HHS Public Access

Author manuscript

Psychiatry Res Neuroimaging. Author manuscript; available in PMC 2023 December 11.

Published in final edited form as:

Psychiatry Res Neuroimaging. 2023 January ; 328: 111577. doi:10.1016/j.pscychresns.2022.111577.

Postnatal Maternal Distress, Infant Subcortical Brain Macrostructure and Emotional Regulation

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Abstract

Background ––—Maternal distress is associated with an increased risk for adverse emotional development in the offspring, including difficulties with emotion regulation. Prenatal maternal distress has been associated with alterations in infant brain development. However, less is known about these associations with postnatal maternal distress, despite this being an important modifiable risk factor that can promote healthy brain development and emotional outcomes in infants.

Methods & Results -—Infants underwent magnetic resonance imaging (MRI) and mothers completed standardized questionnaires concerning their levels of perceived distress 2–5 months postpartum. Infant emotion regulation was assessed at 8–11 months via maternal report. When examining the associations between maternal distress and infant macrostructure, maternal anxiety was associated with infant right pallidum volume. Increased display of negative emotions at 8–11 months of age was associated with larger hippocampal volumes and this association was stronger in girls than boys.

Conclusion -—Findings suggest that postnatal maternal distress may be associated with early infant brain development and emphasize the importance of maternal mental health, supporting previous work. Furthermore, macrostructural properties of infant subcortical structures may be further investigated as potential biomarkers to identify infants at risk of adverse emotional outcomes.

1. Introduction

Maternal distress in the postpartum period, consisting of symptoms of anxiety and/or depression, is prevalent in 10–25% of pregnancies and is associated with reduced or

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dysregulated mother-infant bonding, representing a significant stressor to the infant (Essex et al., 2002; Lebel et al., 2020; Thomas et al., 2017). In turn, postnatal maternal distress poses risks to the emotional development of the offspring and is associated with a range of adverse emotional outcomes that may persist across the lifespan, such as internalizing and externalizing behavioral problems (Rees et al., 2019; Stein et al., 2014; Zou et al., 2019). Internalizing behavioral problems may include anxious, depressed, or withdrawn behaviors that affect one's internal environment (Liu et al., 2004). In contrast, external behavioral problems may include disruptive or aggressive behaviors that affect one's external environment (Liu et al., 2004).

Emotional regulation, defined as the ability to modulate emotional responses, including intensity, duration, or occurrence using age-appropriate strategies, is important for long-term emotional development (Blanchard-Fields & Coats, 2008; Blandon et al., 2008; Cai et al., 2021). Emotional regulation emerges in the first few months of life and continues to mature across the lifespan (Aktar & Pérez-Edgar, 2020; Rutherford et al., 2015). However, infancy through to early childhood is a sensitive period for its development (Aktar & Pérez-Edgar, 2020). During this time, emotion regulation is learned or achieved within the context of caregiver-child interactions. Disruptions in these interactions, such as lower-quality interactions or decreased sensitivity, have been observed in mothers experiencing maternal distress and can adversely affect an infant's emotional development (Feldman., 2003; Thomas et al., 2017), increasing the risk of internalizing and externalizing disorders (Crugnola et al., 2016; Feng et al., 2008; Granat et al., 2017; Maughan et al., 2007). Previous work suggests that high-quality maternal-infant interactions help to regulate the infants stress response and thus support healthy brain development (Center on the Developing Child, 2009; Donnici et al., 2021; National Scientific Council on the Developing Child, 2014). However, low-quality interactions, characterized by decreased sensitivity and negative affect which have been observed in cases of maternal distress, may leave the infant's stress response unregulated (Donnici et al., 2021; Feldman et al., 2003; Kaitz et al., 2009; Thomas, 2017).

Alterations in brain development may underlie associated risks to emotional development in offspring exposed to maternal distress (Lean, 2021). Infancy is a sensitive period for neural development. The brain undergoes rapid and complex structural and functional changes leaving developmental trajectories vulnerable to early experiences. In line with this, evidence suggests maternal distress may alter brain development in infants. For example, postnatal maternal anxiety and depression have been associated with amygdala volume in children (Donnici et al., 2021; Lupien et al., 2011). Furthermore, postnatal maternal anxiety has been negatively associated with left hippocampal volumes in infants (Qiu et al., 2013). However, associations between maternal distress and the developing infant brain have not been fully elucidated, with previous work focusing mainly on limbic structures. As such, research on infant subcortical structures more broadly in association with maternal distress is needed to identify potential early neural markers of risk.

Previous work has found variations in brain structure to predict developing emotional capabilities such as emotional regulation (Graham et al., 2017; Luby et al., 2016; Moog et al., 2021; Pagliaccio et al., 2014). For example, research has found associations between

macrostructure (volume) of limbic areas and later emotion regulation at different stages of development from infants to adolescence (Blanton et al., 2010; Moog et al., 2021; Pagliaccio et al., 2014). This may suggest brain-behavior relationships may be useful predictors of emotional development. However, potential relationships between brain structure and subsequent emotional capabilities early in development during infancy have been limited. Previous research has emphasized the importance of infancy through to early childhood for emotional development, and indicates early interventions are key to promote healthy outcomes, as such, further research in elucidating neural markers to identify those at risk during this developmental period is needed.

Evidence suggests that biological sex of the infants should be considered in examination of these brain-behavior relationships. Sex differences have been found in emotional development including emotion regulation, as well as vulnerability to emotion-related pathologies (Chaplin & Aldao, 2013; Stein et al., 2014; Weinburg & Tronick, 1999). For example, internalizing disorders are more prevalent in girls, while externalizing disorders are more common in boys, both generally and in association with maternal distress (Chaplin et al., 2019; Hick et al., 2019). Together, these results suggest biological sex should be considered in examining relationships between brain structure and predictors of emotional development (Letourneau et al., 2019).

Given the evidence that infancy is a key period for brain development and maternal interactions are essential for healthy emotional development, in the present work we sought to better understand the associations between maternal distress, infant brain development and subsequent emotion regulation to identify risk and resilience factors. We hypothesized that high-quality maternal interactions support heathy brain development of the offspring. Low-quality interactions, characterized by decreased sensitivity and negative affect as observed in cases of maternal distress, may alter developing neural systems and could underlie the risks to emotional development (Feldman et al., 2003; Kaitz et al., 2009; Thomas, 2015). Furthermore, given sex-differences in the vulnerability to emotional outcomes, we hypothesized that biological sex would be an important moderator of this relationship. Based on previous findings, we hypothesized that postnatal maternal distress would be associated with infant subcortical macrostructure. We further predicted that infant subcortical macrostructure would be associated with emotion regulation abilities. Moreover, we hypothesized this association would be moderated by biological sex.

Infants underwent MRI scanning between 2–5 months of age. Subcortical brain structure volumes were extracted from anatomical MRI images. During this period (2–5 months postpartum), maternal distress was measured via self-report on anxiety and depression questionnaires. Infant emotion regulation was subsequently assessed at 8–11 months via maternal report. This study addressed the following questions: What is the association between postnatal maternal distress and infant subcortical macrostructure? Does infant subcortical macrostructure predict emotional regulation in infants in the first year of life? Does biological sex moderate this relationship?

2. Methods

2.1 Participants

Data for this project were obtained via the National Institute of Mental Health Data Archive (NDA identifier: 2340). Data collection occurred between September 2015 and July 2017 at the Children's Hospital of Pittsburgh (Phillips et al., 2021). Inclusion criteria was defined as healthy mothers and full-term infants (> 37 weeks) around the age of 3-months. Exclusion criteria for infants was MRI contraindications (i.e., non-removable metal), premature birth (< 37 weeks), low birth weight (< 5.5lbs), low Apgar scores at 5 minutes (< 7) or prolonged hospital stay for physical illness (Phillips et al., 2021). Exclusion criteria for the mothers included substance use problems (either disorder, or illicit use), age (< 18 years), or cared for her infant less than two hours a day (Phillips et al., 2021). The study was originally approved by the University of Pittsburgh Institutional Review Board (Phillips et al., 2021). Informed consent was obtained from the mothers.

2.2 Procedures

Infants underwent scanning and mothers completed questionnaires regarding their perceived levels of distress 2–5 months postpartum. Infant temperament was later assessed at 8–12 months via maternal report. Participants were selected if mothers had completed questionnaire measures of interest and infant T1-weighted MRI scans were available.

2.3 Maternal Distress

Maternal distress was measured via self-report using questionnaires. The state anxiety component of the state-trait anxiety scale (STAI-S; Spielberger et al., 1983) was used to measure anxiety symptoms and the Edinburgh postnatal depression scale (EPDS; Cox et al.,1987) was used to assess depressive symptoms in mothers during the postpartum period. These measures have been widely used in maternal mental health research (Spry et al., 2020; Meades & Ayers, 2011).

State-Trait Anxiety Inventory—The state subscale of the state-trait anxiety inventory (STAI-S) measures state anxiety, defined as situation-related anxiety or current anxiety level (Spielberger et al., 1983; Dennis et al., 2013). The STAI-S consists of 20 items on a 4-point scale (1=not at all; 4 very much so) (Spielberger et al., 1983). For example: "I am presently worrying over possible misfortunes" (Spielberger, et al.,1983). Scores range from 20–80, with higher scores indicating greater levels of state anxiety (Spielberger et al., 1983). There is no established cutoff score, however, perinatal maternal mental health research suggests scores above 40 may represent clinical significance (Dennis et al., 2013).

Edinburgh Postnatal Depression Scale—The Edinburgh Postnatal Depression Scale (EPDS) measures depression symptoms common in women during pregnancy and postpartum period (Cox et al., 1987). Participants respond based on the frequency of depressive feelings or behaviors experienced over the previous week. For example: "I have been so unhappy that I have had difficulty sleeping" (Cox et al., 1987). The EPDS consists of 10-items on a 4-point Likert scale (0 = never/not at all; 3 = yes, quite often/most of the time). Scores range from 0–30, with higher scores indicating greater levels of depression

symptoms (Cox et al., 1987). There is no established cut-off, however, scores of 10 and greater have been previously used to indicate clinically relevant depression in mothers during the postpartum period (Kozinszky et al., 2015).

2.4 Infant Emotion Regulation

Infant temperament was measured at 8–11 months via maternal report on the Infant Behavior Questionnaire-Revised Short Form (IBQ-R-S) (Putnam et al., 2014). The IBQ-R-S consists of 91 items and 14 scales that assess various dimensions of infant temperament (Putnam et al., 2014). The IBQ-R-S temperament scales can be further divided into three broad temperament dimensions: surgency/extraversion, negative affectivity, orienting/regulation (Putnam et al., 2014). Caregivers respond on a 7-point Likert scale (1 = never; 7 = always) based on the frequency of infant behaviors over the previous 1–2 weeks (Putnam et al., 2014). For example: “after sleeping, how often did the baby cry if someone doesn’t come within a few minutes” (Putnam et al., 2014, p. 5). Scores range from 1–7 on each scale, with greater scores representing greater levels of that temperament dimension (Enlow et al., 2016).

The present study focuses on the negative affectivity dimension of the IBQ-R-S. The negative affectivity dimension of temperament reflects a propensity to respond to everyday situations with negative emotions (Scheper et al., 2017). This dimension encompasses the following scales: sadness, distress to limitations, fear, and falling reactivity or rate of recovery from distress (Putnam et al., 2014). This dimension was chosen as previous research has found negative affectivity is associated with difficulties or impairments in emotional regulation development (Bridgett et al., 2009; Zimmer-Gembeck & Skinner, 2016).

2.5 MRI Acquisition & Image Analysis

Infants underwent MRI scanning at 2–5 months during natural sleep. Anatomical MRI scans were acquired on a Siemens Magnetom Skyra 3T scanner (Hanford et al., 2018; Siemens Healthcare, Erlangen). Three dimensional T1-weighted images were acquired using a Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (Field of view [FOV] = 240 × 224, 1.0 mm voxels, repetition time [TR]= 2.4s, echo time [TE] = 0.000316s, flip angle = 8°) using a 32-channel head coil (Hanford et al., 2018).

Infant T1-weighted images were automatically segmented using Infant FreeSurfer (Zöllei et al., 2020). Infant FreeSurfer is an automatic processing stream for T1-weighted MRI scans in infants (Zöllei et al., 2020). Automatic processing steps include intensity normalization, skull stripping, and segmentation of the cortex, white matter and subcortical structures (Zöllei et al., 2020). Intensity normalization involves standardizing MRI signal intensity which may differ across subjects, scanners, or visits (Sun et al., 2015). Skull-stripping is the process of removing all non-brain tissue from MRI images (Poldrack et al., 2011). Segmentation involves segmenting the brain into its anatomical features including cortical/subcortical brain structures and white/gray matter (Poldrack et al., 2011). It is performed using a multi-atlas approach, in which multiple atlases are first registered to subject space and structure labels are transferred. Labels are then fused into a single segmentation

result, providing higher accuracy than single-atlas approaches (Iglesias & Sabuncu, 2015). Volumetric measurements for anatomical features can then be extracted (Zöllei et al., 2020).

Infant brain subcortical brain structure volumes were extracted as well as cerebral white matter and cerebral cortex volumes to compute total cerebral volumes (TCV). Subcortical brain structures included the left and right: cerebellum cortex, thalamus, caudate, putamen, pallidum, hippocampus, amygdala, accumbens area and ventral diencephalon. An example of an automatic segmentation of an infant T1-weighted MRI scan is provided in Figure 1. All brain parcellations were examined by an expert and found to be of high quality.

2.6 Statistical Analyses

Statistical analyses were performed using SPSS (version 27, IBM, Armonk, NY).

To examine the association between maternal distress (anxiety and depression) and infant brain subcortical structure volumes at 2–5 months, multivariate general linear models were used. Infant brain structure volumes (left and right: cerebellum, thalamus, caudate, putamen, pallidum [globus pallidus], hippocampus, amygdala, accumbens area and ventral diencephalon) were the dependent variables. Maternal anxiety (STAI-S scores) and maternal depression (CES-D or EPDS scores) were the independent variables. The models were adjusted for total cerebral volumes and infant age at scan by including them as covariates. Total cerebral volume (TCV) was included as covariates in each model to account for sex-difference between males and females in brain volumes (Barnes et al., 2010; Duerden et al., 2020). As one model was implemented to address our hypothesis, the alpha level was set at 0.05.

To investigate whether infant subcortical brain structure volumes (2–5 months) may predict later emotional regulation (8–11 months), a generalized linear model with an identity link function was used, with infant temperament (negative affectivity dimension scores) as the dependent variable and infant subcortical structure volumes as the independent variables. The model was adjusted for total cerebral volumes, infant age at scan and infant age at temperament assessment, by including them as covariates. As we had one hypothesis regarding the association between infant emotional regulation outcomes and brain volumes, the alpha level was set at 0.05.

Finally, to address our third aim to determine whether biological sex moderates the relationship between infant subcortical volumes and infant emotional regulation, the interaction variable (biological sex * subcortical structure volume) was included in the models. As we had 9 regions of interest (cerebellum, thalamus, caudate, putamen, pallidum [globus pallidus], hippocampus, amygdala, accumbens area and ventral diencephalon) in the left and right hemispheres, a single model was run to address our hypothesis and the alpha level was set at 0.003.

3. Results

3.1 Participant Demographics

A total of 36 mother-infant pairs were included. Participant demographics for infants are shown in Table 1. The average age of infants at time of MRI scan was 3.36 months (SD = 0.762), and ranged from 2–5 months. The average age of infants at time of temperament measure was 9.25 (SD = 0.692), and ranged from 8–11 months. The average age of mothers was 22.22 (SD = 1.22, range = 4.25). Maternal ethnicity, education, and use of public assistance is reported in Table 1.

3.2 Maternal Anxiety and Depression

To examine maternal distress, perceived levels of anxiety and depression were assessed using self-report questionnaires. Descriptive information regarding maternal distress questionnaires is shown in Table 2. The average maternal depression score determined by EPDS was 5.81 (SD = 5.092) and 7 participants scored above the generally defined cut-off score (≥10) to indicate clinically significant depressive symptoms in this population. Average maternal anxiety scores (STAI-S) were 32.78 (SD = 10.10), and 4 participants scored above the generally defined cut-off score (> 40) in this population to indicate clinically significant anxiety.

3.3 Association between Postnatal Maternal Distress and Infant Subcortical Macrostructure

We first examined the association between maternal distress (anxiety and depression) and infants' subcortical brain structure volumes using a multivariate general linear model, adjusting for total cranial volumes, infant age, and biological sex. Maternal anxiety (STAI-S) was positively associated with infant right pallidum volume ($F(1,30) = 4.519$, $p = 0.042$, Figure 2), suggesting higher anxiety scores were associated with greater right pallidum volumes in infants. This association was only significant when maternal depression (EPDS) was included in the model. These results indicate that maternal anxiety is associated with infant subcortical brain structure, specifically within the right pallidum, and that maternal depression is an important moderator in this association.

3.4 Examining Infant Emotion Regulation

Infant emotion regulation was assessed using the negative affectivity dimension of the IBQ-R-S. The average score for this dimension was 3.589 (SD=0.790). Higher scores on this dimension are associated with impaired emotion regulation (Bridgett et al., 2009; Zimmer-Gembeck & Skinner, 2016).

3.5 Association between Infant Subcortical Macrostructure and Emotion Regulation

We next examined whether infant brain subcortical macrostructure (2–5 months) predicted later infant emotion regulation (8–11 months) using a generalized linear model, adjusting for age at scan and IBQ-R-S assessment, total cranial volume, and biological sex. The results of the generalized linear model are shown in Table 3. Infant negative affectivity scores were positively predicted by left pallidum volume ($B = 0.001$, $p = 0.002$), with larger

volumes predicting impaired emotion regulation. Furthermore, infant outcome scores were negatively predicted by left accumbens area ($B = -0.011$, $p < 0.001$), left hippocampus ($B = -0.002$, $p < 0.001$) and right hippocampus ($B = -0.001$, $p = 0.019$) volumes, indicating that smaller volumes of these structures predict impaired emotion regulation. The results for the associations of the left and right hippocampus are shown in Figure 3. To summarize, we observed infant subcortical macrostructure at 2–5 months, specifically the left pallidum, left accumbens area and hippocampus, predicted or were significantly associated with subsequent emotion regulation at 8–11 months.

As part of exploratory analysis, we further investigated the finer grain temperament dimensions: 1. fear, 2. sadness, 3. distress to limitations, and 3. falling reactivity or rate of recovery from distress. We investigated whether infant macrostructure (2–5 months) predicted subsequent parent-based reports of fearfulness/sadness/distress to limitations/falling reactivity (9–12 months) using separate generalized linear models, adjusting for age at scan and IBQ-R-S assessment, total cranial volume, and biological sex. Of note, significant associations between the volumes of several subcortical structure and subsequent fear (Supplementary Data Table S1) were evident. Infant fear was positively predicted by right amygdala volume ($B = 0.007$, $p = 0.001$) with larger volumes predicting greater fearfulness (Supplementary Data Figure S1). The results for other finer grain temperament dimensions are in Supplementary Tables 2–4.

3.6 Moderating Role of Biological Sex

Finally, we examined the moderating role of sex on the associations between infant subcortical macrostructure and emotion regulation. Associations between infant subcortical macrostructure and subsequent emotion regulation demonstrated regionally-specific associations with biological sex (Table 4). In boys, increased difficulties with emotional regulation were associated with larger left pallidum volumes ($B = 0.01$, $p = < 0.001$). However, a reverse association was seen for girls, whereby infant scores were negatively predicted by the left accumbens area ($B = -0.012$, $p < 0.001$) and left hippocampus ($B = -0.002$, $p < 0.001$;), when correcting for multiple comparisons. The associations between left hippocampus volume and emotion regulation by sex are shown in Figure 4, with females showing a stronger relationship than males.

4. Discussion

The association between postnatal maternal distress and infant subcortical macrostructure were examined in a cohort of mother-baby dyads, as well as the associations between infant subcortical macrostructure and subsequent emotion regulation abilities, taking into consideration the moderating role of biological sex. In support of our prediction, we found an association between postnatal maternal distress and infant subcortical brain structure at 2–5 months. Specifically, maternal anxiety was associated with infant right pallidum volume when accounting for maternal depression.

Our results align broadly with literature that similarly found maternal psychological distress is associated with offspring brain structure. For example, postnatal maternal anxiety has been previously associated broadly with alterations in cerebral white and cortical gray

matter (Lebel et al., 2016; Zou et al., 2019). However, in contrast to previous work, we did not find associations specifically within limbic structures such as the hippocampus or amygdala (Donnici et al., 2021; Lupien et al., 2011; Qiu et al., 2013). Differences in results may be due to variations in the measures, severity, or timing of maternal distress across study samples. For example, previous research investigated maternal trait anxiety rather than maternal state anxiety (Qiu et al., 2013). Furthermore, maternal distress was quite low for both samples in the present study, as opposed to previous research, in which average anxiety scores neared clinical cut-off (Qiu et al., 2013). Moreover, differences may also arise due to differences in the age of offspring at the time of MRI scanning (Tottenham & Sheridan, 2010). The development of subcortical structures spans from infancy into adulthood and, therefore, associations may differ depending on age of offspring. Furthermore, previous work suggests there may be temporal delays for structural alterations of the brain in association with various forms of early life stress (Lee et al., 2020).

The right pallidum has not been previously associated with maternal distress to our knowledge. The pallidum is a structure of the basal ganglia broadly involved in components of movement and cognition, and, recently, it has also been implicated in early child-parent interactions (Abraham et al., 2020). Differences in these results may be due to the focus of previous work which examined limbic structures as opposed to subcortical structures of the basal ganglia.

Our results support previous research that suggests maternal distress may be associated with infant brain structure, emphasizing the importance of maternal mental health for healthy offspring brain development. Given the findings regarding the right pallidum, subcortical structures of the basal ganglia should be considered when examining associations between maternal mental health and infant brain development to gain a better understanding of the relationships between maternal distress and infant brain development.

In support of our second prediction, we found infant subcortical structure volumes at 2–5 months were associated with emotion regulation at 8–11 months. Specifically, our findings suggest larger left pallidum and smaller left accumbens, and left and right hippocampus may predict subsequently impaired emotion regulation. These results are broadly in line with previous work on brain-behavior relationships that have found variations in subcortical structure volumes to predict outcomes relating to emotional development, including emotional regulation. More specifically, our findings that smaller left and right hippocampal volumes may predict impaired emotional regulation is similar to those observed in newborns in association with prenatal maternal distress, as well as adolescence, at risk for depression (Barch et al., 2019; Moog et al., 2021). The hippocampus is a key brain region implicated in emotion regulation as well as stress response modulation. Variations in its structure have been reported across various emotional problems/disorders in both children and adolescence such as anxiety and depression, albeit these relationships have been inconsistent (De Bellis et al., 2000; Gold et al., 2017; Hanson et al., 2015; Rao et al., 2010). Further research is needed to elucidate the role of structural alterations in the hippocampus and emotional problems.

To our knowledge, previous research has not implicated structural alterations in either the left pallidum or nucleus accumbens and emotion regulation. The pallidum and nucleus accumbens are structures of the basal ganglia. The nucleus accumbens is part of the ventral striatum, and is involved in a range of functions, such as emotional and motivational processing (Hyde & Garcia-Rill, 2019). The observed differences in results may be due to the focus of previous work, which has focused on limbic regions.

Given that infant subcortical macrostructure specifically within the left pallidum, left nucleus accumbens, and bilateral hippocampus predicted subsequent emotion regulation, these structures could be further explored as potential predictors or neural biomarkers of risk for adverse emotional development in infants exposed to symptoms of maternal distress. The ability to identify infants at risk could provide the opportunity for early interventions (Savage-McGlynn et al., 2015).

Regarding the role of biological sex, we found the associations between subcortical structure and subsequent emotion regulation were observed in both males and females. However, trajectories of these associations differed by sex. These results align with literature that similarly did not find sex differences in the relationships between subcortical structures and later socioemotional development in infants (Moog et al., 2021; Gold et al., 2017). However, the sex differences in the trajectories of the associations may suggest or emphasizes the importance of examining sex differences in research on brain-behavior relationships. Furthermore, it has previously been suggested that sex differences may depend upon the stage of development and, therefore, may become apparent at a later age (Kaczkurkin et al., 2019; Ortiz-Mantilla et al., 2010). As such, and in line with recommendations by Letourneau and colleagues (2020), biological sex should be considered when evaluating brain-behavior relations between subcortical macrostructure and emotional development.

With regards to our exploratory analysis investigating the finer grain temperament dimension fear, infant macrostructure was associated with later infant fearfulness. Interestingly we found a positive association between right amygdala volumes and subsequent fearfulness. This result aligns well with previous literature which has widely implicated the amygdala in fear processing and fear-related pathology such as anxiety (Ressler, 2010). For example, a similar positive relationship between amygdala volume and fear was observed in children, albeit only in girl and more broadly greater amygdala volumes have been associated with generalized anxiety disorder in children (De Bellis et al., 2000; Qin et al., 2014; van der Plas et al., 2010). Given that fearful temperament is associated with later risk for internalizing disorders such as anxiety it may be useful to further explore these potential early biomarkers (Kochanska et a., 1997).

Relative to other studies, the present study explored how stress relates to a number of subcortical structures within a unique developmental period. Previous work has focused mainly on limbic structures, including the hippocampus and amygdala, when examining associations with both maternal distress and emotional development, with studies targeting children and adolescence. Given that there is currently insufficient identification of young children with emotional development risks and the importance of the early period (infancy-early childhood) for interventions to promote healthy outcomes, identifying potential neural

markers of risk is essential in maximizing outcomes for these individuals (Cooper et al., 2009). In the present study we investigated numerous subcortical structures, linking stress to neural development beyond the limbic system. Moreover, our work suggests that early infancy could be a reasonable period at which to identify children at risk for adverse emotional development (Cooper et al., 2009).

Limitations

A limitation of the present study is the use of maternal reports to assess infant emotion regulation. Although caregiver reports provide insight into an infant's behavior across a variety of contexts, some research suggests psychological distress may bias a mother's perceptions of her infant's temperament (Gartstein & Rothbart, 2003; Leerkes et al., 2003; Liu et al., 2021). As such, future work may benefit from a combination of measures to assess infant emotion regulation, including both lab and caregiver-based assessments.

A second limitation includes the lack of maternal distress measures during the antenatal period. Mothers experiencing psychological distress in the postnatal period are likely to have also experienced distress symptoms during pregnancy (Heron et al., 2004). Moreover, prenatal maternal distress has also been associated with offspring brain structure; therefore, our results may reflect both prenatal and postnatal maternal distress or may be confounded by maternal distress in the prenatal period. Future longitudinal research should consider anxiety and depression symptoms both antenatally and postnatally to better reflect the chronicity of maternal distress during this period (Fitzgerald et al., 2021).

Finally, due to the nature of our data collection (database), several other potential confounding variables were unable to be controlled for in the present project. These include depression and anxiety medication use by the mothers, infant sleep, parental behaviors, genetics, and other forms of early life stress (Brito & Noble, 2014; Choi et al., 2022; Hanson et al., 2015; Kocevska et al., 2017; Rice et al., 2010). These variables have been found to be associated with brain development and as such, should be considered in future work.

5. Conclusions

In conclusion, our findings support an association between postnatal maternal anxiety and infant subcortical brain structure and add to the literature that emphasizes the importance of maternal mental health during this period. Furthermore, the observed associations between infant subcortical macrostructure and subsequent emotion regulation suggest it may be important to examine these relationships further to potentially identify early predictors of emotional development risk. This may, allow for early interventions and, thus, promotion of healthy development in offspring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank the families who participated in this research. Funding for this study was provided by the Canada First Research Excellence Fund (CFREF), the Molly Towell Perinatal Research Foundation and the Natural Sciences and Engineering Council of Canada (NSERC). We thank the investigators who were involved in the original data collection for conducting the study and making the data available: Mary L. Philips, Alison E. Hipwell, Ashley Stiller, Ricki Stiffler, and Genna Bebko. Data used in the preparation of this manuscript were obtained from the NIMH Data Archive (NDA), and were funded by R21 MH106570 (Impact of Maternal Caregiving on Brain-Behavior Relationships in Infants), R01 MH056630 (Pittsburgh Girls Study), and R01 MH115466 (Caregiving Effects on the Early Development of Infant Brain-Behavior Relationships). The raw data are available at nda.nih.gov/edit_collection.html?id=2340.

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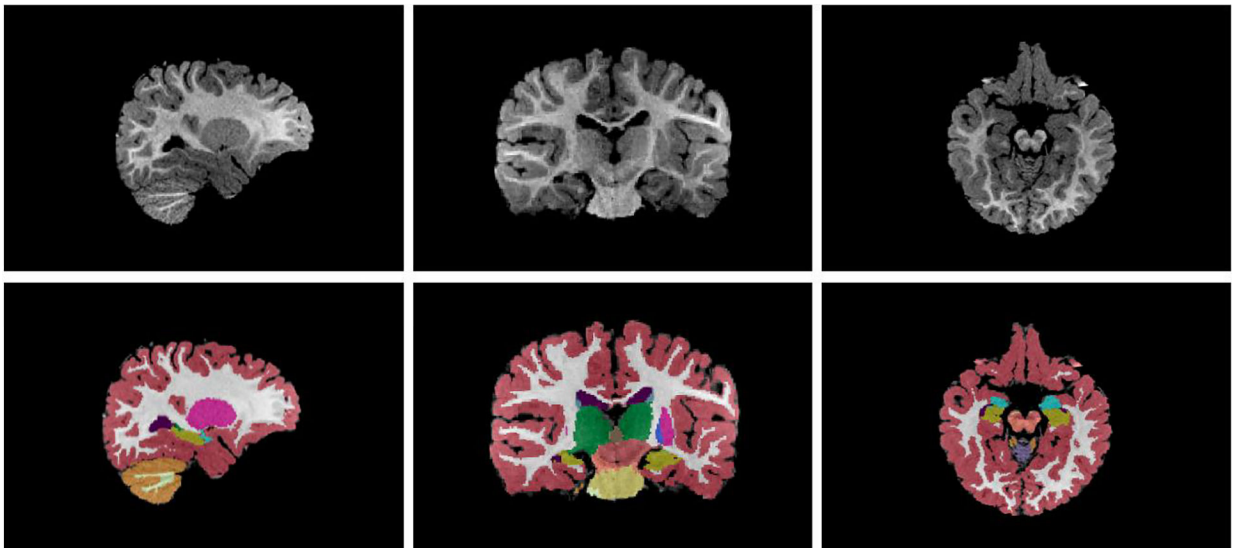

Figure 1.

Example of an automatic segmentation of an infant scan via Infant FreeSurfer

Sagittal (left), coronal (middle), and axial (left) view of an infant T1-weighted MRI scan. Bottom shows segmentation produced by Infant FreeSurfer. Colors represent distinct subcortical regions.

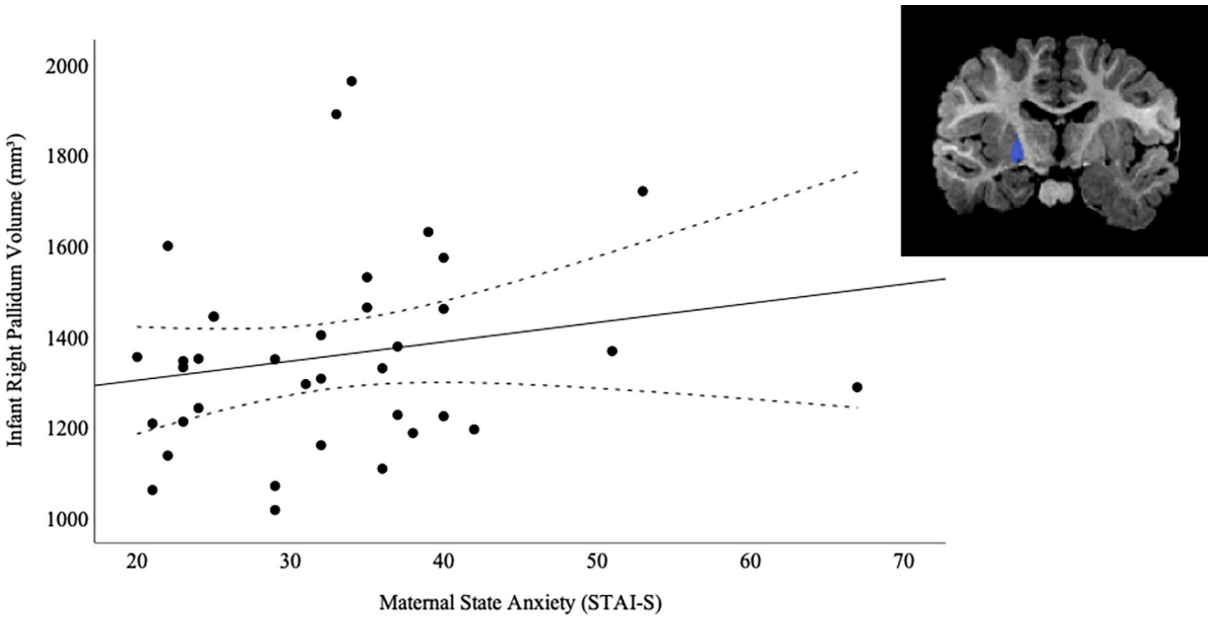

Figure 2.

Association between Maternal State Anxiety and Infant Right Pallidum Volume (mm^3)

Note. Scatterplot depicting association between postnatal maternal anxiety on State-Trait Anxiety Index State Subscale (STAI-S) at 2–5 months postpartum and infant right pallidum volume (mm^3) at 2–5 months. Dashed lines represent 95% confidence interval.

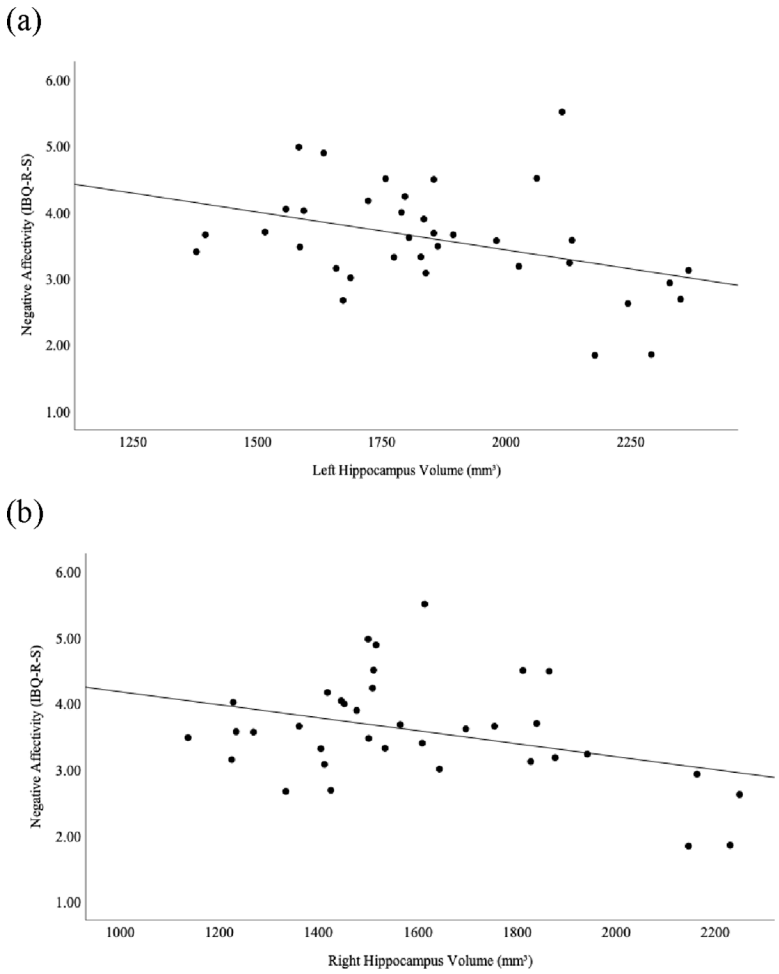

Figure 3.

Associations between Infant Hippocampus Volumes and Subsequent Emotion Regulation (Negative Affectivity Dimension Scores)

Scatterplots depicting associations between infant (a) left and (b) right hippocampus volumes (mm^3) at 2–5 months and subsequent emotion regulation (negative affectivity scores on Infant Behavior Questionnaire-Revised Short Form, IBQ-R-S) at 8–11 months in the high anxiety sample.

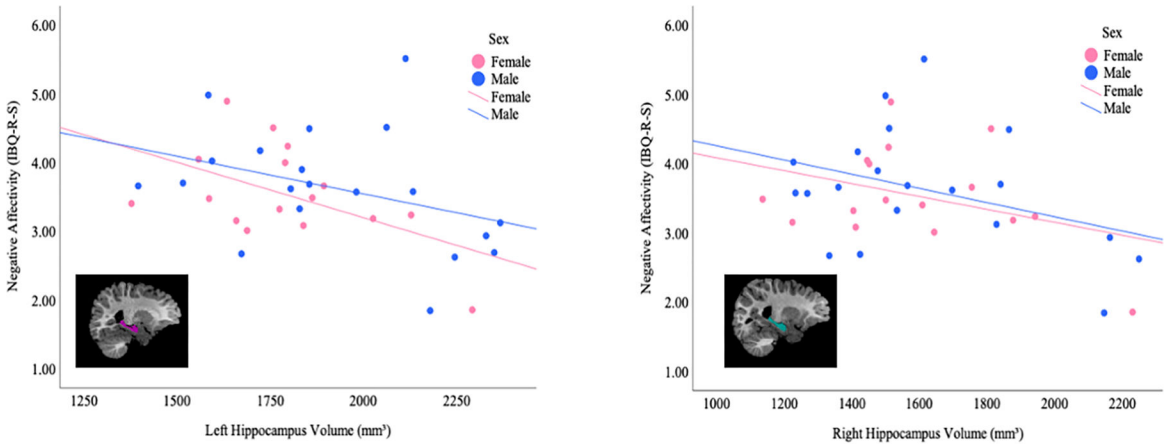

Figure 4.

Associations between Infant Hippocampus Volume and Emotion Regulation (IBQ-R-S Negative Affectivity Dimension Scores) by Biological Sex

Scatterplots depicting the associations between infant (a) left and (b) right hippocampus volumes (mm^3) at 2–5 months and subsequent emotion regulation (negative affectivity dimension scores on Infant Behavior Questionnaire-Revised Short Form IBQ-R-S) at 8–11 months in males and females.

Table 1.

Participant characteristics

Infant Characteristics n	36
Female n (%)	16 (44.4%)
Male n (%)	20 (55.6%)
Age at scan, months M (SD)	3.36 (0.762)
Age at IBQ-R-S M (SD)	9.25 (0.692)
Maternal Characteristics n	36
Ethnicity n (%)	
Caucasian	7 (19.4%)
African American	28 (77%)
Multi-racial	1 (2.8%)
Education	
No diploma or degree	6 (16.7%)
General Educational Development (GED)	3 (8.3%)
High school diploma	22 (61.1%)
Other certificate of training	4 (11.1%)
Bachelor's degree	1 (2.8%)
Use of public assistance	
No public assistance	14 (38.9%)
Use of public assistance	22 (61.1%)

Table 2.

Descriptive information for maternal distress measures

Dataset 1 (n=36)	
STAI-S (M, SD)	32.78 (10.100)
EPDS (M, SD)	5.81 (5.092)
Frequencies	
STAI-S cut off > 40	4 (11%)
EPDS cut off ≥ 10	7 (19.44%)

Maternal depression was assessed using EPDS, Edinburg Postnatal Depression Scale (range 0–30). Maternal anxiety was measured using the State-Trait Anxiety Inventory - State Anxiety Subscale (range 20–80).

Table 3.

Results of a generalized linear model examining the associations between infant subcortical macrostructure (2–5 months) and subsequent emotion regulation (8–11 months).

		95% Confidence Interval		
	Beta Value	**Lower**	**Upper**	**p value**
Sex (Female)	**−1.098**	**−1.489**	**−0.708**	**<0.001**
IBQR Age in Months	**0.575**	**0.235**	**0.915**	**0.001**
Left Cerebellum Cortex	−0.0006	0.000	0.000	0.432
Left Thalamus	0.000	−0.001	0.001	0.550
Left Caudate	−0.001	−0.003	0.000	0.116
Left Putamen	0.000	0.000	0.001	0.236
Left Pallidum	0.001	0.000	0.001	**0.002**
Left Hippocampus	**−0.002**	**−0.003**	**−0.001**	**<0.001**
Left Amygdala	0.000	−0.002	0.003	0.810
Left Accumbens Area	**−0.011**	**−0.017**	**−0.005**	**<0.001**
Left Ventral Diencephalon	0.003	−0.002	0.007	0.201
Right Cerebellum Cortex	<0.001	0.000	0.000	0.846
Right Thalamus	0.000	−0.001	0.000	0.555
Right Caudate	0.001	−0.0006	0.002	0.071
Right Putamen	0.001	−0.0004	0.002	0.064
Right Pallidum	−0.001	−0.003	0.001	0.161
Right Hippocampus	**−0.001**	**−0.002**	**0.000**	**0.019**
Right Amygdala	0.002	−0.00008	0.004	0.059
Right Accumbens area	0.002	−0.003	0.006	0.464
Right Ventral Diencephalon	0.001	−0.003	0.005	0.638
Baby Age at Scan	−0.210	−0.793	0.373	0.479
TCV	−0.00006	−0.000001	0.000006	0.119

Table 4.

Results of generalized linear models examining moderating role of biological sex on the associations between infant subcortical macrostructure (2-5 months) and subsequent emotion regulation (8-11 months).

		95% Confidence Interval		
	Beta Value	**Lower**	**Upper**	**p value**
[Sex=F] * Left Pallidum	0.01	0.0001	0.001	0.032
[Sex=M] * Left Pallidum	**0.01**	**0.0001**	**0.002**	**< 0.001**
[Sex=F] * Left Accumbens Area	**−0.012**	**−0.018**	**−0.006**	**<0.001**
[Sex=M] * Left Accumbens Area	−0.009	−0.015	−0.003	0.003
[Sex=F] * Left Hippocampus	**−0.002**	**−0.003**	**−0.001**	**<0.001**
[Sex=M] * Left Hippocampus	−0.002	−0.003	−0.001	0.004
[Sex=F] * Right Hippocampus	**−0.002**	**−0.003**	**−0.001**	**0.001**
[Sex=M] * Right Hippocampus	−0.001	−0.002	−0.001	0.043

F, female, M, male