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NEURAL BASES OF EMOTIONAL FACE PROCESSING IN INFANCY:
A FUNCTIONAL NEAR-INFRARED SPECTROSCOPY STUDY

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A FUNCTIONAL NEAR-INFRARED SPECTROSCOPY STUDY

Thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Medicine and Health Sciences – Neurosciences of the Pontifical Catholic University of Rio Grande do Sul.

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My heart leaps up when I behold
A rainbow in the sky:
So was it when my life began;
So is it now I am a man;
So be it when I shall grow old,
Or let me die!
The Child is father of the Man;
And I could wish my days to be
Bound each to each by natural piety.
William Wordsworth (1802)

To the children, the parents of humanity.

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ABSTRACT

The neural bases of facial emotion processing in infancy are largely unknown. The environmental factors that may impact facial processing and emotion recognition along the developmental course are also not clearly understood. However, early experiences, particularly involving consistent exposure to familiar caregiver faces, are believed to influence this course. The aim of this study was to investigate the neural correlates of infants' emotional face processing using functional near-infrared spectroscopy (fNIRS), and examine the potential influence of infants' early emotional experiences, indirectly measured by investigating maternal anxiety symptoms. Participants were 29 typically developing 5-month-old infants and their mothers, recruited from a community sample from the Boston greater area, MA, USA. Maternal anxiety was assessed using the trait component of the State-Trait Anxiety Inventory. Infants observed static visual images of a female model portraying happy and fearful expressions, while hemodynamic brain responses were measured using fNIRS. The oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) responses over frontal, parietal and temporal areas were compared for the emotional expressions in infants of mothers reporting low and high levels of anxiety symptoms. Results revealed a significant main effect of emotion (p=.022), driven by greater oxyHb concentration responses for happy compared to fearful faces. There was also a main effect of region (p=.013) induced by a significantly greater oxyHb concentration in temporal compared to frontal cortical regions (p=.031). Additionally, a significant three-way interaction between emotion, hemisphere and anxiety was observed (p=.037). Planned comparisons revealed that infants of high-anxious mothers showed significantly greater left hemispheric activation of oxyHb to happy faces when compared with right (p=.040) and left (p=.033) hemispheric activation of oxyHb to fearful faces. These findings possibly indicate that 5-month-olds can discriminate happy from fearful faces, evinced by the greater activation for the former. The greater activation in temporal as compared to frontal areas was discussed in relation to the ontogenesis of face processing and emotion recognition neural networks. The enhanced response to happy versus fearful faces observed in infants of high-anxious mothers can be related to the presumed altered emotional environment experienced by these infants, compared to that of infants of low-anxious mothers. Therefore, maternal anxiety levels appeared to moderate infants' hemodynamic brain responses to emotional faces.

Keywords: Infants, face processing, emotion, fNIRS, maternal anxiety.

RESUMO

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As bases neurais do processamento da emoção facial na infância são amplamente desconhecidas. Os fatores ambientais que podem afetar o processamento facial e o reconhecimento emocional ao longo do curso de desenvolvimento também são pouco compreendidos. No entanto, acredita-se que as experiências iniciais, particularmente envolvendo exposição repetida a faces emocionais dos cuidadores, influenciem esse curso. O objetivo deste estudo foi investigar os correlatos neurais do processamento de faces emocionais em lactentes usando a espectroscopia funcional no infravermelho próximo (fNIRS), e examinar a possível influência das experiências emocionais iniciais dos lactentes, indiretamente medida pela investigação de sintomas de ansiedade materna. Foram avaliadas 29 crianças de 5 meses de idade e suas mães, recrutadas de uma amostra da comunidade de Boston, EUA. A ansiedade materna foi avaliada usando o componente traço do Inventário de Ansiedade Traço-Estado (STAI-T). Os lactentes observaram imagens visuais estáticas de faces femininas retratando expressões de alegria e medo, enquanto as respostas hemodinâmicas corticais foram medidas usando fNIRS. As respostas de oxihemoglobina (oxiHb) e deoxihemoglobina (deoxiHb) nas áreas frontais, parietais e temporais foram comparadas entre as faces emocionais, e entre filhos de mães com níveis altos e baixos de sintomas de ansiedade. Os resultados demonstraram efeito principal significativo da emoção ($p=0,022$), evidenciado pelo aumento na concentração de oxiHb para faces de alegria em comparação a faces de medo. Ademais, observou-se efeito principal significativo da região ($p=0,013$), induzido por maior concentração de oxiHb nas regiões corticais temporais em relação às regiões corticais frontais ($p=0,031$). Além disso, houve uma interação significativa entre emoção, hemisfério e ansiedade ($p=0,037$). As análises revelaram que filhos de mães com alta ansiedade demonstraram uma resposta hemodinâmica significativamente elevada no hemisfério esquerdo para faces de alegria, em comparação com faces de medo no hemisfério direito ($p=0,040$) e esquerdo ($p=0,033$). Os resultados indicam que lactentes de 5 meses discriminaram faces de alegria em comparação com faces de medo, evidenciado pela maior ativação para a primeira. A maior ativação nas regiões temporais em relação às áreas frontais foi discutida em relação à ontogênese do processamento facial e às redes neurais de

reconhecimento emocional. A resposta mais acentuada, comparando faces de alegria e medo observada nos filhos de mães com alta ansiedade, pode estar relacionada a alterações no ambiente emocional dessas crianças em comparação com os filhos de mães com baixa ansiedade. Assim, os níveis de ansiedade materna parecem moderar as respostas cerebrais hemodinâmicas das crianças às faces emocionais.

Palavras-chave: lactentes, processamento facial, emoção, fNIRS, ansiedade materna.

LIST OF ABBREVIATIONS AND SYMBOLS

ACC: anterior cingulate cortex

BCH: Boston Children's Hospital

BDI: Beck Depression Inventory

BOLD: blood oxygenation level-dependent

CES-D: Center for Epidemiological Studies Depression Scale

deoxyHb: deoxyhemoglobin

DLPFC: dorsolateral prefrontal cortex

EEG: electroencephalography

EPDS: Edinburgh Postpartum Depression Scale

ERP: event-related potential

FA: frontal asymmetry

FFA: fusiform face area

fMRI: functional magnetic resonance imaging

fNIRS: functional near-infrared spectroscopy

HPA: hypothalamic-pituitary-adrenocortical

Hz: hertz

HRF: hemodynamic response function

IDM: infants of depressed mothers

INDM: infants of non-depressed mothers

LCN: Laboratories of Cognitive Neuroscience

MPFC: medial prefrontal cortex

MRI: magnetic resonance imaging

Nc: negative central

nm: nanometers

OFA: occipital face area

OFC: orbitofrontal cortex

oxyHb: oxyhemoglobin

PET: positron emission tomography

PFC: prefrontal cortex

STAI-T: trait component of the State–Trait Anxiety Inventory

STAI: State–Trait Anxiety Inventory

STS: superior temporal sulcus

totalHb: total hemoglobin

vmPFC: ventromedial prefrontal cortex

11β-HSD2: 11β-hydroxysteroid dehydrogenase type 2

µM: µmolar

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1 INTRODUCTION

Faces are ubiquitous in human lives, conveying a wealth of relevant information. Configurational features within the face reveal aspects of a person's identity, gender, ethnicity and age. Facial expressions reflect the emotional states and communicate intentions that orient the behavior during social interactions. As humans are inherently social beings, accurate decoding of facial emotion expressions is considered fundamental for effective navigation in the social world (GROSSMANN; STRIANO; FRIEDERICI, 2007; LEPPÄNEN; NELSON, 2009).

Brain networks related to face and emotion processing emerge early in life, and are believed to be largely shaped by the environmental experiences. Cognitive neuroscience research should clarify how humans develop facial expression processing from early infancy, a knowledge that could be applied in interventions to counteract suboptimal development. While some preliminary results are available from neurophysiological studies, mainly relying on electroencephalogram (EEG) and event-related potentials (ERP) techniques, functional Near-Infrared Spectroscopy (fNRIS) has, to my knowledge, not yet been applied in the attempts to clarify the developmental course of facial expression processing in infants of 5 months of age. The influence of early emotional experiences has also not been explored using fNIRS. The here-presented work was undertaken to close this gap and to contribute to the literature by providing insights about localized brain responses to facial expressions in infants.

The interest in the study of face expressions dates back to Darwin (1872), as he observed that critical affective signals are transmitted through facial expressions, which in turn are promptly recognized, specifically serving as the first means of mother-infant interactions (DARWIN, 1872 cited in YOUNG-BROWNE; ROSENFELD; HOROWITZ, 1977).

> The movements of expression in the face and body, whatever their origin may have been, are in themselves of much importance for our welfare. They serve as the first means of communication between the mother and her infant; she smiles approval, and thus encourages her child on the right path, or frowns disapproval. We readily perceive sympathy in others by their expression; our sufferings are thus mitigated and our pleasures increased; and mutual good feeling is thus strengthened. The movements of expression give vividness and energy to our spoken words. They reveal the thoughts and intentions of others more truly than do words, which may be falsified (Darwin, 1872).

Faces are considered one of the most salient stimuli in the human social environment (TSAO; LIVINGSTONE, 2008). A number of facial expressions have been universally attributed to distinct emotional states. Ekman, Sorenson and Friesen (EKMAN, 1999; EKMAN; SORENSON; FRIESEN, 1969) have observed that humans in diverse cultures exhibit a similar capacity to express and recognize the emotional signals of facial expressions of happiness, surprise, fear, anger, sadness and disgust. The considered universal nature of such facial expressions has raised the hypothesis that humans have an evolutionary innate brain circuitry biased to attend to salient biologically cues from faces (LEPPÄNEN, 2004).

Adults have a highly specialized neural circuitry to process faces (KANWISHER; MCDERMOTT; CHUN, 1997). The neural substrates of face recognition and emotional processing are believed to be intensely integrated to process the relevant and vast amount of information conveyed by faces. Research in animal models, observation of patients with brain lesions, and adult neuroimaging studies congregate a substantial body of information regarding the complex brain circuitry implicated in emotional face processing that was reviewed hereinafter.

Developmental cognitive neuroscience research has shown that key components of face and emotional recognition systems begin to emerge early in life, influencing the development of visual areas that enable the fast detection of relevant cues from faces (LEPPÄNEN; NELSON, 2009). During infancy and childhood, the ability to process faces and decode emotional expressions develops gradually, and appears to reach adult capacity only around the beginning of the third decade of life (RIGHI; NELSON, 2013; SCHERF; SCOTT, 2012). However, during the first year of life, the development of visual orientation and discrimination of different facial expressions progresses significantly.

The capacity to discriminate face expressions is especially relevant for infants' early communications, before the onset of language abilities. Faces are a particularly salient stimulus in infants' lives, and starting as soon as the first hours after birth, empirical experiments have shown that neonates orient preferentially to faces, or face-like shapes compared to non-face-like stimuli (SIMION; GIORGIO, 2015). This phenomenon is believed to relate to an innate network that would facilitate the orientation towards conspecifics' faces, which in turn enhances the success of infants' interaction with the caregiver, essential for the newborns' survival.

The experience with faces impacts the developmental course of the face processing system. Likewise, early emotional experiences, particularly involving consistent exposure to familiar caregiver faces, are believed to influence the developmental course of the emotion

recognition capacities (LEPPÄNEN; NELSON, 2009; MONTAGUE; WALKER-ANDREWS, 2002).

Maternal facial expressions are usually the most prevalent human expressions in the infant's environment (MONTAGUE; WALKER-ANDREWS, 2002). Mother-infant interactions, including the systematic exposure to maternal expressions, constitute the primary environment for infants' emotional experiences (TRONICK, 1989), considered critically important to nurture mother-infant bonding, and to promote the foundation for the development of social and emotional skills (BOWLBY, 1988).

Conditions that affect maternal mental health potentially influence maternal behaviors and the extent to which their infants are exposed to faces and emotions. Maternal anxiety and depression are highly prevalent, and have been systematically related to detrimental effects in the offspring (FIELD, 2011; GOODMAN; GOTLIB, 1999). Infants of anxious and depressed mothers were observed to demonstrate atypical responses to face expressions, including less visual attention to faces (PICKENS; FIELD, 1995) and impaired emotional face discrimination (BORNSTEIN et al., 2011; FIELD; DIEGO; HERNANDEZ-REIF, 2009).

The majority of the studies in the perinatal period (i.e., from pregnancy through the first year postpartum) have focused on depression or on anxiety and depression together. Considerably less is known about the potential effects of anxiety in the offspring. Although anxiety and depression have several neurophysiological and behavioral aspects in common, there may be unique differences in symptom presentation that could affect the development of infants' face processing in distinct ways. While both disorders were correlated to disruption in mother-infant interactions and lower levels of positive emotions (FELDMAN et al., 1997; LOVEJOY et al., 2000; NICOL-HARPER; HARVEY; STEIN, 2007), different patterns of altered communications and of facial emotional expressivity may impact infants' face processing in singular ways.

Over the past several decades' behavioral studies have used different measures of attention and visual preference to infer aspects of recognition of emotional faces during development. Behavioral research has been complemented by neuroimaging findings, in infancy predominantly measuring changes in electrical activity, using EEG and ERP techniques. The EEG is a non-invasive method that has high temporal resolution, yet the localization of the neural activation is not precise (LLOYD-FOX; BLASI; ELWELL, 2010). fNIRS is a relatively novel method used in developmental research that has better spatial resolution as compared to the EEG. Thus, allowing better localization of the neural substrates in stimulus-evoked experiments (ASLIN; SHUKLA; EMBERSON, 2015).

The present study aimed to contribute to the current body of knowledge about the neural underpinnings of emotional face processing during development. An experimental research was conducted to investigate 5-month-old infants' hemodynamic brain responses to happy and fearful facial expressions, comparing responses across broad brain cortical areas using fNIRS. The potential influence of the effects of the emotional environment in infants' emotional face processing was indirectly investigated by assessing maternal self-reported symptoms of anxiety, as indexed by the trait component of the State-Trait Anxiety Inventory (STAI-T; SPIELBERGER et al., 1983).

In the present thesis, the models and studies of neural bases of emotional face processing were reviewed in section 2. In section 3, the fNIRS methodology was presented. Section 4 discussed the relevant literature of behavioral and neural correlates of emotional face processing in typically developing infants. In section 5, maternal anxiety and depression studies were reviewed. The potential mechanisms by which maternal anxiety and depression may affect the offspring in the prenatal and the postnatal period were disclosed in subsections 5.2 and 5.3, respectively. In subsections 5.4 and 5.5, studies of behavioral and neural correlates of emotional face processing in infants of anxious and depressed mothers were reviewed. Sections 4, subsections 5.4 and 5.5 originated the first article of the present thesis (Appendix 1). Subsequently, the rationale, objectives, methods and results of the experimental research conducted were presented. Finally, in the discussion section, the results were examined considering the developmental perspective of emotional face processing, the potential underlying neural substrates implicated, and possible mechanisms mediating the effects observed. The experimental research generated an original article submitted for scientific publication (Appendix 2).

2 NEUROBIOLOGY OF EMOTIONAL FACE PROCESSING

In this section, the most influential models of emotional face processing were reviewed, along with the brain structures and related networks involved in emotional face responses, as indicated by animal research, lesion and neuroimaging adult studies. Next, developmental models and the speculated neural substrates underlying emotional face processing were discussed. Finally, research in affective processing has particularly explored hemispheric asymmetry of frontal EEG activity in relation to emotional valence and motivation. Such studies were reviewed in relation to their proposed neural substrates in the prefrontal cortex.

2.1 MODELS AND NEURAL BASES

Humans have a highly specialized brain network for face processing (NELSON, 2001). The face processing system has been explored extensively, using fMRI and ERP techniques in adults, and by single-cell recordings in non-human primates (ADOLPHS, 2002b; FUSAR-POLI et al., 2009). Recognizing expressions of emotion requires the activation of both emotion-related brain circuits and higher-level face-selective cortical areas (LEPPÄNEN; NELSON, 2009). This process requires the activation of several cortical and subcortical structures, including areas of the temporal-occipital cortex (e.g., occipital face area, OFA), prefrontal cortex (e.g., orbital frontal cortex, OFC), amygdala, insula, and basal ganglia (ADOLPHS, 2002b).

Bruce and Young (1986) proposed an influential model of the theoretical account of face perception, based on studies of behavioral observations of healthy subjects and patients with brain lesions. In this model, after an initial visual structural analysis (i.e., structural encoding stage), the facial information regarding identity, and those related to facial social cues, such as expressions and lip movements, would be carried by distinct streams (CALDER; YOUNG, 2005; RIGHI; NELSON, 2013), and later integrated in cognitive systems related to facial memory.

Building on Bruce and Young's research, Haxby, Hoffman, and Gobbini (2000) proposed the currently dominant neural model of face processing. Integrating neuroimaging studies and evoked potential research, their model describes how the underlying neural systems mediating face perception in humans are organized, emphasizing the distinction

between the neural networks related to the processing of invariant (e.g., identity, gender, race) and variant (e.g., face expression, gaze direction, lip movements) facial aspects (HAXBY; HOFFMAN; GOBBINI, 2002). According to the model, the invariant features of the face enable the recognition of individuals, whereas the variant aspects encode information that facilitates social communication.

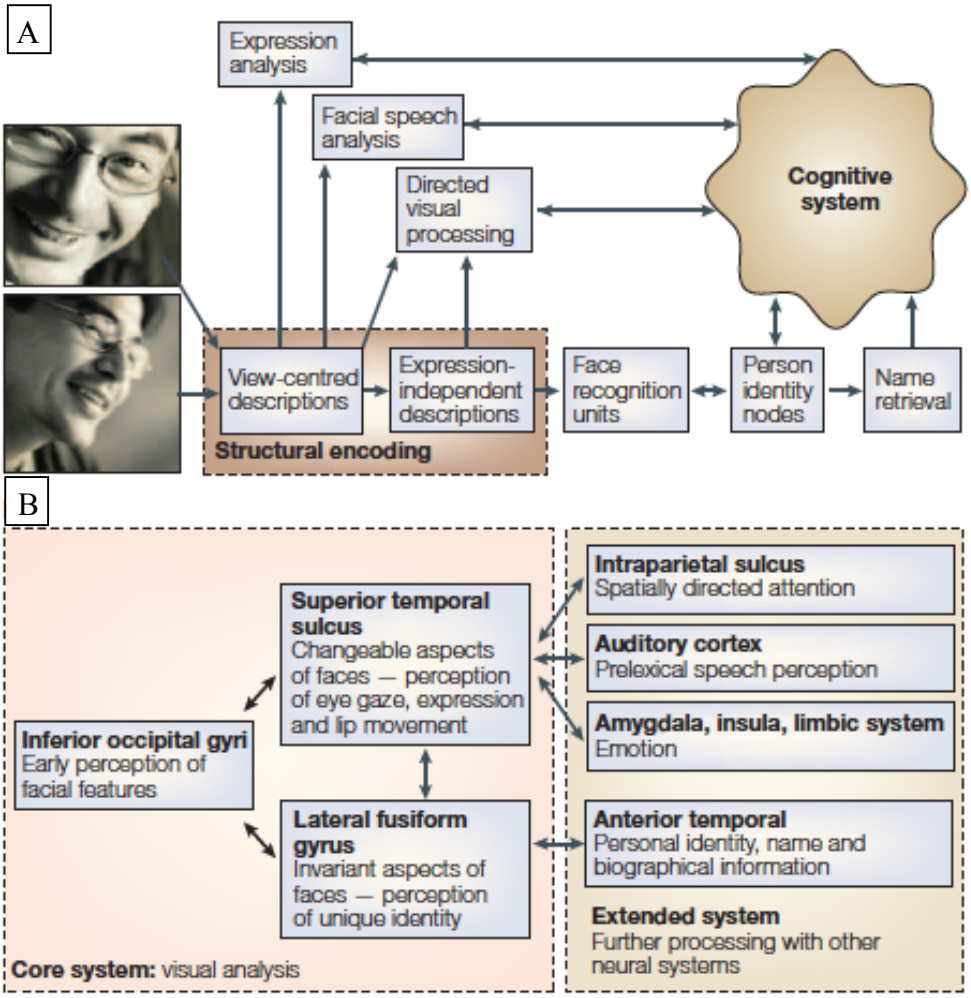
The OFA is located bilaterally in the inferior occipital gyrus, with projections to the fusiform gyrus and the superior temporal sulcus (STS). A particular area in the fusiform gyrus has been largely implicated in face recognition, named the fusiform face area (FFA). The FFA[1] was the first face selective region described (KANWISHER; MCDERMOTT; CHUN, 1997). The initial studies observed that patients with prosopagnosia (i.e., impaired recognition of familiar faces) had lesions in the ventral occipital-temporal cortex (DAMASIO; DAMASIO; VAN HOESEN, 1982). Subsequent studies showed that both FFA and STS responded selectively to faces in evoked potentials experiments in epileptic patients (ALLISON et al., 1999), as well as in single unit recordings in primates (PERRETT et al., 1992).

According to Haxby and colleagues (HAXBY; HOFFMAN; GOBBINI, 2002), the OFA, the FFA, and the STS constitute the "core system" of the face-processing network. The FFA processes the invariant facial signals, whereas the STS processes perceptual representations of changeable facial features. This visual core system projects to distinct areas of the "extended systems", depending on the perceptual features and the related cognitive functions. From the STS, projections to the intraparietal sulcus encode spatially directed attention (i.e., the focus of another's attention); interconnections with the auditory cortex processes speech-related mouth movements; and reciprocal connections with the limbic system (particularly with the amygdala) processes facial expressions. From the FFA, projections to anterior temporal areas relate to personal identity and biographical information. Through reciprocal connections, both core and extended systems facilitate the recognition of the distinct facial signals. The face-processing models by Bruce and Young, and Haxby are illustrated in Figure 1.

---

[1] The FFA, located on the lateral fusiform gyrus bilaterally, has been involved in selective face responses (KANWISHER; MCDERMOTT; CHUN, 1997). However, it has also been activated by other visual categories with which the subject has extensive experience (GAUTHIER et al., 1999). The debate whether the FFA's expertise is restricted to faces or if it is involved in general expertise processing is beyond the scope of this thesis.

Figure 1- Face-processing models



Reproduced from CALDER; YOUNG, 2005 with permission.

(A) Bruce and Young model. An initial structural encoding stage would be directed to separated parallel routes for facial identity, facial expression and lip speech recognition, further redirected to cognitive systems. (B) Haxby model. The core system comprises three occipital-temporal regions that recognize variant and invariant facial features. The extended systems act together with the core system to facilitate face recognition.

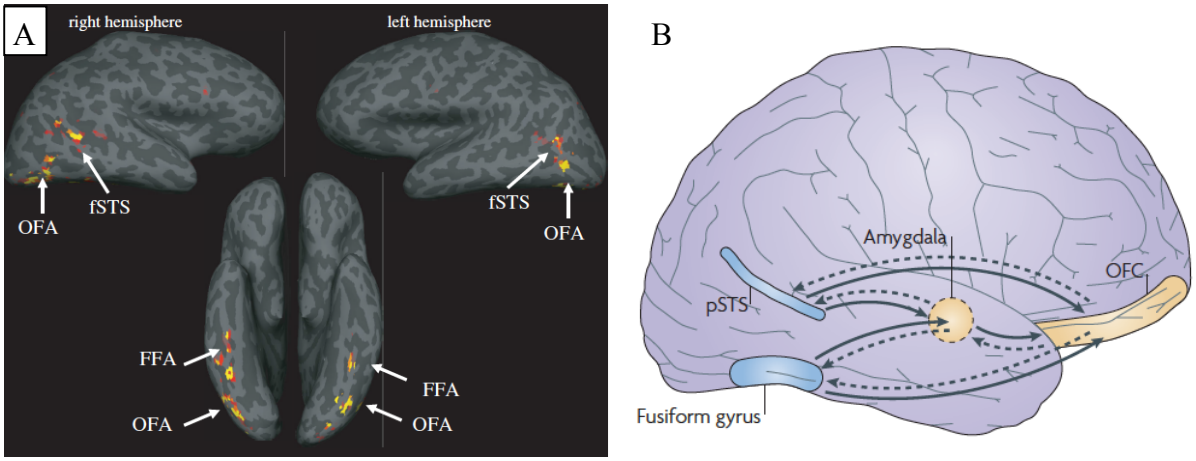
Cognitive neuroscience research has also found evidence of subcortical areas being involved in face processing, not only responding to top-down information from the cortex but receiving early inputs to modulate cortical face processing (JOHNSON, 2005). Such neurophysiological studies have explored face processing in relation to the frequencies of visual input. Accordingly, high and low spatial frequency information about the face appears to be processed by differential neural networks (VUILLEUMIER et al., 2003).

The high spatial frequencies of facial visual input (i.e., fine-grained information of face identity and expressions) are initially processed in visual areas of the occipital cortex, and further directed to either the FFA or to the STS. These areas are engaged in the

processing of detailed facial information, characterized by a highly precise and slow response (JOHNSON, 2005). The FFA, particularly on the right side, is consistently reported in studies of facial identity evaluation, and has been implicated in the processing of invariant facial features, such as gender, race and identity (HAXBY; HOFFMAN; GOBBINI, 2000; RIGHI; NELSON, 2013). By contrast, the STS is engaged in the processing of changeable features of the face, such as eye gaze, speech-related mouth movements, and expressions of emotions (HAXBY; HOFFMAN; GOBBINI, 2002). From the STS, the information of face expressions is directed to emotion-related structures, including the amygdala and insula (HAXBY; HOFFMAN; GOBBINI, 2000).

Nonetheless, the low spatial frequencies, corresponding to the general configuration of facial features (i.e., “coarse” information about faces) are believed to be processed by subcortical pathways, carried through magnocellular channels to subcortical structures including the pulvinar, superior colliculus and amygdala (JOHNSON, 2005). Haxby and collaborators (2000) argued that the processing of variant and invariant aspects of faces is possibly integrated already at the early perceptual level. In an experiment using ERP and MRI in adults, Vuilleumier and colleagues (2003) demonstrated activation of the pulvinar and superior colliculus by low-frequency fearful expressions, showing that these subcortical pathways possibly carry coarse emotional face inputs to the amygdala. In addition, smiling faces increased the rate of reported familiarity in an experiment with adults, demonstrating that emotional expressions influenced face recognition (BAUDOUIN et al., 2000). The main brain areas involved in the processing of emotional faces are illustrated in Figure 2.

Figure 2 - Brain areas related to emotional face processing



Reproduced from KANWISHER; YOVEL, 2006; LEPPÄNEN; NELSON, 2009.
(A) Main face-selective regions in the human brain. OFA, occipital face area; fSTS, face region of the superior temporal sulcus; FFA, fusiform face area. (B) Neural systems involved in face emotional processing. The amygdala and the OFC (orbitofrontal cortex) receive visual information from cortical regions related to invariant (fusiform gyrus) and variant (pSTS; posterior superior temporal sulcus) facials aspects. The amygdala and the OFC may also receive visual information through a faster magnocellular pathway from the early visual cortex or through a subcortical collicular-pulvinar pathway to the amygdala (not shown). The amygdala and the OFC have reciprocal connections and send feedback projections to visual areas, including the fusiform gyrus and STS.

The initial "fast-route" for face detection would be independent of attention and consciousness, quickly enabling the processing of rough emotional cues and further modulating the activity of face-sensitive cortical areas involved in fine-grained processing (through reciprocal connections with FFA and STS) (IIDAKA et al., 2001; VUILLEUMIER et al., 2003).

The subcortical route has been suggested as the main pathway for face processing in human newborns (MORTON; JOHNSON, 1991). The immature visual processing in the first weeks after birth would enable the detection of rough facial features, mainly carried by the subcortical routes and predominantly controlled by the superior colliculi (GAUTHIER; NELSON, 2001; JOHNSON; SENJU; TOMALSKI, 2015). This route could be implicated in the visual preference for faces, or face-like stimuli (compared to other shapes) robustly observed in newborns' empirical experiments (FARRONI et al., 2007; JOHNSON, 2005; MORTON; JOHNSON, 1991). Newborns' innate preference for faces would facilitate the ontogeny of the face-processing system, with the cortical face-processing gradually emerging when infants approach two months of age (JOHNSON, 2005). However, other authors have argued that facial features and their particular spatial distribution would be an optimal

stimulus type to attract newborns' attention and promote the development of the visual system (RIGHI; NELSON, 2013).

A large body of research at both animal and human levels has established the amygdala's primary role in the modulation of emotional processes (LEDOUX, 1993; VUILLEUMIER et al., 2004). The amygdala has reciprocal connections both from/to fast subcortical routes, as well as from/to highly specialized face-cortical areas (ADOLPHS, 2002b; ADOLPHS; TRANEL; DAMASIO, 2003). The amygdala was originally associated with responses to fear (MORRIS et al., 1996), yet more recent studies have demonstrated its association in the processing of salient social and emotional stimuli in general, such as threat or reward experiments, or in emotion regulation of both positive and negative stimuli (HOOKER et al., 2006; KIM; HAMANN, 2007; MORRIS et al., 1996). Furthermore, the amygdala is believed to be involved in gathering and evaluating stimuli and emotional significance, ultimately modulating attention and memory processes (HOOKER et al., 2006).

The prefrontal cortex (PFC) has also been identified as an important area for affective processing, besides its well-known role mediating high-level cognitive functions (ADOLPHS, 2002a) The OFC is a region within the PFC, considered particularly relevant for emotional discrimination and regulation (ADOLPHS; TRANEL; DAMASIO, 2003), participating in both, the "fast-route" for face detection by receiving low spatial frequency information through magnocellular tracts, as well as neuromodulating fine-grained perceptual processing in face-sensitive cortical regions (LEPPÄNEN; NELSON, 2009). Like the amygdala, the OFC has reciprocal connections between face-sensitive cortical areas, including regions in the infero-temporal cortex and the STS (CAVADA et al., 2000), as well as to subcortical structures related to emotion processing (e.g., amygdala, hypothalamus, brainstem nuclei, nucleus accumbens) (LEPPÄNEN; NELSON, 2009). Patients with OFC lesions have impaired capacity to discriminate several facial expressions (HORNAK, 2003), and neuroimaging studies have demonstrated OFC activation for positive and negative facial expressions (O'DOHERTY et al., 2001, 2003).

Another face-processing model was proposed by Valentine (VALENTINE, 1991, 2001), the "face-space framework", supported by computational models using Principal Component Analysis. In this model, faces would be encoded by reference to a facial prototype, in a multi-dimensional face space consisting of distinct featural and configural information, such as gender and race. Face prototypes for different constructs would be stored in memory, and new faces would be analyzed in a norm-based coding model, in relation to their deviation from the prototypical average of the face space. Based on Valentine's model,

Nelson (2001) proposed that the face prototype would be extensively tuned at birth. Pascalis and colleagues (2005) argued that several factors would impact the development of the facial prototype, such as the frequency of exposure to faces of certain individuals (e.g., mother's face would be a prominent stimuli), and the presence of specific facial salient cues, which possibly differs qualitative and quantitative in infants, as compared to adults.

2.2 DEVELOPMENTAL MODELS AND NEURAL BASES

The development of the neural networks for emotional face recognition have been studied in animal models, as well as in behavior and neuroimaging studies in infants. Brain networks related to face perception and emotional processing are believed to interact early in postnatal life, influencing the development of visual areas that enable the fast detection of relevant emotional cues from faces (LEPPÄNEN; NELSON, 2009).

Studies in non-human primates (KORDOWER; PIECINSKI; RAKIC, 1992; MACHADO; BACHEVALIER, 2003) revealed that the neurogenesis of the amygdala is completed at birth (KORDOWER; PIECINSKI; RAKIC, 1992), while connections between visual areas, the amygdala and the OFC are established early in development (i.e., first postnatal week) (LEPPÄNEN; NELSON, 2009; MACHADO; BACHEVALIER, 2003). Additionally, neural networks connecting the OFC and temporal areas are also present at 1 week of age, but they continue to mature during the whole first year (MACHADO; BACHEVALIER, 2003). The observation of these circuitries in animal studies at a notably early stage lead to the suggestion that facial-emotion brain networks would be functional in human infants as they begin to show discrimination of facial expressions (LEPPÄNEN; NELSON, 2009).

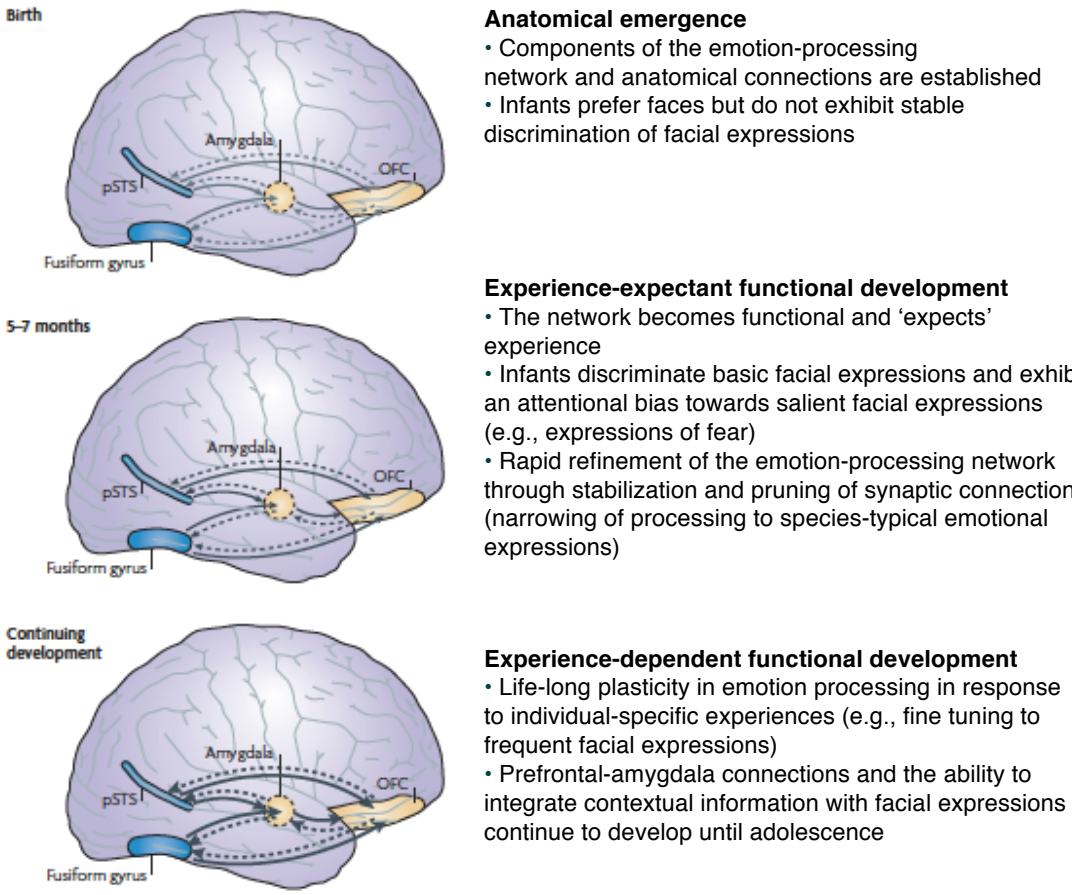
An unique PET study was conducted to investigate face perception in 2-month-old infants with history of hypoxic–ischemic encephalopathy at birth (TZOURIO-MAZOYER et al., 2002). Infants observed female faces compared to dot patterns. The activation for faces was visualized in the inferior occipital cortex, including the FFA akin to adult studies, but additionally over frontal and parietal areas. Although the infants had mild neurological impairments, the observation of neural sensitivity to faces at this age was documented. Other functional studies were conducted mainly with electrophysiological methods, revealing face-specific responses in 3-month-olds and onward (for example, HALIT et al., 2004). These studies were reviewed further down in subsection 4.2.1. Broadly, the face-processing mechanisms appear to be activated by a wider range of stimuli compared to adults (HALIT et

al., 2004). Thereafter, the neural networks are believed to become progressively attuned to human faces through the repetitive exposure to this stimuli across development (GAUTHIER; NELSON, 2001).

The developmental process of face recognition has been defined as "experience-expectant" (GREENOUGH; BLACK; WALLACE, 1987; NELSON, 2001). The innate neural architecture has the potential to become specialized for faces but needs to be primed through experience to enable the face-processing networks to mature. Accordingly, the exposure to faces of conspecifics would provide the foundation for developing perceptual representation of global facial features and face expressions. It remains unclear how long this period would last and what would be the exactly pivotal experiences needed (NELSON, 2001). Leppänen and Nelson (2009) have proposed a subsequent model, accounting for the emotion-recognition development. The emotion-recognition circuitry would functionally emerge between 5 and 7 months of age, sensitive to the exposure to expressions of emotions that would refine the network development (sensitive period). As in the general model for face development, the magnitude of timing and specific influential inputs on this sensitive period remains to be determined. Following this period, the neural circuits would continue to be open to the effects of the environment, through "experience-dependent" mechanisms. The basic facial representations would be influenced by individual experiences, including the frequency and intensity of exposure to distinct facial expressions (environmental factors), genetic factors (e.g., genetic polymorphisms), as well the interactions between those factors.

Hence, the face development processing involves both experience-expectant and experience-dependent mechanisms, as the exposures to faces both enable and largely influence the formation of the mature face processing system (NELSON, 2001). The developmental model of emotion-recognition is reproduced in Figure 3.

Figure 3 - Developmental model of emotion-recognition



Reproduced from LEPPÄNEN; NELSON, 2009 with permission.

Leppänen and Nelson (2009) proposed model of the development of emotion-recognition mechanisms. An experience-expectant neural circuitry emerges at 5–7 months of age, rapidly refined by exposure to universal features of expressions (during a sensitive period, perhaps the first few years of life). The network can be fine-tuned by individual experience-dependent plasticity throughout lifespan. Functional connectivity between emotion networks and prefrontal systems continues to develop until adolescence.

2.3 EMOTIONAL VALENCE, MOTIVATION AND THE PREFRONTAL CORTEX

An expressive number of studies in affective processing, including research about the neural underpinnings of facial expressions of emotions, have investigated patterns of functional brain lateralization over frontal regions, in relation to emotional valence and motivational responses (DAVIDSON, 2002; FOX, 1991)

Observational reports of patients with frontal brain lesions date from more than four decades ago (DAVIDSON, 2002), indicating distinct symptomatology according to the compromised hemisphere. Patients with left frontal brain lesions were more likely to present

depression, showing increased symptomatology as closer the damage was to the frontal pole (DAVIDSON, 1998, 2002). By contrast, patients with right frontal hemisphere injuries more often developed mania (BURGDORF; PANKSEPP, 2006). The general interpretation was that depressive symptoms were associated with left-sided anterior PFC damage, and that this brain area participates in certain forms of positive affect. When damaged, it could lead to deficits in the capacity to experience positive affect, a distinct feature of depression (DAVIDSON, 2004a). Subsequently, a large body of electrophysiological empirical work investigated differential activation patterns comparing left and right frontal brain areas and emotional processing.

The field has particularly explored measures of the EEG power, based on the alpha frequency (COAN; ALLEN, 2004). In the present thesis, EEG alpha power was referred to as EEG power, as no other frequency bands were further explored. Neuroimaging research has correlated the decrease in alpha power to greater cerebral perfusion in fMRI studies (for example, GOLDMAN et al., 2012). Therefore, EEG power is inversely correlated to brain activity, considered an indirect measure of regional cortical activation.

Alpha frequency emerges early in life, appears to mature rapidly over the first few years, and remains relatively stable thereinafter (STROGANOVA; OREKHOVA; POSIKERA, 1999). The EEG frontal asymmetry (FA) is a measure computing the difference between the scores of alpha power, comparing frontal right and left areas (HAGEMANN, 2004). Typically, the alpha frequency band of 8–13 Hz is analyzed in adults, while the frequency band between 3–13 Hz is used to investigate newborns, and frequencies between 6–9 Hz or 3–13 Hz for infants, according to the age of the sample (for example, DIEGO et al., 2004a). There is currently no agreement concerning the appropriate number of electrodes to be used for reliably assessing FA (LUSBY et al., 2014).

Based on the observation of brain lesions and notably on EEG studies, two distinct systems to underlie the mediation of different forms of emotion and motivation were proposed by Davidson and collaborators (DAVIDSON, 1993; FOX, 1991), in the "approach-withdrawal" motivational (or valence) model. The greater relative left FA (vs. right) was associated with the approach system, engaged in appetitive behaviors (e.g, joy, surgency, anger), positive valence emotions, and pleasant stimulus. In turn, greater relative right FA (vs. left), was correlated to the withdrawal system, including avoidance behaviors, processing of certain negative emotions, such as fear and sadness, and unpleasant stimuli. The FA scores may indicate a relative decrease in activation in one of the hemispheres, an increase of either

the right or left hemisphere, or a combination of an increase/decrease of right/left hemispheres (TOMARKEN et al., 1992).

Empirical EEG research both in children and adults have shown that FA is associated with positive/negative affect and with approach/withdrawal behaviors. The studies have identified patterns of individual differences in dimensions of temperament (i.e., biologically-based bias toward distinct patters of feelings and behaviors; KAGAN; SNIDMAN, 1999) and mood disorders (e.g., anxiety and depression) related to lateralization of emotional responses (DAVIDSON, 1998; FOX et al., 2001; MCMANIS et al., 2002; THIBODEAU; JORGENSEN; KIM, 2006). Thereby, FA studies have explored both state- and trait-dependent effects. The former refers to acute emotional responses, such as greater left FA when the infant is smiling or demonstrating approach behaviors (for example, FOX; DAVIDSON, 1988), while the latter describes individual differences for emotional responses and emotional disorders, including anxiety and depression (COAN; ALLEN, 2004; DIEGO; JONES; FIELD, 2010). The EEG method is non-invasive and suitable to collect data from infants, and has been widely used to investigate frontal desynchronization of alpha frequencies in relation to exposure to maternal anxiety and depression. This body of research was reviewed in subsection 5.5.1.

Several areas are speculated to be involved in the FA findings. The PFC is believed to integrate emotional regulation and high-level cognitive functions, influencing affective responses (DAVIDSON, 2003), possibly by regulating limbic and subcortical areas engaged in automatic and fast processing of emotional stimuli, such as the anterior cingulate cortex (ACC) and amygdala (DAVIDSON, 2004b). Subdivisions of PFC are believed to be particularly important in the complex circuitry of affective processing, and are hypothesized to generate the distinct FA patterns observed in EEG studies (DAVIDSON, 1992). The OFC, as previously noted, has been considered relevant for face emotional processing (O'DOHERTY et al., 2003). For instance, patients with bilateral OFC lesions demonstrate impaired ability to discriminate emotional expressions (HORNAK, 2003). Additionally, as the neural activity in the amygdala is transmitted to the frontal lobes, it has been suggested that greater desynchronization of alpha frequencies in the frontal region may reflect greater activity in the amygdala (KAGAN; SNIDMAN, 1999).

In addition to the OFC, neuroimaging and lesion studies in adults have offered support to voluntary and automatic emotion processing functions of the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MPFC), and ventromedial prefrontal cortex (vmPFC) (DAVIDSON, 2003, 2004b). It has been proposed that the DLPFC is involved in emotion-

based decision making, by mediating the influence of emotion on executive functions and cognitive performance (DAVIDSON; IRWIN, 1999). The MPFC has been related to social communication, activated in mutual eye gaze interactions, observed already in 4-month-old infants (GROSSMANN et al., 2008). In adults, this area is activated in complex cognitive processes related to emotional responses, such as active regulation and maintenance of emotional states (WAUGH; LEMUS; GOTLIB, 2014), as well as in experiments of valence evaluation of emotional stimuli (AMODIO; FRITH, 2006). The vmPFC has been implicated in the anticipation of future positive and negative affective consequences. For example, the levels of electrodermal activity in anticipation of a risky choice are decreased in patients with bilateral lesions of the vmPFC compared with controls (BECHARA et al., 1996). The potential networks involved in the FA responses are speculative, since the methodology of EEG is known to have a relatively poor spatial resolution (ASLIN; SHUKLA; EMBERSON, 2015).

Despite the large body of empirical work supporting frontal EEG asymmetry as a moderator/mediator of emotional processing (BATTY et al., 2009; COAN; ALLEN, 2004), substantial inconsistencies have also emerged (HAGEMANN, 2004; NITSCHKE, 1998; REID; DUKE; ALLEN, 1998), and further clarification of the potential involved structures and related mechanisms remain to be better understood.

3 FUNCTIONAL NEAR-INFRARED SPECTROSCOPY (fNIRS)

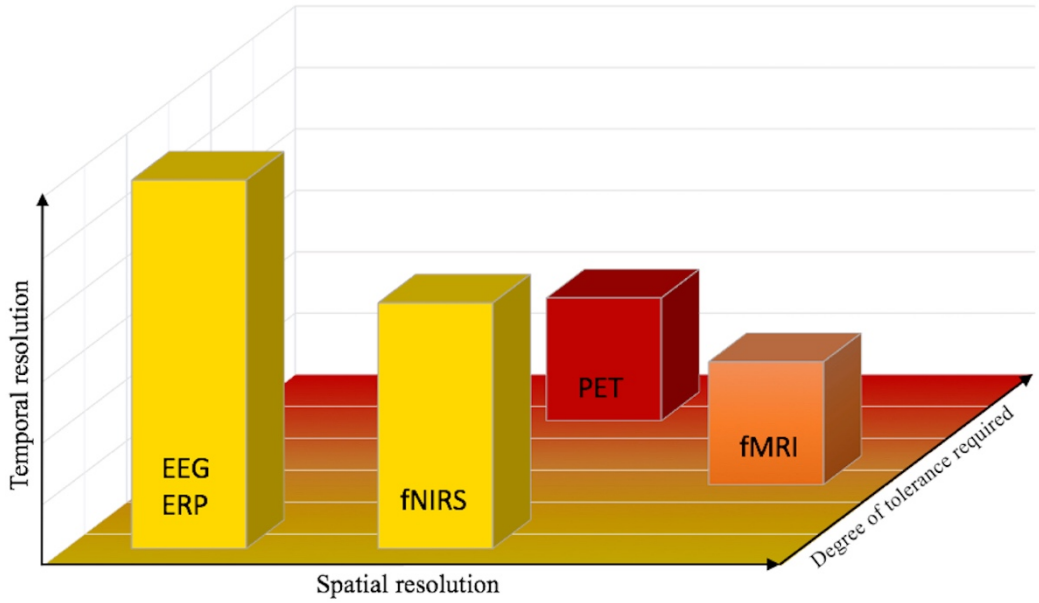
The fNIRS is an optical technique that emerged in the early 1990s, with the development of multichannel optodes (optical sensors) (MINAGAWA-KAWAI et al., 2008). The first study (MEEK et al., 1998) on healthy awake infants obtained hemodynamic occipital responses for visual patterns, presented to infants from 2 days to 3 months of life. However, only in the last decade has fNIRS become widely applied to explore typical and atypical brain development (VANDERWERT; NELSON, 2014). Developmental cognitive neuroscience researchers have used this technique increasingly to complement behavioral studies and other neuroimaging methods, as it is s exceptionally useful for collecting data in awake infants and children who are not easily tested with MRI. Developmental fNIRS studies have investigated sensory and perceptual processing, as well as and several social, emotional, and cognitive functions, such as joint attention and language acquisition (VANDERWERT; NELSON, 2014).

The field of developmental cognitive neuroscience has extensively explored the EEG and ERP techniques, to elucidate neural correlates of behavioral responses (LLOYD-FOX; BLASI; ELWELL, 2010). EEG has exceptional temporal resolution, as the electric responses can be captured in milliseconds of neural events. However, the trajectory of propagation of the electrical potentials through the tissues onto the scalp electrodes cannot be assessed precisely, substantially restricting the EEG's spatial resolution (ASLIN; SHUKLA; EMBERSON, 2015).

fNIRS is a noninvasive method well tolerated in infant populations. It provides a more precise localization of brain activation compared to EEG (LLOYD-FOX; BLASI; ELWELL, 2010). The technique does not require rigid head stabilization and is less sensitive to movement artifacts, offering better spatial resolution than EEG and ERP. Moreover, it has good portability, and is an economical method in comparison to other neuroimaging techniques. Compared to MRI, fNIRS has a better temporal resolution, is silent and offers greater tolerability to movement artifacts, thus allowing the use in more natural experimental settings and in infant-friendly environments (GERVAIN et al., 2011). However, fNIRS is limited to the analysis of the cortical area, since near-infrared light cannot penetrate below approximately 2-3 cm of the cortical surface. The depth resolution varies according to the optical properties of the tissue, as well as with the subject's age (LLOYD-FOX; BLASI; ELWELL, 2010). In addition, as the hemodynamic response to neural activation is relatively slow compared to the electric response, fNIRS is considered to have a moderate temporal

resolution, inferior to that of EEG, yet superior to fMRI (GERVAIN et al., 2011). Figure 4 compares the major advantages and disadvantages across the functional neuroimaging methods used in infancy.

Figure 4 - Neuroimaging methods compared by their properties of spatial resolution, temporal resolution and infant tolerability

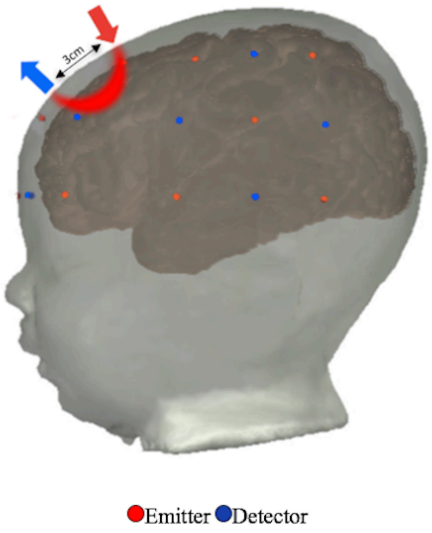


Modified from LLOYD-FOX; BLASI; ELWELL, 2010 with permission.
The degree of tolerance required for each method is illustrated, increasing from low (yellow) to high (red). EEG, electroencephalography; ERP, event-related potential; fNIRS, functional near-infrared spectroscopy; fMRI, functional magnetic resonance imaging; PET, positron emission tomography.

The fNIRS methodology is based on the near-infrared light properties to diffuse through the biological tissue. The near-infrared light spectrum between 650-1000 nm is strongly absorbed by the hemoglobin, yet has a relatively low absorption in human skin, bones and tissues (LLOYD-FOX; BLASI; ELWELL, 2010). This phenomenon called “optical window” allows the light to penetrate about 2-3 cm through skin and skull, reaching around 5 to 10 mm of the cortical surface (HUPPERT et al., 2009), as illustrated in Figure 5. The oxygenated (oxyHb) and the deoxygenated (deoxyHb) hemoglobin chromophores (i.e., a substance that absorbs light at a given wavelength) differ considerably in their absorption spectra of the incident light in the utilized wavelength range (650-1000 nm). Using a brain net containing optodes (i.e., emitter and detector pairs) that emit and detect near-infrared light, relative differences (i.e., attenuation) between the absorption spectra of oxyHb, deoxyHb and

total hemoglobin (totalHb; totalHb= oxyHb + deoxyHb) can be measured. The light attenuation reflects both absorption and scattering mechanisms within the illuminated tissues. By determining the optical pathlength in the tissue and assuming the scattering to be constant (which differs according to the participant's age; LLOYD-FOX et al., 2014), changes in all the chromophores can be expressed in µmolar units (µM) (LLOYD-FOX; BLASI; ELWELL, 2010). Thus, monitoring the changes of the chromophores simultaneously allows a non-invasive measurement of changes in blood oxygenation.

Figure 5 - Schematic model of the fNIRS methodology

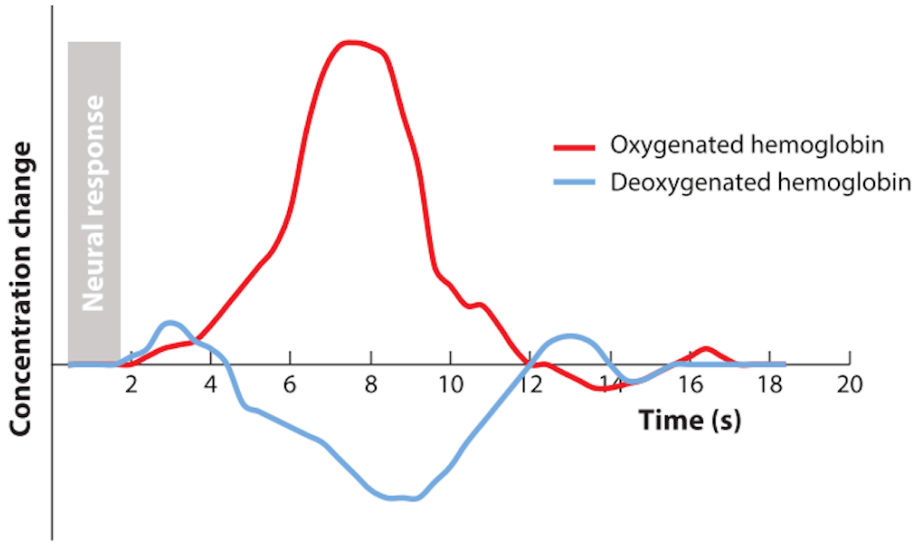


Source: Adapted from Katherine L. Perdue with permission.
The emitter (red) shines the near-infrared lights of 695 and 830 nm wavelengths through the scalp. In the neural tissue, the 830 nm light is absorbed by the oxyHb, whereas the deoxyHb absorbs the 695 nm light. The detector (blue) measures the attenuated light intensity. Each emitter-detector pair constitutes a channel. The light distribution in each channel has a configuration described as a "banana-shape". The maximum depth of the light penetration is located at the center between the emitter and the detector, varying according to the inter-optode distance.

As with the fMRI methodology, fNIRS is based on the principle that a regional neuronal activity is related to local changes in blood flow and oxygenation (LLOYD-FOX; BLASI; ELWELL, 2010). While the basic principles of the neurovascular coupling have been explored in invasive animal studies, the precise association among the neural and vascular responses in the human brain remain unclear (MINAGAWA-KAWAI et al., 2008).

The standard fNIRS response reported in studies with adult participants comprises an increase in oxyHb and totalHb, and concomitant decrease in deoxyHb in the activated cortical area (GERVAIN et al., 2011). Greater neural activity enhances the local oxygen consumption, provoking a rapid increase in the local cerebral blood flow, heightening the oxygen concentration in the activated area. The local oxygen consumption is habitually exceeded by the rate of the oxygen delivered, resulting in a greater oxyHb concentration in the active brain areas. As the local oxyHb concentration increases, it dissipates the deoxyHb (MINAGAWA-KAWAI et al., 2008). Hence, the typical hemodynamic response function (HRF) is characterized by a local excess of oxyHb, and a relatively smaller decrease in deoxyHb, evinced in stimulus-evoked experiments (Figure 6).

Figure 6 - Hemodynamic response function



Reproduced from ASLIN; SHUKLA; EMBERSON, 2015 with permission.
Standard HRF response, showing increase in oxyHb and decrease in deoxyHb after a stimulus-evoked neural activity.

Studies in infant populations have described important variations compared to the hemodynamic responses observed in adults, and the precise meaning of infants' differential responses is not well understood (GERVAIN et al., 2011). In infants, decreased oxyHb concentration (CSIBRA et al., 2004; RAVICZ et al., 2015) increased deoxyHb (HINTZ et al., 2001; MEEK et al., 1998), associated or not to decreased totalHb have been reported (LLOYD-FOX; BLASI; ELWELL, 2010). The greater variability of the infant's HRF has been speculated to reflect differential metabolic demands in developing brain, and/or to be

secondary to the immaturity of the neurovascular coupling (ASLIN; SHUKLA; EMBERSON, 2015; KOZBERG et al., 2013). The oxyHb is the chromophore shown to be more consistent across infant studies, thus it is the most reliable measure in fNIRS work in the developmental population (LLOYD-FOX; BLASI; ELWELL, 2010).

Adult experiments have correlated the fNIRS hemodynamic response to fMRI measurements of the blood oxygenation level dependent (BOLD) sequence. Nevertheless, it is not clear which hemoglobin chromophore is more strongly related to the BOLD signal (LLOYD-FOX; BLASI; ELWELL, 2010). While simultaneous fNIRS-fMRI experiments (for example, STRANGMAN et al., 2002) found the oxyHb (vs. deoxyHb) to be more closely linked to BOLD responses, others (for example, HUPPERT et al., 2006) reported that the greatest correlation was between the BOLD signal and deoxyHb changes.

As previously reviewed, fNIRS allows better spatial location of brain activity than the typically used methods in developmental population (EEG, ERP). Although the hemodynamic measurement is confined to the cortical surface, infants' relatively thin skulls and shallower brain sulci enable better light penetration into the tissue, compared to adults (CSIBRA et al., 2004). Another common issue when collecting data with fNIRS are the high rates of data rejection due to the obstruction of the light by hair, a problem less prevalent in young infants that generally have less dense hair than older children and adults (GOODWIN et al., 2016). Although fNIRS assesses localized hemodynamic responses, it does not consider the anatomical structure of the activated brain region (LLOYD-FOX et al., 2014). The anatomy of the adult brain has been explored extensively, allowing better estimates of the neural substrates underlying fNIRS measurements (HUPPERT et al., 2006; LLOYD-FOX et al., 2014; STRANGMAN; BOAS; SUTTON, 2002). In infants, the brain topography has not been mapped equally well (RAVICZ et al., 2015). Thus, inferences about the regional specificity of the observed responses require caution. While average MRI templates are available for estimated anatomical comparisons (for example, RICHARDS et al., 2016), individual differences are important to be considered and may account for discrepancies among hemodynamic responses. A recent study (LLOYD-FOX et al., 2014), co-registered fNIRS and MRI in 55 infants from 4 to 7 months of age, generating standardized surface maps of the scalp for two groups of infants: 4.5- and 6-month-olds. Reliable localization of the fNIRS optodes over frontal and temporal cortex was observed, facilitating the identification of the inferior frontal gyrus and the STS. Further work expanding comparisons among the whole head for other ages across development are needed to allow better correlations with anatomical brain structures across development (ASLIN; SHUKLA; EMBERSON, 2015)

Several fNIRS techniques are being developed in a number of laboratories worldwide, with a rapid increase in reported works over the last few years, expected to substantially contribute to clarifying the underpinnings of brain development (LLOYD-FOX et al., 2014).

fNIRS has been applied on infants in experiments evaluating face processing, confirming that a distinct cortical response can be observed for faces with this methodology (BLASI et al., 2007). A few recent studies have additionally used fNIRS to investigate emotional face responses in infants, reporting activation in different areas measured in 6 to 7-month-old infants and older. These studies were reviewed in subsection 4.2.3.

4 DEVELOPMENT OF EMOTIONAL FACE PROCESSING

This section briefly reviewed the development of face processing, followed by the discussion of the literature of emotional face processing. Behavioral studies were considered in subsection 4.1, and neural correlates experiments in subsection 4.2, including ERP (4.2.1), EEG (4.2.2) and fNIRS (4.2.3) studies.

Within hours after birth, human newborns already look longer and orient preferentially to faces compared to non-facial shapes (TURATI et al., 2002). A recent study (REID et al., 2017) revealed that even in the uterus, fetuses appear to orient more to up-right than to inverted face-like stimuli. Nevertheless, the ontogeny of newborns' face preferences remains a topic of debate (RIGHI; NELSON, 2013). Yet, it is mostly assumed that humans have an innate ability to orient to faces, speculated to be an adapted mechanism to maximize newborns' interaction with caregivers (FARRONI et al., 2005; NELSON, 2001).

After the initial preference for faces, the repeated exposure and active experience with faces facilitate the emergence of the neural networks that will progressively become specialized in face processing (RIGHI; NELSON, 2013). The role that differential experiences within the first months of life play for face processing has been demonstrated in several developmental studies (JONES et al., 2013; KELLY et al., 2007). Within a few days after birth, infants begin to show a preference for looking at their own mother versus a stranger (PASCALIS; SCHONEN; MORTON, 1995), an ability robustly observed at 3 months of age (PASCALIS et al., 1998), and presumably related to the increased frequency and the characteristics of the mother-infant face-to-face interactions (JONES et al., 2013).

Other studies demonstrated that the face perceptual mechanism is initially broadly tuned, and becomes progressively specialized, shaped by the environmental experiences. Nelson (2001) has proposed that the face developmental process would be based on the mechanism of perceptual narrowing, as previously reported in the language development domain (for example, KUHL et al., 2006). The ability to process facial stimuli would be attuned by the experience, in a way that infants progressively improve the perceptual processing for stimuli they are repeatedly exposed, yet lose the ability to discriminate stimuli to which they are not exposed. Pascalis, de Hann and Nelson (2002) reported that 6-month-old infants could discriminate two monkey faces apart as easily as discriminating two human faces. Yet, 9-month-olds and adults could only discriminate among human faces. This phenomenon was subsequently tested by visually exposing infants at 6 month of age with monkey faces during a 3-month period. When the infants were tested at 9 months, they were

able to discriminate novel monkey faces, a finding not observed in the control group of infants that were not exposed to monkey faces (PASCALIS et al., 2005).

The perceptual narrowing observed for species-specificity faces, was also explored comparing exposure to different races and gender in infancy. At 3 months of age, infants demonstrated visual preference for female faces, but when the primary caregiver was a male, the opposite was observed. Thefore, infants show visual preference matching the primary caregiver's gender (QUINN et al., 2002). The facilitated discrimination among faces that match the same race as the subject, called "other-race effect" has been observed in adults (PASCALIS et al., 2005). Developmental studies have reported this effect in infants, observed as early as in 3 months of age (e.g., BAR-HAIM et al., 2006; KELLY et al., 2007).

The role of emotional experiences in shaping the development of face emotion recognition has been investigated in infants exposed to atypical contexts. In an extreme pervasive environment experienced by children that suffered maltreatment early in life, children were presumably exposed to higher levels of parental expressions of anger and threat. When evaluated in emotion recognition tests, abused children exhibited heightened sensitivity, and a wider perceptual category for detecting facial cues of anger expressions, compared to controls (POLLAK; KISTLER, 2002). In another study investigating emotional faces and ERP responses, maltreated children had enhanced amplitude in attention ERP components (Pb3) for processing angry expressions (POLLAK et al., 2001). The altered perceptual processing to expressions of anger has been speculated to reflect an adaptive mechanism to early detection of threatening social cues (LEPPÄNEN; NELSON, 2009; POLLAK et al., 2001). Children raised in deprived and neglected contexts were investigated in a separate study (MOULSON et al., 2015), exhibiting higher perceptual thresholds for the detection of smiling faces.

The potential effects of emotional experiences in face processing were also studied in typically developing contexts (next subsection), as well as in infants of anxious and depressed mothers, reviewed in subsection 5.4.

Behavioral studies investigating facial expressions have extensively explored aspects of visual discrimination and face recognition. Discrimination refers to the perceptual capacity to distinguish between two or more stimuli (ASLIN, 2007). Infants can discriminate faces based on featural differences of configurational aspects and their arrangements on the face, such as closed versus differential degrees of open mouth, variations of eyes exposure, raised compared to lowered eyebrows, etc (GROSSMANN; VAISH, 2009). Recognition, however, implies also the capacity to identify a distinct emotion across individuals, and despite the

intensity of the facial expression. This ability can be investigated by assessing infants' capacity to categorize distinct facial expressions.

Experimental studies commonly explore looking time measures or visual preferences. Habituation (or familiarization) refers to gradual decreases of visual fixation secondary to a repeated stimulus exposure. Following habituation, the exposure to a new stimulus provokes the recovery of looking when the infant is able to discriminate the new versus the old stimulus, a process referred as post-habituation (post-familiarization or dishabituation). Visual preference is also examined using the visual paired comparison procedure. Using this paradigm, several metrics can be explored comparing two facial expressions presented simultaneously, such as the direction and duration of the first visual fixation, total looking time, mean time of visual fixation, and time to disengage attention of a stimuli (ASLIN, 2007).

Developmental studies also investigate emotional responses by observing infants' social interactions with the mother, engaged in free play activities or during instructed imitative experiments (PORTO; NUNES; NELSON, 2016). Infants' reactions, such as vocalization, facial expressivity and body movements can be measured. A widely used structured experiment is the "still-face" paradigm. The mother (or a researcher) is instructed to display flat affect, mimicking emotional unavailability. Infants typically respond to this paradigm with distress, showing gaze aversion, frowning and crying (FIELD et al., 2007). This paradigm has been widely used to evaluate infants' sensitivity to maternal behavior, infants' communicative skills and their capacity to regulate emotional states (WEINBERG; TRONICK, 1998). Furthermore, emotional studies also investigate multiple sensory modalities simultaneously, such as facial and vocal stimuli. In multimodal experiments, researchers examine the extent to which the processing of one modality may influence the other, and how distinct information is integrated during the development (GROSSMANN, 2010).

4.1 BEHAVIORAL STUDIES

Newborns appear to show distinct reactions to different facial expressions. Field and colleagues (FIELD et al., 1982) conducted a series of experiments observing newborns' behaviors using habituation and post-habituation procedures, during live interaction with a female experimenter. The findings suggested that newborns could not only discriminate facial expressions but that they also attempted to imitate expressions of happiness, surprise, and

sadness. However, the study had a number of methodological constraints (e.g., the lack of a control group), and a subsequent similar controlled study failed to replicate the previous results (FARRONI et al., 2007; KAITZ, 1988). In a more recent study by Farroni and colleagues (2007), habituation and visual preference procedures were applied with newborns between 24 and 120 hours after birth. Neonates showed significantly greater total looking time to happy than to fearful faces, whereas no differences were observed comparing fearful and neutral faces. The results were discussed in relation to the newborn's facial experiences during the first few days of life, presuming that faces expressing happiness were the most prevalent in the newborn's visual world. The authors speculated that happy face expression may be acquired earlier in perceptual development, reflecting infants' emotional experiences from birth onward, which in turn should facilitate infants' interactions with caregivers already within their first few days of life.

Even though there is some evidence that newborns may distinguish a few facial expressions, it is generally not until 3 to 5 months of age that infants are to be able to discriminate among some facial expressions in experimental studies (BAYET; PASCALIS; GENTAZ, 2014). Noteworthy, differential responses to emotions seem to be observed later in experimental contexts compared to those experienced in the infants' rearing environment. In experimental paradigms, infants discriminate between dynamic faces and multimodal stimuli earlier than between unimodal cues such as static faces (GROSSMANN, 2010), possibly because these types of stimuli are more similar to their typical social interactions, or because infants may initially rely on more salient cues, such as synchronous facial and vocal stimuli (LEPPÄNEN; NELSON, 2009). However, for the purpose of the present thesis, the majority of the studies reviewed investigated unimodal visual responses.

Between the ages of 3 and 5 months, infants appear to distinguish happy compared to frowning (GROSSMANN, 2010), surprised (YOUNG-BROWNE; ROSENFELD; HOROWITZ, 1977), sad (MONTAGUE; WALKER-ANDREWS, 2002), and neutral faces (BORNSTEIN; ARTERBERRY, 2003) as observed in empirical studies (BAYET; PASCALIS; GENTAZ, 2014, for a review). Kuchuck and collaborators (1986) reported that 3-month-olds discriminated happy compared to neutral faces, and among different exemplars of happy faces that varied in intensity. Infants' preference for happy (versus neutral) faces increased directly related to the increased degree of the smile, peaking with maximally toothy smiles. The authors also showed that maternal interaction styles possibly influenced infants' visual preferences. Mothers who often attracted their infants' attention to themselves while they were smiling, had infants who detected facial expressions of smiling more readily.

Another experiment (BORNSTEIN; ARTERBERRY, 2003) indicated that 5-month-olds were able to form categories of happy expressions, and that they recognized the same person despite changes in the person's emotional expressions.

Altogether, it seems that infants can discriminate and form categories of happy expressions, compared to several other emotions, before 6 months of age. Facial expressions of happiness and joy are typically the most prevalent affective expressions manifested by caregivers in the infants' rearing context (COHN; TRONICK, 1987; MALATESTA; HAVILAND, 1982). Infants' visual preference for smiling faces over the first months of life possibly contributes to the creation of a positive environment between the infant and the caregiver. Reciprocal positive interactions reinforce and sustain the caregiver's attention, nurturing their bonding, which is considered critical for the infant's survival and for the development of social and emotional abilities (BORNSTEIN; ARTERBERRY, 2003; PARSONS et al., 2010).

Between 5 and 7 months of age, infants' visual acuity has substantially improved (GROSSMANN, 2010), and face perception becomes more reliable. Infants begin to form categories of emotional expressions other than happy, such as sadness (STRIANO; BRENNAN; VANMAN, 2002), and fear (LEPPÄNEN et al., 2009). However, experimental methods vary significantly between the above-referenced studies, thus there are discrepancies regarding the exact age of discrimination appearance. Broadly, discrimination appears to emerge earlier in experiments using a single or a restricted number of identities (BAYET, 2015). After the age of 6 to 7 months, behavior studies reveal more robust data of the infant's capacity to categorize distinct expressions within an emotional category and among multiple identities (BAYET, 2015; LUDEMANN; NELSON, 1988).

Also at some time between 5 and 7 months of age, infants shift their visual preference to fearful faces over other emotions. Studies demonstrated that 7-month-olds looked longer at fearful compared to happy or neutral expressions (LEPPÄNEN et al., 2007; PELTOLA et al., 2009), and were less likely to disengage attention from fearful than to happy faces (PELTOLA et al., 2013). The visual preference for fear is consistently reported after this age both in behavior and neurophysiological studies (NELSON; DE HAAN, 1996; PELTOLA et al., 2013).

The perceptual bias to fear corresponds to the same pattern robustly observed in adult studies, presumed to relate to an evolutionary prioritization to quickly detect potential threats in the environment (LEPPÄNEN; NELSON, 2009). Also around this age, infants can roll over and may begin to crawl. As the locomotion ability improves and infants actively explore

the surroundings, the caregiver's fearful expressions are more likely to happen in the infant's context (LEPPANEN, 2011). Aligned to a plausible evolutionary adaptive mechanism, as infants attune to the caregivers' fearful faces, they are more likely to pay attention and learn to avoid aversive stimuli, heightening their chances of survival (VAISH; GROSSMANN; WOODWARD, 2008).

Also relevant, the ability to process emotional faces is facilitated by familiarity. Infants can discriminate emotional faces expressed by their own mother prior to those expressed by unfamiliar individuals (BARRERA; MAURER, 1981), and of their own-race prior to other-race faces (SAFAR; MOULSON, 2017).

Infants at 10 months of age begin to discriminate expressions in the same valence category despite manipulation of some internal features, indicating comprehension of general classes of affective stimuli (LUDEMANN, 1991). Studies on 8- to 10- month-olds demonstrated that infants begin to understand expression meanings and develop expectations about emotions, such as recognizing congruent emotional reactions to matched experimental conditions (SKERRY; SPELKE, 2014). One-year-olds comprehend expression meanings and are capable to guide their behaviors accordingly. For instance, in an experiment using the visual cliff paradigm, 12-month-olds were significantly less likely to crawl over a mock cliff when observing fearful faces posed by the mothers compared to happy faces (VAISH; GROSSMANN; WOODWARD, 2008).

The reviewed literature indicates a progressive refinement of detection and discrimination among facial expressions within infants' first year of life. It seems that the discrimination initiates with the differentiation of features and their configurational arrangements within the face, and progresses to the association of representations of emotional content. Over time, infants begin to recognize and understand the meaning of different emotional expressions, laying the foundation to later acquire higher social and emotional capacities (QUINN et al., 2011). Towards the end of the first year, infants' behaviors indicate the emergence of social understanding of emotions, evinced by the appearance of anticipatory smiles (SOMERVILLE; FANI; MCCLURE-TONE, 2011), and the capacity to attend to others' expressions to guide their own behavior, as it has been observed in social referencing experiments (QUINN et al., 2011).

4.2 NEURAL CORRELATES

4.2.1 ERP studies

The study of neural correlates of facial processing in infant population has predominantly used EEG and ERP techniques. The EEG is non-invasive and has good tolerability for the use in awake infants, allowing data collection in stimulus-evoked studies. The EEG is an electrophysiological measure of synchronized activation of pyramidal neurons of the cortex. The synchronized electrical activity produces distinct continuous oscillatory frequencies, that can be assessed using electrodes placed at the scalp. The electrical activity can be measured on the order of milliseconds, thus EEG is considered a method of high temporal resolution (NELSON; MCCLEERY, 2008). However, because the electrical signal propagates through the cortical areas, the localization of the neural activation is not precise using this methodology (GERVAIN et al., 2011).

Using the EEG recording, transient changes in neural activation secondary to discrete events can be measured, named ERP. ERPs have been widely used to explore brain activity evoked by perceptual and cognitive functions in infants, including perception discrimination, emotion recognition, and memory (NELSON; MCCLEERY, 2008). Reliable patterns of neural activity have been observed in experimental designs with the presentation of repeated stimuli, such as those of auditory and visual categories (NELSON; MCCLEERY, 2008). The first ERP studies used a limited number of electrodes placed on the scalp, for example, Nelson and de Hann (1996) used electrodes over midline (O2, Pz, Cz, Fz) and lateral scalp (T3 and T4). Subsequently, higher-density arrays of electrodes have been increasingly used, containing 64, 128 and up to 256 electrodes (LEPPÄNEN et al., 2007; NELSON; MCCLEERY, 2008).

Studies of the ontogeny of human visual face processing have reported face-sensitive components in infants, considered potential precursors of components related to facial processing reliably observed in adults (NELSON; MCCLEERY, 2008). In adults, the N170 is a face-selective negative deflection that peaks at 170 ms after the presentation of the stimulus, recorded from electrodes over occipital-temporal areas (LEPPÄNEN et al., 2007). The N170 is developmentally preceded by the N290 (negative deflection at 290 ms post stimulus), and the P400 (positive deflection at 390-450 ms after stimulus onset) (GROSSMANN; STRIANO; FRIEDERICI, 2007; YRTTIAHO et al., 2014). Both N290 and P400 have shown

differential responses to human faces, described in infants between 3 and 12 months of age (HALIT et al., 2004; NELSON; MCCLEERY, 2008).

The Nc component is a negative deflection peaking around 400 ms post stimulus onset, recorded over the frontal areas. The Nc is modulated by attention and orientating processes to salient stimuli in infants, such as a larger Nc reflects a greater allocation of attention. The Nc has been observed already at birth, but its modulation seems to be present from three months of age onward (NELSON; MCCLEERY, 2008).

Between 5 and 7 months of age, infants start to categorize several emotional expressions, and begin to demonstrate sensitivity to ERPs components in response to expressions of the face. Peltola and collaborators (PELTOLA et al., 2009) recorded the Nc component in response to happy and fearful faces of 5- and 7- month-old infants. Five-month-olds looked at either happy or fearful faces for equal periods of time. In accordance, the neural activation evinced a prominent Nc response to both happy and fearful stimuli. By contrast, 7-month-olds allocated greater visual attention to fearful faces (versus happy), and displayed a larger Nc component for this emotion.

As previously noted, around 7 months of age infants' visual preference for fearful faces (compared to other emotion expressions) emerge, and ERP studies corroborate this behavioral pattern. Nelson and de Haan (1996) conducted the first ERP study in infants to evaluate responses to emotional faces. The authors reported that 7-month-old infants evinced a larger Nc when observing fearful compared to happy faces, whereas no differences appeared among fearful versus angry faces. In another study (LEPPÄNEN et al., 2007), the occipital-temporal P400 revealed a larger amplitude to fearful versus happy or neutral faces, similar to the effect observed on the N170 on adults. ERP components of attention allocation and face processing appear to develop sensitivity to emotional expressions after 6 months of age (HOEHL; STRIANO, 2010), with more robust results documented after 7 months of age (DE HAAN et al., 2004; YRTTIAHO et al., 2014).

ERP studies in typically developing infants evinced neural correlates of perceptual face processing, including the N290 and P400, as well as attentional components (Nc). The observed developmental changes in face-sensitive ERP components are considered to reflect the effects of the experiences in the underlying neural systems of face processing.

In a unique ERP study that investigated the effects of the environment in face emotional processing in a typical population, de Haan and collaborators (2004) explored the potential impact of maternal personality (maternal emotional disposition) in 7-month-old infants' emotional face processing. Highly positive mothers (as indexed by the Positive and

Negative Affect Schedule) had infants that looked significantly longer at fearful than happy faces, as compared to infants of lowly positive mothers. A subgroup of these infants who themselves had higher scores in positive temperament (assessed by 5 subscales of the Infant Behavior Questionnaire) revealed a smaller Nc to happy versus fearful faces, as compared to infants with lower scores in positive temperament. The authors speculated that heightened exposure to happy faces (indirectly indicated by maternal higher levels of positive emotionality) resulted in less visual attention for this stimulus type. Additionally, infants own emotional disposition (assessed by the smiling and laughter temperament subscale) mediated the Nc response, indicating that highly positive infants had smaller Nc for happy faces.

4.2.2 EEG studies

The balance between the EEG power in the frontal right and left hemispheres has been explored in response to acute emotional states and in individual differences in emotional processing (FOX, 1991). Some studies have been conducted in typically developed infants, investigating differential patterns of FA. In one of the first reported studies, Fox and Davidson (1986) investigated neonates between 2 and 3 days of life. Newborns were videotaped and had EEG recorded while water, sucrose, and citric acid solutions were orally administrated. The newborns' facial expressions were coded by experimenters and analyzed in relation to EEG power and the discrete stimuli received. Greater left FA, compared to the right, was observed when the newborns displayed an expression of interest, as they received a pleasant taste (sucrose), in comparison to unpleasant (citric acid) or neutral (water) stimuli.

In another experiment (DAVIDSON; FOX, 1982), typically developing 10-month-olds observed a videotaped female model displaying happy or sad emotion expressions. Infants showed a greater relative left FA while exposed to happy faces. Asymmetries in the frontal activation patterns were also reported as 10-month-old infants expressed specific behaviors (FOX; DAVIDSON, 1988). When infants exhibited approach behaviors, such as displaying facial expressions of joy, or reaching with arms for their mothers, an increased left FA emerged. On the contrary, right FA was observed when infants demonstrated active withdrawal behaviors, showing distress and gaze aversion.

Individual differences in emotional dispositions, including emotion regulation and reactivity, have been correlated to distinct FA patterns (CALKINS; FOX; MARSHALL, 1996; FOX et al., 2001). Developmental studies have observed greater right FA in infants with more negative temperaments, such as higher reactivity and inhibition (FOX et al., 2001).

Behavioral inhibition is considered one of the most stable temperamental traits, related to an elevated risk for internalizing disorders, particularly for anxiety (DEGNAN; ALMAS; FOX, 2010; KAGAN; SNIDMAN, 1999). Calkins and colleagues (1996) observed that 4-month-olds with greater motor arousal and higher negative affect showed greater right FA at 9 months of age and behavioral inhibition at 14 months of age. In another longitudinal study (FOX et al., 2001), stability of FA scores between 9 and 24 months were shown to predict infants' levels of inhibition at age 4. Infants were behaviorally evaluated at 4, 24 and 28 months, and resting EEG was collected at 9, 14, and 24 months of age. About 25% of the infants classified as behaviorally inhibited (highly reactive, higher negative affect) at 4 months continued to show this temperamental trait at 4 years old, and presented greater right FA. By contrast, infants rated as exuberant (high sociability, lack of fear, and high approach) displayed more left FA.

4.2.3 fNIRS studies

The major advantage of the fNIRS technology is the possibility to better explore spatial location (compared to EEG/ERP) during stimulus-evoked experiments in awake infants.

Infant's face perception has been explored using fNIRS, with neural correlates observed over several brain areas (VANDERWERT; NELSON, 2014). Differential responses were evinced to faces compared to visual noise stimuli in 4-month-old infants over the occipital cortex (CSIBRA et al., 2004). Five-month-olds showed greater activation over inferior frontal areas while observing dynamic facial stimuli (i.e., variations of eye gaze) (GROSSMANN et al., 2008). Another experiment with 5-month-olds reported bilateral activation of temporal areas in response to dynamic social stimuli, as videoclips of female models were shown moving eye gaze direction, displaying silent mouth movements or performing hand games such as ‘‘peek-a-boo’’(LLOYD-FOX et al., 2009). Greater activation to upright compared to inverted faces appears between 5 and 8 months of age, an effect observed in the right (vs. left) temporal region (OTSUKA et al., 2007). The right parietal area was activated when 5- and 8-month-olds were exposed to frontal versus profile faces (NAKATO et al., 2009), and occipital-temporal regions in 7-month-olds viewing canonical contrasted with scrambled facial images (HONDA et al., 2010).

A few studies have specifically investigated hemodynamic brain responses to facial expressions of emotions during development. Unfortunately, several neural structures

involved in emotional processing are located deep in the brain, such as the amygdala, and cannot be assessed with fNIRS. However, cortical areas speculated to be also implicated in emotional face perception, including the OFC and the STS are potentially accessible to fNIRS technique.

Infants between 6 and 7 months of age were exposed to pictures of a female displaying happy and angry faces, revealing differential hemispheric responses. Greater activation over the left posterior temporal cortex was observed in response to happy facial expressions, whereas the right posterior temporal cortex showed greater responses to angry faces. The authors speculated that the STS was implicated in the observed responses (NAKATO et al., 2011). In another experiment (MINAGAWA-KAWAI et al., 2009), 9- to 13-month-old infants watched videos of their own mothers and of a female stranger producing a smile compared to neutral expressions. The fNIRS channels were positioned over the frontal brain areas, possibly including the OFC. The infants' brain activation was significantly different between the smiling compared and the neutral condition of the infants' own mothers.

In a recent exploratory study (RAVICZ et al., 2015), individual differences in 7-month-olds' temperament (measured with the Revised Infant Behavior Questionnaire Short Form) and brain responses to pictures of women portraying happy expressions (vs. a baseline video) were investigated. Hemodynamic activity was analyzed over the prefrontal area. Infants that scored lower in the negative emotionality dimension, which is considered a positive temperament trait, exhibited a preferential activation in two channels over the left prefrontal cortex (possibly the medial PFC area), compared to the right, in response to smiling faces (vs. baseline video). Greater left (vs. right) activation for a positive/ approach emotion was discussed in terms of the approach-withdrawal model.

5 MATERNAL ANXIETY AND DEPRESSION

The first part of this section provides a general overview of maternal anxiety and depression in the perinatal period, including prevalence estimates and effects in the offspring. In subsection 5.1 the most used self-report instruments to measure maternal anxiety and depression were reviewed. In subsections 5.2 and 5.3 the potential mechanisms and effects in the offspring during pre-and postnatal period were respectively covered. In subsection 5.4 behavioral studies of infants of anxious and depressed mothers were disclosed, followed by studies of neural correlates (5.5), describing EEG (5.5.1) and ERP (5.5.2) experiments.

Anxiety and depression disorders are among the most common of all psychological disorders within the general population, and are responsible for considerable disability worldwide (BAXTER et al., 2013; FERRARI et al., 2013). Women have increased risk for anxiety and depression diagnosis, notably during the years of childbearing age (GAVIN et al., 2005; ROSS; MCLEAN, 2006).

Maternal mental health is a major public health issue, as it affects not only maternal well-being but also the mother's relationship with her offspring, as well as the offspring's health and development (ZELKOWITZ; PAPAGEORGIOU, 2012). Conditions that affect the quality of maternal mental health, particularly from pregnancy to early childhood, may threaten the infant's development and increase the infant's risk for several detrimental outcomes across the lifespan (GLOVER; O'CONNOR, 2002; VAN DEN BERGH, 2008).

Anxiety and depression are the most prevalent mental disorders occurring in the perinatal period, defined as the period of the pregnancy, around childbirth and within the first year post-partum (MUZIK; BOROVSKA, 2010; O'HARA; WISNER, 2014; RIVA CRUGNOLA et al., 2016). Furthermore, elevated rates of maternal anxiety and depression symptoms have been reported as highly prevalent, and they have even at subclinical levels been correlated to adverse outcomes in the offspring (BARNETT et al., 1991; O'CONNOR; HERON; GLOVER, 2002). Infants of anxious and depressed mothers show increased vulnerability to cognitive and emotional problems throughout childhood, adolescence, and adulthood (BARNETT et al., 1991; GLASHEEN; RICHARDSON; FABIO, 2010; HAY et al., 2008).

During the first years of life, the exposure to maternal disrupted emotional mood and behaviors is believed to be particularly detrimental for the infant's development. As reviewed earlier, the emotion-recognition networks are believed to be established early in life, and functional around 5–7 months of age. The neural substrates are thought to be progressively

refined by the exposure to expressions, particularly during this sensitive period that is, albeit not clearly defined, believed to comprise the first few years of life (LEPPÄNEN; NELSON, 2009). Thus, the exposure to different patterns of emotions and emotional face expressions on a daily basis experienced by infants of anxious and depressed mothers may impact the establishment of basic networks of face perception and emotion recognition. As a result, infants exposed to these environments appear to have an increased risk to present atypical perceptual responses to faces.

Prenatal stress, anxiety and depression lead to an increased risk of preterm birth and low birth weight (FIELD et al., 2004), which in turn is related to behavior and mental problems (FIELD, 2011). Infants have increased rates of difficult temperaments (e.g., highly reactive, fearful, and inhibited) if their mothers were anxious and depressed during pre- and postnatal periods (AUSTIN et al., 2005; DAVIS et al., 2004). These temperaments are well-recognized predictors of adult anxiety disorders (KAGAN; SNIDMAN, 1999). Additionally, maternal anxiety and depression have been correlated to childhood behavioral problems and increased rates of psychiatric diagnosis, including attention-deficit/hyperactivity disorder (VAN DEN BERGH; MARCOEN, 2004), conduct disorders, anxiety and depression (O'CONNOR et al., 2003).

Anxiety and depression share several symptomatic presentations, are modulated by common genetic factors, and are frequently comorbid (GRUPE; NITSCHKE, 2013; MÖLLER et al., 2016). Both disorders are linked to a vulnerability to general affective distress, yet differences in the distress factors were suggested to be specific to each disorder, such as physiological hyperarousal would be related to anxiety, whereas anhedonia would occur in depression (CLARK; WATSON, 1991). In the clinical presentation, depression is more associated to persistent depressed mood and to deficits in the capacity of experiencing positive affect, whereas anxiety is characterized by the persistence of worry and fear. Among both disorders, symptoms of nervousness, irritability, disturbed sleep and impaired concentration overlap (GRUPE; NITSCHKE, 2013).

The incidence and prevalence estimates of maternal anxiety and depression vary considerably among the studies, depending on the measures utilized, the diagnosis criteria and the timing of assessments (GAVIN et al., 2005). Within the general population, there is a wide variation in the estimates of the prevalence of anxiety and depression. Around 10-20% of women will exhibit symptoms of depression during pregnancy and/or the postpartum period (DUNKEL SCHETTER; TANNER, 2012). Clinically diagnosed depression varies

between 5–12.9% during the perinatal period (FAIRBROTHER et al., 2016; GAVIN et al., 2005; RECK et al., 2008).

Only recently have anxiety disorders in the perinatal period received more scientific attention, and the prevalence is still unclear, but estimates for increased symptoms range as high as 39% (LEACH; POYSER; FAIRWEATHER-SCHMIDT, 2015). Clinical anxiety studies are predominantly based on small samples, and have reported prevalence between 1.2% to 17.1% during pregnancy and the postpartum period, depending on the type of anxiety disorder (FAIRBROTHER et al., 2016; RECK et al., 2008; ROSS; MCLEAN, 2006). A recent meta-analysis (GOODMAN; WATSON; STUBBS, 2016) about clinically anxious mothers estimated 8.5% of prevalence for one or more anxiety disorders during the first postpartum year.

The prevalence of comorbid depressive and anxiety symptomatology in perinatal samples ranges from 10% to 50% (FALAH-HASSANI; SHIRI; DENNIS, 2016; FARR et al., 2013). Clinical studies in the postpartum period report comorbid anxiety in a third of women with a major depression episode (AUSTIN et al., 2010). Population-based prevalence estimates of comorbid postpartum anxiety and depression are lacking, but general population-based rates in adults estimated that 50% of anxiety cases had comorbid depression, whereas one third of adults with depression presented comorbid anxiety (FARR et al., 2013).

5.1 SELF-REPORT INSTRUMENTS

A large number of the studies about maternal mental health and child outcomes relies on symptoms scales, rather than a clinical diagnosis of anxiety and depression. Although effects appear to be more robust for the clinical samples, community-based studies have also shown important adverse outcomes in children of mothers with heightened self-reported anxiety and depressive symptoms (O'CONNOR et al., 2002; STEWART et al., 2003). Several self-report instruments have been widely used in perinatal samples and up to one year following childbirth, a number were validated by the authors, and further correlated with clinical evaluations and confirmed diagnoses (MEADES; AYERS, 2011). The present thesis mainly focused on this body of scientific research. For convenience, the terms "maternal anxiety" and "maternal depression" were used to refer to both clinical and subclinical types of studies.

Diverse instruments have been used in the perinatal period to explore associations with maternal and infants' behaviors and neurophysiological findings. For depression evaluation,

among the most used scales are: The Beck Depression Inventory (BDI; BECK; STEER; CARBIN, 1988), the Center for Epidemiological Studies Depression Scale (CES-D; cited in FIELD et al., 2002), and the Edinburgh Postpartum Depression Scale (EPDS; cited in FALAH-HASSANI; SHIRI; DENNIS, 2016). To assess anxiety, the most widely used instrument (GRUPE; NITSCHKE, 2013) is the State Trait Anxiety Inventory (STAI; SPIELBERGER et al., 1983). The Beck Anxiety Inventory is also frequently used (BAI; cited in CLARK; WATSON, 1991). Furthermore, some instruments explicitly include dimensions of anxiety and depression, such as the Hospital Anxiety and Depression Scales and the Symptom Checklist-90-R (SCL-90-R) (for example. in OTTE et al., 2015).

The BDI is a self-report questionnaire composed of 21 items that measure manifestations of depression in the past 2 weeks. It has a mean internal consistency of .81, ranging from .73 to .92 (BECK; STEER; CARBIN, 1988). Several authors have argued that the BDI is not specific to depression, reporting poor discriminant validity against anxiety (RICHTER et al., 1998).

The CES-D is a 20-item scale questioning about depressive symptoms during the past week. Items are rated according to the experienced frequency, from ‘‘rarely or none of the time’’ to ‘‘most or all of the time”, and include questions about depressive mood, feelings of hopelessness and sleep disturbances, for example. A score of 16 or above is considered significant for symptomatic depressed subjects, typically used as a cut-off in maternal mental health research (for example, DIEGO et al., 2002). The scale has high internal consistency in community and clinical populations (Cronbach's α .85−.90). Many researchers have also questioned the validity of certain CES-D items, some of them have been regarded as potentially confoundable with anxiety constructs (e.g., CARLETON et al., 2013).

The EPDS is considered the gold standard screening tool for depression in perinatal population (DUNKEL SCHETTER; TANNER, 2012), however it is not the most used instrument. It consists of 10 items scored on a 4-point scale ranging from 0 to 3. Cut off points from 9 to 13 are used (total possible 30), and high internal consistency (Cronbach's α .82–0.84) is reported. Notably, as the BDI and the CES-D, the EPDS also has been shown to measure both depressive and anxiety symptoms, and cannot reliably distinguish between depression and anxiety (BROUWERS; VAN BAAR; POP, 2001). For instance, sample questions of the EPDS include “I have been anxious or worried for no good reason” and “I have felt scared or panicky for no very good reason”.

The STAI (SPIELBERGER et al., 1983) has two subscales with 20 items each. The state subscale (STAI-S) assesses a transitory anxiety experienced at a specific moment,

whereas the trait component (STAI-T) measures symptoms more generally, related to a propensity to respond with elevated anxiety. Items are answered in a range from 1 (not at all/almost never) to 4 (very much/almost always). Several studies attested the construct and concurrent validity of the STAI, with internal consistency Cronbach's α ranging from .86 to .95, and mean of test-retest reliability r=.88 at multiple time intervals (SPIELBERGER, 1989). The original scale (1970) was revised to improve specificity, and items potentially confounded with depression were replaced, it was then named STAI-Y (SPIELBERGER et al., 1983). The STA-Y is the most popular version used and typically referred as simply "STAI". Some authors suggested that the STAI is also associated with depression, and argued it measures negative affect in general (GRUPE; NITSCHKE, 2013). However, in perinatal samples it has been considered a robust and specific measure of anxiety, has good predictive validity and in some studies, it was validated against clinical interview (MEADES; AYERS, 2011).

The scores of the above-referenced measures are commonly used either as continuous variables, or as dichotomized values in order to compare groups of controls to anxious and/or depressed mothers. The latter means creating a proxy for diagnostic categories (DUNKEL SCHETTER; TANNER, 2012). Most studies in this area are based on depression scales. However, considering the high incidence of comorbid anxiety and depression, their shared features and genetic basis, some authors have argued that it might be impossible to statistically control for symptoms of anxiety and depression to study these disorders separately (FIELD, 2011; GRUPE; NITSCHKE, 2013). It has been proposed to denominate it all stress-related or negative affect measures, when using scales that rate symptoms of both disorders interchangeably (FIELD, 2011; GRUPE; NITSCHKE, 2013). Thus, although most of maternal mental health studies focused on depression symptoms scales, many researchers in the field consider that the findings relate to anxiety as well (MATTHEY et al., 2003).

5.2 PRENATAL PERIOD

5.2.1 Mechanisms and effects in the offspring

Maternal anxiety and depression are related to elevated levels of stress. The mechanisms between the exposure to high levels of maternal stress and related outcomes in the offspring have been studied both in animal models and human studies (GLOVER; O'CONNOR, 2002). During the gestational period, altered concentrations of maternal stress

hormones (e.g., glucocorticoids), may be transmitted across the placenta and affect the fetus (VAN DEN BERGH et al., 2008). Another hypothesis accounts for abnormalities in the blood flow through the uterine arteries, potentially affecting the nutrients and oxygen supply required for a healthy fetus development (TEIXEIRA; FISK; GLOVER, 1999). Recent studies support the fetal programming hypothesis[2], as the effects of the environment particularly during sensitive periods in utero can impact the fetal phenotype permanently, leading to long-term outcomes across the lifetime. Monk and colleagues (KINSELLA; MONK, 2009; MONK; SPICER; CHAMPAGNE, 2012) argued towards a high susceptibility of the placenta for epigenetic dysregulation, and its critical role in regulating the intrauterine environment.

Elevated maternal stress during pregnancy provokes dysregulation of stress-regulating systems: the hypothalamic-pituitary-adrenocortical (HPA) and the autonomous nervous system. The HPA regulates the corticotropin-releasing hormone, vasopressin, and glucocorticoid among other hormones, whereas the autonomous nervous system controls the levels of catecholamines (e.g., noradrenaline, adrenaline), inducing sympathetic activation (GLOVER; O'CONNOR, 2002). The placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) is a pivotal enzyme that converts cortisol into inactive cortisone, regulating the glucocorticoids influx to the placenta (MONK; SPICER; CHAMPAGNE, 2012). Maternal stress and heightened catecholamine levels both in the mother and the fetus impair the 11β-HSD2 activity, compromising the placental glucocorticoid barrier (GLOVER; O'CONNOR, 2002). The glucocorticoids increase affects the fetal brain development as shown in animal studies, and is speculated to mediate the observed findings in human brain studies (MONK; SPICER; CHAMPAGNE, 2012), potentially as a consequence of epigenetic dysregulation through alterations in synaptogenesis and neurotransmitter functions (OTTE et al., 2015). Heightened corticoid levels have also been linked to increased rates of premature births (FIELD et al., 2004). The adverse biochemical and physiological effects on the fetus and the newborn are believed to mediate the observed alterations in the infant's perception and behavior observed in the studies further reviewed (FIELD, 2011).

Besides the effect on disrupting the placental barrier, greater levels of catecholamines may also contribute to elevating the uterine artery resistance (FIELD et al., 2004). In a cohort study, pregnant women reporting high levels of anxiety symptoms showed an increased

[2] The Developmental Origins of Health and Disease (DOHaD) hypothesis relates to short- and long-term consequences of the conditions of the developmental environment accounting for health and disease risk (VAN DEN BERGH, 2008).

uterine artery resistance index, compared to subjects describing low anxiety, assessed between 28 and 32 weeks of gestation (TEIXEIRA; FISK; GLOVER, 1999). Greater blood flow resistance is associated with restricted inflow of oxygen and nutrients, resulting in a fetal intrauterine growth restriction, as well as in an increased risk of pre-eclampsia (VAN DEN BERGH et al., 2008). Although noradrenaline does not seem to be directly transferred from mother to fetus, it has been hypothesized that greater maternal muscular and vascular tones might lead to enhanced cortisol and stress in the fetus (VAN DEN BERGH et al., 2008).

Recent neuroimaging studies (QIU et al., 2015; SANDMAN et al., 2015) in infants and children whose mothers experienced elevated levels of anxiety and depression, either during pregnancy and the postnatal period, evidenced alterations of developmental trajectories of brain circuitries. Such alterations were mainly observed in the PFC and the reciprocal connections with the amygdala, known to play an important role in emotional processing and regulation.

Prenatal exposure to anxiety and depressive symptoms was correlated to alterations in brain structures and neural networks in newborns, infants and in children up to 6-9 years old (QIU et al., 2015; RIFKIN-GRABOI et al., 2013). In one study (RIFKIN-GRABOI et al., 2013), neonates were evaluated between 6 and 14 days of life, and significant alterations in the microstructure of the right amygdala were observed. Compared to controls, newborns of prenatally depressed mothers showed lower fractional anisotropy in the right amygdala, a measure of delayed neuronal maturity. Qiu and collaborators (2015) also evaluated 6-month-olds exposed to maternal depression assessed at 26 weeks (as indexed by CES-D), using MRI and resting-state fMRI. Considering the whole group, 6-month-olds had widespread connections between the amygdala and cortical areas. The infants exposed to higher levels of depressive symptoms showed heightened left functional connectivity of the amygdala with temporal cortex and insula, as well as the bilateral ACC, medial OFC and vmPFC. Such regions are involved in emotional regulation as previously reviewed.

The altered patterns observed, however, are not linear, and might be influenced by the timing of exposure to maternal symptoms. For instance, another experiment (POSNER et al., 2016) reported decreased connectivity between the amygdala and dorsal PFC in infants with 2 weeks of life. In this sample, maternal depression scores (assessed with CES-D) were obtained at the end of the pregnancy (34-37 weeks), and the neural alterations were further correlated with fetal heart rate reactivity.

A prospective longitudinal study (SANDMAN et al., 2015) included measures of maternal depressive symptoms (CES-D) at 19, 25 and 31 weeks of gestation and an MRI scan

of the offspring between 6 and 9 years of age. Compared to controls, children of depressed mothers had lower cortical thickness in the right frontal lobes. The researchers also observed a stronger association between maternal depression scores at 25 weeks of gestation and cortical thinning, enhanced by 19% within the whole cortex, and by 24% in the frontal lobes, particularly in sub regions of the right PFC (i.e., right superior, medial orbital and frontal pole), compared to controls. Notably, similar findings (i.e., lower gray matter volumes in the amygdala and frontal areas) have also been reported in MRI studies of depressed adults (SACHER et al., 2011 cited in SANDMAN et al., 2015).

Other studies investigated anxiety and depression pre- and postnatally. In one study (QIU et al., 2013), mothers' STAI-T was measured at 26 weeks of pregnancy, and again when the infants were at 3 months of age. Newborns underwent MRI to assess hippocampus development at 3 months, and a subsample was scanned again at 6 months of age. No bilateral hippocampal volume differences were observed at birth. However, greater levels of anxiety during pregnancy were correlated to infants' slower growth of right and left hippocampus during the first 6 months of life. The levels of postnatal maternal anxiety were associated differently to right and left hippocampus growth. Greater anxiety levels were positively associated to right hippocampal growth, whereas they were negatively related to left hippocampal volume at 6 months of age.

In addition, continuous exposure to depressive symptoms from the postnatal period through childhood was correlated to alterations in the amygdala size. Lupien and collaborators (2011) examined postnatal CES-D maternal scores longitudinally (at 5, 17, 30, 42, 60, 84, and 156 months postpartum). The mothers who showed continuous higher CES-D scores, had their children MRI scanned at 10 year of age. Compared to children not exposed to maternal depressive symptoms, the children of the symptomatic mothers had significantly larger left and right amygdala volumes, as well as increased levels of salivary glucocorticoids.

Hence, exposure to maternal anxiety and depression during pregnancy and in the postnatal period seem to affect the offspring's' brain development, including the PFC, amygdala, and their connectivity. Disruptions in the underlying substrates of affective-processing may reflect altered stress reactivity responses which could, in turn, lead to heightened vulnerability for mood anxiety disorders in this population. However, despite the increasing work in the field, the precise mechanisms mediating the exposure to a dysregulated intrauterine and extrauterine environment, and adverse child neurodevelopmental outcomes remain to be better clarified.

5.3 POSTNATAL PERIOD

5.3.1 Maternal behaviors and mother-infant interaction

In the postnatal period, maternal symptoms of anxiety and depression may jeopardize the quality of the relationship between the mother and the infant. Affected mothers have an increased risk of demonstrating poor parenting behaviors, possibly impairing the quality of mother-infant emotional interactions (KERTZ et al., 2008). Additionally, mothers experiencing anxiety and depression are believed to display different frequencies and intensities of particular facial expressions. The atypical exposure to specific facial expressions in the course of daily mother-infant interactions may influence infants' perception and responses to emotional faces (DE HAAN et al., 2004; JONES et al., 2013).

During the interactions with the infant, the mother demonstrates attention, facial expressions, vocalization and touch to engage in social and emotional experiences with her infant. In turn, the infant is receptive to the maternal behavior, recognizes her face and voice and progressively attunes to her emotional state. These early interactions are crucial to the formation of attachment and strongly influence the infant's social and emotional basic regulation skills (BOWLBY, 1988; TREVARTHEN, 2011), ultimately implicated in the achievement of emotional competence and socialization abilities (FELDMAN, 2007).

Several aspects of maternal behaviors during the interactions with their infants can be evaluated, including the dimensions of maternal attention, emotional tone, sensitivity and facilitation. Attention can be measured as the time the mother dispenses focusing on the infant and the infant's activity, making eye contact and vocalizing. Maternal emotional tone is analyzed observing the posture, and the affective tone in facial and vocal expressions. Sensitivity accounts for the mother's capacity to appropriately detect and respond to infant's cues, the degree of accurate interpretation of infant's signals and the coordinated, prompt responses that are expected (BOWLBY, 1988; FELDMAN, 2007). Facilitation refers to the capacity to assist and encourage the infant's activities, showing availability and active engagement without taking over or being intrusive. Contingency is explored by evaluating aspects of social communication between the mother and the infant. Interactive contingency consists of moment-to-moment adjustments in social relationships, including the capacities of predictability and coordination that each individual makes in response to changes in the partner's behavior (BEEBE et al., 2011; RIVA CRUGNOLA et al., 2016).

Theses dimensions are explored observing the mother-infant relationship during home visiting or in experimental settings, rated with observational scales and qualitative reports. Maternal sensitivity and responsivity are considered key aspects to promote contingent interactions. Contingency, in turn, is considered the foundation of social communication (BEEBE et al., 2011). Those processes are related to positive health and development outcomes in the offspring, and promote the development of higher social and affective functions in the individual (PAPOUŠEK, 2007; PARSONS et al., 2010).

Maternal anxiety and depression have been consistently related to altered maternal behaviors and disruption of the mother-infant interactions. Murray, Fiori-Cowley, Hooper and Cooper (1996) observed that depressed mothers were less sensitive, expressed fewer empathic and imitation responses than non-depressed mothers. Mothers with depression were also shown to smile less, display more flat affect and negative facial expressions and interact with infants in a withdrawn and muted style (Diego, & Hernandez-Reif, 2009 (BORNSTEIN et al., 2011). Additionally, depressed mothers were less likely to identify happy infant faces accurately when compared to controls and anxious mothers (ARTECHE et al., 2011).

Weinberg and Tronick (1998) observed maternal depression and related alterations the in mother-infant relationship, indicating disruptions in all the communicative domains analyzed: face, voice, and touch. Depressed mothers spent less time looking at, talking to, and touching their infants. They also showed fewer positive and more negative face expressions compared to non-depressed mothers. Cohn and Tronick (1989) pointed that depressed mothers presented two distinct interaction styles: withdrawal and intrusive. Withdrawal depressed mothers are less engaged with their infants, display more flat and sad affect, are less playful, and make less vocalizations, rarely using motherese (i.e., altered speech patterns when talking to the infant). Intrusive mothers, on the contrary, are overly reactive, tend to interfere with the infant's activities showing rough physical contact, and demonstrate more loud and fast vocalizations. Different characteristics of infants' behavior during interactions were also observed in these domains. Infants of withdrawn depressed mothers spent more time fussing and crying, whereas infants of intrusive depressed mothers were more avoidant when interacting with their mothers (COHN; TRONICK, 1989).

Anxious mothers also show less sensitivity during interactions, and the behaviors have been described as more intrusive (FELDMAN, 2007), and controlling (ZELKOWITZ; PAPAGEORGIOU, 2012). Nicol-Harper, Harvey, and Stein (2007) showed that high trait anxiety mothers (indexed with STAI-T) had less sensitive responsivity and reduced positive

emotional tone while interacting with their 10- to 14-month-old infants, compared to low anxiety mothers.

To evaluate the influence of maternal anxiety symptoms in early mother-infant communications, Beebe and colleagues (2011) videotaped face-to-face interactions of 119 dyads from a community sample. The mothers' anxiety was assessed using STAI-T, and data was collected when infants were 4 months of age. The authors specifically analyzed attention, affect, spatial orientation, and touch in self- and interactive contingency modalities. The presence of maternal anxiety altered all the modalities analyzed in the dyadic interactions, evincing general greater discrepancies in mother-infant communication. For instance, mothers with anxiety symptoms spent more time gazing at their infant's face, but showed lower empathic coordination to their infant's emotional face expressions. The authors pondered: "Vigilant visual monitoring, without empathic emotional response, suggests that mothers may be "looking through" the infants' faces, as if the infant is not "seen" or experienced." The observed intermodal discrepancies are considered disrupted forms of communication, and are thought to be confusing for the infants. Anxious mothers are presumably self-absorbed in their heightened worry, over-aroused/fearful states, resulting in behavior patterns of emotional distancing and disengagement. It has been hypothesized that such patterns could result from a self-protective attempt to decrease arousal and avoid further distress (KAITZ; MAYTAL, 2005).

Field and collaborators (2005a) used a median split to compare spontaneous and imitative interactions of depressed mothers with high and low anxiety (STAI) with their infants. Compared to the low anxious depressed mothers, the high anxious depressed mothers spent less time smiling, showing exaggerated faces, imitating and playing with their infants. High anxious depressed mothers also spent more time moving their infants' limbs, whereas no differences in the amounts of time of vocalizing and touching were observed between the groups.

Riva Crugnola (2016) recruited dyads from a community sample and observed mother-infant free play interactions using a microanalytic approach. Mothers completed EDPS and STAI scales. Researchers that were blind to the maternal status videocoded the interactions on contingency (evaluating dyadic matched and mismatched states), and global emotional states (positive, negative or neutral). The authors observed that depression was correlated with both negative maternal states and negative dyadic matches, as well as to infant positive/mother negative mismatches. Anxiety scores were also correlated with both negative maternal states and infant negative states, but those dyads had increased mismatches,

observed when one of the partners showed negative states. They further conducted multiple regression analysis revealing that anxiety was a stronger predictor of less adequate styles of mother-infant emotion regulation than depression.

While many studies have shown altered maternal behaviors in anxious and depressed mothers, some studies found minor or no evidence of significant impairment of mother-infant interactions, even in clinical samples (KAITZ et al., 2010; WEINBERG; TRONICK, 1998). In a study following clinical depressed mothers longitudinally, Campbell and collaborators (1995) found that mothers who were capable to engage in positive mother–infant interactions despite their symptoms were less likely to develop a chronic course of depression.

Overall, maternal anxiety and depression have both been related to diminished sensitivity, responsivity and less contingent interactions with their infants. Maternal anxiety behaviors have only been studied more recently, and the limited number of studies available reported more intrusive and poorly contingent interactions (BEEBE et al., 2011). The intrusiveness and overactive behaviors of anxious mothers appear to be more closely similar to the observed behaviors of depressed mothers with intrusive style.

Both anxiety and depression disorders are related to infants' reduced exposure to positive affect (AKTAR; BÖGELS, 2017; BORNSTEIN et al., 2011; JONES et al., 2013). However, there may be differences in symptom presentation that possibly contribute to infants' perceptual and social development in different ways. For instance, maternal depressive symptoms have been associated with infants' increased exposure to sadness and flat affect (FIELD; DIEGO; HERNANDEZ-REIF, 2009; HERNANDEZ-REIF et al., 2006). In contrast, mothers with anxiety experience excessive fear and worry (AKTAR; BÖGELS, 2017), thus the frequency with which infants are specifically exposed to fearful emotional stimuli may greater than in infants of depressed mothers.

5.4 BEHAVIORAL STUDIES

Most of the literature has focused on depression, and the results on infants of depressed mothers (IDM) reported here were predominantly collected with depression self-report symptom scales. However, as previously noted, such scales have been shown to invariably assess anxiety symptoms as well. Thus, the reported outcomes for IDM may also be related to maternal anxiety symptoms.

Infants of anxious and depressed mothers have been observed to display a number of atypical behaviors during emotion-related experiments, such as showing less interest for facial

expressions and for face-voice pairs (FIELD; DIEGO; HERNANDEZ-REIF, 2009), less smiling and vocalizations (FIELD et al., 2005), longer periods required to habituate to faces (HERNANDEZ-REIF et al., 2006), and impaired discrimination among different emotions (BORNSTEIN et al., 2011; HERNANDEZ-REIF et al., 2002).

Hernandez-Reif, Field, Diego, and Largie (2002) evaluated newborns of depressed mothers (indexed by CES-D) while they were exposed to their own mother and a female stranger. IDM oriented less to their mothers and a stranger faces and voices as early as the first hours of life, compared to newborns of healthy mothers. They required significantly more trials and longer periods than the infants of non-depressed mothers (INDM) to habituate to their mother's face-voice pairing, and they were more likely to fail to discriminate their mother from a stranger.

A subsequent study (HERNANDEZ-REIF et al., 2006) analyzed infants of mothers reporting high levels of depression in the prenatal period (measured with the CES-D, including comorbid anxiety), that continued to report depression when the infants were 3 month of age. Infants were tested in a multimodal experiment, with a video of a female model portraying happy and sad faces and voice stimuli. IDM required longer time to habituate to faces, particularly to happy expressions. Additionally, IDM appeared to discriminate sad from happy expressions, but only if they were first habituated to the sad expression, thus suggesting that they may have not perceived sad expressions as a novelty.

A previously above-referenced study (FIELD et al., 2005) reported that depressed mothers with high levels of anxiety symptoms were less positive (i.e., showed less smiling) and less engaged with their 3-month-old infants during interactions, compared to depressed mothers reporting lower levels of anxiety. Infants of highly anxious depressed mothers also spent less time smiling, and more time in distress and crying, but equivalent amounts of time on other analyzed behaviors: imitation, vocalization, gaze aversion and motor activity.

Striano, Brenann and Vanman (2002) investigated 6-month-olds' abilities to discriminate increasing intensities of smiling and frowning expressions, compared to neutral stimuli. Additionally, the potential influence of self-reported maternal depressive symptoms, collected with a modified version of the Inventory to Diagnose Depression was explored. Infants were tested in visual paired comparison procedure, and observed during a face-to-face mother-infant interaction. All infants discriminated between emotional expressions compared to neutral faces. IDM, however, revealed a visual preference for happy faces, showing greater looking time for smiling faces in general, and a trend for preference for the most intense smiling stimuli. Depressed mothers' scores were additionally correlated to infants' longer

gazing at their mothers while they were smiling. The findings were interpreted as related to the possible diminished exposure to smiling faces in the IDM, that would, in turn, enhance their visual preference for a relatively novel stimulus, as compared to INDM.

In experiments applying the still-face procedure (FIELD et al., 2007; FIELD, 1984), 3-month-olds IDM exhibited less distress and fewer negative expressions compared to the typical response of INDM, presumably related to being more accustomed to a less expressive environment characterized by their mothers' relatively flat affect and less interactive behaviors (FIELD, 1984). The IDM also showed less interactive behaviors (i.e., fewer positive and negative behaviors) during the observed spontaneous mother-infant interactions. Evaluating the still-face paradigm in infants of clinically anxious mothers, Kaitz and colleagues (2010) also observed less negative emotions when compared to infants of healthy mothers.

The experience with disrupted behaviors and atypical exposure to emotional faces seem to influence infants' visual responses to faces. Infants appear to have less visual attention to emotional faces, and show distinct stimuli preferences as compared to INDM. The systematic exposure to an environment with flatter affect and negative emotions, possibly contribute to reflect infants' greater preference for happy faces, and less distress in experiments that mimic emotional unavailability, such as the still-face procedure.

The main findings of the studies with infants of anxious and depressed mothers that focused on behavioral and neural correlates of emotional face responses are summarized in Figure 7.

5.5 NEURAL CORRELATES

5.5.1 EEG studies

A pattern of greater right FA has been suggested to reflect a vulnerability for emotional disorders, as observed in studies on the offspring of depressed mothers. Several studies have reported patterns of greater relative right FA in anxious and depressed mothers, as well as in their infants, compared to healthy mother-infant dyads (DAWSON et al., 1997; DIEGO et al., 2006; FIELD et al., 1995, 2003; THIBODEAU; JORGENSEN; KIM, 2006). Most of the EEG studies reviewed in this section were recorded using lycra stretchable caps (manufactured by Electro-Cap, Inc.) positioned on infant's head according to the international 10-20 system, focusing in electrodes at frontal and parietal sites (for example, using

electrodes on F3, F4, P3, P4, referenced to the vertex Cz; DIEGO et al., 2006; JONES; FIELD; FOX, 1997).

Thibodeau, Jorgensen and Kim (2006) conducted a meta-analytic review about anxiety, depression and resting EEG FA studies including infants and adults. Data from 1,088 infants were analyzed, with a mean age of 3.9 months (ranging from newborns to 17 months). IDM had greater right FA than INDM. The FA differences were robust for newborns up to 13- to 15-month-old infants. Notably, results yielded that younger samples showed larger FA effects than older ones.

Stable patterns of right FA have been reported in IDM compared to INDM, investigated at the neonatal period (JONES et al., 1998), as well as at 1 and 3 months of age (JONES; FIELD; FOX, 1997). In another study (JONES et al., 1997) to evaluate stability across infancy, IDM were followed from 3 months to 3 years. Of the initial 32 infants studied at 3 months of age, 15 were analyzed at 3 years of age. Seven of the eight children who had exhibited right frontal EEG asymmetry as infants still showed the EEG asymmetry pattern at the 3-year visit. Children with relative right FA at 3 years of age were more behavioral inhibited during an exploratory play task, and children of depressed versus non-depressed mothers were less empathic during a simulated maternal distress paradigm.

To study the effects of prenatal anxiety on the fetus and the newborn in a wide range of behavior and physiological measures, 166 women were evaluated in the second trimester of pregnancy using the STAI-T scale, and measures of depression and (CES-D) anger (FIELD et al., 2003). Women classified as highly anxious (STAI-T>38) also scored high on measures of depression and anger. During the prenatal period, these mothers had greater urinary levels of norepinephrine and lower dopamine than lowly anxious mothers. Analyzing the fetus, highly anxious women had more fetuses with growth delays and greater motor activity. Newborns of highly anxious mothers had greater right FA compared to neonates of lowly anxious mothers. EEG data was obtained with the infant in a quiet alert state. Newborns of anxious mothers also had lower vagal tone, as well as low dopamine and serotonin levels.

Field, Pickens and Fox (1998) also examined induced acute emotional responses with EEG. Three-month-olds IDM and INDM watched videos of a female model displaying happy and sad facial and vocal expressions. The INDM exhibited greater relative right FA when viewing sad compared to happy face-voice stimuli. Yet, no differences on FA were found for IDM. In a subsequent study (DIEGO et al., 2004b), 3- to 6-month-old IDM and INDM had EEG recorded while observing their own mothers versus strangers posing happy, sad and surprised expressions. In both groups, infants demonstrated greater right FA during their

mothers' and strangers' sad compared to happy expressions. However, IDM had significantly greater right FA compared to INDM throughout the different expressions performed by either the mother and stranger. Furthermore, IDM were less interested in facial expressions, displayed less positive and more negative affect, and greater levels of salivary cortisol, collected after the experiment.

Using a prospective longitudinal design, Lusby and collaborators (2014) enrolled pregnant mothers that had previously been clinically diagnosed with anxiety or depression disorder. Data was collected during pregnancy, and at 3 and 6 months postpartum. EEG was collected from 16 left and right scalp sites, and the frequency band between 6-9 Hz was used to compute EEG power. At 3 and 6 months of the infant's age, mothers and infants were observed during interactions, while infants' EEG was recorded. The authors reported greater right FA only for infants that had symptomatic mothers during pregnancy and the postpartum period. The presence of depression just in the postpartum evaluation was not correlated to the EEG findings.

A few studies recorded EEG while the infants were observing emotional faces, during facial presentation of their own mothers and strangers (DIEGO et al., 2002, 2004b), or while observing videos of female models displaying face-voice emotions (FIELD; PICKENS; FOX, 1998). The results are presented in Figure 7, along with behavioral studies that directly evaluated emotional face processing.

Although many studies reported FA patterns, there also have been studies showing null results (FIELD; PICKENS; FOX, 1998; VANMEENEN, 2005). The specific neural substrates and mechanisms that could be driving the observed FA patterns are currently unknown. It has been suggested frontal hemispheric desynchronization could reflect asymmetric inputs originating in the amygdala (KAGAN; SNIDMAN, 1999) or driven by thalamic rhythmicity (ALLEN; COAN; NAZARIAN, 2004). Genetic components, alterations during pregnancy, and the post-natal period, or combination of these aspects may be involved.

Figure 7 - Studies of behavior and neural correlates of emotional face processing in infants of anxious and depressed mothers

Authors	Participants (n)	Mean age[a]	Maternal assessment	Method	Findings/Results
Hernandez-Reif et al.,	20 (10 IDM)	45 h	CES-D	Habituation and dishabituation to mother	IDM required more trials and took longer to habituate to their

2002				and stranger face-voice	mothers' face and voice IDM failed to discriminate their own mothers from a stranger
Field, 1984	28 (14 IDM)	3.0 mo	BDI STAI	Mother-infant interaction, still-face procedure and infant behavior coding	IDM showed less distress in still-face procedure (less negative facial expressions and less vocalizations)
Pickens & Field, 1995	84 (27 IDM)	3.1 mo	BDI	Mother-infant interaction and infant facial expression coding	IDM displayed more sad and anger expressions and less interest expressions
Diego et al., 2002	27 (Intrusive=14, Withdrawn=13)	3.3 mo	CES-D	Mother-infant interaction, Visual preference for mother and stranger facial expressions Infant behavior coding EEG recorded during visual preference	Infants of intrusive mothers looked longer to surprise and sad than to happy expressions performed by a stranger, displaying a concomitant greater right FA activity
Peláez-Nogueras et al. 1996	48 (24 IDM)	3.4 mo	BDI	Mother-infant interaction, still-face and still-face-with-touch procedures	IDM displayed less distress and negative behaviors in still-face procedure IDM submitted to still-face-with-touch procedure showed more positive affect (more smiles and vocalizations)
Hernandez-Reif et al. 2006	32 (16 IDM)	3.5 mo	CES-D	Habituation and dishabituation to face-voice	IDM required longer time to habituate to faces, particularly to happy faces
Field et al., 1998	24 (12 IDM)	3.7 mo	BDI DIS	Visual preference for face-voice (video) Infant facial expression coding EEG recorded during visual preference	INDM looked longer to sad face-voice stimuli than IDM, and exhibited greater right FA while exposed to sad comparing to happy stimuli. No differences on FA were found for IDM
Field et al., 2007	28 (14 IDM)	4 mo	CES-D SCID	Mother-infant interaction, still-face procedure and infant behavior coding	IDM showed less smiling and vocalizing, more gaze aversion and motor activity during mother-infant interaction. IDM showed less motor activity and less distress behavior (less gaze aversion, distress brow and crying) during still-face procedure
Diego et al., 2004	60 (30 IDM)	4.2 mo	BDI	Visual preference for mother and stranger facial expressions Infant behavior coding EEG recorded during visual preference	IDM exhibited less positive affect and looked less at their mothers' surprise and sad expressions. IDM looked less at all strangers' facial expressions, showed less positive affect during happy and surprise and more negative affect during surprise expressions IDM had significantly greater right FA compared to INDM in all different expressions of both the mothers and strangers IDM and INDM showed greater right FA during their mothers'

					and strangers' sad versus happy faces
Bornstein et al., 2011	28 (14 IDM)	5.1 mo	BDI SCID	Habituation and visual paired comparison procedure	IDM and INDM habituated to neutral and happy faces IDM failed to discriminate between neutral and happy faces following habituation
Striano et al., 2002	46 (Maternal depression analyzed as a continuous variable)	6 mo	IDD	Visual paired comparison procedure comparing neutral from progressively higher intensities of smiling and frowning faces. Mother-infant interaction and infant behavior coding	Infants of mothers with higher depression scores showed greater looking preference for all smiling faces, and to high intensity smiling and frowning expressions Infants of mothers with higher depression scores looked longer at their own mothers while they were smiling
Otte et al., 2015	81 (Maternal anxiety analyzed as a continuous variable)	10. 1 mo	STAi	Multimodal face-voice compounds ERP recorded with EEG during face-voice compounds	Infants of mothers with higher maternal anxiety scores showed larger P350 and P150 amplitudes after fearful vocalizations, preceded by either happy or fearful faces.

[a]Mean age is presented in hours or months (mo).
BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies-Depression scale; DIS, Diagnostic Interview Schedule; EEG, electroencephalogram; ERP, event-related potentials; FA, frontal asymmetry; IDD, Inventory to Diagnose Depression, IDM, infants of depressed mothers; INDM, infants of non-depressed mothers; SCID, Structured Clinical Interview for DSM-IV; STAI, State–Trait Anxiety Inventory; STAi, Anxiety subscale of the SCL-90-R
Modified from PORTO; NUNES; NELSON, 2016.

5.5.2 ERP studies

Recent studies have investigated the potential impact of prenatal anxiety symptoms in the offspring's sensory processing, reporting associations between higher levels of anxiety and distinct patterns of neural correlates examined with ERPs. In one ERP study (OTTE et al., 2015; see Figure 7) multimodal processing was examined in 9-month-old infants exposed to maternal anxiety during pregnancy (10% of the mothers also reported previous treatment for depression). Infants were exposed to happy and fearful facial and vocal stimuli. Infants prenatally exposed to higher levels of anxiety showed significantly greater P350 amplitudes, and a trend for larger P150 amplitudes after fearful vocalizations, regardless of the preceding visual emotion type. This pattern can potentially relate to an increased sensitivity to threatening input. Enhanced attention to threat is a well-established correlate of anxiety disorders.

In another experiment (VAN DEN HEUVEL et al., 2015), maternal anxiety symptoms evaluated during the second trimester of gestational age were correlated to enhanced ERP

auditory responses in their 9-month-old infants. Infants' ERP were collected during an oddball auditory paradigm. When presented with repetitive uninformative sounds that typically lead to a progressive decrease of neural responses (i.e., neural habituation), infants of mothers reporting greater levels of anxiety showed higher N250 amplitudes. This auditory component is believed to be the precursor of the adult's N2 component, associated with auditory orienting responses. Interestingly, the authors also measured self-reported levels of maternal mindfulness during the same gestational period. Mindfulness is considered a positive trait and has been successfully explored in interventions to reduce anxiety symptoms, including in prenatal populations. Mothers with a greater mindfulness trait had infants that showed lower N250 amplitudes, the opposite pattern of infants of highly anxious mothers.

To date, studies of ERP responses specifically focusing on emotional faces and the influence of maternal anxiety or depression were only performed on children and adolescents. Altered responses were observed in children of anxious parents, that were less likely to habituate to fear-relevant multimodal visual/auditory stimuli than controls (TURNER; BEIDEL; ROBERSON-NAY, 2005). Also in children of mothers with a history of major depressive disorder, who exhibited less attention to sad faces than children of never depressed mothers (GIBB et al., 2016).

6 RATIONALE

Developmental research has investigated behavioral and neural correlates of emotional face processing, revealing that components of face and emotion networks are functional early in life. Neuroimaging studies have predominately used EEG/ERP techniques, lacking a more precise localization of the underlying neural substrates of emotional face processing. fNIRS studies have been increasingly used in infant population, providing better information of the brain areas involved in stimulus-evoked responses. Infants' hemodynamic brain responses to emotional face stimuli were recently explored using fNIRS, in experiments performed on infants of 6-7 months of age and older, focusing on limited brain regions.

The emotional experiences within the caregiving context were shown to alter the behavior and neural correlates of emotional face recognition in clinical populations (i.e., infants of clinically depressed mothers and maltreated children) (BORNSTEIN et al., 2011; POLLAK; SINHA, 2002), in infants of mothers with elevated symptoms of depression (DIEGO et al., 2004b), as well as in typically developmental contexts (e.g, in relation to distinct aspects of maternal personality, DE HAAN et al., 2004).

Maternal anxious and depressive symptoms are highly prevalent and may negatively affect maternal behaviors, mother-infant relationship, and the extent to which infants are exposed to emotional faces. Although anxiety and depression share several neurophysiological and behavioral aspects, there may be differences in symptom presentation that contribute to the development of infant's face processing in distinct ways. Maternal anxiety has been considerably less explored than depression, and the potential impact on infants' behavior have only recently been investigated. Greater maternal anxiety symptoms were related to disruption of particular aspects of mother-infant interaction, such as greater intrusiveness and overreaction. Anxious mothers experience elevated fear and worry and less positive affect, possibly resulting in atypical frequencies and intensities of expressing this emotions during daily interactions with their infants.

The present study aimed to used fNIRS technique to contribute to elucidate the underlying brain regions activated in response to facial expressions in 5-month-old infants. Previous fNIRS experiments were performed on older infants, and had restricted the analysis to limited brain areas. Furthermore, to my knowledge, any reported work to date has specifically investigated the potential role of early emotional experiences, as indexed by elevated maternal anxiety symptoms, on infants' brain responses to facial expressions of emotion using fNIRS.

The behavioral and neural underpinnings of face processing are believed to undergo substantial modification throughout development, influenced and shaped by the experiences in the environment. Better understanding of the neural developmental pathways can also clarify aspects of the mature face-processing system. Furthermore, exploring fNIRS responses in relation to potential influences of the early emotional rearing environment, such as the occurrence of elevated maternal anxiety symptoms, can contribute to the literature by providing insights about which brain areas and related neural networks may be affected.

7 OBJECTIVES

7.1 GENERAL AIM

The aim of this study was to use fNIRS to investigate 5-month-olds' hemodynamic brain responses to emotional faces over broad cortical areas, exploring the potential influence of maternal anxiety symptoms, as an indirect measure of the infants' early emotional environment.

7.2 SPECIFIC AIMS

I. Analyze individual differences in 5-month-old infants' fNIRS hemodynamic brain responses to happy and fearful face stimuli.

II. Explore the use of fNIRS for localization and lateralization of cortical emotional responses comparing broad cortical areas (i.e., frontal, temporal, parietal).

III. Investigate the influence of maternal anxiety symptoms in relation to 5-month-old infants' fNIRS hemodynamic brain responses to emotional face stimuli.

IV. Investigate the potential influence of maternal anxiety symptoms in infants' fNIRS hemodynamic brain responses specifically in relation to hemisphere lateralization.

8 METHODS

8.1 PARTICIPANTS

Twenty-nine typically developing 5-month-old infants (mean age 154 days ± 4.4; range 145-160; 14 females) and their mothers were recruited from a community sample in the greater Boston area, MA, USA. Families were contacted from a list of registered local births by the Laboratories of Cognitive Neuroscience, Division of Developmental Medicine of the Boston Children's Hospital. Twenty additional infants were tested but were excluded from the final sample for the following reasons: more than 25% of channels were rejected for artifacts (n=8), poor cap placement exceeding 1.5 cm deviation from ideal in any direction (n=5), equipment failure (n=3), cap refusal (n=2), and insufficient number of trials completed (n=2). The attrition rate of 40% is similar to previous infant fNIRS studies (LLOYD-FOX; BLASI; ELWELL, 2010). In addition, 7 other infants were excluded from the current study due to missing data on maternal anxiety symptoms (n=5), and for informed maternal medication use (opioids) during the gestational period (n=2). All participants in the final sample were typically developing infants, born full-term, with no history of pre- or perinatal complications, vision problems, developmental delay, or any neurological disorder. Prior to all the study sessions, written informed consent was collected from each participant's parent or primary caregiver. Written informed consent was also obtained from the parent for use of the photos of participants in this study. The experimental protocol was approved by the Boston Children's Hospital Institutional Review Board.

8.2 STATE-TRAIT ANXIETY INVENTORY

Maternal trait anxiety was assessed with the trait component of the State-Trait Anxiety Inventory (STAI-T; SPIELBERGER et al., 1983). The STAI is a reliable instrument used with both clinical and non-clinical populations. It comprises two different self-report scales that measure state and trait anxiety. Each scale (state, trait) is composed of 20 items answered on a four-point scale (1-4). The state anxiety scale explores current feelings of anxiety, worry, and tension in response to a specific situation or a certain period of time. In contrast, the trait scale assesses how a person generally feels, measuring an individual's proneness to experience anxiety (MEADES; AYERS, 2011). Samples of the trait scale items include "I feel nervous and restless" and "I worry too much over something that really doesn't matter". Trait

anxiety is considered a stable characteristic in the individual, believed to reflect a predisposition to appraise situations as stressful, and to respond with higher levels of anxiety to perceived threats (MEADES; AYERS, 2011). The authors (SPIELBERGER et al., 1983) reported coefficients of internal consistencies ranging from .90 to .91, and test-retest coefficients ranging from .65 to .75.

Although there are no established clinical cut-offs for the STAI-T, the inventory has been widely applied in perinatal populations (VAN DEN BERGH et al., 2005), and in mothers along the first year after childbirth, with scores above 40 reported significant for higher levels of anxiety (AUSTIN et al., 2005; GRANT; MCMAHON; AUSTIN, 2008; HART; MCMAHON, 2006).

STAI-T was validated against clinical interviews in perinatal samples (MEADES; AYERS, 2011). Additionally, perinatal STAI-T above 40 was similar to clinical diagnostic interviews to predict postnatal clinical anxiety (GRANT; MCMAHON; AUSTIN, 2008). During the postnatal period, higher levels of STAI-T were associated with increased maternal ratings of difficult infant's temperament and behavior (MCMAHON et al., 2001), as well as to reduced levels of maternal sensitivity, and lower levels of maternal emotional tone during the interaction with her infant (NICOL-HARPER; HARVEY; STEIN, 2007).

In the present study, a STAI-T score of 40 was used as the cut-off, as previously done in other maternal anxiety studies (AUSTIN et al., 2005; GRANT; MCMAHON; AUSTIN, 2008; HART; MCMAHON, 2006; NICOL-HARPER; HARVEY; STEIN, 2007). Mothers were classified as either low-anxious (scores 20-39), or high-anxious (scores above 40). In the current sample, the range of maternal STAI-T varied from 23 to 60 (possible 20-80). The low-anxious mothers' mean score was 31.6 (SD= 4.8), ranging from 23 to 39, whereas the high-anxious mothers' mean score was 48.5 (SD=7.2), ranging between 40 to 60.

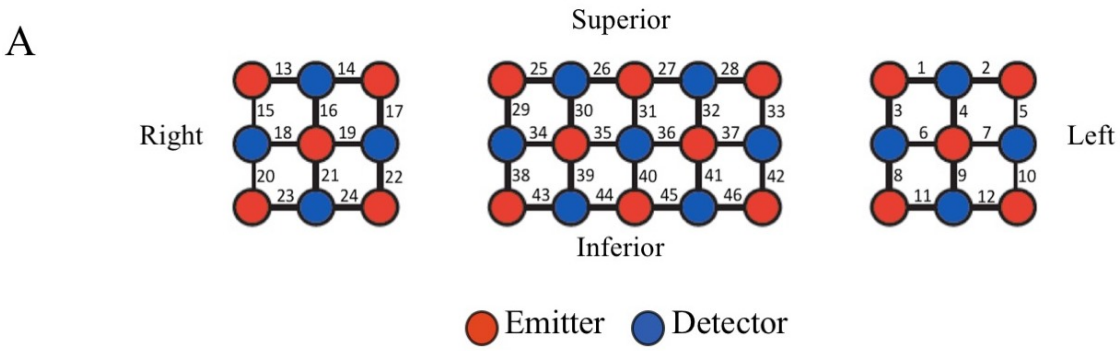
Maternal scores on the Beck Depression Inventory (BDI) were also collected. However, very little variability was observed in the present community sample. Therefore, this study focused only in the maternal STAI-T scale.

8.3 FUNCTIONAL NEAR-INFRARED SPECTROSCOPY

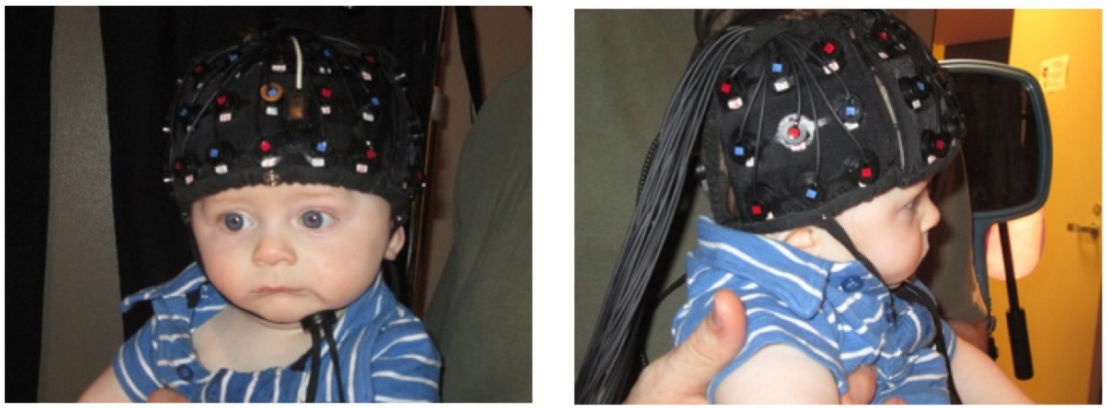
To record the hemodynamic responses, a Hitachi ETG-4000 multi-channel system was used in the study (ETG-4000, Hitachi Medical Corporation, Tokyo, Japan). The Hitachi ETG-4000 optical topography instrument produces two near-infrared wavelengths, of 695 and 830 nm. The flexible head cap, which contains a probe with 18 emitters and 15 detectors of near-

infrared light, was customized for this experiment, with a fixed inter-optode distance of 3.0 cm. Each emitter-detector pair formed a channel, resulting in a total of 46 channels. Figure 8 A illustrates the probe design. Before the recording session, the fNIRS cap was carefully positioned on the infant's head, covering an area over the frontal, parietal and temporal cortices as presented in Figure 8 B. The emitters shone near-infrared lights of 695 and 830 nm onto the scalp. The shorter light wavelength (695 nm) was absorbed by the deoxyHb, whereas the oxyHb absorbed the longer light (830 nm). Then, the attenuated light was measured by the detectors. Data were collected at every 100 ms (10 Hz). For the present study, channels 31 and 40 were excluded for being positioned at midline. The remaining 44 channels were divided into frontal, parietal and temporal regions, as shown in Figure 9 .

Figure 8 - fNIRS probe layout

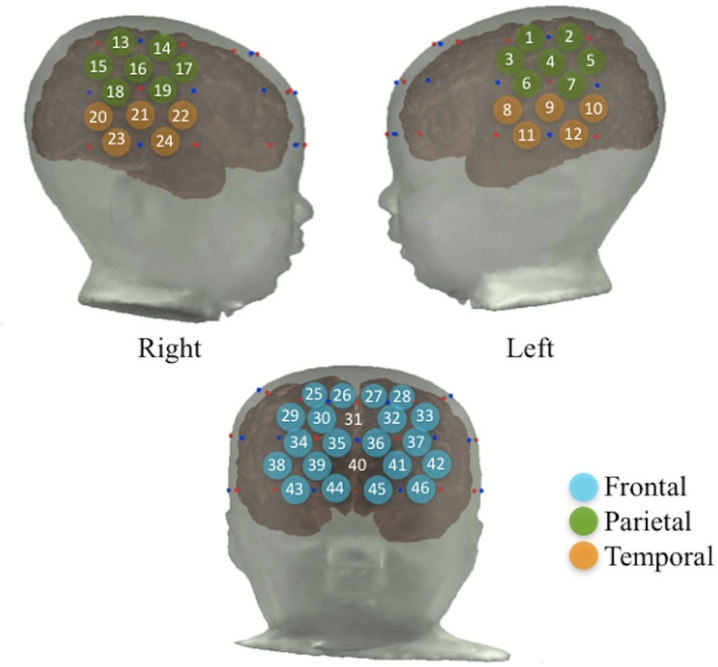


B



Source: A) Adapted from Katherine L. Perdue B) LCN, BCH. Reproduced with permission.
A) Probe design showing emitters (red) and detectors (blue), consisting 46 fNIRS channels (numbers).
B) Probe placed on infant's head during study session, frontal and lateral views.

Figure 9 - Regions of interest in the study

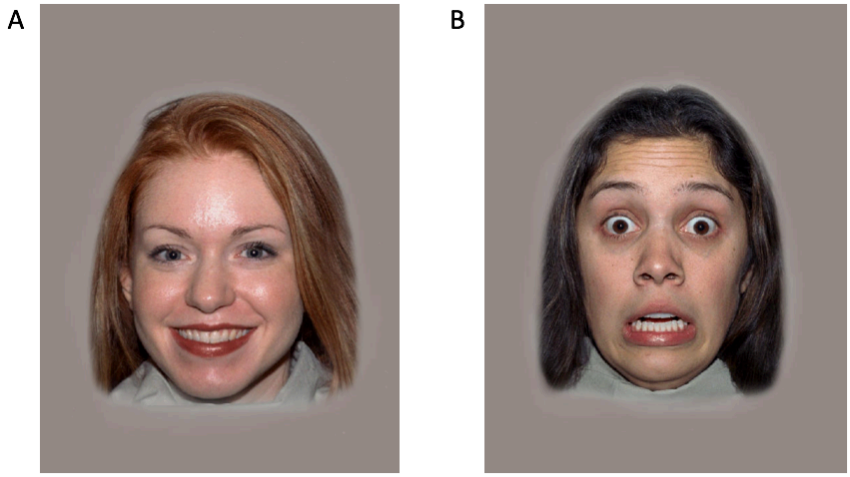


Source: Adapted from Katherine L. Perdue with permission. (Appendix 2)
Layout of lateral and frontal views of the approximate locations of fNIRS channels on the infant's head. Regions of interest in the study: frontal, parietal and temporal areas.

8.4 STIMULI AND DESIGN

The experimental design comprised 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) (Figure 10). As in other experiments involving infants, the female model's race matched the race of the infant's mother (for example, VANDERWERT et al., 2015).

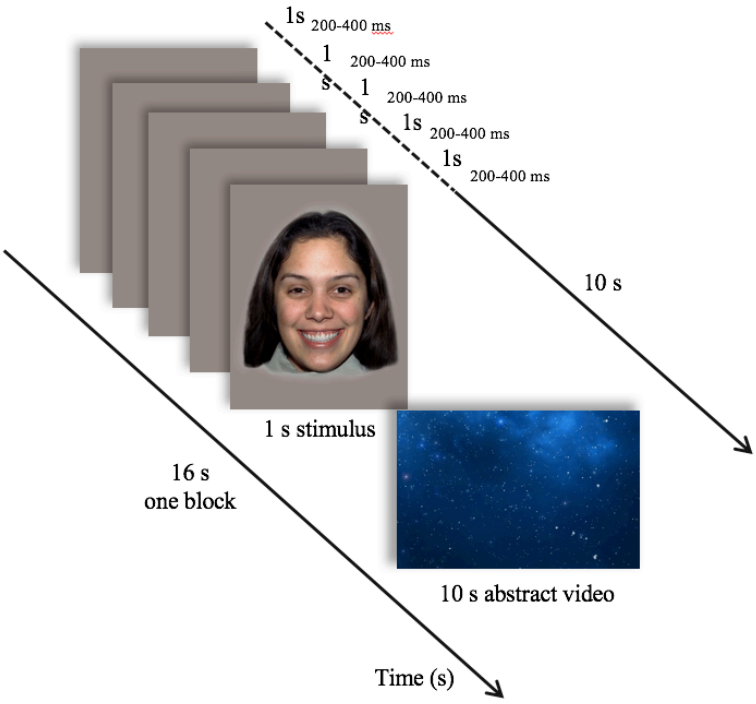
Figure 10 – Examples of images used in the experiment A) Happy expression B) Fearful expression



Modified from NimStim Face Stimulus Set (TOTTENHAM et al., 2009), reproduced with permission.

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 was presented, with up to 10 blocks of each of the 3 stimulus types selected (happy, fearful and angry facial expressions). Within each block, 5 facial stimuli in the same emotional category were presented. For example, 5 happy faces with different female models were presented in a row, followed by an abstract animation. Facial images were displayed on the screen for 1s, with a randomly generated 200–400 ms inter-stimulus interval before the presentation of the next face. The abstract animation was shown for 10s. Including the presentation of the faces, the abstract animation, and the inter-trial intervals between each face, each block lasted a total of 16 s; see Figure 11. The order in which blocks of emotion faces were presented was counterbalanced across participants. If the infant became unsettled or distressed, the experiment was stopped. To limit the number of comparisons in the study, the analysis was restricted to happy and fearful stimuli, since both emotions are good representation of the approach/withdrawal model. Happy is a positive/approach emotion and fear a negative/withdrawal emotion. In contrast, anger is a negative emotion related to an approach motivation, with discrepant findings reported in studies of neural correlates (FOX, 1991).

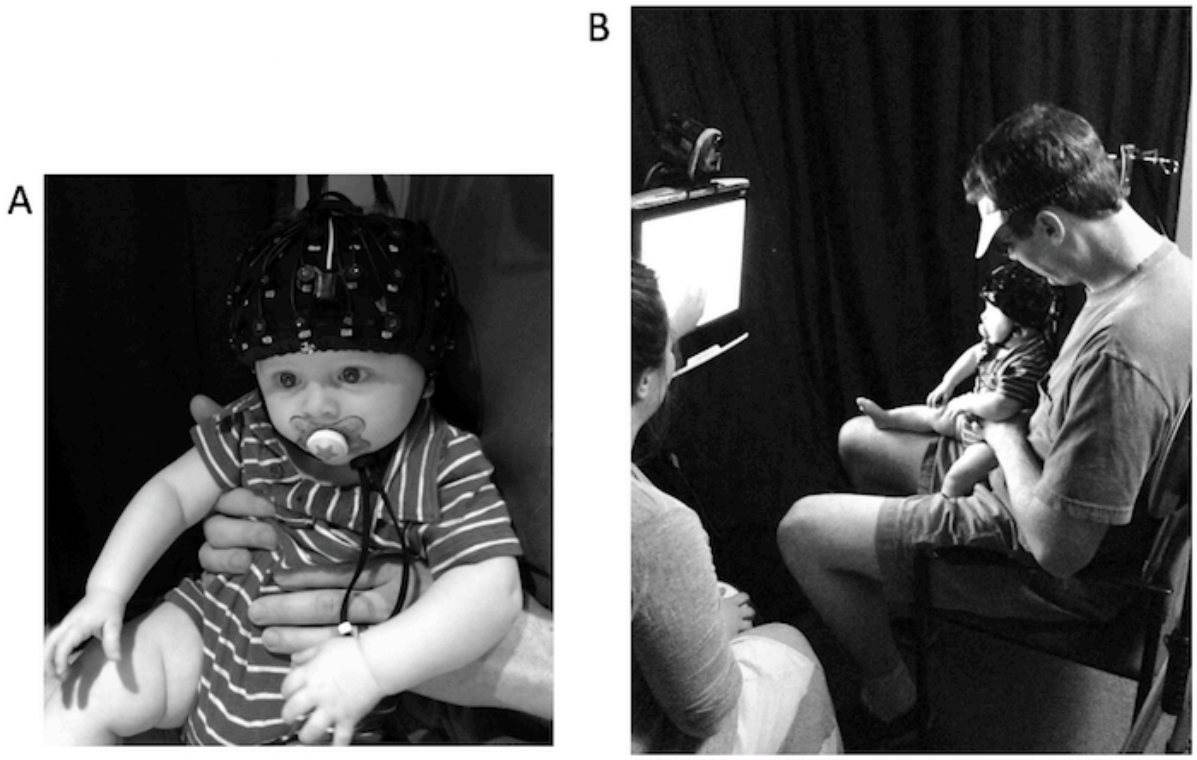
Figure 11 - Experimental design



Source: Author, 2017 (Appendix 2).
Each block had five images of a different female model displaying the same emotional category (happy, fearful or angry). Each image was shown for 1 s, with 200–400 ms inter-stimulus time randomly generated, followed by a 10 s abstract video. Each block lasted 16 s. The experiment included 30 blocks in total, 10 of each emotional category.

Testing took place in a soundproof room with standardized dimmed lights. Infants were seated on their caregiver's lap approximately 70 cm from a 17-inch computer screen, on which the images were presented (See Figure 12). Images' measures were 16.5 cm high and 14 cm wide. Parents were instructed to refrain from speaking to the infant during the experiment, and asked to wear a visor to shield their view of the computer screen, preventing them from influencing the infants' responses to the visual stimuli. During the entire task, an experimenter was seated next to the infant and parent to redirected the infant's attention to the monitor before the start of each trial, if needed. The sessions were scheduled by the parents around the time of the day their infant was habitually awake and content. If necessary, session breaks were taken. The sessions were video-recorded to assess infants' attention to the stimuli.

Figure 12 - Infant and parent during a study session



Source: LCN, BCH. Reproduced with permission.

8.5 DATA PROCESSING

Hemodynamic data from happy and fearful trials were included into the analysis. Video recordings of each session were analyzed to verify if the infant was looking to the stimulus, and coded by researchers blind to the emotional category, using the SuperCoder software (SuperCoder 1.7.1, Purdue University, West Lafayette, IN, USA). Inter-rater reliability was maintained at 0.90 with 15% coding overlap. Blocks were excluded if the infant failed to look at the screen for at least 50% of the time while the stimulus was presented. As in other infants' experiments (for example, RAVICZ et al., 2015), an *a priori* threshold of three trials for each emotion category was used for inclusion in the study. In the final sample, infants completed a mean of 21.5 ± 5.9 total trials (range 09-29), 7.5 ± 2 happy, 7 ± 1.9 fear, and 7.1 ± 2.3 anger trials (n =29).

The software HOMER2 (MGH-Martinos Center for Biomedical Engineering, Boston, Massachusetts), a MATLAB (The MathWorks, Inc., Natick, Massachusetts) package, was

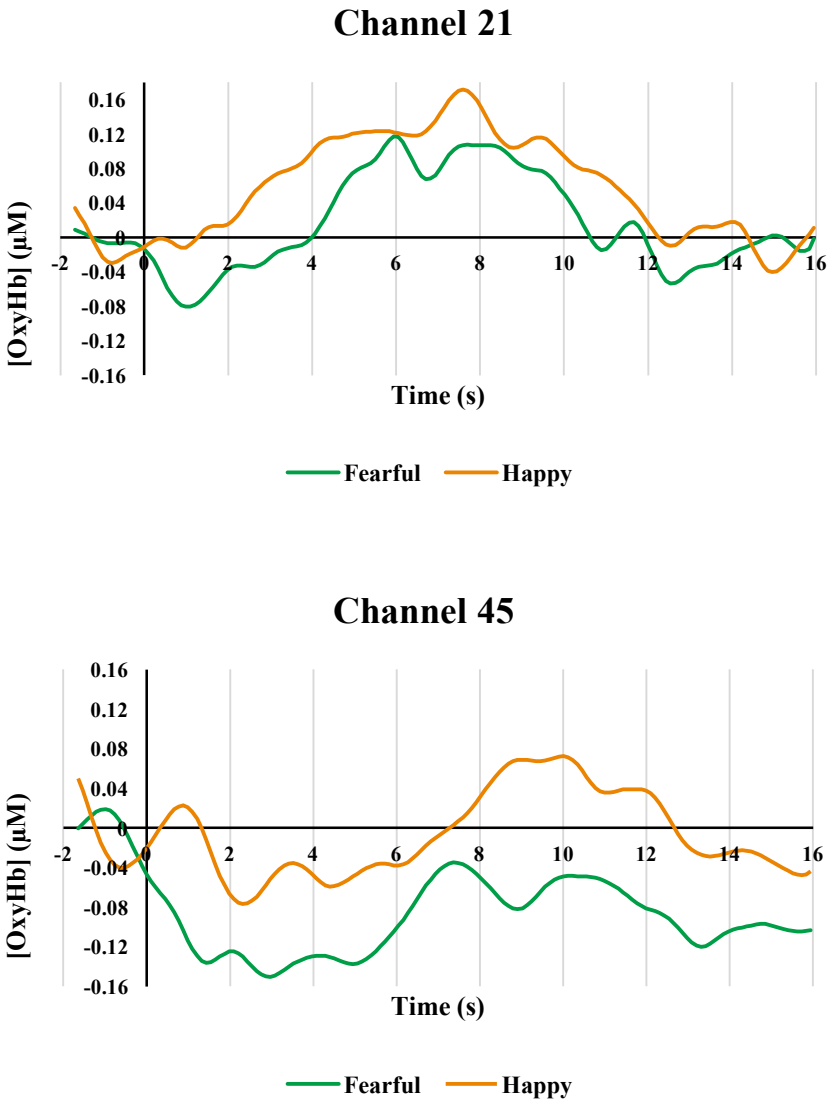
used to process the fNIRS data. The attenuated light intensities measured by the detectors were converted to μmolar units of optical density. Several types of noise had to be considered to process the NIRS data, including instrumentation (e.g., electrical noise from the computer or other hardware), physiological oscillations (e.g., local changes in vascular tone) and head and body movement artifacts (HUPPERT et al., 2009; LLOYD-FOX; BLASI; ELWELL, 2010). The data was filtered using a 0.05-0.80 Hz bandpass filter. Bandpass filtering removes sources of noise related to instrumentation drift (frequencies bellow 0.05) and to physiological artifacts (expected to be above 0.80Hz). To correct motion artifacts, wavelet motion correction with an interquartile range of 0.5 was utilized (MOLAVI; DUMONT, 2012).

The filtered, motion-corrected data were used to calculate the concentration variance of each hemoglobin chromophore (oxyHb, deoxyHb, totalHb) applying the modified Beer–Lambert law and assuming a pathlength factor of 5 (DUNCAN et al., 1995), as implemented in HOMER2 (HUPPERT et al., 2009). As in other fNIRS studies (for example, WATANABE et al., 2008), chromophore concentrations were baseline-corrected using the 2 s prior to stimulus presentation.

Prior studies with infants have observed that oxyHb is a more robust and reliable measure of stimulus-evoked hemodynamic responses than deoxyHb and totalHb (for a review, LLOYD-FOX; BLASI; ELWELL, 2010). Hence, the present study focused on oxyHb to determine the time window for the analysis.

For each infant, the oxyHb hemodynamic responses of the accepted trials were averaged for each channel and emotion condition. Then, a grand average was calculated for each channel and emotion condition. The grand averaged time course of the oxyHb hemodynamic responses across all infants was subsequently visually inspected. Based on the visual inspection, a time window between 0 and 12 s was selected for analysis. This window included the range of maximum changes (or amplitude) in concentration for oxyHb. For example, the grand averaged time courses of oxyHb responses on channel 21 and 45 are illustrated in the Figure 13.

Figure 13 - Grand averaged time courses of the changes in oxyHb concentration in response to happy and fearful facial stimuli for Channel 21 (Temporal) and 45 (Frontal)



Source: Author, 2017.

Next, for each subject the maximum change in the concentration of oxyHb and deoxyHb was extracted for each channel and emotion, subsequently winsorized for extreme outliers (if they were beyond the quartiles by three times the interquartile range), and averaged over the channels in the regions of interest (frontal, parietal and temporal) for statistical analysis. The stimulus-evoked mean responses of oxyHb and deoxyHb by each emotion, region, and hemisphere across all subjects are shown in Table 1.

Table 1 - Mean of maximum changes in oxyHb and deoxyHb concentration across all infants by emotion, hemisphere, and region (n=29)

Cortical area	Chromophore	Emotion/ Hemisphere			
		Happy		Fear	
		Right	Left	Right	Left
Frontal	oxyHb	-.009 (.19)	.000 (.18)	-.090 (.17)	-.115 (.15)
	deoxyHb	-.007 (.11)	-.007 (.10)	.008 (.09)	-.011 (.10)
Parietal	oxyHb	.095 (.25)	.062 (.24)	-.063 (.21)	-.042 (.23)
	deoxyHb	-.019 (.11)	-.030 (.13)	.055 (.13)	.012 (.11)
Temporal	oxyHb	.081 (.35)	.169 (.38)	-.042 (.23)	-.001 (.38)
	deoxyHb	-.065 (.13)	-.017 (.18)	-.013 (.13)	.020 (.16)

Values expressed in μM (SD).
Source: Author, 2017.

8.6 STATISTICAL ANALYSES

Statistical analysis was conducted using IBM SPSS Statistics 21.0 (IBM Corporation, Armonk, New York). Differences between low- and high- anxious groups for demographic variables and characteristics of participants were investigated by means of independent sample t-tests and chi-square tests.

Repeated measures omnibus analyses of variance (ANOVAs) were conducted separately to analyze oxyHb and deoxyHb data. The model included 3 within-subject factors: emotion category (happy, fear), region (frontal, parietal, temporal) and hemisphere (right, left). Maternal STAI-T classification was included as the between-subject factors with two levels (anxiety: low, high). When the omnibus ANOVA yielded significant effects, post hoc comparisons were carried out using Bonferroni correction. When the omnibus ANOVA revealed significant interaction effects, post hoc tests were carried out with planned comparisons.

9 RESULTS

STAI-T scores were significantly different between the groups (t_{27}= -7.548, p< 0.001). The high-anxious mothers' mean score (±SD) was 48.5 (±7.2), compared to the low-anxious mothers' mean score of 31.6 (±4.8). Low- and high-anxious groups were comparable in terms of all socio-economic and demographic characteristics analyzed: maternal age, maternal education, marital status, ownership of the house, combined family income in the past 12 months, infant age, infant gender, infant race, birth weight, and type of delivery (Table 2).

Table 2 - Demographic variables and characteristics of participants

Parameters	Total (n=29)	Low anxiety (n=20)	High anxiety (n=9)	*p*
Maternal descriptive				
Maternal age in years	33.56±3.79	33.18±3.96	34.41±3.43	.429
Education				.529
Master or equivalent/PhD	23 (79.3)	15 (75.0)	8 (88.8)	
Bachelors	5 (17.2)	4 (20)	1 (11.1)	
High school	1 (3.5)	1 (5)		
Marital status				.632
Married/Cohabiting	29(100)	20 (100)	9 (100)	
Ownership of the house				.454
Owned	16 (55.2)	10 (50.0)	6 (66.7)	
Rented	13 (44.8)	10 (50.0)	3 (33.3)	
Combined family income in the past 12 months[a]				.762
$100,000 and greater	19 (73.1)	12 (70.6)	7 (77.8)	
$25,000 through $75,000	6 (23.1)	4 (23.5)	2 (22.2)	
Less than $5,000	1 (3.8)	1 (5.9)		
Infant descriptive				
Infant age at test in days	153.8±4.0	153.9±4.4	153.7±4.6	.946
Female	14 (48.3)	8 (40.0)	6 (66.7)	.245
White[b]	24 (82.8)	16 (80.0)	8 (88.9)	.782
Birth weight[b] in grams	3.539±332	3.536±351	3.546±307	.941
Type of delivery				.396
Vaginal	20 (69.0)	15 (75.0)	5 (55.6)	
C-section	9 (31.0)	5 (25.0)	4 (44.4)	

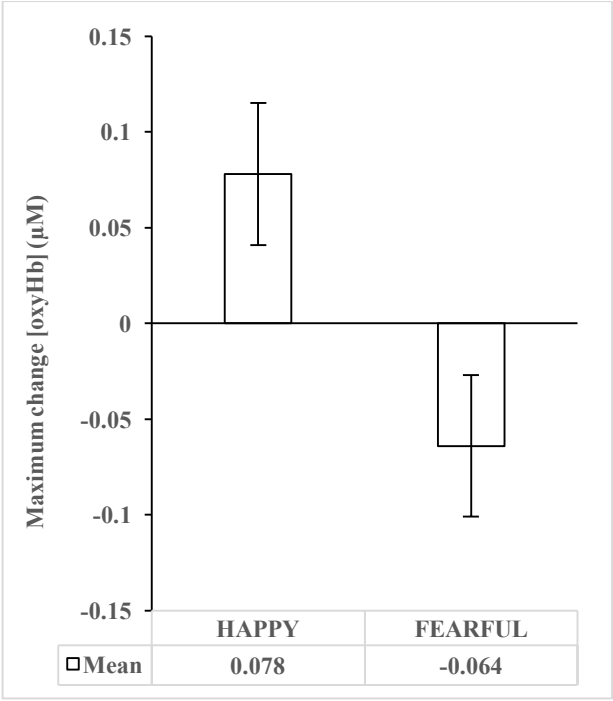
Note: Data presented as No. (%) or mean±SD.
[a] Missing data in 3 participants.
[b] Missing data in 1 participant.
Source: Author, 2017 (Appendix 2).

9.1 OxyHb RESULTS

9.1.1 Main effect of emotion

For the oxyHb data, the omnibus ANOVA revealed a significant main effect of emotion, $F_{1,27}$=5.887, p=.022, η_p^2=.179. Post hoc analysis (Bonferroni) showed that the main effect of emotion was driven by significantly greater oxyHb concentration for happy compared to fearful faces. For happy faces, the oxyHb concentration increased relatively to baseline, whereas for fearful faces, the oxyHb concentration decreased in comparison to baseline (Figure 14).

Figure 14 - Main effect of emotion (p=.022)



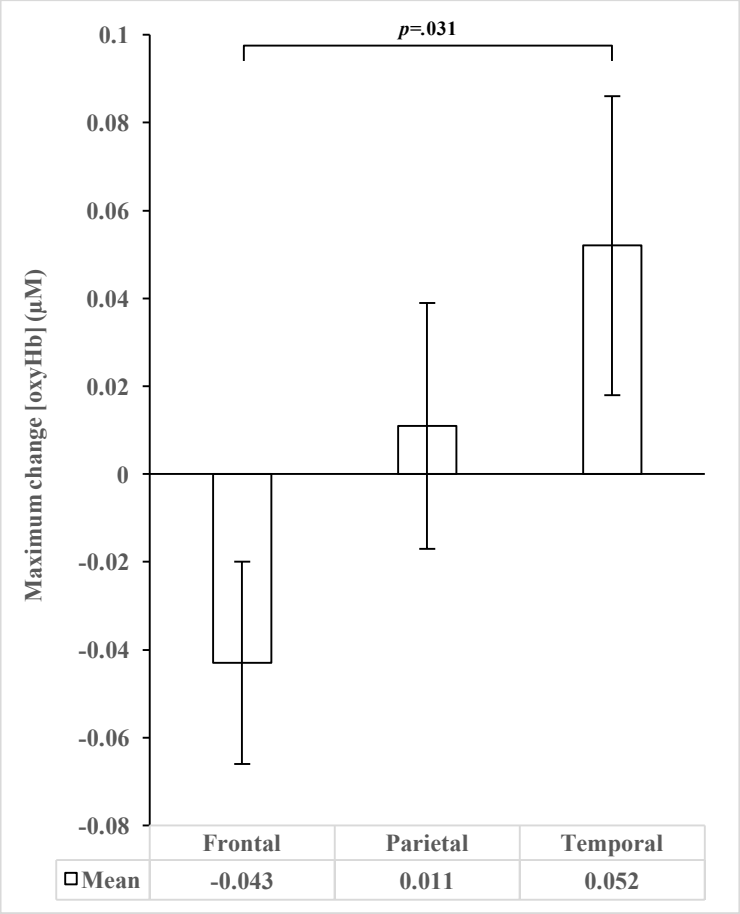
Maximum change in oxyHb (µM) (presented as mean ± SE) for happy and fearful stimuli (n=29).

9.1.2 Main effect of region

There was also a significant main effect of region, $F_{2,54}$=4.888, p=.013, η_p^2=.153. Post hoc comparisons (Bonferroni) showed that the main effect of region was driven by significantly greater oxyHb concentration in temporal compared to frontal regions (p=.031). OxyHb concentration did not significantly differ neither between frontal and parietal areas,

nor between parietal and temporal areas. Post hoc inspection of results revealed that there was a relative increase in oxyHb concentration from baseline over temporal regions, which significantly differed from the relative decrease of oxyHb concentration from baseline over frontal regions. The main effect of region is illustrated in Figure 15.

Figure 15 - Main effect of region (*p*=.013)



Maximum change in oxyHb (µM) (presented as mean ± SE) in the frontal, parietal, and temporal areas (n=29).

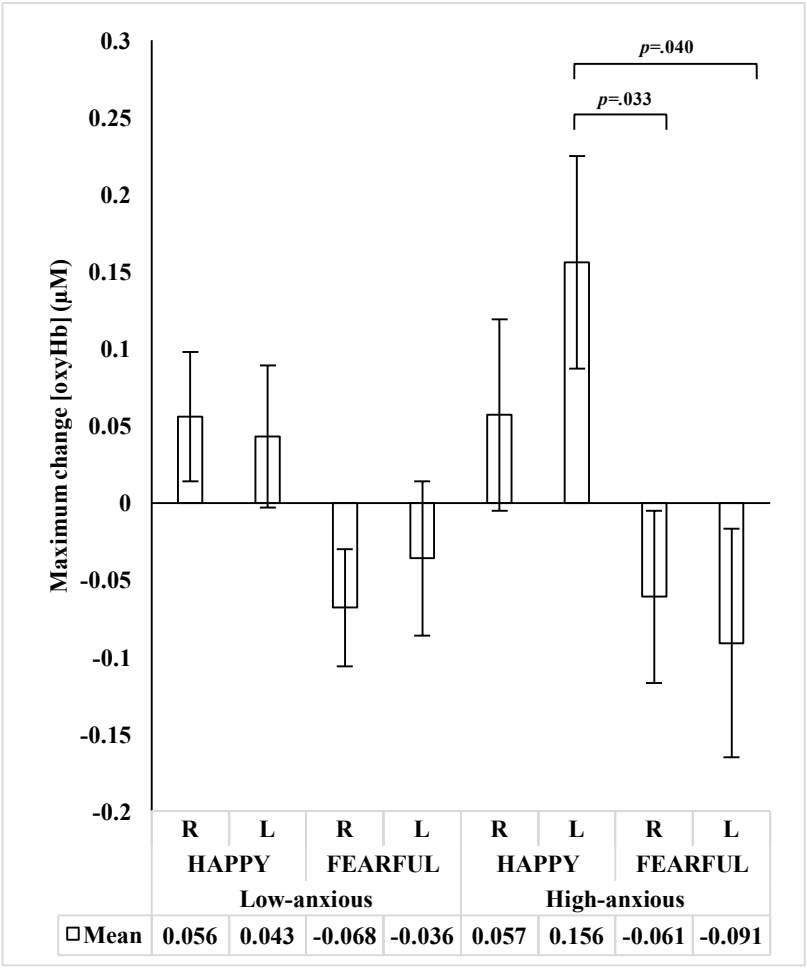
9.1.3 Maternal anxiety symptoms and infants fNIRS responses to emotional faces

A significant three-way interaction between emotion, hemisphere and anxiety, $F_{1,27}$=4.816, *p*=.037, partial η_p^2= .151 also emerged. Inspection of the results revealed that maternal anxiety levels moderated the extent to which infants showed alterations in oxyHb to emotional faces.

Post hoc tests (planned comparisons, uncorrected) revealed that maternal anxiety levels moderated the extent to which infants showed alterations in oxyHb responses to

emotional faces. Infants of high-anxious mothers showed significantly greater left hemispheric activation of oxyHb to happy faces when compared with right (p = .040) and left (p = .033) hemispheric activation of oxyHb to fearful faces. Infants whose mothers reported lower levels of anxiety showed no significant differences in the oxyHb activation to happy versus fearful faces. In summary, infants of low-anxious mothers showed more attenuated responses to happy versus fearful faces, and no hemispheric differences. In contrast, infants of high-anxious mothers showed more exaggerated responses to happy versus fearful faces, and greater lateralization in their responses (Figure 16).

Figure 16 - Three-way interaction between emotion, hemisphere, and anxiety (p=.037)



Infants of high-anxious mothers showed greater left hemispheric [oxyHb] for happy faces compared to left (p = .033) and right (p =.040) [oxyHb] for fearful faces. Maximum change in oxyHb (µM) (mean ± SE) for happy and fearful faces are presented comparing right (R) and left (L) hemisphere responses for infants of low- and high-anxious mothers (n=29).

9.2 DeoxyHb RESULTS

For deoxyHb, the omnibus ANOVA revealed a marginal effect of region, $F_{2,54}=2.977$, $p=.077$, $\eta_p^2=.099$. However, the results were not significant after post hoc analysis.

10 DISCUSSION

In the present study, fNIRS was used to explore individual differences in the neural correlates of happy and fearful emotional face stimuli in 5-month-old infants, exploring cortical responses over frontal, parietal, and temporal cortical areas. Subsequently, infants' brain hemodynamic responses to emotional faces were examined in relation to self-reported maternal anxiety symptoms.

The results revealed an effect of emotion, in that overall, happy faces induced greater activation than fearful faces. There was also an effect of region, with emotional faces eliciting greater hemodynamic responses over temporal compared to frontal areas. Finally, maternal anxiety symptoms influenced infants' neural responses to emotional faces. Specifically, infants of high-anxious mothers showed a more pronounced differential hemodynamic response to happy versus fearful faces, when compared to infants of low-anxious mothers. These differential patterns of activation were predominantly observed over the left hemisphere. Each of these findings were discussed below.

10.1 MAIN EFFECT OF EMOTION

Within all infants, a greater activation for happy compared to fearful faces was evinced. Developmental behavioral studies corroborate that infants' ability to discriminate positive expressions precedes the discrimination of negative emotions, such as fearful and sad faces (BAYET; PASCALIS; GENTAZ, 2014; BORNSTEIN; ARTERBERRY, 2003). Infants were previously observed to demonstrate visual preference for happy faces, reported as early as within the first days of life (BAYET; PASCALIS; GENTAZ, 2014; FARRONI et al., 2007).

Happy faces are usually the most prevalent emotional expressions displayed by caregivers in the infants' typical rearing context (COHN; TRONICK, 1987; MALATESTA; HAVILAND, 1982). Over the first months of life, infants' visual preference for smiling faces and expressions of joy may contribute to establishing a positive environment, sustaining the caregiver's attention and nurturing their bonding, crucial for assuring infant's survival and for promoting adequate development of social and emotional skills (BORNSTEIN; ARTERBERRY, 2003; PARSONS et al., 2010).

Infants of 5 months of age can discriminate happy faces from other emotional expressions (i.e., neutral, sad, angry and surprised faces; BAYET; PASCALIS; GENTAZ,

2014; BORNSTEIN; ARTERBERRY, 2003) and can form categories within happy face expressions (KUCHUK; VIBBERT; BORNSTEIN, 1986). Between 5 and 7 months of age infants begin to categorize diverse emotional expressions other than happy, and to show sensitivity to ERP components related to facial expressions (PELTOLA et al., 2009). Seven-month-olds consistently distinguish between positive (happy) and negative (anger or fear) emotions. Around the same time, infants shift their visual preference towards fearful faces, the typical pattern observed in adults (LEPPÄNEN; NELSON, 2009; NELSON; DE HAAN, 1996). The perceptual bias to fear is reliably observed in behavior and neurophysiological studies after the age of 7 months, and is believed to be related to early identification of potential environmental threats (LEPPÄNEN; NELSON, 2009).

It has been suggested that during early stages of development, infants demonstrate a 'positivity bias', evinced by a visual preference for positive emotions, whilst a 'negativity bias' emerges at the second half of the first year of life, as infants develop sensitivity to fearful expressions (VAISH; GROSSMANN; WOODWARD, 2008).

Interestingly, animal studies may suggest possible mechanisms associated with the later emergence of the fearful visual preference in human infants (LEPPÄNEN; NELSON, 2009). Experimental research in rodents has described a neural mechanism believed to facilitate the formation of social attachment in altricial rats (MARCHESINI et al., 2000; MORICEAU; SULLIVAN, 2004). Accordingly, neural networks related to reward associations would be present from birth, whereas circuitries involved in aversion learning would emerge later, around the time the pups begin to leave the nest to explore the environment (i.e., postnatal day 10). As rat pups depend heavily on their mother for survival, the impaired fear/avoidance learning would be a sensitive period to facilitate maternal odor preference and approach behaviors, inducing attachment to the maternal nipple. Noteworthy, maternal behaviors during interactions include potentially painful stimuli such as pushing and biting, yet experimental presentation of odors paired to similar painful stimulations not just failed to evoke aversion learning, but induced pups to prefer the specific odors (MARCHESINI et al., 2000; MORICEAU; SULLIVAN, 2004). The authors hypothesized that the immaturity of fear-related circuitry, including the amygdala, would promote attachment with the caregiver, enhancing chances of survival. Thus, the early positivity bias in human infants might also be due to such immature circuitry of fear/aversion reactions.

In humans, it is also possible that the preference for positive faces observed during the first months of life relates to the predominance of such faces in the environment, and this familiarity-based preference would shift to greater attention to fear as threat-sensitivity

circuitries evolve, around 6-7 months of life, and facial expressions of fear may emerge in the infants' context.

Recently, other infant studies of emotional face processing have used the fNIRS technique. Hemodynamic responses to happy and angry faces were observed in 6 to 7-month-olds over the posterior temporal cortex of typically developing infants (NAKATO et al., 2011). Angry faces activated the right temporal region, whereas happy faces activated the left temporal region. The authors discussed the interhemispheric differences based on lesion and fMRI adult studies, which have described hemisphere lateralization (beyond the frontal areas) in accordance to the approach/withdrawal model (ADOLPHS, 2002a; WAGER et al., 2003). Another study (RAVICZ et al., 2015) observed PFC responses to happy faces (vs. abstract shapes video) in 7-month-olds, with a frontal asymmetrical activation over two channels in the MPFC when comparing infants scores of high and low negative emotionality temperament factors. Infants with a more positive trait (lower levels of negative emotionality) showed preferential activation over the left MPFC for happy faces. However, happy stimulus was not compared to other emotional faces, thus the findings can be related to responses to faces in general.

In the present study, 5-month-olds demonstrated a greater activation to happy compared to fearful stimuli, a pattern that is in accordance with the developmental literature. To the extent to my knowledge, this is the youngest age emotional face expression responses were reported in infants using fNIRS.

Notably, happy faces elicited an increase of oxyHb concentration relative to the baseline, whereas fearful faces evoked a decrease of oxyHb compared to the baseline. In addition, deoxyHb concentrations did not show significant responses for emotional faces. The standard hemodynamic response observed in adults' fNIRS studies consists of an increase in oxyHb and totalHb, accompanied by a relatively smaller decrease in deoxyHb (GERVAIN et al., 2011). The localized neural activity heightens the oxygen consumption, inducing a prompt increase of local cerebral blood flow with higher oxygen delivery, which usually exceeds the neural demand for oxygen, generating the typical HFR observed in adults in stimulus-evoked experiments (GERVAIN et al., 2011). However, several studies have reported atypical hemodynamic responses in infants, with a decrease of oxyHb concentration (CSIBRA et al., 2004; RAVICZ et al., 2015), and an increase of deoxyHb (MEEK, 2002), accompanied or not by a decrease of totalHb (LLOYD-FOX; BLASI; ELWELL, 2010). It has been hypothesized that the greater discrepancies observed on the infant's HRF might be related to heightened metabolic demands for neural activity in the immature brain, such as related to greater energy

consumption in the unmyelinated white matter (MEEK, 2002). Thus, the oxygen consumption rate possibly exceeds the increase in the blood flow during neural activity, contributing to the altered HRF in infants.

The vascular coupling in the adult brain shows an established relationship of increase in neural activity resulting in increase in local blood flow. This relationship appears to fail to follow a linear response in the infant's brain, yet the mechanisms related to the observed atypical patterns remain unclear. The immaturity of the neurovascular coupling includes the gradual development of the neurovascular signaling regulation, the process of cerebral angiogenesis, and the vascular remodeling of brain vases (KOZBERG et al., 2013). Greater variability in both oxyHb and deoxyHb patterns in infants are assumed to accrue from the immaturity of the neurovascular coupling (LLOYD-FOX; BLASI; ELWELL, 2010).

Another hypothesis proposes that the altered pattern could be secondary to the activation of a metabolically highly demanding focal area that would reallocate the surrounding blood flow. As a result, a decrease of blood flow and of oxyHb would be recorded in a determined region, that is adjacent to the prominent active focal area ("stealing effect" in HAREL et al., 2002). However, this is unlikely to be the case in the current study design, that broad cortical areas were analyzed.

A pattern of increased deoxyHb with or without decreased oxyHb was also observed in BOLD fMRI studies with infants and adults (MEEK, 2002; SAKATANI et al., 2006). The findings have been speculated to be related to a decreased neural activity, or local brain deactivation (SAKATANI et al., 2006). The BOLD signal is believed to be more closely associated with the deoxyHb signal, a chromophore with high inconsistency across infants' studies (LLOYD-FOX; BLASI; ELWELL, 2010), thus similar inferences in the developing brain should be interpreted cautiously.

Finally, given that a decrease in oxyHb was seen to fearful but not happy faces, the present findings also suggest that the oxyHb HRF response direction is sensitive to the specific stimulus presented and not a global feature of the infant brain response or response to faces in general.

10.2 MAIN EFFECT OF REGION

While observing emotional faces, infants exhibited a greater hemodynamic response in temporal versus frontal areas. It is possible that 5-month-olds discriminated the stimuli based on the distinct configurational aspects of happy in comparison to fearful expressions, such as

variations in the mouth shape, differential degrees of the eye aperture, and variation in the eyebrows position.

Facial perceptual processing of variant aspects of faces is attributed to regions of the occipital-temporal cortices, particularly the posterior STS (ADOLPHS, 2002a; LEPPÄNEN; NELSON, 2009). In contrast, areas of the PFC, particularly the OFC, are involved in the discrimination and modulation of emotional responses (ADOLPHS, 2002a; LEPPÄNEN; NELSON, 2009). The OFC has reciprocal connections with the amygdala and the occipital-temporal cortices, involved in emotional face processing as observed in animal an adult studies (CAVADA et al., 2000; O'DOHERTY et al., 2003). These streams are believed to become functional around the ages of 5 to 7 months, coinciding with the time infants become capable to distinguish between facial expressions of emotions (LEPPÄNEN; NELSON, 2009). However, this brain circuitry is believed to be extensively refined by experience, and possibly continues to develop until adolescence or later (LEPPÄNEN; NELSON, 2009).

The discrimination between facial expressions is believed to initiate with the differentiation of features of the face (i.e., configural processing), progress to a holistic processing (related to both facial aspects and their spatial arrangements in the face), and gradually the recognition of the expressions become associated with representations of emotional content. Over time, infants begin to recognize and understand the meaning of distinct expressions, laying the foundation for acquiring higher social and emotional capacities, such as social referencing, anticipation of emotional states, and cooperation during interactions (QUINN et al., 2011).

In the current sample, it is possible that the processing of the affective cues might be still functionally emerging in 5-month-olds, resulting in the less pronounced response observed in the frontal areas. Emotional faces induced activation over PFC areas in older infants, between 9 and 13 months of age, while observing happy and neutral faces of their own mothers and a female model (MINAGAWA-KAWAI et al., 2009). In that study, PFC hemodynamic responses were reported when the infant was observing their own mother smiling, but not for a female stranger. Moreover, the mothers' brain responses were also recorded, showing increased activation in the OFC to their own infants' smiling compared to neutral faces. It is possible that the prefrontal responses to emotional signals may initially develop within social experiences with the caregiver, evincing responses to familiar faces, and later generalize to other social contexts and unfamiliar faces. Aligned to this hypothesis, research on adults has reported OFC activation to positive affective signals, and reward representation related to positive cues (O'DOHERTY et al., 2001, 2003). The activation for

the mothers' faces may relate to the presence of a positive affect response for the maternal face, which would not be elicited by an unfamiliar woman smiling.

Developmental fNIRS studies investigating configurational aspects of face processing reported activation over parietal, temporal and occipital areas (Vanderwert & Nelson 2014). Temporal areas were activated in infants between 5 and 8 months while viewing upright compared to inverted faces (OTSUKA et al., 2007), right parietal areas in 5- and 8-month-olds while observing frontal versus profile faces (NAKATO et al., 2009), whereas canonical versus scrambled facial images (i.e., face-shaped matched visual noise) elicited responses in occipital-temporal regions in 7-month-old infants (HONDA et al., 2010). Nonetheless, studies exploring emotional and social aspects, such as joint attention (GROSSMANN; JOHNSON, 2010), or comparing the infant's own mother's face to unfamiliar faces (MINAGAWA-KAWAI et al., 2009), have shown increased hemodynamic responses over frontal areas.

The studies that investigated infant's brain responses to emotional faces using fNIRS have used restricted coverage of the infant's head, observing hemodynamic responses either in frontal (MINAGAWA-KAWAI et al., 2009; RAVICZ et al., 2015), or in temporal-parietal regions (NAKATO et al., 2011). Hence, a comparison of cortical hemodynamic activation between wide brain areas was not feasible. In the present study, a fNIRS probe with increased coverage over the cortex was used, allowing for comparisons of responses between broad areas of the frontal, temporal and parietal cortices. A significant increase of oxyHb concentration in relation to the baseline was observed over temporal areas, whereas a significant decrease of oxyHb concentration from the baseline was evinced in the frontal areas. As previously noted, altered HRF patterns were observed in infants, suggesting that the differential underlying processes might be related to development. The typical activation response was observed in the temporal areas, whereas the decrease in the oxyHb concentration over frontal areas were possibly due to an immaturity of the neurovascular coupling, which may be greater in the frontal compared to temporal areas, or due to a deactivation response.

10.3 MATERNAL ANXIETY SYMPTOMS AND INFANTS fNIRS RESPONSES TO EMOTIONAL FACES

The results revealed an interaction between emotion, hemisphere and anxiety. Infants of high-anxious mothers appeared to have a more pronounced hemodynamic response to happy versus fearful faces, a pattern particularly observed over the left hemisphere, in

comparison to infants of low-anxious mothers. Several mechanisms that could explain the observed association are further discussed.

The importance of sensitive caregiving and contingent interactions for an optimal social and emotional development has been emphasized for a long time (TRONICK, 1989). Emotional experiences in the caregiving context were shown to affect children's and infants' perceptual abilities and their underlying neural correlates, as reported in previous emotional face processing studies both in adverse contexts (BORNSTEIN et al., 2011; POLLAK; KISTLER, 2002) and in healthy environments (DE HAAN et al., 2004).

Conditions that affect maternal mental health can impact the quality of caregiving behaviors and alter the mothers' expressions of emotions. Mothers experiencing elevated anxiety symptoms, even without meeting clinical diagnostic criteria, were observed to communicate in disrupted ways with their infants (AKTAR; BÖGELS, 2017; BEEBE et al., 2011). Beebe and collaborators (2011) observed that highly anxious mothers were less empathic and less contingent during interactions with their infants. Interestingly, their infants were shown to respond with greater levels of approach and expressivity coordination to maternal facial signals, perhaps in a tentative to process their mothers dysregulated communication signals. It has been speculated that infants of highly anxious mothers could be more sensitive to maternal emotional signals, and possibly to emotional signals in general (DE ROSNAY et al., 2006).

The systematically altered maternal behaviors may affect the extent to which infants are exposed to positive and negative emotions during daily interactions with their mothers. In the current sample, it is possible that infants of high-anxious mothers were relatively less exposed to happy faces (particularly to high-intensity expressions), and more exposed to neutral and fearful faces, as compared to dyads of mothers with lower levels of anxiety and their infants. Thus, the greater hemodynamic response observed in infants of high-anxious mothers may reflect an enhanced neural activity to process a less commonly experienced stimulus (i.e., happy), compared to a more familiar one (i.e., fearful).

These results are aligned with previous studies of infants of highly symptomatic depressed mothers, according to which such infants are presumably less exposed to happy expressions and more familiarized with sad expressions in their environment, as compared to infants of healthy mothers (FIELD; DIEGO; HERNANDEZ-REIF, 2009; STRIANO; BRENNAN; VANMAN, 2002). In those studies, infants of depressed mothers exhibited greater attention to high-intensity smiles, compared to neutral faces (STRIANO; BRENNAN; VANMAN, 2002), as well as less attention to sad versus happy faces (HERNANDEZ-REIF et

al., 2006). A separate study (CRESWELL et al., 2008) compared mothers with social anxiety and controls. Infants of anxious mothers were more likely to show reduced looking to high- versus low-intensity fearful faces, the opposite pattern observed in the controls, potentially due to being more exposed to maternal fearful faces. Although the present study was not conducted in a clinical sample, the findings are in accordance of a lower activation (i.e., greater decrease of oxyHb concentration in relation to baseline) for fearful faces in infants of high-anxious mothers, particularly over the left hemisphere. This inference, however, should be interpreted cautiously. As previously noted, the interpretation of patterns of decrease in oxyHb are not clearly understood.

Furthermore, extant data supports the heritability of emotional disorders. The offspring of anxious parents have an increased risk to develop anxiety disorders (TURNER; BEIDEL; ROBERSON-NAY, 2005). Anxiety has been characterized by a higher aroused functional state, associated with an attentional bias for threatening stimuli (BRADLEY et al., 1999; CISLER, JOSH, M; KOSTER, ERNST, 2011). A number of studies have described biases for attention and negative emotions processing, particularly for fear (FOX; RUSSO; DUTTON, 2002; GEORGIOU et al., 2005). However, an altered response to other emotions, such as anger, disgust (ROSSIGNOL et al., 2007), and happiness (BRADLEY et al., 1999; MOREL et al., 2014; WATERS et al., 2008), have also been observed both in studies of self-reporting symptoms (ROSSIGNOL et al., 2005) and clinical populations, including children and adolescents (MONK et al., 2008; WATERS et al., 2008; WESSING; ROMER; JUNGHÖFER, 2017). This recent body of research suggests that anxiety amplifies vigilance for emotional stimuli in general.

MRI studies about the offspring of anxious and depressed mothers have recently reported associations between greater levels of maternal symptoms and alterations in infants' brain areas involved in emotional responses. For instance, Qiu and colleagues (2015) found that greater maternal depressive symptoms during pregnancy were associated to enhanced connectivity between the amygdala, areas of the PFC and left temporal region. Other studies observed anatomic alterations in infants and children exposed to elevated maternal depressive and anxiety symptoms in the postnatal period, reporting greater amygdala volumes (LUPIEN et al., 2011) and altered hippocampal growth (QIU et al., 2013), respectively.

Altogether, it is possible that the greater hemodynamic responses of infants of high-anxious mothers are related to heritable patterns for anxiety disorders, or of higher sensitivity to emotional stimuli, and /or a combination of a genetic predisposition and the exposure to altered emotional environments in the perinatal period.

In contrast to EEG studies exploring acute emotional responses, an overall lateralized activation for happy versus fearful faces was not observed. However, for infants of high-anxious mothers, a greater activation to happy versus fearful stimuli was observed particularly over the left hemisphere. Happy faces induce positive and approach emotions, and have been correlated to greater left FA in EGG studies previously reviewed. A preferential activation for approach emotions over the left hemisphere, particularly in a region of left superior temporal cortex was reported in a meta-analysis of emotional responses in neuroimaging adult studies (WAGER et al., 2003). Greater activation over the left temporal region (versus right) was also described in a fNIRS study of 6 to 7-month-olds while observing happy faces compared to angry faces (NAKATO et al., 2011). However, the EEG FA findings are mainly observed in frontal areas, and most of the EEG studies reporting greater left FA observed this pattern when the infant was actively experiencing positive emotions and approach behaviors (for example, FOX; DAVIDSON, 1988). Infants' behaviors while observing faces were not directly evaluated in the current experiment, making it difficult to further interpret this finding.

The present findings were not aligned to previous EEG studies of IDM that indicate a pattern of greater relative right FA. Several aspects should be noted. First, a number of the EEG studies reporting greater right FA focused on the effects of prenatal maternal depression, as well as on elevated anxiety and depression in pre- and postnatal period, investigating resting EEG in neonates and infants. The neurophysiological findings could be related to the anxiety and depression adverse effects in the fetal development, and relatively less to the postnatal environment. In the present study, however, data of maternal anxiety in the prenatal period was not collected, a limitation of the study.

Second, the vast majority of the EEG studies have focused on depressed subjects, and a number of inconsistencies have been reported in the EEG literature. Many studies failed to demonstrate right FA or described inverse patterns, noticeably when evaluating comorbid depression and anxiety (DAWSON et al., 1997; LUSBY et al., 2014; VANMEENEN, 2005), or anxiety alone (ENGELS et al., 2010; THIBODEAU; JORGENSEN; KIM, 2006). Empirical support for distinct anxiety profiles has been observed in adult EEG research (NITSCHKE; HELLER, 2005; NITSCHKE, 1998). Accordingly, anxious apprehension (related to worry and anticipatory anxiety) induces greater left FA, whereas anxious arousal (related to fear and panic), generates greater right FA as well as greater relative right posterior activation (ENGELS et al., 2010). Thus, the inconsistencies in comorbid studies could reflect different types of anxiety associated with depression.

Third, the present work was not focused in clinical maternal anxiety. It is possible that the degree of the maternal symptomatology in the evaluated community sample was not powerful enough to be related to relative right FA. Finally, EEG studies are based on measures of the EEG alpha power. The specific relationship patterns between EEG power and fNIRS responses are not well established. The hemodynamic responses could be less sensitive than EEG regarding changes in the approach/withdrawal model (DOI; NISHITANI; SHINOHARA, 2013). Further studies using simultaneous EEG and fNIRS measures should clarify this.

In summary, although the anxiety-related findings are preliminary, refer to a small sample and should be interpreted cautiously until they can be replicated, they suggest that differences in the cortical hemodynamic responses to facial emotional processing could be related to alterations in the rearing environment, including elevated maternal anxiety symptoms.

11 LIMITATIONS

Several limitations should be considered. This study investigated a relatively small sample, with little variation regarding socioeconomic aspects. The high education and socioeconomic levels indicate that the current sample is skewed towards the higher end of socioeconomic stratum. While 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, such as economic status and cultural differences (AKTAR; BÖGELS, 2017). Hence, the present findings may not be generalizable and should be replicated in diverse samples.

Another limitation is that infants' emotional experiences were not directly evaluated. However, based on previous studies (for example, BEEBE et al., 2011), maternal emotionality presumably affects the extent to which infants are exposed to different emotions and facial expressions in a daily basis. In future studies, it should be useful to confirm this assumption and collect measures of infants' experiences, such as direct observation of mother-infant interactions. Additional information regarding the infants' behavior and genetic polymorphisms would also be informative in future experiments.

Also, in the current study, prenatal assessment of maternal anxiety symptoms was not collected. Thus, it is possible that the presented results may be overly attributed to postnatal factors.

Finally, the implications of the investigated elevated symptoms of maternal anxiety may be different from those of a clinically diagnosed anxiety disorders.

12 CONCLUSION

The present study contributes to the field of developmental cognitive research about the neural bases of emotional face processing in early infancy. Using fNIRS, a relatively novel neuroimaging technology, it was possible to evince hemodynamic activation of cortical brain areas in response to static visual stimuli of happy and fearful facial emotion expressions. Typically developing 5-month-old infants exhibited greater hemodynamic responses to happy compared to fearful faces. This finding is consistent with previous developmental behavioral studies, which have shown that infants can discriminate positive emotions prior to negative emotions. Emotional faces elicited greater activation over temporal compared to frontal areas. The temporal areas analyzed likely cover the posterior region of the STS, considered a key structure in the perceptual processing of changeable aspects of faces (including facial expressivity) and has been studied extensively in animals and adults. Developmental models suggest that the networks involved in face perception and emotion recognition, including the STS, become particularly attuned to environmental experiences around 5 and 7 months of age. Hence, the greater hemodynamic activation in temporal areas likely reflects the functional emergence of those networks, as previously reported in other fNIRS studies that specifically showed temporal activation for dynamic faces in 5-month-olds, as well as for emotional faces in infants between 6 and 7 months of age. To my knowledge, the present study is the first fNIRS experiment reporting activation for emotional faces in infants at 5 months of age.

The second part of this work aimed to investigate the potential influence of the emotional environment experienced by the infant in this particularly sensitive period of the emergence of emotion-recognition networks. The mother-infant relationship, alongside with the indubitable role in assuring the infant's survival, is critical to promote the foundation of social and emotional skills. Due to the repeated exposure to maternal expressions and the critical role of mother-infant interactions for infant bonding and health development, the exposure to maternal emotional faces are considered a distinct class of stimuli, which presumably influences the emerging neural networks more than any other emotional face in the infants' context. The present findings, although observed in a small sample size, suggest that infants' hemodynamic brain responses to emotional faces may be influenced by alterations in the early emotional environment, likely related to elevated maternal anxiety symptoms. Infants of high-anxious mothers showed a more pronounced response to happy versus fearful expressions, particularly observed over the left hemisphere. Infants of high-anxious mothers could have been systematically less exposed to high-intensity happy facial

expressions during mother-infant interactions, and the altered patterns reflect a greater hemodynamic response to process a less familiar stimulus. Alternatively, this result could reflect an innate predisposition of infants of anxious mothers to demonstrate greater sensitiveness to emotional responses, or could relate to both heritable and environmental aspects. Further studies should elucidate these effects with longitudinal designs. In any event, the results indicated altered hemodynamic brain responses for emotional face processing in infants exposed to elevated levels of maternal anxiety symptoms.

Despite the high prevalence of maternal anxiety and the potential impact on infants' emotional development, to my knowledge this is the first study to explore infants' emotional face processing and maternal anxiety using fNIRS. Further research should clarify the observed developmental differences and their neural correlates using clinical samples, or promoting longitudinal studies in risk populations. Expanding the research on individual differences throughout development can enable the discovery of precocious neural underpinnings that may mediate the later onset of clinical symptoms, ultimately allowing better intervention strategies for children at risk.

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ATTACHMENT A – Confirmation of original article submission to the Journal of Cognitive Neuroscience

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APPENDIX A – Review article published in the Jornal de Pediatria

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REVIEW ARTICLE

Behavioral and neural correlates of emotional development: typically developing infants and infants of depressed and/or anxious mothers

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KEYWORDS
Infant;
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Abstract
Objectives: To describe the main findings of studies of behavioral and neural correlates regarding the development of facial emotion processing during the first year of life in typically developing infants and infants of depressed and/or anxious mothers.
Sources: Comprehensive, non-systematic review of the literature on studies about individual differences in facial emotion processing by newborns and infants over the first year of life.
Summary of the findings: Maternal stress related to depression and anxiety has been associated to atypical emotional processing and attentional behaviors in the offspring. Recent neuro- physiological studies using electroencephalogram and event-related potentials have begun to shed light on the possible mechanisms underlying such behaviors.
Conclusions: Infants of depressed and/or anxious mothers have increased risk for several adverse outcomes across the lifespan. Further neurobehavioral investigations and the promotion of clinical and developmental research integration might eventually contribute to refining screening tools, improving treatment, and enabling primary prevention interventions for children at risk.

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PALAVRAS-CHAVE
Lactente;
Mães Deprimidas;
Ansiedade;
Face;
Emoção;
Comportamento

Bases neurais e comportamentais do desenvolvimento emocional: lactentes com desenvolvimento típico e lactentes filhos de mães deprimidas e/ou ansiosas

Resumo

Objetivos: Descrever os principais achados de estudos de correlação entre o comportamento e as bases neurais em relação ao processamento de emoções faciais durante o primeiro ano de vida de lactentes com desenvolvimento típico e lactentes de mães deprimidas e/ou ansiosas.

Fontes: Análise abrangente e não sistemática da literatura de estudos sobre diferenças individuais no processamento de emoções faciais de neonatos e lactentes ao longo do primeiro ano de vida.

Resumo dos achados: O estresse materno relacionado à depressão e ansiedade tem sido asso- ciado a alterações no processamento emocional e na alocação da atenção da prole. Estudos neurofisiológicos recentes utilizando electroencefalograma e potenciais relacionados a eventos começam a esclarecer os possíveis mecanismos inerentes a esses comportamentos.

Conclusões: Lactentes filhos de mães deprimidas e/ou ansiosas têm maior risco de problemas de saúde física e mental durante toda vida. O avanço de estudos neurocomportamentais e a promoção de integração entre a pesquisa clínica e de desenvolvimento poderão contribuir para refinar as ferramentas de triagem, melhorar o tratamento e permitir intervenções de prevenção primária para crianças em risco.

Introduction

The ability to recognize and understand facial expressions of emotion is a fundamental skill in daily interactions with others, and plays a particularly important role early in life, before the onset of language.[1] Face recognition is one of the most salient cues for social interaction and affective communication. Facial expression recognition develops gradually during infancy and childhood, and appears to continue to develop until early adulthood.[2] During the first year of life, however, the development of visual orientation and the discrimination of different emotions progresses rapidly.[3] Over the past several decades, behavioral studies[4---6] have used different measures of visual preference to infer aspects of recognition of emotional faces. More recently, new methods to elucidate distinct correlates of brain activation have provided significant contribution to the field. Two of the most used methods, known as electroencephalogram (EEG) and event-related potentials (ERP), are reviewed here.

Evidence has become available that stress exposure during pregnancy and the postnatal period leads to several long lasting detrimental outcomes in the offspring, including behavior and cognitive problems and neurodevelopmental delay.[7] Studies on maternal negative affective states, including both depression and anxiety, indicate a detrimental effect on the child's health and development, increasing the risk for a wide range of disorders such as low birth weight and preterm birth, cognitive and motor developmental delay, achievement deficits, and psychiatric disorders.[8] Infants of depressed and anxious mothers have increased vulnerability to cognitive and emotional problems throughout their lifespan.[7,8]

Psychological stress, depression, and anxiety are closely linked and often coexist.[7] Approximately 10---20% of women will exhibit symptoms of depression during pregnancy and/or the postpartum period.[7] Anxiety disorders in the perinatal period have received more scientific attention only recently and their prevalence is still unclear, yet estimates range as high as 30%.[9] The outcomes of anxiety and depression are often studied together, as the symptoms frequently overlap, and their coexistence is a marker of severity.[9,10]

The mechanisms between maternal negative affective states and the infant outcomes are studied both in animal and human clinical research. During pregnancy, maternal stress induces the dysregulation of the hypothalamic- pituitary-adrenocortical (HPA) system, elevating the cortisol levels and inducing sympathetic activation with release of catecholamines.[7,9] The latter is associated to increased uterine artery resistance, reducing the blood flow to the fetus, with restricted inflow of oxygen and nutrients.[10,11]

The higher levels of maternal cortisol adversely affect fetal brain development, possibly due to epigenetic dysregulation through alterations in synaptogenesis and neurotransmitter functions.[11,12] There is evidence of disruption of the fetal HPA system, with adverse physiological and bio- chemical effects on the fetus and newborn[10] that can persist throughout infancy, resulting in altered infant perception and behavior.

In the postnatal period, maternal anxiety and depression are related to less sensitive and inconsistent care when interacting with infants, providing suboptimal levels of general stimulation, and disrupting the mother-child relationship and the formation of attachments.[8,13] Accumulating evidence indicates that the emotional environment of the infants' daily experiences influences their developmental trajectory of facial recognition.[14] Typically, the mother is the most present person in an infant's life, and the mother's facial expressions are the most prevalent in their experience.[14] Mothers with depression and anxiety smile less, display more flat affect and negative

facial expressions, and interact with infants in a with- drawn and muted style.[14,15] As a result, infants of depressed and/or anxious mothers have systematically atypical social experiences compared to infants of healthy mothers.[14,16] Understanding the possible mechanisms by which maternal stress related to depression and anxiety affects an infant's development is a key to further developing better intervention strategies and prevention programs.

This review examines the findings of studies about maternal depression and anxiety on face recognition by the infant, both regarding behavior and neurophysiology. It begins with a brief review of typically developing infants in order to set the stage for the discussion that follows, focused on infants of depressed and/or anxious mothers.

Behavioral studies

The majority of early emotional behavioral studies mea- sure looking time or visual preference. Visual fixation gradually decreases to a repeatedly presented stimulus, a phenomenon referred to as habituation (or familiarization); presentation of a new stimulus leads to recovery of looking if the infants can discriminate the old from the new stimulus (dishabituation).[3] This measure can be used to examine the ability to discriminate different visual stimuli, such as one face from another or one object from another, or in the current context, one facial expression from another. Another method to measure visual preference is the visual paired comparison procedure, in which looking time and duration of the first visual fixation are measured comparing two expressions seen at the same time.[3]

Emotional information can also be inferred from multisensory modalities presented simultaneously, such as facial and vocal stimuli. Multimodal studies investigate how different sensory stimuli may influence the processing and perception of each other.[5,17] For example, studies analyzing congruent and incongruent face---voice pairs (*i.e.*, same or different emotion presented by the face---voice) attempt to elucidate how emotional information is integrated.[5]

Furthermore, emotional responses are measured observing infants' specific behavioral reactions, such as facial expressions, vocalization, imitation, or body movements. One commonly used paradigm is the still-face, in which the mother (or the experimenter) is instructed to show flat affect, mimicking emotional unavailability. Infants typically respond with distress, manifested by less motor activity, frowning, gaze aversion and crying.[13,18,19]

Neural correlates - Electroencephalogram (EEG)

The EEG is a measure of electrophysiological brain activity that represents synchronized activation of large populations of cortical pyramidal neurons firing together. The synchronization of electrical activity generates different continuous frequencies of oscillation, measurable by electrodes placed at the scalp. EEG is a non-invasive method that can be used in infant-friendly environments and has an excellent temporal resolution.[20] The study field of emotional development has especially explored the pattern of frontal EEG power in the alpha frequency.[20,21] Alpha frequency appears early in life, matures rapidly over the first few years, and thereafter remains relatively stable.[22] Alpha power is inversely related to brain activity, confirmed with hemodynamic and metabolic measures (*i.e.*, negatively correlated with cerebral perfusion in functional magnetic resonance imaging (fMRI) and with cerebral glucose metabolism using positron emission tomography (PET)).[16,21] Therefore, EEG alpha power is used as an inverse indicator of regional cortical activation. The EEG frontal asymmetry (FA) is a measure computing the difference between the scores of alpha power comparing frontal right and left areas.[21,23]

A large body of empirical work measuring FA relates different patterns of activation to differentially specialized types of emotions.[20,21] Greater relative left FA is associated with approach behaviors (such as joy, anger, and surgency) and with the expression of positive affect. In turn, greater relative right FA is associated with avoidance and withdrawal behaviors, as well as the expression of certain negative emotions, such as fear and sadness. The studies[16,21---24] of FA are related to both trait and state measures, considering individual differences in affective style and emotional disorders, and acute affective response, respectively.

Neural correlates - Event-related potentials (ERPs)

ERPs are the most common method used in infancy to investigate the neural correlates of a variety of perceptual and cognitive functions. ERPs are transient changes in brain activity that occur in response to a discrete event, extracted from the EEG recording. Electrical brain activity is measured during the presentation of repeated stimuli, revealing reliable patterns according to each stimuli category. It is successfully used to investigate perception discrimination, emotion recognition, and memory in infants and adults.[25]

Studies in infants have identified several components involved in visual human face processing: P1 (positive deflection that peaks around 120 ms after stimulus onset), N290 (negative deflection at 290 ms post stimulus), P400 (positive deflection at 390---450 ms for infants between 3 and 12 months of age), Nc (Negative central deflection peak- ing around 400 ms after stimulus), and positive slow wave (PSW, positive deflection beginning around 800 ms after stimulus).[25,26] The precise meaning of each component and the developmental trajectory remain to be clarified both in children and in adults, although a number of recent studies have begun to shed light on this subject. Specifically, consistent evidence relates similar face-sensitive processing for both the N290 and the P400 to the N170, a component reliably studied in face processing in adults.[25] Additionally, the Nc is considered an index of attention and orienting to salient stimuli in infants, stimuli that recruit more attention appear to enhance the amplitude of the Nc.[27]

The electrophysiological processes underlying multi- modal sensory integration in emotion began recently to be examined throughout development. Auditory ERP components can be explored in paradigms using simultaneous face-voice stimuli.[5] Some authors have shown that the previously described Nc and a positive component (Pc, a component with similar characteristics of the PSW, possibly equivalent to it) are also sensitive in crossmodal face-voice stimuli. The enhanced amplitude of the Nc is related to attention orienting to unexpected/unfamiliar stimuli, while

the Pc evinces a larger amplitude to familiar stimuli.[17] Other researchers refer to infants' responses to auditory stimuli as the P150-N250-P350-N450 ERP complex, and consider the N450 equivalent to the Nc.[28] These infant components are believed to be precursors of children's and adults' components (P1, N1, N2, P2, P3a, and N4) and can already be observed at birth.[28]

Typically developing infants

Studies with newborns reveal that infants already look longer and preferentially orient to face-like stimuli several hours after birth,[29] suggesting they have some ability to orient to the most salient social stimuli in their environment: faces. The developmental process is defined as ''experience expectant'': the innate neural architecture has the potential to become specialized for face processing, but it needs to be primed through experience, allowing the face-processing pathway to mature.[26]

A few studies[30---32] have shown that newborns already react distinctly to different facial expressions. Field et al.[30,31] conducted a series of studies with newborns, both term and preterm, using dishabituation procedure and behavior observation. The authors reported that newborns were able to discriminate and imitate happy, surprise, and sad expressions (although there was no control group in this study). In a more recent dishabituation study, term newborns showed increased looking time to happy compared to fearful faces presented at the same time, and no difference between neutral and fearful categories.[32]

Even though there is evidence that newborns might differentiate some facial expressions, it is not until 3---4 months of age that infants can reliably distinguish among happy compared to some other emotional expressions.[5] Infants at 3 months of age can discriminate among happy and surprised faces,[5] and between happy and sad faces of their own mothers or a stranger.[6] In another experiment,[4] 3-month-olds discriminated between happy and neutral faces and within the positive emotional category (*i.e.*, different degrees of happy), demonstrating increasing positive visual preference with the intensity of the smile rising, peaking with maximally toothy smiles. In this study, maternal style to the infants' perceptual sensitivity was categorized. Mothers who actively encouraged their infants to attend to them more often had infants who detected facial expressions of smiling more readily, a possible reflection of the effects of early experience with the mother's interaction styles.[4]

Accordingly, happy faces appear to be the first to be discriminated in infants comparing to all other facial expressions.[29] The infant's early preference for positive emotions is believed to be related to the necessity of bonding at this attachment formation stage.[29] As the infant pays more attention, the caregiver smiles and the infant imitates it back, promoting a positive environment and strengthening their relationship, crucial to the infant's survival.[4,29]

The studies on infants after the age of 7 months present more consistent data of the infant's ability to categorize other expressions than happiness.[5] In fact, at some point between 5 and 7 months of age, infants develop a preference for fearful faces over other emotions.[1] Seven-month-old infants look longer to fearful than to neutral or happy faces, and are less likely to disengage attention from fearful faces.[1,33] This pattern is typically seen in adults, possibly to prioritize the identification of potential environmental threats.[1] As infants begin to crawl, and their locomotion ability improves this response, thus may reflect an adaptive increase in vigilance in response to cues of threat in the environment.[1,33]

In a multimodal face-voice experiment, 5-month-old infants reliably detected emotional vocal changes, but only if there was a simultaneous presentation of faces, suggesting that facial cues might facilitate infants' perception of emotional voice tones.[34] In another study, 7-month-old infants recognized face-voice common affect, displaying preference for face and voice emotionally congruent matching stimuli rather than incongruent ones, even when voice was played out of synchrony with the face.[5]

Neural correlates

Stable patterns of FA emerge early in life and are related to individual differences in emotional trait dispositions, such as emotion regulation and reactivity.[16,20,21] Infants with more difficult temperaments (*i.e.*, highly reactive, fearful, and inhibited) show greater relative right FA.[7,10] FA is also observed in acute affective response, indicating a current emotional state. Fox and Davidson[35] conducted a series of studies examining FA during a variety of elicitors producing positive or negative emotions. Newborns were tested with water, sucrose, and citric acid solutions while concomitant EEG was recorded. The solutions elicited facial expressions that the experimenters coded as interest and disgust, which were associated to greater left FA in response to a pleas- ant taste (sucrose) compared to unpleasant (citric acid) or neutral tastes.[35]

Typically developing 10-month-old infants watched videotaped segments of a female model displaying happy or sad facial expressions. The infants showed greater relative left FA when observing the happy expressions.[36] In another study,[23] the same authors documented asymmetrical EEG activation in the frontal cortex when 10-month-old infants were observed while exhibiting specific behaviors. Infants showed greater left FA when expressing approach behaviors like reaching with hands for their mother and eliciting facial expressions of joy accompanied by positive vocalizations. When the same infants displayed behaviors such as gaze aversion and distress (*i.e.*, active withdrawal behavior), there was greater relative right FA.[23] In a similar posterior study, 6-month-old infants who demonstrated fear and sadness (while a stranger was approaching) had greater right FA.[37]

In the first study in infants using ERPs to analyze differences in response to facial emotional states, Nelson and De Haan[27] reported that 7-month-old infants evinced a larger Nc when seeing fearful instead of happy faces, and showed no differences when tested only on negative emotions (angry and fear). The authors also reported variations on the amplitude of two positive components, an early and a later positive component, both of greater amplitude to happy rather than to fearful faces. Additional studies corroborate with the finding of enhanced Nc amplitude and attentional response to emotional face stimuli.[1,23,33]

In a multimodal processing study, 7-month-old infants demonstrated a larger Nc for emotionally incongruent face-voice pairs of happy and angry stimuli, whereas congruent stimuli elicited larger amplitude for the Pc.[17] The pattern of an attenuated Nc and a larger Pc was related to the recognition of the congruent pairing.[17] Recently, 9-month-old infants revealed modified auditory ERP components (larger positivity on P150 and P350 and smaller negativity in N250 and N450) for either happy or fearful vocalizations when preceded by visual exposition to fearful faces.[38] Both P150 and P350 are related to orienting attention; therefore, the authors concluded that fearful faces enhanced attentional levels, modulating ERP responses.[38]

Infants of depressed and anxious mothers

Maternal depression and anxiety are implicated in atypical behaviors in infants since birth.[9] Infants of depressed and anxious mothers are believed to have higher arousal and less attentiveness,[12] showing less orientation to facial expressions and face---voice pairs in experimental conditions and in live face---voice interactions.[15] Studies of behavior and neural correlates are beginning to improve insights into the mechanisms underlying the presumably slower sensory processing and delayed attention in these infants.

Most of the studies on maternal negative affective states are based on symptoms scales rather than a confirmed diagnosis of maternal depression and anxiety. Although self-report scales do not provide a clinical diagnosis, they have been correlated with confirmed diagnoses on clinical evaluations.[8,9,22] It is particularly noteworthy to emphasize that the use of depression symptoms scales has been shown to invariably assess a wide range of anxiety symptoms, as well as other negative affective states such as anger and irritability.[10,11] Therefore, although the majority of studies reviewed here rely on depression symptoms scales, it is believed that the related outcomes may be secondary to maternal anxiety aspects as well.[8---10]

Studies on newborns indicate that infants of depressed mothers (IDMs) orient less to faces and voices as early as during the first hours of life. Hernandez-Reif et al.[39] tested full-term newborns of depressed and non-depressed mothers for visual preference and habituation to the mother's face---voice, comparing to a female stranger. IDMs required one-third more trials and almost twice as long as the infants of nondepressed mothers (INDMs) to habituate to their mother's face---voice pairing. In the post-test visual preference phase, IDMs failed to discriminate their mothers from a stranger. In a subsequent experiment,[40] a group of mothers were evaluated longitudinally for continuity of depressive symptoms pre- and postnatally, including comorbid anxiety. Their 3-month-old infants were exposed to video clips of female models with face and voice stimuli for happy and sad conditions. As earlier reported in newborns, IDMs required longer time to habituate to faces, particularly to happy facial expressions. Unexpectedly, IDMs were able to discriminate sad from happy expressions but only if they were first habituated to sad, thereby indicating that they may not perceive sad expressions as a novelty.[40]

Using a still-face procedure, 3-month-old IDMs exhibited less distress and fewer negative expressions comparing to the typical response of INDMs, possibly related to being more accustomed to a less expressive environment characterized by their mothers' relatively flat affect and less interactive behaviors.[18,19] Beyond that, IDMs had a less interactive behavior (*i.e.*, fewer positive and negative behaviors) during the recorded spontaneous mother-infant interactions, when mothers were instructed to engage with their infant in play, as they would usually do at home.[19] In a study[13] that added a tactile component to the still-face procedure, mothers were asked to maintain a neutral face while touching the infant. Three-month-old IDMs showed more positive affect, manifesting more smiles and vocalizations than infants in the still-face control group without touching. The authors suggest that providing touch stimulation can increase infants' attention and positive affect, thus improving the interactions of depressed mothers and their infants.[13]

Five-month-old infants of mothers with a confirmed diagnosis of depression were successfully habituated to neutral or smiling faces, but they later failed to discriminate between the facial expressions.[14] Striano et al.[41] investigated 6-month-old IDMs and INDMs and found that all infants were able to discriminate neutral from progressively higher intensities of smiling and frowning faces. IDMs, however, presented a looking preference for all smiling faces, and a greater preferential looking to high intensity smiling and frowning expressions, a pattern not observed in INDMs.

Hence, there is evidence that IDMs show less interest in faces, orient poorly to synchronized visual and vocal stimuli, and have diminished sensitivity to changes in facial expressions from birth and throughout the first months of life.[15] The abnormalities are speculated to be related to deficits in attentiveness, as well as altered perceptual skills, per- haps secondary to atypical visual and/or auditory sensory processing.[14,15]

Neural correlates

There is consistent evidence that IDMs show greater relative right FA than do infants whose mothers are not depressed. This pattern is reported from newborns studies, remaining stable throughout infancy up to childhood.[16,20] The right FA bias is also exhibited by depressed adults, which remains stable even after a remission of the depressive symptoms.[22] Relative right FA is also associated with anxiety.[11]

During face-to-face interactions, 3-month-old IDMs compared to INDMs were less responsive to facial expressions, looked longer at sad faces, and displayed less positive and more often negative faces themselves.[42] Another group of 3-month-old watched videos of a female model displaying happy and sad facial and vocal expressions. The INDMs exhibited greater relative right FA when viewing sad compared to happy face---voice stimuli. No differences on FA were found for IDMs, possibly because the EEG data were analyzed during the whole experiment, rather than accounting for only the periods when the infants were actually looking at the videos.[43] In a subsequent study, the same researchers analyzed 3---6-month-old IDMs' and INDMs' EEG responses to mothers' and strangers' happy, surprised, and sad facial expressions. This time, the researchers only computed the EEG data for the periods when the infants were attending to facial expressions. Both groups of infants showed greater

Table 1 Studies of behavior and neural correlates on infants of depressed and/or anxious mothers.

Authors	Participants (*n*)	Mean age[a]	Method	Findings/results
Hernandez-Reif et al., 2002[39]	20 (10 IDMs)	45 h	Habituation and dishabituation to mother and stranger face---voice	IDMs required more trials and took longer to habituate to their mothers' face and voice IDMs failed to discriminate their own mothers from a stranger
Field, 1984[18]	28 (14 IDMs)	3.0 mo	Mother-infant interaction, still-face procedure, and infant behavior coding	IDMs showed less distress in still-face procedure (less negative facial expressions and less vocalizations)
Pickens & Field, 1995[42]	84 (27 IDMs)	3.1 mo	Mother-infant interaction and infant facial expression coding	IDMs displayed more sad and anger expressions and less interest expressions
Diego et al., 2002[44]	27 (intrusive = 14, withdrawn = 13)	3.3 mo	Mother-infant interaction, visual preference for mother and stranger facial expressions Infant behavior coding EEG recorded during visual preference	Infants of intrusive mothers looked longer to surprise and sad than to happy expressions performed by a stranger, displaying a concomitant greater relative right FA activity
Peláez-Nogueras et al., 1996[13]	48 (24 IDMs)	3.4 mo	Mother-infant interaction, still-face and still-face-with-touch procedures	IDMs displayed less distress and negative behaviors in still-face procedure IDMs submitted to still-face-with-touch procedure showed more positive affect (more smiles and vocalizations)
Hernandez-Reif et al., 2006[40]	32 (16 IDMs)	3.5 mo	Habituation and dishabituation to face---voice	IDMs required longer time to habituate to faces, particularly to happy faces
Field et al., 1998[43]	24 (12 IDMs)	3.7 mo	Visual preference for face---voice Infant facial expression coding EEG recorded during visual preference	INDMs looked longer to sad face---voice stimuli than IDM, and exhibited greater relative right FA while exposed to sad comparing to happy stimuli. No differences on FA were found for IDM
Field et al., 2007[19]	28 (14 IDMs)	4 mo	Mother-infant interaction, still-face procedure, and infant behavior coding	IDMs showed less smiling and vocalizing, more gaze aversion and motor activity during mother-infant interaction. IDMs showed less motor activity and less distress behavior (less gaze aversion, distress brow and crying) during still-face procedure

Table 1 (*Continued*)

Authors	Participants (*n*)	Mean age[a]	Method	Findings/results
Diego et al., 2004[24]	60 (30 IDMs)	4.2 mo	Visual preference for mother and stranger facial expressions Infant behavior coding EEG recorded during visual preference	IDMs exhibited less positive affect and looked less at their mothers' surprise and sad expressions. IDM looked less at all strangers' facial expressions, showed less positive affect during happy and surprise and more negative affect during surprise expressions IDMs had significantly greater relative FA compared to INDMs in all different expressions of both the mothers and strangers IDMs and INDMs showed relative greater right FA during their mothers' and strangers' sad *vs.* happy faces
Bornstein et al., 2011[14]	28 (14 IDM)	5.1 mo	Habituation and visual paired comparison procedure	IDMs and INDMs habituated to neutral and happy faces IDMs failed to discriminate between neutral and happy faces following habituation
Striano et al., 2002[41]	46 (Maternal depression analyzed as a continuous variable)	6 mo	Visual paired comparison procedure comparing neutral from progressively higher intensities of smiling and frowning faces. Mother-infant interaction and infant behavior coding	Infants of mothers' with higher depression scores showed greater looking preference for all smiling faces, and to high intensity smiling and frowning expressions Infants of mothers' with higher depression scores looked longer at their own mothers while they were smiling
Otte et al., 2015[12]	81 (Maternal anxiety analyzed as a continuous variable)	10.1 mo	Multimodal face---voice compounds ERP recorded with EEG during face---voice compounds	Infants of mothers' with higher maternal anxiety scores showed larger P350 and P150 amplitudes after fearful vocalizations, preceded by either happy or fearful faces.

h, hours; mo, months; IDMs, infants of depressed mothers; INDMs, infants of non-depressed mothers; EEG, electroencephalogram; ERPs, event-related potentials; FA, frontal asymmetry.
[a] Mean age is presented in hours or months.

right FA during their mothers' and strangers' sad *vs.* happy expressions; however, IDMs had significantly greater FA compared to INDMs throughout the different expressions of both the mothers and strangers. IDMs were less interested in facial expressions, showed less positive and more negative affect, and evinced increased salivary cortisol levels after the experiment.[24]

Diego et al.[44] further investigated infants of mothers with two different styles of depressive behavior, intrusive and withdrawn. Accordingly, the interaction style and the biochemical profiles differ between the two styles. The withdrawn mothers tended to have more flat affect, less frequent vocalizing as well as touching, and lower dopamine levels. Their infants also showed lower dopamine levels

and displayed greater relative right FA. Intrusive mothers showed rough physical contact and quick and loud verbal behavior when interacting with their infants. In the study, 3-month-old infants observed their own mother and a stranger, in happy, surprised, and sad expressions. Infants of intrusive mothers looked longer to surprise and sad expressions compared to happy ones performed by a stranger, and displayed a concomitant greater relative right FA activity. These infants also had an increased salivary cortisol, possibly reflecting a higher response to the stressful stimulus. The nature of the different maternal depressive styles and how they affect the infants' physiology and behavior have not yet been fully understood and require further research.

As previously reviewed, ERP provide an excellent tool to temporarily correlate behavior and neural response and is easily administered throughout development.[25] A growing number of studies have been performed in children and adults, expanding the research on neural vulnerability markers for psychopathological disorders, including depression and anxiety.[25] In infancy, a few studies on auditory ERP and maternal affective disorders have begun to demonstrate neural processing alterations, providing insights into the underlying developmental pathways that remain to be better clarified.

In a recent study using ERP and multimodal processing, Otte et al.[12] analyzed 9-month-old infants exposed to maternal anxiety during pregnancy (10% of the mothers also reported previous treatment for depression). Infants were presented with happy and fearful facial and vocal stimuli. Infants prenatally exposed to higher levels of anxiety exhibited significantly larger P350 amplitudes and a trend for larger P150 amplitudes after fearful vocalizations, regardless of the preceding visual emotion type, potentially related to an increased attention to fearful vocal stimuli. The findings corroborate studies in children and adults that anxiety symptoms heightened the sensitivity to threat-related information.[12]

The findings of studies on infants of depressed and anxious mothers are summarized in Table 1.

Conclusions

In summary, infants of depressed and anxious mothers have increased risk for several detrimental outcomes across the lifespan. They exhibit more difficult temperaments (*i.e.*, highly reactive, fearful, and inhibited) and higher incidence of attentional, emotional, and behavioral problems —such as depression, anxiety, and conduct disorders[9,10] — throughout childhood, adolescence, and adulthood.[7,9,10]

During the first year of life, these infants display a number of atypical behaviors, including less interest in facial expressions, less smiling and vocalizations, more time required to habituate to faces and to face-voice pairs, and failure to discriminate between different emotions.[15] Impairments in sensory and perceptual processing as well as reduced attentiveness may underlie such behaviors. Recent neurophysiological studies have begun to shed light on the possible mechanisms linking maternal depression and anxiety to outcomes in infants. EEG studies specifically analyzing facial emotion recognition corroborate findings from the extant literature of a relative right FA asymmetry and its association with depression and negative effects. Comparing to INDMs, IDMs show significantly greater relative right FA across different emotional expressions.[24] A recent unique ERP study described a correlation between maternal anxiety and infants' enhanced ERP components to fearful stimuli, potentially related to an increased bias to threat in these infants.[12]

Further research is needed to better clarify the potential mechanisms related to infants' negative outcomes. Expanding the research with current behavior and neurophysiological methods, as well as exploring new tools such as near-infrared spectroscopy, can help detect biologically-based markers that may mediate these associations from the earliest stages of life, months and years prior to adverse clinical outcomes. Fostering clinical and research integration, by incorporating investigation tools in clinical practice or promoting longitudinal studies in risk populations, for example, should facilitate studying individual differences throughout development and enable the potential identification of precocious neural changes in infants associated with the later onset of clinical symptoms. Beyond that, developmental research might eventually contribute to refining screening tools, improving treatment and enabling primary prevention interventions for children at risk.

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Conflicts of interest

The authors declare no conflicts of interest.

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APPENDIX B – Original article submitted to the Journal of Cognitive Neuroscience

The influence of maternal anxiety on 5-month-old infants' hemodynamic brain responses to emotional faces – a fNIRS study

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ABSTRACT

Early emotional experiences, particularly those made in the caregiving context, are believed to impact the development of emotional face processing. The aim of this study was to investigate the neural correlates of infants' emotional face processing, examining the potential influence of maternal anxiety symptoms. Participants were 29 typically developing 5-month-old infants and their mothers, recruited from a community sample. Maternal trait anxiety was assessed using the trait component of the State-Trait Anxiety Inventory, and explored as an indirect measure of the infant's emotional environment. Infants were shown photographs of women portraying happy and fearful expressions, while hemodynamic brain responses were measured using functional Near-Infrared Spectroscopy (fNIRS). We analyzed the oxyhemoglobin (oxyHb) responses over frontal, parietal and temporal areas, comparing infants of mothers reporting low and high levels of anxiety symptoms. Five-month-olds showed a greater activation to happy compared to fearful faces, and the response for emotional faces was greater over temporal than over frontal areas. When compared to infants of low-anxious mothers, infants of high-anxious mothers exhibited a more pronounced differential hemodynamic response to happy versus fearful faces over the left hemisphere. Our findings suggest that infants' differential hemodynamic brain responses to emotional faces are potentially influenced by alterations in the early emotional environment, including maternal anxiety.

Keywords: Infants, face processing, emotion, fNIRS, maternal anxiety

INTRODUCTION

As social beings, humans' accurate decoding of facial emotion is considered fundamental for effectively navigating the social world (Grossmann, Striano, & Friederici, 2007; Leppänen & Nelson, 2009). The environmental factors that shape the developmental course of facial emotion processing, as well as their underlying neural substrates, are largely unknown. However, early experiences, particularly involving consistent exposure to familiar caregiver faces, are believed to largely influence this course (de Haan, Belsky, Reid, Volein, & Johnson, 2004; Nelson, 2001).

Alterations in the early social environment resulting from maternal mental health conditions, such as anxiety and depression, may negatively impact mother-infant interactions, and possibly influence infants' perception and behavior (Bornstein, Arterberry, Mash, & Manian, 2011; Field, Diego, & Hernandez-Reif, 2009; Glasheen, Richardson, & Fabio, 2010; Jones, Slade, Pascalis, & Herbert, 2013). Infants' perception of emotion may be affected by either the disruption of the quality of emotional interactions with their mothers, or due to atypical exposure to particular facial expressions in the course of daily mother-infant interactions (de Haan et al., 2004; Jones et al., 2013). Maternal anxiety and depression are often studied together, yet considerably less work has investigated the effects of maternal anxiety alone, and more subtle conditions (i.e., subclinical levels of emotional disorders) that are highly prevalent (Glasheen et al., 2010)**.** While both maternal anxiety and depression are related to infants' reduced exposure to positive affect (Aktar & Bögels, 2017; Bornstein et al., 2011; Jones et al., 2013), there may be differences in symptom presentation that uniquely contribute to infants' perceptual and social development. For instance, maternal symptoms of depression may be associated with infants' increased exposure to sadness and flat affect (Field et al., 2009; Hernandez-Reif, Field, Diego, Vera, & Pickens, 2006). In contrast, mothers with anxiety experience excessive fear and worry (Aktar & Bögels, 2017), possibly heightening the frequency with which infants are specifically exposed to fearful emotional stimuli.

The experience with a systematically atypical social environment has potential consequences for the development of underlying neural systems that subserve emotional face processing (de Haan et al., 2004; Pollak, Klorman, Thatcher, & Cicchetti, 2001). Behavioral studies show that infants of anxious and depressed mothers show less attention to faces, and more often fail to discriminate among different emotions compared to infants of healthy mothers during the first months of life (Bornstein et al., 2011; Field et al., 2009; Jones et al., 2013; Porto, Nunes, & Nelson, 2016). A recent study (Otte, Donkers, Braeken, & Van den Bergh, 2015) examined the influence of prenatal exposure to maternal anxiety on infants'

electrophysiological responses (event-related potentials; ERPs) to emotional stimuli. Infants of anxious mothers showed larger P350 amplitudes to fearful vocalizations that were preceded by happy or fearful facial expressions, potentially revealing increased sensitivity to threatening input. Enhanced attention to threat is a well-established correlate of anxiety disorders (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007). For instance, attention bias to fear is reported in both clinically and non-clinically anxious groups, including children, and in a broad range of tasks and neural correlates studies (Bar-Haim et al., 2007; Rossignol, Philippot, Douilliez, Crommelinck, & Campanella, 2005; Williams et al., 2007).

Other studies using the electroencephalogram (EEG) have examined the impact of maternal anxiety and depression on infants' cortical maturation, specifically in frontal regions associated with emotion processing and regulation (Diego, Field, Jones, & Hernandez-Reif, 2006; Field et al., 2003; Field, Fox, Pickens, & Nawrocki, 1995). Based on the approach/withdrawal motivational model, greater activation over the left (vs. right) frontal lobe is associated with approach and positive emotions, whereas relatively greater right (vs. left) frontal activity relates to withdrawal and negative emotions (Davidson, 1993; Fox, 1991). Multiple studies have indicated patterns of greater relative right (vs. left) frontal EEG alpha activation in infants of anxious and depressed mothers comparing to infants of healthy mothers (Dawson, Panagiotides, Klinger, & Spieker, 1997; Diego et al., 2006; Field et al., 2003, 1995; Thibodeau, Jorgensen, & Kim, 2006). This pattern of cortical activity has also been correlated with avoidance and withdrawal behaviors in pediatric and adult populations (Davidson, 1998; Fox, Henderson, Rubin, Calkins, & Schmidt, 2001; McManis, Kagan, Snidman, & Woodward, 2002; Thibodeau et al., 2006), and is considered a marker of increased susceptibility to anxiety and depression (Davidson, 1998).

The EEG is a functional neuroimaging technique widely used in infants' studies. However, it offers limited spatial resolution (Lloyd-Fox, Blasi, & Elwell, 2010). Functional Near-Infrared Spectroscopy (fNIRS) is a relatively novel method applied to infant populations. fNIRS is an optical imaging technique that explores 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). fNIRS provides a more precise localization of brain activation (albeit confined to the cortical surface), and is less sensitive to motion artifacts than EEG (Lloyd-Fox et al., 2010). Thus, fNIRS allows better spatial resolution of brain activity during cognitive tasks, when compared to EEG.

Recent studies employed fNIRS to explore infants' brain responses to emotional face stimuli. Minagawa-Kawai et al. (2009) investigated infants at 9–13 months of age exposed to videos of their own mothers and of an unfamiliar woman, portraying a smile versus neutral faces. Infants exhibited greater activation for their own mothers smiling (vs. neutral faces), over the frontal region, an area possibly including the orbitofrontal cortex (OFC). In a separate study (Nakato, Otsuka, Kanazawa, Yamaguchi, & Kakigi, 2011), differential hemispheric activation was observed in 6.5-month-olds over the posterior temporal cortices, while viewing pictures of women expressing happy and angry faces. The authors reported greater activation over the left temporal cortex in response to happy facial expressions, while angry faces activated the right temporal cortex. In a subsequent exploratory study, Ravicz and colleagues (2015) analyzed individual differences in 7-month-olds' temperament (assessed with the Revised Infant Behavior Questionnaire Short Form) and hemodynamic prefrontal responses to pictures of women portraying happy expressions. Infants with lower negative emotionality scores (considered a positive temperament trait) showed a preferential activation in the left (vs. right) prefrontal cortex in response to smiling faces. Taken together, the brain areas reported in these studies are believed to involve the prefrontal cortex including the OFC, in addition to the superior temporal sulcus (STS), cortical regions related to facial processing and emotional arousal in neuroimaging adult studies (Adolphs, 2002; Wager, Phan, Liberzon, & Taylor, 2003). However, none of the previous studies specifically investigated the potential role of experience (i.e., differences in rearing environments and associated caregiver characteristics) in shaping infants' brain responses to facial expressions of emotion.

The aim of this study was to use fNIRS to investigate 5-month-olds' hemodynamic brain responses to happy and fearful faces, exploring the potential influence of maternal anxiety symptoms, as an indirect measure of the infants' early emotional environment. We explored the use of fNIRS to detect possible hemisphere lateralization in emotional processing by comparing the responses to happy and fearful stimuli, based on the above-referenced approach/withdrawal model. Happy is a positive/approach emotion, whereas fear is a negative/withdrawal emotion.

We predicted that 5-month-olds would discriminate happy from fearful faces, evinced by a greater hemodynamic response to the former. We hypothesized that the hemodynamic response would be more pronounced in frontal and temporal areas, regions previously reported as involved in emotional face processing in infants. Based on previous EEG studies showing specific frontal activation patterns, we expected that 1) if infants could discriminate happy faces, the response would be lateralized to the frontal left region (i.e., greater left,

relative to right, as such activation has been related to positive/approach emotions), and 2) infants of high-anxious mothers would exhibit the opposite pattern, with greater lateralization to the right (vs. left) frontal region, indicating a withdrawal response observed in previous EEG studies of infants of anxious and depressed mothers. Previously reported EEG findings were mainly observed over frontal areas. As fNIRS has a better spatial resolution than EEG, we were interested in exploring potential lateralized responses over broad cortical areas. Thus, we compared between frontal, parietal and temporal regions.

METHODS

Participants. Twenty-nine typically developing 5-month-olds (mean age 154 days ± 4.4; range 145-160; 14 females) and their mothers were recruited from a community sample in the greater Boston area to participate in a longitudinal study of emotion processing. Twenty additional infants were tested but were excluded from the present study for the following reasons: more than 25% of channels were rejected for artifacts (n = 8), poor cap placement exceeding 1.5 cm deviation from ideal in any direction (n = 5), equipment failure (n = 3), cap refusal (n=2), and insufficient number of trials completed (n=2). The 40% attrition rate is consistent with other infant fNIRS studies (Lloyd-Fox et al., 2010). We excluded seven other infants from the final sample due to missing data on maternal anxiety symptoms (n=5), and maternal medication (opioids) used during pregnancy (n=2). All participants were typically developing infants born full-term, with no history of pre- or perinatal complications, vision problems, or developmental delay. Written informed consent was obtained from all parents before the study sessions. The experimental protocol was approved by the local Institutional Review Board.

State-Trait Anxiety Inventory. Maternal trait anxiety was assessed using the trait component of the State-Trait Anxiety Inventory (STAI-T; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). STAI-T is a self-report questionnaire comprising 20 items answered on a four-point scale (1-4). Examples of items include “I feel nervous” and “I am worried”. 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). STAI-T was validated against clinical interviews in perinatal samples (Meades & Ayers, 2011). Although clinical cut-offs for the STAI-T are not available, the inventory has been widely used in perinatal populations and during the first postnatal year, with scores above 40 reported significant for elevated levels of anxiety (Austin, Hadzi-Pavlovic, Leader,

Saint, & Parker, 2005; Grant, McMahon, & Austin, 2008). Greater STAI-T scores were associated with increased maternal ratings of difficult infant temperament and behavior (McMahon, Barnett, Kowalenko, Tennant, & Don, 2001), as well as to lower levels of maternal sensitivity, and reduced levels of maternal emotional tone during mother-infant interactions (Nicol-Harper, Harvey, & Stein, 2007). In the current study, the STAI-T score of 40 was used as the cut-off, as previously done in other maternal anxiety studies (Austin et al., 2005; Grant et al., 2008; Nicol-Harper et al., 2007). Mothers were classified as either low-anxious (scores 20-39), or high-anxious (scores above 40). In our sample, the range of maternal STAI-T was 23-60 (possible 20-80), low-anxious mothers mean scores were 31.6 (±4.8; range 23-39), whereas high-anxious mothers mean scores were 48.5 (±7.2; range 40-60).

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 1 A. Prior to recording, the fNIRS cap was carefully placed on the infant's head, covering an area over the frontal, parietal and temporal cortices (Figure 1 B). 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 deoxygenated (deoxyHb) and oxygenated (oxyHb) hemoglobin respectively, and the attenuated light was measured by the detectors. Data were collected at every 100 ms (10 Hz). For this study, two channels were excluded for being positioned at midline (channels 31 and 40). The remaining 44 channels were divided in frontal, parietal and temporal regions as presented in Figure 2.

Stimuli and design. Color images of female models exhibiting happy, fearful, and angry facial expressions, selected from the NimStim Face Stimulus Set (Tottenham et al., 2009) were used in the experiment. The models' race matched the self-reported race of the infant's mother. 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 3 stimulus types (happy, fearful and angry faces). Within each block, five facial stimuli in the same emotional category were presented. For example, five happy faces with different female

models were presented in a row, followed by an abstract animation. Facial images were displayed on the screen for 1s, with a randomly generated 200–400 ms inter-stimulus interval between each face. The abstract animation was shown for 10s. Including the presentation of the faces, the abstract animation, and the inter-trial intervals between each face, each block lasted a total of 16 s; see Figure 3. The order in which blocks of emotion faces were presented was counterbalanced across participants. If the infant became unsettled or distressed, the experiment was stopped. To limit the number of comparisons in the study, we focused on the analysis of happy and fearful stimuli since both emotions provide a good representation of the approach/withdrawal model, as previously noted. Anger, however, is a negative emotion with an approach motivation and showed discrepant findings in studies of neural correlates (Fox, 1991).

The experiment was performed in a soundproof 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 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. The sessions were video-recorded to assess infants' attention to the stimuli.

Data processing. Prior infant studies have shown that oxyHb is a more reliable measure of neural activation than deoxyHb and totalHb (see Lloyd-Fox et al. 2010 for a review). Therefore, we focused on the statistical analyses in the oxyHb chromophore. Video recordings of each session were coded by researchers blind to the emotional category, using the SuperCoder software (SuperCoder 1.7.1, Purdue University, West Lafayette, IN, USA). Inter-rater reliability was maintained at 0.90 with 15% coding overlap. Blocks were excluded if the infant failed to look at the screen for at least 50% of the time the stimulus was presented. Based on previous infant experiments (for example, Watanabe, Homae, Nakano, & Taga, 2008), an a priori threshold of three trials for each emotion category was used for inclusion in the study. In the final sample, infants completed a mean of 21.5 ± 5.9 total trials (range 09-29), 7.5 ± 2 happy, 7 ± 1.9 fear, and 7.1 ± 2.3 anger trials (n =29).

The software HOMER2 (MGH-Martinos Center for Biomedical Engineering, Boston, Massachusetts), a MATLAB (The MathWorks, Inc., Natick, Massachusetts) package, was used to process the fNIRS data. The fNIRS raw data was converted to optical density units

and filtered using a 0.05-0.80 Hz bandpass filter. Wavelet motion correction with an interquartile range of 0.5 was used to correct motion artifacts. The filtered, motion-corrected data were used to calculate the concentration variance of each hemoglobin chromophore (oxyHb, deoxyHb, totalHb) using the modified Beer–Lambert law, as implemented in HOMER2 (Huppert, Diamond, Franceschini, & Boas, 2009). As in other fNIRS studies (for example, Watanabe et al., 2008), chromophore concentrations were baseline corrected using the 2 s prior to stimulus presentation.

For each infant, the hemodynamic responses of the accepted trials were averaged for each channel and emotion condition. Then, a grand average was calculated for each channel and emotion condition. The grand averaged time course of the hemodynamic responses across all infants was subsequently visually inspected. Based on the visual inspection, a time window between 0 and 12 s was selected for analysis. This window included the range of maximum changes (or amplitude) in concentration for oxyHb. Next, the maximum oxyHb change for each channel and emotion was extracted for each infant, and was winsorized for extreme outliers (if they were beyond the quartiles by three times the interquartile range), and averaged over the channels in the regions of interest (frontal, parietal and temporal) for statistical analysis.

Statistical Analyses. Statistical analysis was conducted using IBM SPSS Statistics 21.0 (IBM Corporation, Armonk, New York). Differences between low- and high- anxious groups for demographic variables and characteristics of participants were investigated by means of independent sample t-tests and chi-square tests. Repeated measures omnibus analyses of variance (ANOVAs) were conducted to analyze de oxyHb responses. The model included 3 within subject factors: emotion category (happy, fear), region (frontal, parietal, temporal) and hemisphere (right, left). Maternal STAI-T classification was included as the between-factors with two levels (anxiety: low, high). When the omnibus ANOVA yielded significant effects, post hoc comparisons were carried out using Bonferroni correction.

RESULTS

Low- and high-anxious groups were comparable in terms of all socio-economic and demographic characteristics analyzed: maternal age, maternal education, marital status, ownership of the house, combined family income in the past 12 months, infant age, infant gender, infant race, birth weight, and type of delivery (Table 1).

The omnibus ANOVA revealed a significant main effect of emotion, $F_{1,27}$=5.887, p=.022, η_p^2=.179. Post hoc analysis showed that the main effect of emotion was driven by significant greater activation in response to happy faces than to fearful faces (Figure 4). There was also a significant main effect of region, $F_{2,54}$=4.888, p=.013, η_p^2=.153 (Figure 5). Post hoc inspection of results revealed significantly greater activation over temporal areas, compared to frontal areas (p=.031). No other region differences were observed. A significant three-way interaction between emotion, hemisphere and anxiety, $F_{1,27}$=4.816, p=.037, partial η_p^2 = .151 also emerged (Figure 4). Inspection of the results revealed that maternal anxiety levels moderated the extent to which infants showed alterations in oxyHb to emotional faces. Infants whose mothers reported higher anxiety symptoms showed relatively greater oxyHb to happy faces and lower oxyHb to fearful faces, with effects most pronounced over the left hemisphere. Infants whose mothers reported lower levels of anxiety did not show differential hemispheric activation of oxyHb response to happy versus fearful faces.

DISCUSSION

This study used fNIRS to analyze individual differences in the neural correlates of happy and fearful emotional face stimuli in 5-month-old infants over frontal, parietal, and temporal cortical areas, exploring the relation between self-reported maternal anxiety symptoms and infants' brain responses to emotional faces. We observed an effect of emotion, in that overall, happy faces induced greater activation than fearful faces. We also observed an effect of region, with emotional faces eliciting greater hemodynamic responses over temporal than over frontal areas. Finally, we found some evidence that maternal anxiety symptoms influenced infants' neural responses to emotional faces. Specifically, infants of high-anxious mothers showed a more pronounced differential hemodynamic response to happy versus fearful faces, when compared to infants of low-anxious mothers. These differential patterns of activation were observed over the left hemisphere. Each of these findings is discussed below.

Emotion. Infants showed a greater activation when seeing happy faces, compared to fearful ones. Prior evidence indicates that infants discriminate positive emotions (i.e., happy faces) prior to negative emotions (fear, angry and sad faces; Bayet, Pascalis, & Gentaz, 2014; Bornstein & Arterberry, 2003). A number of developmental behavioral studies reported a visual preference for happy faces, starting as early as the first days of life (Bayet et al., 2014; Farroni, Menon, Rigato, & Johnson, 2007). Happy faces are the most prevalent emotional expressions displayed by caregivers in the infants' rearing environment (Malatesta &

Haviland, 1982). Over the first months of life, the infant's preference for smiling faces and expressions of joy may contribute to promoting a positive environment that sustains the caregiver's attention and nurtures their bonding, which is considered critical for the infant's survival and for the development of social and emotional abilities (Bornstein & Arterberry, 2003; Parsons, Young, Murray, Stein, & Kringelbach, 2010).

Before 5 months of age, infants reliably discriminate happy faces compared to other emotional expressions (i.e., neutral, sad, angry and surprised faces; Bayet et al., 2014; Bornstein & Arterberry, 2003). Yet, it is not until 7 months of age that infants consistently discriminate between expressions other than happy (Bayet et al., 2014), and begin to shift their visual preference towards fearful faces, the typical pattern observed in adults (Leppänen & Nelson, 2009; Nelson & de Haan, 1996). The perceptual bias to fear is reliably observed in behavior and neurophysiological studies after the age of 7 months, and is believed to be related to early identification of potential environmental threats (Leppänen & Nelson, 2009).

Data from our sample involving 5-month-olds support this developmental trend: Specifically, happy faces elicited an increase of oxyHb concentration relative to the baseline, whereas fearful faces evoked a decrease of oxyHb compared to the baseline. The standard hemodynamic response observed in fNIRS studies on adults consists of an increase in oxyHb and totalHb, and a relatively smaller decrease in deoxyHb (Gervain et al., 2011). The neural activity heightens the oxygen consumption, leading to a prompt increase of local cerebral blood flow with higher oxygen delivery that typically exceeds the demand for oxygen (Lloyd-Fox et al., 2010). This typical hemodynamic response function (HRF) is characterized by a local excess of oxyHb in stimulus-evoked experiments (Gervain et al., 2011). However, a number of studies have described atypical responses in infants, with decrease of oxyHb concentration (Csibra et al., 2004; Ravicz et al., 2015), increase of deoxyHb (Meek, 2002), and/or decrease of totalHb (Lloyd-Fox et al., 2010). The higher variability of the infant's HRF might be related to greater metabolic demands in the immature brain (Meek, 2002), as well as to the immaturity of the neurovascular coupling (Gervain et al., 2011). The last explanation embraces the gradual development of the neurovascular signaling regulation, as well as cerebral angiogenesis and vascular remodeling (Kozberg, Chen, DeLeo, Bouchard, & Hillman, 2013). A pattern of increased deoxyHb with or without decreased oxyHb was also observed in blood oxygen level dependent (BOLD) fMRI studies in infants and adults (Meek, 2002; Sakatani et al., 2006). The findings have been speculated to be related to a decreased neural activity, or local brain deactivation (Sakatani et al., 2006). However, the BOLD signal is believed to be more closely associated with the deoxyHb signal, a chromophore that shows

a high inconsistency across infants' studies (Lloyd-Fox et al., 2010), hence this inference should be interpreted cautiously. In addition, given that a decrease in oxyHb was seen to fearful but not happy faces, our findings suggest that oxyHb HRF response direction is sensitive to the specific stimulus presented and not a global feature of the infant brain response or response to faces in general.

Region. Our study also showed that infants exhibited a greater activation over temporal in relation to frontal areas when exposed to happy and fearful face stimuli. A possible explanation is that 5-month-olds were able to recognize differential configurational aspects between the distinct emotional faces (e.g., open vs. closed mouth, differential degrees of exposure of the eyes, eyebrows variations). Facial perceptual processing of changeable aspects of faces has been attributed to regions of the occipital-temporal cortices, particularly the STS (Adolphs, 2002; Leppänen & Nelson, 2009). Whilst areas of the PFC, particularly the OFC, are involved in the discrimination and modulation of emotional responses (Adolphs, 2002; Leppänen & Nelson, 2009). The OFC has reciprocal connections with the amygdala and the occiptal-temporal cortices, believed to be functional around 5 to 7 months of age, when infants become capable to distinguish between facial expressions (Leppänen & Nelson, 2009). This circuitry, however, is subjected to extensive refinement by experience and possibly continues to develop until adolescence (Leppänen & Nelson, 2009). The discrimination between facial expressions is believed to initiate with differentiation of features and their spatial arrangements in the face, which is progressively associated with representations of affective content. Over time, infants begin to recognize and understand the "meaning" of distinct expressions, laying the foundation for acquiring higher social and emotional capacities (e.g., social referencing, cooperation; Quinn et al., 2011).

In our sample, it is possible that the processing of the affective cues might be still functionally emerging in 5-month-olds, resulting in the less pronounced response observed in the frontal areas. In prior work, activation over the PFC has been reported in older infants, between 9 and 13 months of age, in response to happy versus neutral faces (Minagawa-Kawai et al., 2009). Interestingly, these responses were significant only when the infant was observing their own mother smiling, but not for a female stranger. Moreover, the mothers' brain responses were also recorded and showed increased activation in the OFC to their own infants' smiling compared to neutral faces. It seems that the prefrontal responses to emotional cues may initially develop within social experiences with caretakers, and later generalize to other social contexts (Minagawa-Kawai et al., 2009).

Previous developmental fNIRS studies evaluating configurational aspects of face processing have documented responses over parietal, temporal and occipital areas (for a review, Vanderwert & Nelson 2014). Temporal areas were activated in infants between 5 and 8 months observing upright compared to inverted faces (Otsuka et al., 2007), right parietal areas in 5- and 8-month-olds observing frontal versus profile faces (Nakato et al., 2009), and occipital-temporal regions in 7-month-olds viewing canonical compared to scrambled facial images (Honda et al., 2010). However, studies exploring social and emotional aspects, such as joint attention (Grossmann & Johnson, 2010), or comparing the infant's own mother's face to unfamiliar faces (Minagawa-Kawai et al., 2009), have shown increased hemodynamic responses over frontal areas.

The fNIRS studies that specifically investigated infants' brain responses to emotional faces, restricted the measurements to a limited brain area, either frontal (Minagawa-Kawai et al., 2009; Ravicz et al., 2015), or temporal-parietal (Nakato et al., 2011). Thus, they did not allow a comparison of activation between wide brain areas. In the present study, we used an increased coverage over the cortex, enabling comparisons of activation between broad areas of the frontal, temporal and parietal cortices. We observed a significant increase of oxyHb concentration related to baseline over temporal areas, whereas oxyHb concentration decreased significantly from baseline in the frontal areas. As previously noted, altered HRF patterns were observed in infants, suggesting that the differential underlying processes might be related to development. The typical activation response was observed in the temporal areas, whereas the decrease in the oxyHb concentration over frontal areas are possibly due to an immaturity of the neurovascular coupling, or to a deactivation response.

Maternal anxiety symptoms and infants fNIRS responses to emotional faces. We observed an interaction between emotion, hemisphere and anxiety. Infants of high-anxious mothers appeared to have a more pronounced hemodynamic response to happy versus fearful faces, a pattern particularly observed over the left hemisphere, in comparison to infants of low-anxious mothers. Hereafter, we discuss several mechanisms that could explain the observed association.

Early experiences, particularly those made in the caregiving context, play a critical role in the course of the development of face processing (de Haan et al., 2004; Jones et al., 2013). Conditions that affect maternal mental health potentially impact maternal behaviors and the extent to which their infants are exposed to faces and emotions. Mothers with heightened anxiety symptoms, even at a subclinical level, may communicate in altered ways

with their infants (Aktar & Bögels, 2017; Beebe et al., 2011). Higher levels of maternal anxiety symptoms have been associated with a disruption of mother-infant interaction, often involving high levels of intrusive behavior and lower levels of sensitivity to infants' cues (Beebe et al., 2011; Feldman, Greenbaum, Mayes, & Erlich, 1997; Nicol-Harper et al., 2007). Anxious mothers have also been described as over-aroused, worried and fearful. When interacting with their infants, they are shown to smile less, respond less empathically to infants' distress, and engage with their infants with greater 'emotional distance' (i.e., emotional withdrawal; Aktar & Bögels, 2017; Beebe et al., 2011).

These systematically altered maternal behaviors likely affect the extent to which infants are exposed to positive and negative emotions. In our sample, it is possible that infants of high-anxious mothers experienced relatively less exposure to happy facial expressions, and more exposure to fearful emotions. Thus, their greater hemodynamic response may reflect an enhanced neural activity to process a less commonly experienced stimulus (i.e., happy), compared to a more familiar one (i.e., fearful). These results are aligned with previous studies of infants of highly symptomatic depressed mothers, who are presumably less exposed to happy expressions and more familiarized with sad faces than infants of healthy mothers (Field et al., 2009; Striano, Brennan, & Vanman, 2002). Compared to controls, infants of depressed mothers exhibited greater attention to high-intensity smiles (vs. neutral) faces (Striano et al., 2002), and attended less to sad (vs. happy) faces (Hernandez-Reif et al., 2006). In a separate study (Creswell et al., 2008) comparing mothers with social anxiety and controls, infants of anxious mothers were more likely to show reduced looking to high- versus low-intensity fearful faces, the opposite pattern observed in the controls, again potentially due to being more exposed to maternal fearful faces. We observed similar patterns of neural activation in our sample of infants whose mothers report anxiety symptoms, even at a subclinical level. Specifically, we showed lower activation (i.e., greater decrease of oxyHb concentration in relation to baseline) for fearful faces in infants of high-anxious mothers, compared to infants of low-anxious mothers over the left hemisphere. This inference, however, should be interpreted cautiously. As previously mentioned, the interpretation of patterns of decrease in oxyHb are unclear and still a matter of debate.

In contrast to the EEG literature, we did not find an overall lateralized activation for happy faces. However, on the left hemisphere, infants of high-anxious mothers showed a greater activation to happy versus fearful stimuli, compared to infants of low-anxious mothers. Happy faces induce positive and approach emotions, and have been correlated to preferential activation over the left hemisphere (beyond the frontal areas) in adult

neuroimaging studies (Adolphs, 2002, Wager, 2003). Greater activation on the left hemisphere (vs. right) was also described in a fNIRS study of 6-7-month-olds while observing happy faces (Nakato, 2011). In our study, we did not evaluate the infant's behavior while observing emotional faces, which makes it difficult to interpret the differential patterns evinced between low and high-anxious groups.

Contrary to our hypothesis, infants of high-anxious mothers did not show a pattern of greater right (vs. left) frontal activation, as has been reported with EEG. Several aspects should be noted. First, most of the EEG studies reporting greater relative right frontal activation have focused on depressed subjects, as well as on the effects of anxiety and depression on the prenatal period. However, inconsistencies among studies exist, with many studies failing to observe the frontal asymmetry effect or describing inverse patterns, noticeably when evaluating comorbid depression and anxiety (Dawson et al., 1997; Lusby, Goodman, Bell, & Newport, 2014), or anxiety alone (Engels et al., 2010; Thibodeau et al., 2006). Second, our study did not use a clinical diagnosis of maternal anxiety. It is possible that the degree of the maternal symptomatology in our community sample was not powerful enough to be related to right frontal asymmetry. Finally, EEG studies are based on measures of the EEG alpha power, and the relation between EEG power and fNIRS are not well established (Doi, Nishitani, & Shinohara, 2013). Thus, it is possible that hemodynamic responses are less sensitive than EEG regarding changes in the approach/withdrawal model.

In summary, although our findings must be interpreted cautiously until they can be replicated, they suggest that potential brain hemodynamic differences in early facial emotional processing could be related to alterations in the rearing environment, particularly to elevated maternal anxiety symptoms.

Limitations

The conclusions drawn from this study must take a number of limitations into consideration. We analyzed a relatively small sample, with 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, such as economic status and cultural differences (Aktar & Bögels, 2017). Hence, our findings may not be generalizable. Furthermore, we did not directly evaluate infants' emotional experiences. However, based on previous studies (Beebe et al., 2011), we assumed that maternal emotionality systematically affects the extent to which infants are exposed to different emotions. Finally, the implications of the investigated

elevated symptoms of maternal anxiety may be different from those of a clinically diagnosed anxiety disorder.

Conclusions and future directions

The present findings add to the body of studies on emotional face processing during infancy. Five-month-olds exhibited a greater response to happy compared to fearful faces, and a greater activation over temporal compared to frontal areas. Additional findings suggest that infants' hemodynamic brain responses may be influenced by alterations in the early emotional environment, likely related to elevated maternal anxiety symptoms. Despite the high prevalence of maternal anxiety and the potential impact on infants' emotional development, to our knowledge this is the first study to explore infants' emotional face processing and maternal anxiety using fNIRS. Further research should clarify the observed developmental differences and its neural correlates using clinical samples, or promoting longitudinal studies in risk populations. Expanding the research on individual differences throughout development can enable the discovery of precocious neural underpinnings that may mediate the later onset of clinical symptoms, ultimately allowing better intervention strategies for children at risk.

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Table 1. Demographic variables and characteristics of participants.

Parameters	Total (n=29)	Low anxiety (n=20)	High anxiety (n=9)	*p*
Maternal descriptive				
Maternal age in years	33.56±3.79	33.18±3.96	34.41±3.43	.429
Master or equivalent/PhD	23 (79.3)	15 (75.0)	8 (88.8)	.529
Marital status				.632
Married/Cohabiting	29(100)	20 (100)	9 (100)	
Ownership of the house				.454
Owned	16 (55.2)	10 (50.0)	6 (66.7)	
Rented	13 (44.8)	10 (50.0)	3 (33.3)	
Combined family income in the past 12 months[a]				.762
$100,000 and greater	19 (73.1)	12 (70.6)	7 (77.8)	
Infant descriptive				
Infant age at test in days	153.8±4.0	153.9±4.4	153.7±4.6	.946
Female	14 (48.3)	8 (40.0)	6 (66.7)	.245
White[b]	24 (82.8)	16 (80.0)	8 (88.9)	.782
Birth weight[b] in grams	3.539±332	3.536±351	3.546±307	.941
Type of delivery				.396
Vaginal	20 (69.0)	15 (75.0)	5 (55.6)	
C-section	9 (31.0)	5 (25.0)	4 (44.4)	

Note: Date were presented as No. (%) or mean±SD.
[a] Missing data in 3 participants.
[b] Missing data in 1 participant.

Figure 1: A) fNIRS probe layout. fNIRS channels (labeled by numbers) corresponding to 46 emitter-detector pairs. B) Probe on infant during study session.

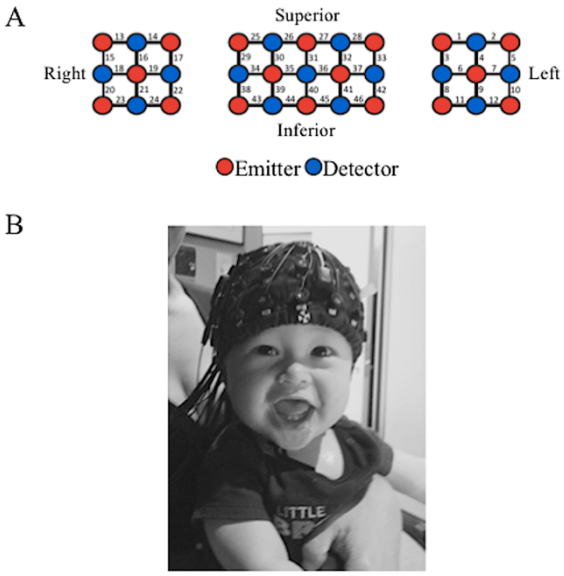


Figure 2: Lateral and frontal views of the approximate locations of fNIRS channels (emitter-detector pairs) on the infant's head. Regions of interest in the study: frontal, parietal and temporal areas.

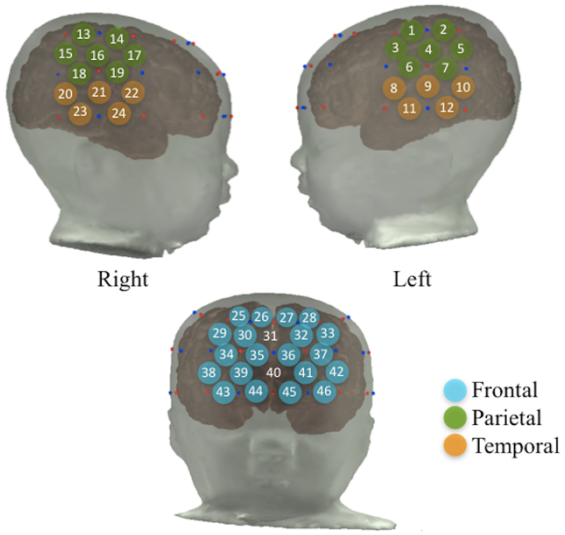


Figure 3: Schematic diagram of experimental design. Each block included five images of a different model portraying the same emotional expression (happy, fearful or angry). Each image was presented for 1 s with a randomly generated 200–400 ms inter-stimulus time, followed by a 10 s abstract video, totalizing 16 s for each block. The experiment included 30 blocks in total, 10 of each emotional category.

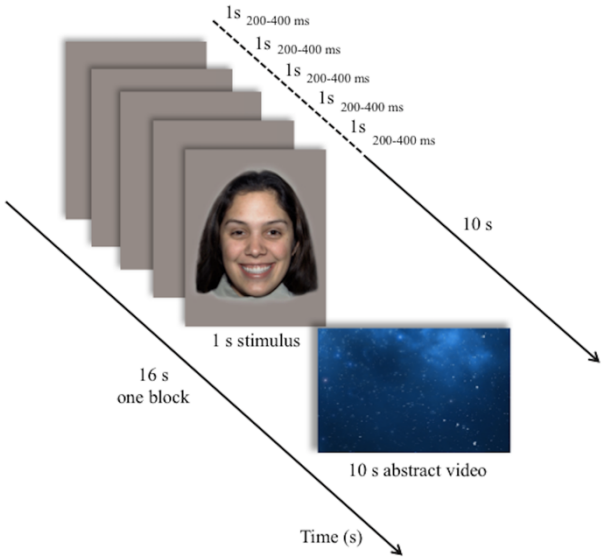
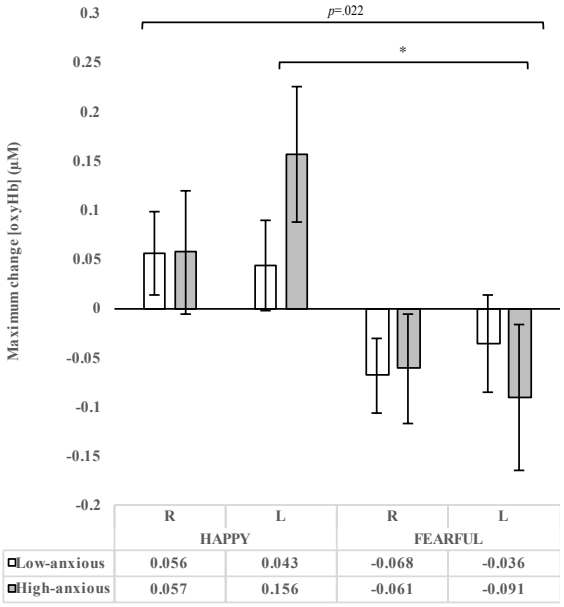
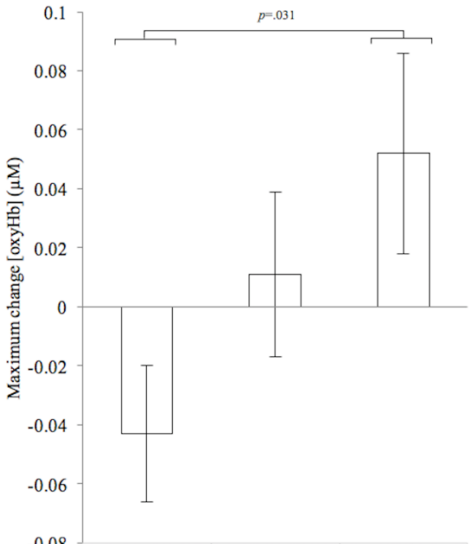


Figure 4: Main effect of emotion (p=.022), and three-way interaction between emotion, hemisphere, and anxiety *p=.037. Maximum change in oxyHb (μM) (presented as mean ± SE) for happy and fearful faces are presented comparing right (R) and left (L) hemispheres for infants of low- and high-anxious mothers (n=29).



	R	L	R	L
	HAPPY		FEARFUL	
Low-anxious	0.056	0.043	-0.068	-0.036
High-anxious	0.057	0.156	-0.061	-0.091

Figure 5: Main effect of region (p=.031). Maximum change in oxyHb (µM) (presented as mean ± SE) in the frontal, parietal, and temporal areas. (n=29).



	Frontal	Parietal	Temporal
Mean	-0.043	0.011	0.052

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