect (Weinberg, Beeghly, Olson, & Tronick, 2008). Guided by this behavioral literature, we hypothesized that maternal depression (which may manifest as reduced positive affect and greater anger) might be more correlated with infants' processing of positive and angry emotional faces. In contrast, we expected that

maternal anxiety might be more strongly correlated with infants' neural activation patterns when processing fearful emotional expressions.

Methods

Participants

Mother-infant dyads were recruited from a community sample in the greater Boston area to participate in a longitudinal study of emotion processing. A total of 43 5-month-olds (145.9 ± 8.3 days; range 120-160) and 48 7-month-olds (204.2 ± 9.5 days; range 183-218) and their mothers were included in the final sample. An additional 20 5-month-olds and 33 7-month-olds were tested but fNIRS data were excluded for the following reasons: more than 25% of channels were rejected for artifacts (5-month-olds: n=9; 7-month-olds: n=17), poor cap placement exceeding 1.5 cm deviation from ideal in any direction (5-month-olds: n=5, 7-month-olds: n=10), equipment/technical malfunction (5-month-olds: n=2, 7-month-olds: n=5), cap refusal (5-month-old: n=1, 7-month-old: n=1), and insufficient number of trials completed (5-month-olds: n=3). Additionally, 3 participants (5-month-olds: n=3) were excluded due to maternal self-report of medication use during pregnancy (opiate antipsychotic), 2 participants (5-month-old: n=1, 7-month-olds: n=2) were excluded due to subsequent ASD diagnosis reported at the 2- or 3-year follow-up, and 9 participants (5-month-olds: n=5, 7-month-olds: n=4) due to missing data on maternal anxiety and depression symptoms.

All participants were typically developing infants born full-term, with no known history of pre- or perinatal complications, vision problems, or developmental delay. The 5- and 7-month-olds groups were comparable in terms of all socio-economic and demographic characteristics analyzed: maternal age, maternal education, marital status, ownership of the house, total family income in the past 12 months, infant gender, infant race and type of delivery. Differences between groups were explored by means of independent sample t-tests and chi-square tests (Table 1). Written informed consent was obtained from all parents before the study sessions. The experimental protocol was approved by the local Institutional Review Board.

Materials and Procedure

Maternal Depression and Anxiety Symptoms. Mothers had the option to complete assessments of depression and anxiety electronically, through a secure link, or via paper copies

by having the assessments mailed to then. Assessments were delivered prior to the laboratory session. If not complete on the day of the session, mothers were asked to complete them during their session. The majority of mothers completed the questionnaires one day prior to the session, but ranged from 36 days prior to or 15 days following the session. Mothers symptom reports of depression and anxiety symptoms were significantly positively correlated (r = .642, p <.001).

State-Trait Anxiety Inventory. Maternal trait anxiety was assessed using the trait component of the State-Trait Anxiety Inventory (STAI; Spielberger, 1989). Trait anxiety is considered a stable characteristic in the individual, reflecting a predisposition to appraise situations as stressful and to respond with anxiety to perceived threats (Meades & Ayers, 2011). The inventory has been widely used and validated against clinical interviews in perinatal populations and during the first postnatal year (Meades & Ayers, 2011). The STAI scale has also been associated with depression, and some authors argued that it measures negative affect in general (for example, (Balsamo et al., 2013)**.** In the present sample, maternal STAI mean score was 35.3 ± 9.4; range 21-62, which according to established norms, ranges from "no or low anxiety" to "high anxiety". There were no significant differences between 5-month-olds (35.6 ± 9; range 23-60) and 7-month-olds (35.1 ± 9.8; range 21-62) groups (t (89) = .229, p = .819).

Beck Depression Inventory. Maternal depression symptoms were assessed using the Beck Depression Inventory (BDI; Beck, Steer, & Carbin, 1988). The BDI is one of the most used instruments in research on non-clinically depressed samples, as a screening tool and to study the impact of maternal depression symptoms across pregnancy and the postpartum period (Lovejoy, Graczyk, O'Hare, & Neuman, 2000). In the current sample, maternal mean BDI score was 6.5 ± 4.7; scores ranged from 0 to 22; or from "none" to "moderate" depression. There were no significant differences between 5-month-olds (6.7 ± 4.5; range 0-20) and 7-month-olds (6.3 ± 4.29; range 0-22) groups (t (89) = .497, p = .621) on maternal depression scores.

functional Near-infrared Spectroscopy (fNIRS). A Hitachi ETG-4000 multi-channel system was used in the study (ETG-4000, Hitachi Medical Corporation, Tokyo, Japan). A flexible head cap containing a probe with the near-infrared light optodes (18 emitters and 15 detectors) was customized for this experiment, with the inter-optode distance fixed at 3.0 cm. The probe has a total of 46 channels consisting of emitter-detector pairs, as shown in the layout of the Figure 1A. Prior to recording, the fNIRS cap was placed on the infant's head, covering an area over the frontal, parietal and temporal cortices (Figure 1B). Near-infrared light at 695 and 830 nm was transmitted via optical fibers onto the scalp at the positions of the emitters. The light at both wavelengths was absorbed by the deoxyHb and the oxyHb respectively, and the attenuated light was measured by the detectors. The data was collected at every 100 ms (10 Hz).

Stimuli and design. Color images of female models exhibiting high-intensity happy, fearful, and angry facial expressions, selected from the NimStim Face Stimulus Set (Tottenham et al., 2009) were used in the experiment. The experiment was presented in a block design using the E-Prime Application Suite for Psychology (E-Prime 2.0, Psychology Software Tools, Sharpsburg, PA, USA). A maximum of 30 blocks were presented, with up to 10 blocks of each of the three stimulus types (happy, fearful and angry faces). Within each block, five different female models portraying the same emotional category were presented for 1s, with a randomly generated 200–400 ms inter-stimulus interval between each face, followed by an abstract video of geometric shapes shown for 10s. Including the presentation of the faces, the abstract video, and the inter-stimulus intervals between each face, each block lasted a total of 16 s; see Figure 2. The order of blocks of emotional faces presentation was counterbalanced across participants. The experiment was performed in a sound attenuated room with standardized dimmed lights. Infants completed the task while sitting on their caregiver's lap, at approximately 60 cm from a 17-inch computer screen. Parents were instructed to wear a visor to shield their view of the computer screen, thereby preventing them from cueing infants to the visual stimuli. They were also asked to refrain from speaking and interacting to the infant during the session. An experimenter sat next to the infant and parent during the entire task and redirected the infant's attention to the monitor before the start of the trials if necessary. Session breaks were also taken if necessary. If the infant became unsettled or distressed, the experiment was stopped. The sessions were video-recorded to assess infants' attention to the stimuli.

Anatomical localization. The regions of interest (ROI) were defined by averaged anatomical localization for each channel based on age-appropriate MRIs as previously described ([redacted], under review). Briefly, MRI templates were selected from a database (Richards, Sanchez, Phillips-Meek, & Xie, 2016; Sanchez, Richards, & Almli, 2012) with age and head circumference matched to the experimental group. Previously described geometrical methods were used to project channel location to the cortical regions (Lloyd-Fox et al., 2014). A total of sixteen ROIs were divided over the frontal, parietal and temporal cortices, each formed by 2, 3, or 4 channels. Frontal regions were divided in ventral and dorsal Superior Frontal Gyrus (vSFG; dSFG), Inferior Frontal Gyrus (IFG), Middle Frontal Gyrus (MFG), and dorsal Middle Frontal Gyrus (dMFG). Temporal and parietal regions were defined as Inferior Temporal Gyrus (ITG), Middle Temporal Gyrus (MTG), Superior Temporal Gyrus (STG), Temporal-parietal junction area (TPJ). For visualization purposes, channels and ROIs locations were estimated on an average 7.5 month-old MRI template (Richards et al., 2016) (Figure 3).

Data processing. Video recordings of each session were coded by researchers who were blind to the emotional category, using the SuperCoder software (SuperCoder 1.7.1, Purdue University, West Lafayette, IN, USA). Consistent with prior research in infants (Lloyd-Fox et al., 2017; Perdue et al., 2019; Ravicz et al., 2015), blocks were excluded if the infant failed to look at the screen for at least 50% of the entire block in which stimuli were presented. This ensured that the hemodynamic responses were derived from blocks in which infants provided their full attention. A randomly selected 20% of the sample was double coded, with an average inter-coder agreement of 95% for block inclusion decision. Based on previous work (for example, Ravicz et al., 2015), an a priori threshold of three blocks for each emotion category was used for inclusion in the study.

HOMER2 (Huppert, Diamond, Franceschini, & Boas, 2009), a MATLAB (The MathWorks, Natick,

Massachusetts) package, was used to process the fNIRS data. The fNIRS raw data was converted to optical density units and wavelet motion correction with an interquartile range of 0.5 was used to correct motion artifacts (Behrendt, Firk, Nelson, & Perdue, 2018). Slow drift and cardiac artifact were filtered using a 0.05-0.80 Hz bandpass filter. The filtered, motion-corrected data was used to calculate the concentration variance of each hemoglobin chromophore (oxyHb, deoxyHb, totalHb) using the modified Beer–Lambert law and assuming a pathlength factor of 5 (Duncan et al., 1995). Chromophore concentrations were baseline corrected using the 2 s prior to stimulus presentation.

The oxyHb is the most consistent chromophore across infant studies (Lloyd-Fox, Blasi, & Elwell, 2010), thus the statistical analysis was focused on oxyHb responses. For each infant, the hemodynamic responses of the accepted blocks were averaged for each channel and emotion condition. Then, grand average oxyHb waveforms were calculated across all participants and ROIs for the overall hemodynamic responses for visual inspection. The time window of ± 2 s from the grand mean oxyHb peak was selected for analysis. This window included the range of maximum changes (or amplitude) in concentration for oxyHb. The mean peak oxyHb activation for 5- and 7-month-olds was at 8.6 seconds post stimulus onset. The mean oxyHb activation was calculated between 6.6 and 10.6 seconds for each participant in each condition and ROI.

Results

Missing data and preliminary analyses. Each ROI was inspected for extreme and outlying values, defined as oxyHb values falling 3 times outside of the inter-quartile range, and winsorized prior to running analyses. In total 19 oxyHb values were winsorized. All models were run with and without the inclusion of extreme values; no differences in results were observed. We report results from models including winsorized values.

As is typical in neuroimaging studies involving infants, 63% (91of 144) of infants provided valid fNIRS data for analyses. The average number of blocks provided by infants was 26.62 (range 11 to 30 blocks). Prior to analyses, we examined whether maternal depression and anxiety symptoms was associated with likelihood of an infant having missing data (due to refusal to participate in task, due to insufficient signal quality related to excessive motion, or due to providing too few valid blocks to be included in analyses). No significant associations were observed between (p values > .05). For infants whose data was included in analyses, there were no significant associations between maternal depression and anxiety and the number of blocks

provided for the task (*p* values > .05).

Primary analyses. We ran a series of linear mixed models to examine the effects of maternal depression and anxiety symptoms on infant frontal asymmetry and cortical activation patterns to emotional faces. A diagonal covariance structure best fit the data in all models. Residuals of all models were visually inspected and confirmed as normally distributed. First, a principal components analyses was used to create a composite total negative affect score. The first factor was extracted from the PCA and used as the independent variable in subsequent analyses.

Our first model tested our hypothesis that maternal depression and anxiety would be associated with greater frontal asymmetry (greater right versus left frontal activation, specifically) in key frontal regions. We further hypothesized that this would be most pronounced for negative versus positive images. For all models, main effects of laterality, condition, maternal negative affect, and their interactions were tested. Child age and gender and family income were explored as covariates. Gender and family income were not significantly associated with cortical activation and was therefore not included in models. Child age was associated with cortical activation in one region (MFG, p = .03). There were no differences in results when age was not included in the model. Therefore, all results are reported without this covariate.

Results of models indicated no main effect of laterality, interaction between laterality and condition, interaction between laterality and maternal negative affect, or three-way interaction between laterality, condition, and maternal negative affect for all frontal regions (all p values > .05). Thus, we found no evidence for frontal asymmetry generally, or as varying as a function of maternal negative affect exposure to negative or positive images.

Our next question was whether maternal negative affect was associated with cortical activation more generally in frontal and non-frontal, temporal regions. To test this question, we replicated approaches in our in prior work with this same sample ([redacted], under review). For each regions of interest, oxyHb responses was entered as the dependent variable, emotional condition (happy vs. fearful vs. angry) was entered as within subject factors. We extended these prior models by added the composite negative affect score as a between-subjects continuous factor. To control for multiple comparisons, we applied an FDR correction to all models. As reported in prior work on this sample ([redacted], under review), there was a significant main effect of condition on infants' oxyHb values in the dSFG (*p* = .023). Additional main effects of condition emerged in our study for the dMFG (p = .033). However, neither of these results survived FDR correction for multiple comparisons.

In terms of the effects of maternal negative affect on infants' neural response to emotions, there was a significant main effect of maternal negative affect on oxyHb on the left IFG, *p* = .04, in that higher scores of maternal negative affect were associated with greater activation in this region. A significant interaction between condition and maternal negative affect emerged for the right STG, *p* = .022, which did not survive FDR correction, whereby greater maternal negative affect was associated with greater activation to angry faces (*r* = .334, *p* = .004) but not happy (*r* = -.118, *p* = .328) or fearful (*r* = -.008, *p* = .949) faces in this region.

Unique effects of maternal depression and anxiety. We were also interested in the potentially unique effects of depression and anxiety on infants' neural activation to facial emotions. To test

this question, we repeated the previous model but entered maternal depression or maternal anxiety scores as a between subjects variable. Results from the model including maternal anxiety revealed no significant main effect of anxiety (*p* values ranged from .218 to .928). No significant interactions emerged between maternal anxiety and condition in oxyHb activation in the STG (*p* = .054 to 968).

However, results from the model including maternal depression revealed a main effect of maternal depression on oxyHb on the left IFG, *p* = .006, which survived FDR correction. Post hoc inspections revealed that this effect was driven by a significant positive association between maternal BDI scores and oxyHb responses (*B* = .139, *p* = .007) in the IFG, which survived FDR correction, see figure 4. A significant interaction between condition and maternal depression emerged for the right STG, *p* = .024, which did not survive FDR correction, whereby greater maternal depression was associated with greater activation to angry faces (*r* = .304, *p* = .020) but not happy (*r* = -.120, *p* = .319) or fearful (*r* = -.088, *p* = .465) faces.

Discussion

In the present study, we applied multichannel fNIRS as a tool to investigate associations between maternal depression and anxiety symptoms and 5- and 7-month-old infants' neural responses to positive and negative facial expressions. Building off prior EEG work , we expected that higher maternal negative affect would be associated with infants' frontal asymmetry to emotional faces. We specifically hypothesized higher maternal negative affect would be associated with greater right versus left frontal activation, specifically in anterior cortical regions, and most strongly when infants viewed negative emotional faces. However, this hypothesis was not supported.

We also expected that maternal negative affect would be associated with activation levels in other key frontal and temporal cortical regions of interest. Results indicated that higher maternal negative affect, and specifically maternal depression, was associated with infants' greater activation in the left inferior frontal gyrus. Further, higher maternal negative affect, and specifically depression, was associated with greater activation in the right superior temporal gyrus, specifically to angry, but not fearful or sad faces, although the effect size was small and did not survive correction.

Finally, we explored whether maternal depression and anxiety might have explain unique variance in cortical activation patterns. We hypothesized that anxiety would more strongly predict neural activation patterns to fearful images, whereas depression would more strongly predict activation to angry and happy faces. This hypothesis was partially supported. We found no significant associations between maternal anxiety and neural activation for any region. Yet, maternal depression was specifically associated with infants' neural activation (in temporal regions) to angry faces, but not happy faces. This effect size was small and did not survive correction.

This is one of the first studies to use fNIRS to test associations between maternal depression and anxiety symptoms and neural activation patterns in infants. In terms of specific effects, we found that higher levels of maternal depression were associated with greater activation in the left inferior frontal gyrus. Effects did not vary by child age, indicating that neurodevelopmental alterations secondary to maternal depression exposure were evident by at least 5 months of age. Unlike prior work involving clinical samples, our sample involved mothers with normative

variability in maternal depression and anxiety symptoms. Findings suggest that even when not at a clinically significant level, maternal depression can have a significant impact on shaping cortical development, as early as 5 months of age.

Effects of maternal depression were primarily localized to the inferior gyrus. In addition to speech and semantic processing, the IFG is largely known for its support of executive processes, especially involving making judgements of, making or comparisons between stimuli (Petrides, 2005). A growing body work supports the IFG's involvement in self-referenced or other-referenced social processes, including the categorization of memory encoding (Frühholz, Fehr, & Herrmann, 2009; Frühholz & Grandjean, 2013) and evaluation of emotional stimuli (Marumo, Takizawa, Kawakubo, Onitsuka, & Kasai, 2009). The IFG has also been specifically implicated in the development of empathy starting in infancy (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). Neural models reveal subregions of the inferior gyrus, which includes a lateral zone (situated ventral to Broca's area) in the pars orbitals and a ventral zone in the frontal operculum of the inferior frontal gyrus (Dapretto et al., 2006). These subregions have been shown to support convergence between networks that support processing of semantic and emotional content across various modalities of communication (Belyk, Brown, Lim, & Kotz, 2017). The left IFG (which is where we found significant effects) more so than right, appears to be involved in integrating and performing executive processes on social or emotional information, representing in posterior cortices following sensory processing (Frühholz & Grandjean, 2013).

Our findings suggest that maternal depression may alter neural circuits in infants that associated with discriminating different facial expressions of emotion. This may further indicate that higher maternal depression leads to greater attunement to facial emotional cues, which starts in the first months of life, when infants begin to attend to facial emotion expressions. Whether this greater attunement is adaptive or maladaptive at this early stage in life is an open question. Our findings implicating the IFG in emotion processing are consistent with two additional studies involving infants. In one, increased inferior frontal cortex activation was observed when infants of 7 months of age (which parallels ages in our study) viewed facial emotions (Krol, Puglia, Morris, Connelly, & Grossmann, 2019). In a second study, PET was used to investigate neural correlates of face processing in 2-month-olds. Specifically, infants showed increased activation of the IFG (as well as other face sensitive cortical regions, including the fusiform face area), when viewing neutral female faces (Tzourio-Mazoyer et al., 2002). fMRI work involving adults has also demonstrated increased IFG activation during facial emotion processing (Sabatinelli et al., 2011), emotion recognition and empathy (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Seitz et al., 2008; Shamay-Tsoory et al., 2009).

In terms of the direction of effects, infants whose mothers reported higher levels of depression showed greater IFG activation to both positive and negative emotions. Increased activation of the IFG has also been documented in adults with diagnoses of depression. Specifically, depressed adults showed greater IFG activation during an emotion processing task when compared with non-depressed adults (Fitzgerald, Laird, Maller, & Daskalakis, 2008). The increased IFG activation may signal a precursor to maladaptive emotional adjustment, which may then increase risk for later life depression. Longitudinal follow up of these children will be an important direction to test this hypothesis.

Unexpectedly, effects of maternal depression on neural activation in temporal brain regions

were of small size and did not survive correction for multiple statistical comparisons. These specific effects were observed in the STG, which, along with other regions in the temporal lobe, including the TPJ, subserve emotional face processing and general social processing respectively (Leppänen & Nelson, 2009). Consistent with hypothesis, associations between maternal depression and activation in the superior temporal gyrus were only observed for angry faces, but not positive or fearful faces. However, given the modest effect size, this result should be interpreted with caution.

Also noteworthy is that all associations between our composite estimated of maternal negative affect and infant neural activation were specifically driven by mother's reports of maternal depression, but not anxiety. Effects were not driven by a difference in severity of depression versus anxiety symptoms, as highest scores of depression fell in the moderate range, whereas highest scores of anxiety fell in the severe range. Our findings therefore have critical implications for early identification of risk, such that infants reared by mothers who report even moderate levels depression may be at higher risk for maladaptive neurodevelopmental and socio-emotional outcomes, even when compared with mothers who report severe levels of anxiety.

Several limitations associated with the research approach should be mentioned. The task we used in this study involved static images of emotional faces. A valuable future direction will be to present more dynamic displays of facial emotions (i.e. from neutral to happy or angry expressions) and to directly evaluate mother-infant interactions. In addition, future research should examine the role of maternal touch, responsiveness, and affective displays as accounting for associations between maternal depression and infant neural response patterns. The present sample showed little variation regarding social and economic aspects. While such homogeneity is desired for testing the efficacy of the method, it limits the exploration of other aspects that might mediate the risk or protection of infants' exposure to maternal anxiety and depression, such as economic status and cultural differences (Aktar & Bögels, 2017). Hence, our findings may not be generalizable to other populations.

Furthermore, our findings revealed variability in key inferior frontal cortical regions in association with maternal depression. There may be specific subregions of the inferior frontal cortex, or other subcortical regions, that contributed to activation patterns. However, these are not detectable using the spatial resolution provided by fNIRS. Analyses were only limited to oxyHb response patterns, but future work should also consider effects on signal changes associated with deoxyHb. Finally, depression and anxiety symptoms were assessed only at one time point in this study, using self-report instruments which have inherent reporting bias. Given the risks associated with prenatal and or chronic maternal affected disorders, the continuity of maternal symptoms during distinct phases of infants' development should be considered in association with neurodevelopmental trajectories (Lusby, Goodman, Bell, & Newport, 2014; Qiu et al., 2015; Soe et al., 2016).

In summary, results from this study support an association between maternal depression symptoms and differential cortical hemodynamic responses (primarily in the left IFG) while infants observed emotional faces. These findings contribute to the elucidation of neural underpinnings that may signal increased risk for atypical emotional development in the first year of life. Findings hold important implications for understanding how maternal mental health may influence infants' early neural development, offer new methods for early risk

detection, and contribute to efforts to develop highly effective and targeted intervention programs for vulnerable families.

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Table 1. Demographic variables and characteristics of participants

	Total (n=91)	5-month-olds (n=43)	7-month-olds (n=48)	*P*
Maternal descriptive				
Maternal age[a] (years)	32.70 ± 4.09	32.73 ± 4.29	32.66 ± 3.95	.935
Masters /PhD or equivalent	63 (69.3)	34 (79.1)	29 (60.4)	.213
Married/Cohabiting	90 (98.9)	43 (100)	47 (97.9)	.509
Ownership of the house				.450
Owned	58 (63.7)	26 (60.5)	32 (66.6)	
Rented	31 (34.1)	17 (39.5)	14 (29.1)	
Total family income in the past 12 months[b]				.359
U$100,000 and greater	63 (75)	31 (79.5)	32 (71.1)	
U$50,000 through U$99,999	16 (19)	6 (15.4)	10 (22.2)	
Less than U$49,999	4 (4.7)	2 (5.1)	2 (4.4)	
Infant descriptive				
Male	49 (53.8)	22 (51.2)	27 (56.3)	.632
White[a]	75 (82.4)	36 (83.7)	39 (81.3)	.557
Type of delivery				.494
Vaginal	69 (75.8)	34 (79.1)	35 (72.9)	
C-section	22 (24.2)	9 (20.9)	13 (27.1)	

Note: Data presented as No(%) or mean±SD.
[a] Missing data in 1 participant.
[b] Missing data in 7 participants.

Figure 1. (to appear in color) A) fNIRS probe layout. fNIRS channels (labeled by numbers) corresponding to 46 emitter-detector pairs. B) Probe on 5-month-old infant during study session.

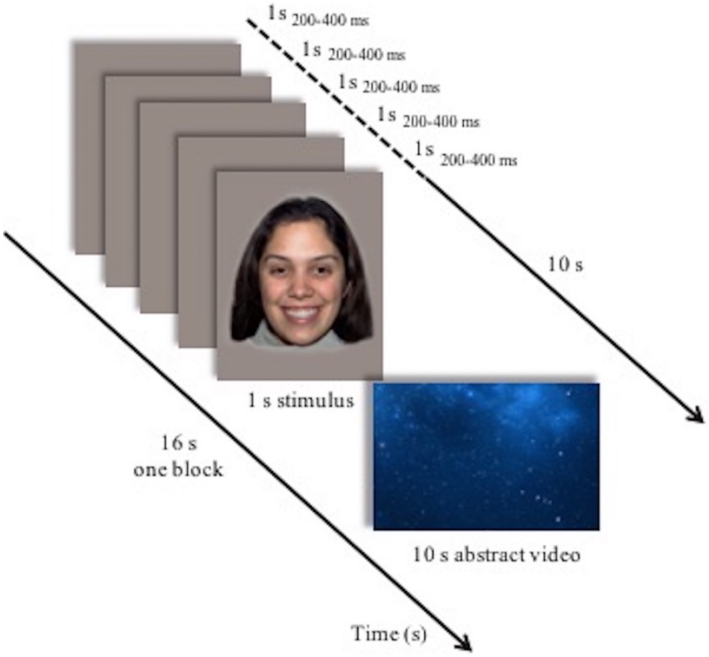

Figure 2. (to appear in color) Schematic diagram of experimental design. Each block included five images of a different model portraying the same emotional expression (happy, fearful or angry). Each image was presented for 1 s with a randomly generated 200–400 ms inter-stimulus time, followed by a 10 s abstract video, totalizing 16 s for each block. The experiment included 30 blocks in total, 10 of each emotional category. Stimuli reproduced with permission (Tottenham et al., 2009).

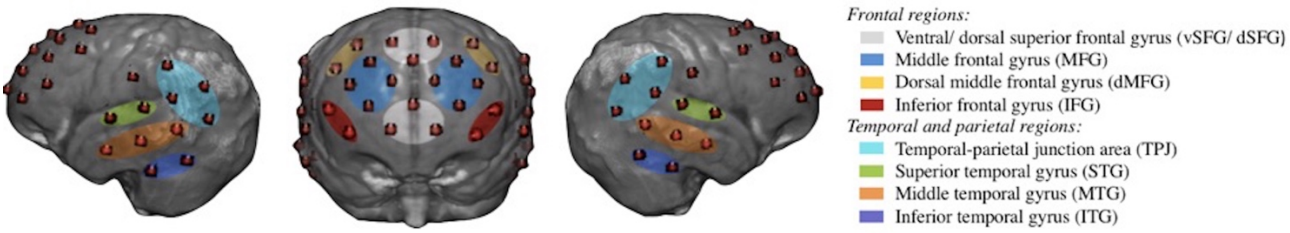

Figure 3. (to appear in color) Modeled locations of fNIRS channels and ROIs. Frontal and lateral views computed on an average 7.5 month-old MRI template (Richards et al. 2016).

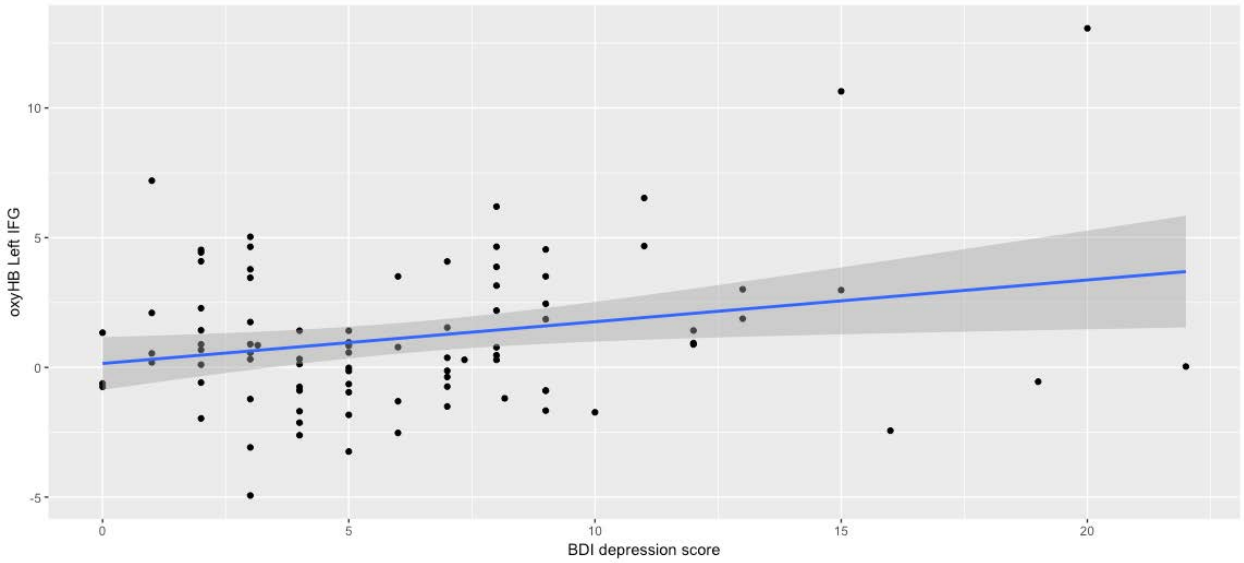

Figure 4. Positive association between maternal depression scores (BDI) and infants' oxyHb responses to emotional faces in the left IFG.