Responsiveness to Infant Cues in Postpartum Depressed and Non-Depressed Mothers: Functional Neural Correlates and their Relation to Behaviour

by

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Abstract

Postpartum depression (PPD) is the most common maternal birth complication, affecting approximately 5-20% of women. PPD disrupts the normal repertoire of parenting abilities and is thought to have long-term consequences for the developing infant, even after the mothers’ depression remits. Despite its prevalence and potentially enduring effects, we understand very little about the neural correlates of PPD. Recent evidence suggests that postpartum depression (PPD) is associated with reduced amygdala (AMY) response to negative stimuli. However, given the anhedonic features of PPD, it is also important to consider the brain response of depressed mothers specifically to positive infant stimuli and to other positively valenced stimuli. In the current work, mothers with clinically determined PPD (n=31) and without PPD (n=23) viewed smiling pictures of infants (both their own and other), and positive non-infant stimuli during an fMRI. Four studies were completed which examined: 1) multidimensional measures such as current parenting stress, early experiences (e.g., being parented themselves as well as experiences of trauma), current mood and anxiety levels, and relationship satisfaction to better characterize our sample of mothers with and without PPD, 2) PPD and Non-PPD mothers’ response to infants and other positive non-infant stimuli, using AMY region-of-interest as well as amygdala connectivity analyses, 3) subregion-level differences in AMY response and connectivity during the viewing of infant and non-infant stimuli 4) whether and/or how behavioural measures of maternal sensitivity and responsiveness (quality of mother-infant interaction) relate to brain response in the AMY as a whole as well as at the subregion level.
Knowing how a depressed mother’s brain responds to her own and other infants is critical as many of the symptoms of PPD focus on the mother-infant dyad and involve a subjective evaluation of one’s parenting abilities. This work adds to the existing literature that examines the brain response of mothers with PPD to various stimuli. Furthermore, it has the long-term potential to inform treatment and intervention programs designed for PPD.

Keywords: Mothering; Postpartum Depression; fMRI; Amygdala
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Relative to Non-PPD mothers, PPD mothers score higher on the following factors: Maternal Worry ($F(1,36) = 11.906, p = .001, \eta^2_p = 0.249$), Negative Self-Image ($F(1, 36) = 9.727, p = .004, \eta^2_p = 0.213$), Lability ($F(1, 36) = 4.248, p = .047, \eta^2_p = 0.106$), and Need for Nurturance ($F(1, 36) = 12.693, p = .001, \eta^2_p = 0.261$). On these factors, higher scores reflect more distress.

Relative to Non-PPD mothers, PPD mothers score lower on the following factors (see Figure 9b): Maternal Self-Confidence ($F(1, 36) = 6.935, p = .012, \eta^2_p = 0.162$), Feel About Children ($F(1, 36) = 7.588, p = .009, \eta^2_p = 0.213$), Interest in Sex ($F(1, 36) = 12.507, p = .001, \eta^2_p = 0.258$), Relationship with Father ($F(1, 36) = 5.229, p = .028, \eta^2_p = 0.127$), Care Taking ($F(1, 36) = 14.475, p = .001, \eta^2_p = 0.287$), and Social Confidence ($F(1, 36) = 6.810, p = .013, \eta^2_p = 0.159$). On these factors, lower scores reflect more distress.

As compared to Non-PPD mothers, mothers with PPD are less accepting ($F(1, 42) = 8.071, p = .007, \eta^2_p = 0.161$), available ($F(1, 42) = 5.194, p = .028, \eta^2_p = 0.110$), cooperative ($F(1, 42) = 4.949, p = .032, \eta^2_p = 0.105$) and sensitive ($F(1, 42) = 6.963, p = .012, \eta^2_p = 0.142$) in their interactions with their infants. Furthermore, they have lower overall scores on the AMSS ($F(1, 42) = 7.298, p = .010, \eta^2_p = 0.148$).

Mothers with PPD, relative to Non-PPD mothers, also show poorer quality maternal care overall as measured by scores on the MBQS ($F(1, 42) = 5.151, p = .028, \eta^2_p = 0.109$).

As compared to Non-PPD mothers, mothers with PPD spend more time holding their infants ($F(1, 42) = 8.823, p = .005, \eta^2_p = 0.174$).

Relative to Non-PPD mothers, mothers with PPD groom their infants more frequently ($F(1, 42) = 5.067, p = .030, \eta^2_p = 0.108$). They also try to engage their infants in play with toys less frequently ($F(1, 42) = 4.193, p = .047, \eta^2_p = 0.091$) and their infants play with toys less frequently ($F(1, 42) = 4.597, p = .038, \eta^2_p = 0.099$). Finally, PPD also mothers laugh and smile with their infants less frequently in a 20-minute interaction ($F(1, 42) = 4.343, p = .043, \eta^2_p = 0.094$).
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11b. Average BOLD response in the right AMY was greater for OwnView compared to Other View in PPD mothers (87 voxels, p=0.0246, z=3.76, peak x=26, y=0, z=-12). There were no differences in left AMY response to OwnView-OtherView. There were also no differences in AMY response to OtherView-NonInfantView.

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12b. In comparison to Non-PPD mothers, PPD mothers demonstrate increased BOLD response to Non-InfantView in the right AMY (54 voxels, p=0.0472, z=3.24, peak x=26, y=0, z=-14).

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19a. right BLA
19b. left BLA
19c. right CMA
19d. right SFA
19e. left SFA

Figure 20. From univariate ANOVAs, where group (Non-PPD vs. PPD) and parity (primiparous vs. multiparous) served as between subjects factors and connectivity parameter estimates from the PPI analysis served as the dependent variables, an interaction between group and parity was observed for bilateral BLA and SFA to bilateral IC connectivity. More specifically, across subregions, Non-PPD mothers show greater connectivity with the IC if they are multiparous, whereas multiparous mothers with PPD show decreased subregion to IC connectivity. Parity x Group interactions were not observed for CMA to insula connectivity. Furthermore, Parity x Group interactions were not observed for BLA, CMA or SFA subregion to other brain region connectivity (e.g., ventral striatum, precuneus, etc.).

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21a. Left. In Non-PPD mothers, AMY BOLD response for OwnView-OtherView was significantly correlated with Ainsworth Total (r=.518, p=.040). In PPD mothers, AMY BOLD response for OwnView-OtherView was significantly correlated with Ainsworth Total (r=.401, p=.034).
21b. Right. In Non-PPD mothers, no significant relationship was observed between AMY BOLD response for OwnView-OtherView and Ainsworth Total, or any subscales (shown for visualization purposes, only). In PPD mothers, AMY BOLD response for OwnView-OtherView was significantly correlated with Ainsworth Total ($r=.460$, $p=.014$).

Figure 22. AMY response for OwnView-OtherView with MBQS. BOLD response in the bilateral AMY for the contrast OwnView-OtherView, was significantly correlated with MBQS (L: $r=.370$, $p=.013$; R: $r=.342$, $p=.023$). To demonstrate that there are no group differences in these relationships, the effects for Non-PPD and PPD mothers have been plotted separately on the same graph.

22a. Left. In Non-PPD mothers, no significant relationship was observed between BOLD response and MBQS. In PPD mothers, BOLD response was significantly correlated with MBQS ($r=.383$, $p=.044$).

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23a. Left

23b. Right

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p = .032; Right r = .300, p = .048). There were no significant correlations between SFA or CMA connectivity with any measures of maternal behavior. Notably, when depression status (Non-PPD vs. PPD is controlled for using Pearson partial correlation, the relationship between bilateral BLA to left IC connectivity and maternal sensitivity disappears. For visualization purposes, only, the relationship between BLA to IC connectivity and maternal sensitivity and acceptance has been plotted separately for Non-PPD and PPD mothers.

24a. Left

24b. Right
Responsiveness to Infant Cues in Postpartum Depressed and Non-Depressed Mothers: Functional Neural Correlates and their Relation to Behaviour

1 General Introduction

1.1 Postpartum Depression (PPD)

Although pregnancy and childbirth signal a period of excitement, anticipation and delight for many new mothers, for some, this time period is accompanied by transient low mood, tearfulness and worry. In approximately 5-20% of mothers, these feelings develop into more severe PPD (O’Hara & Swain, 1996; Lanes, Kuk & Tamim, 2011; O'Hara, Neunaber, Zekoski, 1984; Halbreich & Karkun, 2006). In fact, PPD is the most prevalent perinatal complication experienced by mothers (Ross, Dennis, Blackmore & Stewart, 2005). It is characterized by the same symptoms that occur during a major depressive episode, including depressed mood or anhedonia lasting for two or more weeks, as well as some combination of sleep or eating disturbances, restlessness or agitation, lack of energy, inability to concentrate, and feelings of hopelessness, worthlessness and guilt experiences (Ross, et al., 2005; Cox, Murray & Chapman, 1993; Cooper & Murray, 1998; O’Hara & Swain, 1996). It is distinguishable, however, by timing of onset. Furthermore, many of the symptoms of PPD focus on the mother-infant dyad and involve excessive worry or guilt surrounding parenting abilities. The greatest onset of PPD is within the first 3 months postpartum (Gavin et al., 2005; Cox, et al., 1993; Cooper & Murray, 1995; O’Hara & Swain, 1996). Risk factors include stressful recent life events, a history of interpersonal violence, marital conflict, low postpartum social support, poor self-perceived maternal health, history of MDD during pregnancy or another time of life, PPD with a previous pregnancy, and low socioeconomic status (Dennis, Heaman & Vigod, 2012; O’Hara & Swain, 1996; Milgrom et al., 2008; O’Hara, Arndt & Stuart, 2007; Robertson, Grace, Wallington & Stewart, 2004). Although some studies have suggested PPD symptomology tends to resolve within the first 6 months postpartum, a recent study by Dennis and colleagues (2012) found stability in symptomology throughout the first postpartum year.
1.1.1 Mothering and Child Outcomes

PPD disrupts the normal repertoire of parenting abilities. Mothers with PPD tend to interpret their infant’s behaviour more negatively (Field et al., 1993). Additionally, they tend to be more intrusive and irritated, and respond less sensitively and contingently to their infants when compared with mothers without PPD (Stanley, Murray & Stein, 2004; Cohn, Campbell, Matias, & Hopkins, 1990; Murray, Fiori–Cowley, Hooper, & Cooper, 1996; Fleming, Ruble, Flett, & Shaul, 1988). Mothers with PPD also engage in less positively synchronous interactions (Field et al., 1990) and are less affectionate with their infants (Fleming et al., 1988; Stanley et al., 2004).

The atypical mother-infant interactions observed in mothers with PPD can have lasting effects on the developing infant. For example, children of mothers with PPD demonstrate insecure and disorganized attachment at 1-year follow-up, as well as poor cognitive outcome at 18 months (Hayes, Goodman & Carlson, 2012; Cicchetti, Rogosch & Toth, 1998; Murray et al., 1996). Notably, boys appear to be more vulnerable to the developmental effects of this style of parenting than girls (Murray et al., 1996). Infants of mothers with PPD also display an altered physiological profile that includes greater relative right frontal EEG asymmetry associated with decreased empathy during the toddler/preschool years, and lower vagal tone, which is a proxy for stress vulnerability (Diego et al., 2004; see for Field, Diego & Hernandez-Reif, 2010 for review). They also demonstrate social or interactional difficulties when engaging with their peers at 5 years (e.g., more physical than creative play and more negative reactions to friendly approaches from peers; Murray, 1992; Murray et al., 1996). They also show more problematic behaviours according to the Child Behaviour Checklist (internalizing, externalizing and total problems) and Conner’ Parent Rating Scale (total index) than children of non-depressed mothers (Nulman et al., 2012).

These psychosocial outcomes extend into adolescence, and potentially into adulthood. For example, there is evidence that children of mothers with PPD are more likely to develop MDD at 16 years of age (Murray et al., 2011). As such, the presence of recurrent maternal depression has been shown to play a mediating role in the intergenerational transmission of depression (Halligan et al., 2007). Additionally, children of mothers with PPD are more likely to develop anxiety disorders than children of mothers without PPD at 13 years (Halligan et al.,
A different pattern of brain response (e.g., in the insula, ACC and caudate) to sad films was observed in 8 year-old children of mothers with PPD, even in the absence of current mood differences, when compared to children of non-depressed mothers (Levesque, et al., 2011). The relationship between maternal PPD and subsequent affective/internalizing psychopathology, as well as aggressive behaviour, in adolescent offspring may be mediated by factors such as childhood resilience, insecure attachment, and family adversity (Murray et al., 2011; Averdijk, Malti, Eisner & Ribeaud, 2012). Thus, in addition to the negative impact of depression on the mother herself, these detrimental and enduring effects of PPD on the developing infant highlight the need for etiological research with PPD.

1.1.2 Infant Communication

Maternal communication represents only one half of the mother-infant dyad; Although their repertoire of behaviours is more limited, infants also demonstrate stereotyped patterns of communication from a very early age. Their primary means of communication involves gaze direction, vocalizations and facial expressions (Yale, Messinger, Cobo-Lewis & Delgao, 2003). Smiles tend to be coordinated with gazes towards the mothers’ face, and this relationship increases with age (Yale et al., 2003). Furthermore, they tend to coordinate mother-directed gaze with positive facial expressions and intense vocalizations (Colonnesi, Zijlstra, van der Zande & Bogels, 2012). For example, during a videotaped interaction, when infants positively vocalize in combination with a smile, 80% of the time they also direct their gaze towards the mother (Colonnesi et al., 2012). Additionally, positive facial expressions tend to be directed towards the mother more than father (Colonnesi et al., 2012). This highlights the importance of studying a mother’s response to her own infant’s communicative patterns (such as facial expressions) in any studies of early maternal responsiveness.

1.1.3 Face Processing

Some studies have sought to examine whether the perinatal period is associated with an altered pattern of mothers’ responsiveness to facial expressions, whether they be her own infant’s or other. Indeed, Pearson and colleagues (2009) demonstrated that the ability to encode negative emotional faces (e.g., those signaling threat, harm or sadness) is enhanced in late pregnancy. The authors speculate as to whether this increasing vigilance towards negative stimuli may be adaptive for the soon-to-be mother. This begs the question of whether this mechanism may
become overactive in mothers who go on to develop PPD, postpartum anxiety, or other altered mood states postpartum. Interestingly, a recent study found that mothers with PPD were less likely to accurately identify happy infant faces in a morphed emotion labeling task (Arteche et al., 2011). Whether this decreased ability to detect positive emotions from infant faces at lower intensity translates into reduced maternal responsiveness to positive affect at the behavioural level remains to be investigated.

### 1.2 Neurobiology

#### 1.2.1 Maternal Behaviour

Over the past 15 years, neuroimaging research has been trying to uncover the interplay between affective, experience-related, reward and attention systems that allow for typical human maternal behaviour. This literature includes approximately 20 fMRI studies where mothers and non-mothers are presented either pictures of their own infants or age-matched unfamiliar infants (Bartels & Zeki, 2004; Leibenluft et al., 2004; Nitschke et al., 2004; Strathearn et al., 2008), recorded infant cries (Swain et al., 2008; Musser, Kaiser-Laurent & Ablow, 2012; Kim et al., 2010; Kim et al., 2011; Seifritz et al., 2003), and videotapes of infants (Noriuchi, Kikuchi & Senoo, 2008). All studies demonstrate that many of the same hypothalamic, limbic, and cortical sites important for emotional or social processing, reward-processing or for regulation of maternal behaviour in other mammals are implicated in response to infant stimuli (see Figure 1 and Table 1 for summary). For example, Leibenluft, Gobbini, Harrison and Haxby (2004) observed greater brain response in socioemotional processing regions, such as the amygdala (AMY), insula, anterior cingulate cortex (ACC), and superior temporal sulcus (STS) when mothers were viewing pictures of their own child (aged 5-12 years). Seifritz et al. (2003) also found greater BOLD response in the amygdala when parents listen to their own baby’s cry. Additionally, Bartels & Zeki (2004) demonstrated increased BOLD response in reward processing regions, such as the striatum, thalamus, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) when viewing pictures of one’s own child. Nitschke, et al. (2004) found that positive mood ratings correlate with increased activation in the OFC, a brain region important for reinforcement processing and inhibitory control, when viewing pictures of one’s own infant. Strathearn et al., (2008) also found that smiling infant faces, compared to neutral and sad faces, activate dopamine-associated reward processing
regions, including the ventral tegmental area (VTA)/substantia nigra (SN) and the dorsal putamen. Although this work is informative, there is wide variation in stimulus modality, sample size, postpartum stage of the mothers, standardization of the stimuli, and analysis methods, making comparison across studies difficult.

Studies have also sought to investigate the link between mediating factors, such as breastfeeding and quality of care in the family of origin, and the brain response of new mothers to their infants. For example, mothers who self-report higher maternal care in childhood show greater BOLD response in the middle frontal gyrus, superior temporal gyrus and fusiform gyrus, whereas mothers who self-report lower maternal care show greater BOLD response in the hippocampus in response to infant cries (Kim et al., 2010). Additionally, in response to infant cries, mothers who breastfeed show higher response in brain regions important in socioemotional and reward processing including the superior frontal gyrus, insula, precuneus, striatum, and AMY as compared to formula-feeding mothers, in the first month postpartum (Kim et al., 2011; see Table 1 for summary).

Examining the relationship between brain response to infants and measures of maternal behaviour is also of interest. One recent study identified a positive correlation between brain response to infant cries and later maternal sensitivity in the right superior frontal gyrus and right lateral globus pallidus/AMY region (Musser et al., 2012). This effect has been demonstrated previously (e.g., right superior frontal gyrus and AMY response to infant cries and maternal behaviour; Kim et al., 2011). Others have looked at how maternal synchrony and intrusiveness are related to brain response to video clips of mother-infant interactions (Atzil et al., 2011). They found that mothers who display greater synchrony in their interactions show higher response in the left nucleus accumbens, whereas mothers who display greater intrusiveness show greater response in the right AMY. This group also found a correlation between blood oxytocin concentration and left nucleus accumbens and right AMY response to the video clips, only in synchronous mothers. It should be noted that all of these studies have been conducted in non-clinical populations. The relationship between maternal behaviour and brain response to infants in mothers who are experiencing mood changes postpartum is still poorly understood.

We recently published a study which looked at the brain response to positive infant pictures in healthy mothers (Barrett et al., 2011). Here, we found that there was greater BOLD
response in the AMY when mothers were viewing pictures of their own infant, consistent with previous research. Interestingly, we also found that level of AMY response was related to trait anxiety, where greater trait anxiety was related to reduced amygdala response. Furthermore, we found that poorer quality of maternal experience, as measured lower scores on an affect-attachment factor of a maternal attitudes questionnaire that we administer, was significantly related to reduced AMY response to own compared to unfamiliar infant faces. We also found that greater levels of distress during parenting were related to reduced AMY response to own compared to unfamiliar infant faces. This suggests that, in human mothers, infant-related AMY function may be an important factor in maternal anxiety/mood, in quality of mothering, and in individual differences in the motivation to mother.

### 1.2.2 Major Depression (MDD)

There is a vast and growing body of literature examining brain functioning in individuals with and without MDD. From this, there is conflicting evidence with respect to whether there is increased or decreased activation in response to emotional stimuli in MDD. For example, a recent meta-analysis conducted by Fitzgerald et al. (2008) identified six papers in which individuals viewing smiling or positive faces showed a decrease in activation in patients with MDD in the posterior cerebellum, left OFC, pregenual and posterior cingulate and medial and lateral temporal regions including the parahippocampal gyrus. Alternatively, three papers reported increased activation in the subgenual (and posterior) cingulate and a number of medial, inferior and lateral frontal regions when individuals with MDD were viewing positive faces (Fitzgerald et al., 2008). Despite these inconsistencies, Price & Drevets (2010) have reviewed the existing functional and structural neuroimaging data and proposed a neural network that they believe is altered in individuals with MDD. It is comprised of the mPFC, AMY, ventral striatum and pallidum, medial thalamus, hypothalamus, as well as the periaquedunctal grey (PAG) and other regions in the brainstem (see Price & Drevets, 2010). With respect to face stimuli, in particular, MDD is associated with altered activity in emotion-related brain regions, especially in limbic structures such as the AMY (Hamilton et al., 2012; Gil, Teissedre, Chambres & Droit-Volet, 2011; Arteche et al., 2011; Anand et al., 2005; Dannilowski et al., 2007). Furthermore, there appears to be a valence specificity in the AMY response to emotional face stimuli in MDD, where there is higher activation to negative stimuli, but lower activation to positive stimuli (Hamilton et al., 2012; Suslow et al., 2010; Victor et al., 2010). Functional, structural and post-
mortem studies have also found abnormalities in the left subgenual cingulate cortex in individuals with MDD (see Hasler, 2010). This body of research is informative in the present context since MDD and PPD share many symptom characteristics. Additionally, some studies find overlap in the pathophysiology of these disorders. For example, lower striatal D2/3 receptor BPND is common to both PPD and unipolar depression (Moses-Kolko et al., 2012).

1.2.3 PPD

Despite its prevalence and pervasive costs for the developing infant, our understanding of the neural bases of PPD relies on only a few recent studies (Moses-Kolko et al., 2010; Moses-Kolko et al., 2012; Moses-Kolko et al., 2011; Silverman et al., 2011; Silverman et al., 2007; Laurent & Ablow, 2013; Laurent & Ablow, 2012; for review see Moses-Kolko et al., 2014). In terms of brain response to emotional stimuli, currently, only 6 functional neuroimaging studies have been conducted on mothers with PPD.

Silverman et al., 2007; Silverman et al., 2011. Silverman and colleagues report on two studies where they used emotionally-valenced words to examine the brain response in mothers with postpartum depression, using fMRI. In Silverman et al. (2007) they used a region of interest approach to investigate fronto-limbic-striatal activity in mothers with PPD to emotional word-probes. They found that mothers without PPD (as defined by a score of 0-4 on the EPDS) show greater BOLD response in the AMY to negative words than do individuals with PPD (as defined by scores >12 on the EPDS). They also found that mothers with PPD viewing negative words show decreased BOLD response in the posterior orbitofrontal cortex and increased BOLD response in the insula. Finally, they also show decreased BOLD response to positive words in the striatum in mothers with PPD. As a result, they propose that the function of brain regions known to play a critical role in affectively relevant decision-making processing of affectively relevant information, and reward/motivation are altered in mothers with PPD. In Silverman et al. (2011) they again used a region of interest approach to examine whether the AMY responds differentially to negative versus neutral words in mothers with and without PPD. As predicted, they found that individuals with increasing PPD severity, as defined by EPDS score, displayed reduced BOLD response. This differs from the findings of existing neuroimaging studies of individuals with MDD that show increased AMY response to negative stimuli (Hamilton et al., 2012). A major limitation of these two studies is their use cutoff scores on a non-clinical
questionnaire to categorize mothers as PPD or Non-PPD. They also do separate region of interest analyses on areas broadly hypothesized to play a role in emotion and reward, while failing to look at regions known, from work with rodent models, to play a more specific role in mothering such as the ventral tegmental area and hypothalamus. Finally, the first study used only 8 subjects (4 PPD and 4 non-depressed), and in their second study data from 4 of the 7 PPD subjects came from their first study.

Moses-Kolko et al., 2010; Moses-Kolko et al., 2011. Moses-Kolko et al. (2010) used a negative emotion face-matching task to examine the brain response in mothers with postpartum depression, using fMRI. Specifically, they examined brain regions implicated in emotion regulation: the AMY and dorsomedial prefrontal cortex. They found that mothers with PPD (as defined by DSM-IV TR criteria) show lower activation in the left dorsomedial prefrontal cortex to negative faces versus shapes. They also found that left AMY activation was negatively correlated with PPD symptom severity and that right AMY activation was positively correlated with lack of infant-related hostility. Finally, connectivity analysis decreased top-down effective connectivity (Grainger Causality) between the left dorsomedial prefrontal cortex and left AMY in response to negative adult faces in mothers with PPD. They suggest that brain regions known to play a critical role in processing negative emotions in faces are altered in mothers with PPD.

Moses-Kolko et al. (2011) used a monetary reward card task to examine the integrity of reward functioning in mothers with and without PPD. They found that habituation of the typically observed ventral striatal reward response was faster in mothers with PPD compared to non-depressed mothers. This leads the authors to suggest that the neural processing of rewards might be altered in mothers with PPD. It is important to note that neither of these studies examined the brain response of mothers to infant stimuli, specifically, despite the fact that much of the symptomology of PPD focuses on mothering abilities, and the mother-infant dyad.

Laurent & Ablow 2012; Laurent & Ablow, 2013. Laurent and Ablow (2012), for the first time, examined the brain response in mothers to child stimuli, in particular. More specifically, they presented primiparous mothers of 18-month old children with their own child’s cry sounds, the cry sounds of an unfamiliar child or to control sounds during fMRI. These mothers were classified as “depressed” if they met diagnostic criteria for a major depressive episode at some point during the perinatal period and if they reported ongoing minor symptoms
of depression. Using a whole-brain analysis, they examined the brain response to own children’s
cry, other cry and/or control sound separately in Non-PPD and PPD mothers, as well as group
differences. They identified that Non-PPD mothers showed a greater brain response to their own
child’s cry as compared to a control sound in a distributed network of paralimbic and prefrontal
regions. PPD mothers did not show this pattern of brain response. From the group analysis, they
identified that Non-PPD mothers showed a greater response in the striatum (caudate and nucleus
accumbens) and the medial thalamus when listening to their own child cry as compared to a
control sound. When listening to their own child cry versus an unfamiliar child cry, Non-PPD
mothers demonstrated greater BOLD response in the right occipital fusiform and lingual gyri.

Laurent & Ablow (2013) again examined the brain response in mothers of 18-month old
children to child stimuli, in particular. However, in this study, they presented primiparous
mothers with pictures of their own and other children’s “joy” and “distress” faces during fMRI.
These mothers were classified as “depressed” according to the same criteria as in the previous
described study. Again, using a whole-brain analysis, they examined group differences in brain
response to own and other “joy” faces and own and other “distress” faces. While they identified
no significant group differences in BOLD response to one’s own child’s joy faces-other joy
faces, mothers who reported less current depressive symptomology showed greater BOLD
response in the right insula and left inferior OFC during this contrast. For the own distress-other
distress contrast, Non-PPD mothers showed a greater BOLD response in the left dorsal ACC and
in the right occipital pole. In both of these studies, the authors focus only on whole-brain
analyses, which are not driven by apriori theoretical knowledge or predictions regarding
functional neuroanatomy of mothering. Thus, they may miss potentially informative results in
smaller brain regions (e.g, the AMY) due to overcorrecting for multiple comparisons.
Furthermore, they fail to examine the possibility that, while response-level differences may not
be easily identified, differences in the pattern of connectivity between brain regions important in
mothering, affect and/or reward may still exist in mothers with and without PPD.

**Resting State Connectivity.** There are only two existing studies examining brain
connectivity differences in PPD and Non-PPD mothers. Chase, Moses-Kolko, Zevallos, Wisner,
& Phillips (2013) examined connectivity of the default mode network during resting-state fMRI.
They observed a negative coupling between the AMY and posterior cingulate cortex.
Furthermore, using seed-based connectivity analyses, they found that posterior cingulate cortex-
right AMY connectivity was positively correlated with posterior cingulate cortex-parahippocampal connectivity. Thus, they suggest that the parahippocampal gyrus may influence the altered posterior cingulate cortex-right AMY connectivity, and that this is not due to changes in the overall connectivity of the default mode network in mothers with PPD. Deligiannidis et al. (2013) also used resting-state functional connectivity analysis to look at corticolimbic connectivity in mothers with and without PPD. They used seeds in the ACC, DLPFC, hippocampus and AMY and found that Non-PPD mothers show stronger connectivity among these regions, compared to mothers with PPD.

1.2.4 Amygdala (AMY)

The AMY is a mass of grey matter located in the anterior part of the temporal lobe, comprised of at least two main divisions: the basolateral AMY (BLA) and the centromedial AMY (CMA), from rodent work. Human work suggests there is at least one other functionally and structurally distinct subnuclei: the superficial AMY (SFA). Rodent work suggests that the BLA includes the lateral, basolateral, basomedial and cortical nuclei and is primarily glutamatergic (with GABAergic interneruons), whereas the primarily GABAergic CMA is comprised of the central and medial extended AMY. Rodent work suggests that the AMY has extensive reciprocal connections with brain systems including those involved in sensory/visceral functions (e.g., sensory cortical association areas, thalamus, olfactory cortex), brain stem/hypothalamic functions (e.g., hypothalamus, periaquiductal gray, reticular formation), and emotional forebrain functions (e.g., orbital and medial prefrontal cortex, anterior cingulate cortex, ventromedial striatum, insular cortex; Price, 2003).

In general, the AMY guides behaviour in response to motivationally, emotionally and socially relevant stimuli (Adolphs, 2003). Relevant to mothering, in rodents, the CMA inhibits neophobic responses by nulliparous females through olfactory stimulation (Fleming, Vaccarino, & Luebke, 1980; Numan, Numan, & English, 1993). The earliest work with non-human primates by Kluver and Bucy (1937, 1939) as well as Brown and Shafer (1888), described severely aberrant social behaviour following AMY lesions. Similarly, in humans, the AMY is vital in normative interpretations of a social phenomenon: facial expressions (Adolphs, Tranel, Damasio & Damasio, 1994; Anderson, Spencer, Fulbright & Phelps, 2000). Initially, the AMY was implicated predominantly in the detection of fear (Adolphs, Tranel, Damasio & Damasio, 1995;
Anderson & Phelps, 2000), however, upon further analyses, it was found that impairments were individually specific, thus differing between subjects based on task, emotion and analysis used (Adolphs, 1999). It appears that individuals with AMY lesions have deficits in judging social emotions from the eyes of others more severe than that for basic emotions (Adolphs, Tranel, Baron-Cohen, 2002). This implicates the AMY in attaching reward and punishment values to stimuli of social significance, as opposed to playing a role in motivational behaviour in general (Adolphs, 2003). Thus, the role of the AMY in social cognition, a skill necessary for normative mothering, suggests that it may be a region of particular interest when studying the neural correlates of mothering.

1.3 Summary

Although this existing work examining the neural correlates of PPD reflects important first insights into its underlying neuropathology, it is important to examine the brain response in mothers with PPD to infant stimuli, in particular, as the disorder impacts mothering abilities and the mother-infant dyad. Additionally, as PPD is characterized by an altered emotional, cognitive and behavioural response towards a stimulus that is typically interpreted as rewarding (e.g., one’s own infant), any investigation of the neurophysiology of this disorder should also utilize stimuli that are positively valenced. To better elucidate the underlying neuropathology of PPD, it is also important to understand whether the pattern of brain response is specific to their own, or generalizable to all infants, or even to all positive stimuli. To address the above concerns and further our understanding of the neurobiology of PPD, we propose a block-design fMRI that will examine: 1) Brain response in mothers with PPD to positive stimuli, 2) Brain response in mothers with PPD to infant stimuli of varying familiarity, 3) Functional connectivity within various brain networks during the viewing of infants, in mothers with and without clinically determined PPD, 4) How the brain response during viewing of infant stimuli relates to measures of maternal behavior, outside of the scanner.

1.4 Overview of Studies

The primary objective is to investigate the neural underpinnings of depressed human mothers’ response to infants. Relatedly, it is important to understand whether the pattern of brain response in mothers with and without PPD is specific to their own, or generalizable to all infants. This may eventually allow for more targeted intervention programs (e.g., effective interventions
with any infant, or only with one’s own). Furthermore, despite the fact that, to-date, predominantly negative stimuli have been used, it is important to examine the brain response of mothers to positively valenced stimuli, as PPD involved symptoms of anhedonia towards a typically salient stimulus. Research suggests that mothers with PPD exhibit a negative bias in processing infant facial expressions (Arteche et al., 2011). This is clinically relevant, as research indicates that facial expressions are a primary means of communicating emotion for a developing infant and that infant facial expressions are coordinated with infant-directed gaze from the mother (Yale, et al., 2003; Colonnesi, et al., 2012), leading to ‘en face’ behaviour between the two, which has been described as species-typical maternal behaviour (Klaus, Trause, & Kennell, 1975). This indicates that infant visual stimuli elicit maternal arousal and may reflect maternal motivation. As such, we will utilize stimuli derived from one’s own as well as an unfamiliar infant during fMRI to examine brain response and connectivity in new mothers with and without PPD. Examining this will have important implications for the treatment of PPD.

1.4.1 Study 1

As aforementioned, risk factors for PPD include low postpartum partner support, stressful life events, a history of abuse, and more (see General Introduction). As a result, in Study 1 we will characterize our sample of women with and without PPD using a number of well-known risk factors, such as current parenting stress, quality of early care in one’s family of origin, history of early neglect and/or abuse, relationship satisfaction, as well as current mood and anxiety symptoms (Dennis, Heaman & Vigo, 2012; O’Hara & Swain, 1996; Milgrom et al., 2008). This multidimensional assessment will allow us to examine whether the sample of postpartum women we have recruited differ on measures beyond their experience of a major depressive episode in the current pregnancy. We predict that our group of mothers with PPD will demonstrate overall greater burden across our various measures. In this, we will confirm a well-known set of risk factors for PPD. Furthermore, we will examine specific factors, such as attitudes and behaviour when interacting with one’s infant (e.g., sensitivity), also known differ in mothers with PPD (e.g., reduced maternal sensitivity). As such, this study will serve as a proof of principle, demonstrating that our sample of PPD mothers indeed fits with samples from other studies of PPD mothers according to multiple demographic and clinical variables. Because our sample of women were recruited based on clinical diagnosis of depression, for Study 2-4, diagnostic
category (PPD vs. Non-PPD) will be used as the main predictor variable in relation to fMRI and behavioural measures.

1.4.2 Study 2

Recent views suggest that the normative functional role of the AMY includes assisting with both the identification of a salient stimulus and the convening of necessary resources for an adaptive response to said stimulus (Cunningham & Brosch, 2012). As such, in Study 2, we hope to examine whether blood-oxygen-level dependent (BOLD) response in the AMY will be greater when mothers view their own as opposed to an unfamiliar baby, and whether this difference will be preserved in mothers with PPD. We predict that Non-PPD mothers will indeed show greater BOLD response in the AMY when they view their own infants, however we expect that this difference will be blunted in mothers with PPD. We also expect to see an altered pattern of cortico-limbic connectivity in PPD compared to Non-PPD mothers. It is also possible that mothers with PPD will display an altered response to all emotional stimuli and that the response is not specific to infant faces. As a result, in Study 2 we will also investigate the brain response in mothers with and without PPD to positive non-infant pictures (e.g., scenes, animals, food).

1.4.3 Study 3

For Study 3, we will examine whether subregions in the AMY display unique connectivity patterns during the viewing of infant stimuli in mothers with and without PPD. Some researchers suggest that a primary role of the AMY is characterizing the social reinforcement value of other individuals (Adolphs, 2003), which is why it is engaged with people view emotional facial expressions. Relatedly, the lateral ventral subregion as compared to the medial ventral and dorsal subregions of the AMY appear to play different functional roles in emotional face processing. For example, recent work by Whalen and colleagues suggests that a portion of the lateral ventral subregion (approximately equivalent to the basolateral nuclei) may act as a sensory input and convergence centre, the medial ventral subregion (which appears to include overlap between the basolateral and superficial nuceli) may be responsible for integrating contextual and motivation information (with connections to the orbito- and medial-prefrontal cortices), and the dorsal subregion (equivalent to centromedial nuclei) may project to neuromodulatory centres responsible for increasing arousal (see Davis et al., 2010). Although this work was derived from studies that contrasted BOLD response to negative, neutral and
positive stimuli, it is possible that we would see similar relationships with varying familiarity (and thus, social relevance) of stimuli (e.g., own versus other babies). Fortunately, Amunts et al., (2005) recently compiled probabilistic maps based on AMY cytoarchitecture for the three most well delineated and studied AMY subregions: the basolateral, centromedial, and superficial nuclei. Relating functioning in these subregions during viewing of emotional infant and non-infant stimuli to interconnected networks will also be of interest. We may observe differential connectivity to these subregions in patients with PPD when they view their own compared to another infant in other brain regions involved in interpreting the hedonic quality of stimuli and affective states (e.g., orbital frontal cortex, pregenual and posterior cingulate, temporal and striatal regions; Fitzgerald, Laird, Maller & Daskalakis, 2008).

1.4.4 Study 4

In Study 4, we will relate behavioural measures of maternal sensitivity and responsiveness (quality of mother-infant interaction) to neural activation. To do this, we will first examine maternal behavior in association with brain activity in the AMY, thought to differentially respond to familiar and unfamiliar infant stimuli in PPD mothers. We predict that maternal behaviour will be dependent upon normative AMY functioning, as the AMY plays a role in socioemotional processing (Adolphs, 2003; Adolphs, Baron-Cohen and Tranel, 2002; Pessoa, 2010) and maternal behavior (Fleming, Vaccarino, and Luebke, 1980; Barrett and Fleming, 2011). Although no study has related maternal sensitivity to the mother’s brain response to positive infant stimuli, one study has used infant cry stimuli (Musser, Kaiser-Laurent and Ablow, 2012). Similar to their results, we may also observe a positive correlation between maternal sensitivity and brain response to infant cues in the AMY. However, this relationship may change, as we will be using positive rather than negatively valenced stimuli presented in a different modality (visual). Atzil et al. (2011) found that mothers who display greater intrusiveness show greater response in the right AMY, which contradicts findings regarding maternal sensitivity in that region (e.g., greater maternal sensitivity to greater AMY response). We hope to reconcile these findings using highly standardized positive infant stimuli, of varying familiarity, as well as positive non-infant stimuli.
2  General Methods

There were three phases to the study: 1) Diagnostic Interview and Photography Session, 2) fMRI Session, 3) Home Visit. A similar paradigm has been used successfully in previous work in our lab (Barrett, et al., 2012; Wonch et al., 2016; see Figure 2 for a study timeline). This study was approved by the Research Ethics Boards of St. Joseph’s Healthcare (SJH), Hamilton, ON, Canada and the University of Toronto at Mississauga (UTM), Mississauga, ON, Canada. Informed written consent was obtained from all participants.

2.1  Subjects

All participants were right-handed, English speaking women, 20-40 years of age, with singleton, full-term babies. They presented with no contraindications to fMRI (e.g., metallic implants) and had corrected or normal vision. According to structured clinical interview (Composite International Diagnostic Interview-Venus (CIDI-V; Martini et al., 2009), all participants reported no serious medical or neurological condition, no substance dependence in the past year (except caffeine or nicotine) and no current or history of psychotic or bipolar disorder, according to Diagnostic and Statistical Manual fourth edition text revision (DSM-IV TR; American Psychiatric Association, 2000) criteria. Additionally, the Children’s Aid Society was not involved in the care of the baby and mothers did not present with suicidal, homicidal or infanticidal risk. Mothers with no history of or current psychiatric illness (Non-PPD, n=23) were recruited from the maternity ward at SJH. Mothers who met DSM-IV TR criteria for Major Depressive Episode, with perinatal onset (PPD, n=31) were recruited from the Women’s Health Concerns Clinic at SJH. A principal investigator (MS) provided clinical care to these participants. Since PPD mothers were recruited from an outpatient psychiatric clinic, some were receiving treatment in the form of selective serotonin reuptake inhibitors (SSRI use n=13; no medication n=18). Diagnosis of PPD was made approximately one week prior to fMRI scan. To ensure a representative sample, these mothers were not excluded from the study and medication status was considered in all analyses. Symptom type and severity after the initial clinical diagnosis was assessed one week after diagnosis (and at the time of the scan) using the Edinburgh Postnatal Depression Scale (EPDS), a self-report measure of PPD severity and the State-Trait Anxiety Inventory, Trait version (STAI-T). These measures of mood reflect moment-to-moment changes in affect and are not necessarily consistent with the clinical diagnosis based
on DSM-IV for Major Episode Depressive Episode with perinatal onset.

Mothers participated at 2-5 months postpartum. This range was chosen as this was the minimum age based on our previous work (Barrett et al., 2012) at which positive (i.e. smiling) facial expressions were produced by infants in a relatively consistent manner. However, due to the often time-limited nature of PPD keeping the time period under 5 months was ideal (Cox et al., 1993). Prior to the fMRI, mother-baby pairs attended a laboratory session at SJH where a minimum of 50 positive infant facial expressions were photographed (by Kathleen E. Wonch (graduate student) and Cynthia de Medeiros (research assistant)). Five observers then rated these images on a 9-point scale (1='not at all positive’ and 9='extremely positive’). Twenty of the most positive infant face pictures (average rating of 5 or higher) were chosen for use in the fMRI protocol. The images were standardized for overall brightness, and framed and masked to present just the face area. Own baby stimuli were matched by randomly choosing another baby from our stimulus set. For their participation, mothers were provided with $100 remuneration plus the cost of parking.

### 2.2 fMRI

**2.2.1 Affect Rating Task (ART)**

PPD and Non-PPD mothers completed an Affect Rating Task (ART) during an fMRI session at the Imaging Research Centre at SJH. The ART was presented using E-Prime software and timing was synchronized with the acquisition of functional images. During each ART run, three conditions were presented four times using a block-design: 1) smiling own infant face (Own); 2) smiling other infant face (Other); 3) positive non-infant stimuli (e.g., scenes, animals, food; Non-Infant). Prior to each condition-block, a 1.5s visual cue was presented (Set A, Set B, Set C) followed by a 4s fixation cross. Cue to condition-block assignment was randomized across participants. For each 40s condition-block, 5 unique picture stimuli were presented randomly for 4s. After this, mothers had 4s to make a subjective rating of their emotional response to each stimulus (‘How does this picture make you feel?’), made on a 9-point scale (1='not at all positive’ and 9='extremely positive’). Each condition-block was followed by a jittered 8-10s inter-stimulus fixation cross (see Figure 3). PPD mothers may interpret infant faces more negatively than Non-PPD mothers (Arteche et al., 2011). Thus, mothers were instructed to rate the infant faces for the degree of emotional intensity they felt internally when viewing them,
rather than on the emotional intensity conveyed by the facial expressions. It is also possible that PPD mothers would display an altered response to all emotional stimuli. Consequently, each mother also viewed 20 Non-Infant, control images from the International Affective Picture System based on pre-chosen emotional subset categories defined by Mikels et al. (2005): amusement, contentment and undifferentiated positive.

2.2.2 Acquisition

MRI scanning was conducted using a General Electric 3-T short-bore scanner with 32 parallel-receiver channels (General Electric, Milwaukee, WI). BOLD response to infant faces was acquired using T2 weighted interleaved echo-planar imaging (EPI). 256 volumes were obtained from each participant, consisting of 42, 3mm thick axial slices (repetition time=2.7ms, echo time=35ms, flip angle=90°, resolution=64x64 over 24cm field of view).

2.2.3 Preprocessing

fMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB’s Software Library, www.fmrib.ox.ac.uk/fsl). Pre-statistic processing included: motion correction using MCFLIRT (Jenkinson et al., 2002); brain extraction using BET (Smith, 2002); spatial smoothing using a FWHM 5mm Gaussian kernel; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=75.0s). Participants were excluded from further analysis if they exhibited greater than 2mm movement. The first four images were discarded to ensure the scanner had achieved steady state during image acquisition. Warped functional images were combined to create a mean study-specific template for coregistration with individual functional data. Registration to this template was carried out using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich). In the following description, ‘Own’ refers to own baby pictures, ‘Other’ refers to other baby pictures and ‘NonInfant’ refers to all positive nonbaby pictures. Ten experimental conditions were included as regressors: OwnSet (instructions), OwnView, OwnRate, OtherSet (instructions), OtherView, OtherRate, NonInfantSet (instructions), NonInfantView, NonInfantRate, and ThankYou (end of task message). BOLD response when the mothers were viewing infant faces (View) was modeled separately from the time they were making a
subjective rating of the infant faces, as AMY activation can be inhibited by cognitive activity (Drevets & Raichle, 1998; Phan et al. 2002).

2.2.4 Region-of-Interest (ROI) Analysis

An AMY region of interest (Gil et al., 2011) was anatomically defined using the Harvard-Oxford anatomical atlas, at 70% probability threshold. We recognize that the human AMY is comprised of distinct subregions, each with their own afferents and efferents (Amunts et al., 2005; Ball et al., 2007; McDonald, 2003; Price, 2003). Subregions are also differentially involved in the processing of emotional face stimuli, especially in anxious individuals (Etkin et al., 2004; Etkin et al., 2009). In Study 2, we chose to examine the AMY as a whole for comparison with the extensive work that uses this approach to examine the functional significance of the AMY in MDD. In Study 3, we examined three AMY subregions: the basolateral (BLA), centromedial (CMA) and superficial (SFA). These subregions were defined according to the Amunts et al. (2005) probabilistic maps, with voxels identified as belonging to the BLA, CMA or SFA if they presented with the highest likelihood of belonging to said subregions, respective of neighbouring structures (e.g., hippocampal regions). This approach has been supported by recent work by Bzdok et al. (2013). In Study 4, the average AMY ROI, as well as the ROIs for the BLA, CMA and SFA, were used to examine the relationship between brain response and maternal behavior, outside of the scanner using Spearman correlation, as mentioned below.

We examined the View conditions rather than the conditions during which mothers were actively using the response box to respond to the pictures (Rate). The mean time series of AMY ROI voxels was generated for OwnView, OtherView and NonInfantView conditions in the right and left AMY and subregions (defined using the abovementioned anatomical masks). In order to examine both familiarity and specificity related differences, we examined AMY response to the following contrasts: OwnView-OtherView (familiarity) and OtherView-NonInfantView (specificity). To replicate our previous work (own positive-other positive contrast from Barrett et al., 2012), we first examined these contrasts in Non-PPD and PPD mothers, separately. Next, we conducted group-level analyses in FSL, masked for the bilateral AMY, where Z statistic images (Gaussianised T/F) were cluster thresholded \((z>2.3)\) and a cluster significance threshold of \(p=0.05\) was applied (Worsley, 2001). This represents a more sensitive alternative to voxel-based
thresholding where a z-statistic is used to define contiguous clusters with estimated significance level (from GRF-theory), which is then compared with the cluster probability threshold. For group-level analyses in Study 2, we examined both contrast—level (OwnView-OtherView and OtherView-NonInfantView) and condition-level (e.g., OwnView, OtherView and NonInfantView) effects, as well as the overall BOLD response across conditions (e.g., in OwnView, OtherView and NonInfantView, combined). In Study 3, we examined contrast—level (OwnView-OtherView and OtherView-NonInfantView) differences in each of the three AMY subregions (as defined above). To examine PPD and anxiety symptom severity EPDS and STAI-T scores were entered into SPSS-21 for analyses with AMY (subregion ROI and connectivity parameters) mean signal change across contrast conditions. Medication status was used as a covariate in the group-level model.

2.2.5 Psychophysiological Interaction (PPI) Analysis

Again, in order to examine both familiarity and infant-related connectivity differences, separate PPI models were conducted for OwnView-OtherView and OtherView-NonInfantView, respectively. Mean deconvolved time course was extracted from seed regions in the left and right AMY to serve as the psychophysiological variable. We restricted our bilateral AMY/subregion seed regions to those voxels within the anatomical ROIs defined above that showed an overall enhanced BOLD response relative to baseline in all three of our conditions combined (OwnView, OtherView and NonInfantView). PPI interaction terms were calculated as the cross product of the physiological variable and the task regressor. In each task model, separate analyses were computed for the right and left AMY/subregions with 3 regressors: task condition (OwnView-OtherView or OtherView-NonInfantView), PPI interaction term and left or right AMY time course. Although not specifically of interest, all other task conditions were also included as regressors. The PPI interaction term was then brought to a second-level group analysis (Non-PPD, PPD), with medication status entered as a covariate. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Z>2.3 and a (corrected) cluster significance threshold of P<0.05 (Worsley, 2001). For any cluster of voxels identified as significantly connected with the AMY in Non-PPD or PPD mothers, mean time series data was extracted and entered into SPSS-21 for analysis with covariates of interest using one-way ANOVA.
2.3 Other Demographic and Clinical Data

2.3.1 Questionnaires

**Demographic Questionnaire**: A comprehensive measure, used in Fleming laboratory projects with mothers for many years, which includes questions regarding childbirth experiences, medical issues, education, socioeconomic status, relationship and family factors including parity (Giardino, Gonzalez, Steiner & Fleming, 2008).

**Childbearing Attitudes Questionnaire (CAQ)**: A 76-item scale that includes 3-6 items for each of 16 issues about infants and childbirth (Ruble et al., 1990).

**The Edinburgh Postnatal Depression Scale (EPDS)**: A self-report scale designed to screen for PPD (Cox, Holden & Sagovsky, 1987). A cutoff score of 12 is indicative of PPD.

**State-Trait Anxiety Inventory (STAI)**: Measures components of state and trait anxiety (Spielberger, Goruch & Lushene, 1970; Spielberger, 1996).

**Parenting Stress Index (PSI)**: A self-report instrument of 120 items that yields a Total Stress score as well as separate scores for three sources of stress (parent, child and life events) (Abidin, 1990). On all scales, higher scores indicate greater stress.

**The Childhood Trauma Questionnaire (CTQ)**: A 28-item brief self-report questionnaire that retrospectively assesses 5 types of childhood abuse experiences (physical, emotional and sexual abuse; emotional and physical neglect) (Bernstein et al., 1994).

**The Parental Bonding Instrument (PBI)**: A 25-item checklist of attitudes and behaviours of the subject’s parents during the subject’s first 16 years of life (Parker, Tupling & Brown, 1979).

2.3.2 Videotaped Mother-Infant Interactions

At Visit 3 (Home Visit), the mother and infant participated in a 20 minute videotaped non-feeding interaction session followed by a 10-minute divided attention task. Mothers were asked to interact, as they normally would, while remaining within the camera's view. During the last 10-minute period, mothers completed a set of questionnaires while still caring for their infant.
Ainsworth Maternal Sensitivity Scale (AMSS): The AMSS consists of four nine-point Likert rating scales: acceptance vs. rejection; accessibility vs. ignoring and neglecting; cooperation vs. interference; and sensitivity vs. insensitivity (Ainsworth & Wittig, 1969). Higher scores indicate higher quality of maternal interactions.

Behavioral Evaluation Strategies and Taxonomies (BEST): At 3-4 months coded behaviours include 4 maternal factors comprised of individual behaviors; they are designated 1) Maternal Attention, 2) Maternal Vocalizations, 3) Maternal Sociality, 4) Maternal Instrumental and 5) Infant Behaviours (Educational Consulting, Inc., Hobe Sound, FL, USA). BEST generates duration and frequency data for the abovementioned maternal behaviors by the use of a computer keyboard with keys indexed for each behavior (Mileva-Seitz et al., 2012).

Maternal Behaviour Q-Sort (MBQS)-Mini: In this, mothers were coded according to a 25-item forced-sort procedure (original 90-item sort described in Pederson et al., 1990; Pederson, Moran & Bento, 1999), where single-item descriptors of the quality of interaction with one’s infant are assigned to be most-like to most-unlike mom and compared against scoring for an ideal, or prototypical mom, to produce a global rating of maternal sensitivity (see Pederson & Moran, 1995).

The resulting data, summarized in Study 1, was used to examine brain-behaviour relations in Study 4 through analysis in relation to the aforementioned BOLD response data generated in Study 2 and Study 3. A graduate student (KW; for the AMSS and MBQS) and research assistant (AD; for the BEST) underwent training by coders experienced and trained to reliability with each system. Training included joint viewing, discussion and coding of videos of mothers interacting with 3-month old infants from a separate series of studies conducted in the laboratory (the Maternal Adversity, Vulnerability and Neurodevelopment study). This series of studies follows a similar interaction protocol (e.g., 20-minute free play with child followed by 10-minute distraction task) to the current work. Joint coding of these videos was continued until inter-rater reliability of .80 or greater was reached for 10 videos in a row. After this, the trainer coded 10 videos from the current sample with the trainee (KW/AD) in order to establish reliability with the current sample. The sample included videos of 5 PPD and 5 Non-PPD mothers, chosen at random. Here, inter-rated reliability was also established to be .80 or greater.
Split-half intra-rater reliability coefficients were also all above .80 for each of the aforementioned behavioural coding schemes, for both PPD and Non-PPD populations.

2.3.3 Data Analysis

Demographic and clinical variables from Study 1 were analyzed with SPSS-21 using a univariate ANOVA or chi-square test, where appropriate. Spearman correlations were used to examine the relationship between ART, other demographic/clinical variables (e.g., EPDS, STAI-T) and maternal behavior measures (e.g., AMSS, MBQS) with our fMRI contrasts (OwnView-OtherView and Other-View-NonInfantView) and conditions of interest (OwnView, OtherView and NonInfantView) for Study 2 (AMY ROI and connectivity parameters), Study 3 (AMY subregion ROI and connectivity parameters) and Study 4 (AMY/subregion ROI and connectivity parameters). Further details on Study-specific analyses are included in Study Methods and/or Results. Alpha level for significance was set at .05.

3 Study 1: Multidimensional Indicators of PPD.

Postpartum depression (PPD) is one of the most common complications following childbirth. It is characterized by many of the same symptoms as major depressive disorder, including significantly decreased mood and loss of interest or pleasure in previously enjoyable activities (American Psychiatric Association, 2000). However, uniquely, PPD is postpartum in onset and often includes excessive concern or guilt surround one’s parenting abilities. This period of low mood also often extends beyond the usual 2-weeks needed to meet the criteria for a diagnosis of major depression. Epidemiological studies estimate that anywhere from 5-20% of women will experience an episode of depression in the first year postpartum and that even more experience some form of postpartum mood changes, without meeting the full criteria for a major depressive episode (O’Hara & Swain, 1996; Lanes, Kuk & Tamim, 2011; O’Hara, Neunaber, Zekoski, 1984; Halbreich & Karkun, 2006). In fact, while Cox, Murray & Chapman (1993) did not find a difference in the point prevalence of depression at 6-months in mothers versus non-mothers, they did find a three times greater onset in the first 5 weeks postpartum. While some studies suggest that symptoms of PPD may spontaneously resolve around 6 months (e.g. Cox, Murray & Chapman, 1993), other work has identified symptom stability across the first
postpartum year (Dennis et al., 2012). Known risk factors for PPD include: prior history of depression during pregnancy or during another time period, PPD during another pregnancy, low household income, low postpartum social support, stressful recent life events, interpersonal violence, marital conflict, low socioeconomic status and poor self-perceived maternal health (Dennis, Heaman & Vigod, 2012; O’Hara & Swain, 1996; Milgrom et al., 2008; O’Hara, Arndt & Stuart, 2007; Robertson, Grace, Wallington & Stewart, 2004).

Mothers with PPD demonstrate an altered repertoire of parenting abilities relative to mothers without PPD. For example, they tend to be more intrusive, irritated, and negative in their interactions with their infants (Murray et al., 1996; Cohn et al., 1990), they also tend to interpret their infant’s behaviour more negatively (Field et al., 1993). Additionally, they are less affectionate with their infants (Fleming et al., 1988; Stanley et al., 2004) and respond less sensitively and contingently to their infants (Murray et al., 1996; Fleming et al., 1988; Stanley et al., 2004). They also demonstrate less positively synchronous interactions with their babies compared to mothers without PPD (Field et al., 1990).

Given what we know about the relationship between parenting and child development, it is not surprising that children of mothers with PPD tend to fare more negatively from a social, emotional cognitive and behavioural perspective, than children reared by mothers who are not depressed. For example, children of mothers who were depressed postpartum show overall poor cognitive outcome at 18 months (Murray et al., 1996). Notably, male children were found to be the most vulnerable to these effects. They were also identified to have more difficulties in social interactions with their peers at 5 years of age, as evidenced by more physical than creative play and more negative reactions to friendly approaches. They have also been identified to have higher rates of mood and anxiety disorders at 13 years (Halligan et al., 2007) and higher rates of mood disorders at 16 years (Murray et al., 2011). It appears that other risk factors may interact with maternal PPD to predict the intergenerational transmission of mood disorders. For example, Halligan et al. (2007) found that 84% of mothers with PPD at initial presentation experienced another major depressive episode prior to the 13-year follow-up. Murray et al. (2011) also found that child vulnerability factors (e.g., attachment style and weak ego resilience), as well as family adversity, accounted for approximately 81% of the effect of PPD on adolescent depression. This work highlights the importance of studying moderators and mediators of the relation between maternal depression and child outcomes.
In the current work, we will characterize our sample of women with and without PPD using a number of questionnaire- and observation-based measures of current parenting stress, quality of early care in one’s family of origin, history of early neglect and/or abuse, relationship satisfaction, attitudes towards parenting, current mood and anxiety symptoms, as well as behavioral indicators of maternal sensitivity. As aforementioned, this multidimensional assessment will allow us to examine whether the sample of postpartum women we have recruited differ on measures beyond their experience of a major depressive episode in the current pregnancy. Furthermore, it will allow us to confirm a well-known set of risk factors and behavioural profile of mothers with PPD (e.g., Dennis, Heaman & Vigo, 2012; O’Hara & Swain, 1996; Milgrom et al., 2008; Murray et al., 1996; Fleming et al., 1988; Stanley et al., 2004), serving as a proof of principle that our community sample of women fits the typical profile of mothers with PPD. We predict that our group of mothers with PPD will demonstrate overall greater burden across our various risk factors (e.g., higher parenting stress, poorer quality of early care in their family of origin, reduced maternal sensitivity, etc.).

3.1 Abbreviated Methods

Our study population consisted of mothers, 2-5 months postpartum, with (n=28) and without (n=17) PPD, as determined by diagnostic interview (CIDI-V), who are 20-40 years of age, with singleton, full-term babies. As part of our multidimensional assessment of maternal factors, we assessed maternal behavior (e.g., AMSS, MBQS and BEST), maternal attitudes (e.g., CAQ) and maternal mood (e.g., EPDE, STAI-T/S, PANAS) as well as well-known risk factors such as early life experiences (e.g., CTQ, PBI), stress (e.g., PSI) and relationship quality (e.g., DAS; Dennis, Heaman & Vigo, 2012; O’Hara & Swain, 1996; Milgrom et al., 2008). Please see Figure 2 for a timeline of when these measures were collected. Demographic and clinical variables from Study 1 were analyzed with SPSS-21 using a univariate ANOVA or chi-square test, where appropriate. Alpha level for significance was set at $p < .05$.

3.2 Results

Mothers with and without PPD were recruited to be matched on all demographic variables, and indeed, they did not significantly differ on any demographic variables of interest (e.g., age, parity, feeding method, education and delivery method; see Table 2). As such, these
variables were not included in subsequent analyses. Of note, medication status (SSRI vs. None) was not a significant predictor in any model and, thus, was not included in subsequent analyses.

### 3.2.1 Questionnaire Measures

As the following analyses are exploratory, all questionnaire variables were entered into a single multivariate ANOVA. In the initial model, the following 20 dependent variables (DVs) were included: 3 PSI subscales, EPDS at Visit 2, STAI-T at visit 2, 5 CTQ subscales, Care and Protect subscales of PBI for mother and father, 4 DAS subscales, and PANAS positive and negative. Group (PPD vs. Non-PPD) served as the single independent variable. Alpha value for significance was set at \( p < .05 \). Following this, the analysis was repeated using only those variables that were significant from model 1. The following 8 variables served at the DVs: Parental Distress from PSI, EPDS Visit 2, STAI-T Visit 2, Emotional Abuse and Neglect from CTQ, Care Mom from PBI and PANAS positive and negative affect. Post-hoc power analysis using G-Power (Faul, Erdfelder, Lang, & Buchner, 2007) indicated that, for a MANOVA with 8 response variables, a sample size of 60 was needed to detect an effect size of 0.3 with 80% power at \( \alpha = 0.05 \). As only 42 mothers completed all questionnaires, it is important to note that we are somewhat underpowered for this analysis.

Mothers with PPD reported more parental distress subscale of the parenting stress index (e.g., I feel trapped by my parental responsibilities; I give up more of my life to meet my child’s needs than expected; since having a child I feel I cannot do things I like doing) in mothers with PPD, relative to mothers without PPD (\( F(1, 40) = 20.849, p = .001, \eta_p^2 = 0.343 \); see Figure 4). Mothers with PPD reported more depressive symptomology, as measured by higher EPDS score at Visit 2, than mothers without PPD (\( F(1, 40) = 12.906, p = .001, \eta_p^2 = 0.244 \) see Figure 5a). Mothers with PPD also reported more trait anxiety (STAI-T at Visit 2) than mothers without PPD (\( F(1, 40) = 44.366, p = .001, \eta_p^2 = 0.526 \); see Figure 5b). Mothers with PPD demonstrate less positive affect (\( F(1, 40) = 6.772, p = .013, \eta_p^2 = 0.146 \); see Figure 5c) and more negative affect (\( F(1, 40) = 10.575, p = .002, \eta_p^2 = 0.209 \); see Figure 5c) than mothers without PPD. Mothers with PPD reported higher levels of emotional abuse (\( F(1, 40) = 6.125, p = .013, \eta_p^2 = 0.145 \); see Figure 6) and neglect (\( F(1, 40) = 8.866, p = .005, \eta_p^2 = 0.181 \); see Figure 6), compared to mothers without PPD. Mothers with PPD report lower quality of care from their own mothers (\( F(1, 40) = 7.119, p = .011, \eta_p^2 = 0.151 \); see Figure 7)
3.2.2 Maternal Attitudes

Group differences in all factors from the Maternal Attitudes Questionnaire with Cronbach’s Alpha’s greater than 0.5 were examined using a single multivariate ANOVA. The chronbach’s alpha for Feelings of Dependency and Information Seeking was <0.5, thus, these factors were excluded from further analysis. In the initial model, the following 14 dependent variables (DV) were included: Maternal Worry, Negative Self-Image, Lability, Need for Nurturance, Maternal Self-Confidence, Feel About Children, Interest in Sex, Relationship with Mother, Relationship with Father, Relationship with Husband, Care Taking, Social Confidence, Feeling Tied Down, and Attachment. Group (PPD vs. Non-PPD) served as the single independent variable. Alpha value for significance was set at $p<.05$. Following this, the analysis was repeated using only those variables that were significant from model 1. The following 10 variables served as the DVs: Maternal Worry, Negative Self-Image, Lability, Need for Nurturance, Maternal Self-Confidence, Feel About Children, Interest in Sex, Relationship with Father, Care Taking, and Social Confidence. Post-hoc power analysis using G-Power (Faul, Erdfelder, Lang, & Buchner, 2007) indicated that, for a MANOVA with 10 response variables, a sample size of 64 was needed to detect an effect size of 0.3 with 80% power at $\alpha = 0.05$. As only 38 mothers completed this questionnaire, it is important to note that we are somewhat underpowered for this analysis.

Relative to Non-PPD mothers, PPD mothers score higher on the following factors (see Figure 8a): Maternal Worry ($F(1,36) = 11.906, p = .001, \eta_p^2 = 0.249$), Negative Self-Image ($F(1, 36) = 9.727, p = .004, \eta_p^2 = 0.213$), Lability ($F(1, 36) = 4.248, p = .047, \eta_p^2 = 0.106$), and Need for Nurturance ($F(1, 36) = 12.693, p = .001, \eta_p^2 = 0.261$). On these factors, higher scores reflect more distress. Relative to Non-PPD mothers, PPD mothers score lower on the following factors (see Figure 8b): Maternal Self-Confidence ($F(1, 36) = 6.935, p = .012, \eta_p^2 = 0.162$), Feel About Children ($F(1, 36) = 7.588, p = .009, \eta_p^2 = 0.213$), Interest in Sex ($F(1, 36) = 12.507, p = .001, \eta_p^2 = 0.258$), Relationship with Father ($F(1, 36) = 5.229, p = .028, \eta_p^2 = 0.127$), Care Taking ($F(1, 36) = 14.475, p = .001, \eta_p^2 = 0.287$), and Social Confidence ($F(1, 36) = 6.810, p = .013, \eta_p^2 = 0.159$). On these factors, lower scores reflect more distress.
3.2.3 Behavioural Measures

All behavioural measures of mothering (AMSS, MBQS and BEST) were entered into a single multivariate ANOVA. The following 13 dependent variables (DVs) were included: Ainsworth Total score and all subscales (Acceptance, Availability, Cooperation and Sensitivity), MBQS, time spent holding infant, looking at/interacting with infant and looking away from infant, as well as frequency of mother showing toy to infant, infant playing with toy, grooming and mother laughing/smiling at infant. Group (PPD vs. Non-PPD) served as the single independent variable. Alpha value for significance was set at p<.05. We did not observe differences between Non-PPD and PPD mothers in time spent looking at/interacting with infant and/or looking away from infant. As such, the analysis was repeated with only the remaining 11 significant behavioural variables. Post-hoc power analysis using G-Power (Faul, Erdfelder, Lang, & Buchner, 2007) indicated that, for a MANOVA with 11 response variables, a sample size of 68 was needed to detect an effect size of 0.3 with 80% power at α = 0.05. As only 44 mothers completed the mother-infant interaction video, it is important to note that we are somewhat underpowered for this analysis.

As compared to Non-PPD mothers, mothers with PPD are less accepting ($F(1, 42) = 8.071, p = .007, \eta^2 = 0.161$; see Figure 9a), available ($F(1, 42) = 5.194, p = .028, \eta^2 = 0.110$; see Figure 9a), cooperative ($F(1, 42) = 4.949, p = .032, \eta^2 = 0.105$; see Figure 9a) and sensitive ($F(1, 42) = 6.963, p = .012, \eta^2 = 0.142$; see Figure 9a) in their interactions with their infants. Furthermore, they have lower overall scores on the AMSS ($F(1, 42) = 7.298, p = .010, \eta^2 = 0.148$; see Figure 9a). Mothers with PPD, relative to Non-PPD mothers, also show poorer quality maternal care overall as measured by scores on the MBQS ($F(1, 42) = 5.151, p = .028, \eta^2 = 0.109$; see Figure 9b).

As compared to Non-PPD mothers, mothers with PPD spend more time holding their infants ($F(1, 42) = 8.823, p = .005, \eta^2 = 0.174$; see Figure 9c). They also groom their infants more frequently ($F(1, 42) = 5.067, p = .030, \eta^2 = 0.098$; see Figure 9d). Relative to Non-PPD mothers, PPD mothers try to engage their infants in play with toys less frequently ($F(1, 42) = 4.193, p = .047, \eta^2 = 0.091$; see Figure 9d) and their infants play with toys less frequently ($F(1, 42) = 4.597, p = .038, \eta^2 = 0.099$; see Figure 9d). PPD also mothers laugh and smile with their infants less frequently in a 20-minute interaction ($F(1, 42) = 4.343, p = .043, \eta^2 = 0.094$; see 9d).
3.2.4 Correlations

The analyses revealed a very high degree of collinearity in the data. Rather than summarizing this vast amount of data, we have chosen to use the relationship between EPDS from visit 2 (time of the fMRI) and each of the following questionnaire measures to display this high degree of interrelationship among the various measures: STAI-trait anxiety from visit 2 (time of the fMRI), CTQ total score, PSI total score, quality of early care with one’s own mother, overall quality of one’s intimate relationship and maternal worry from the Maternal Attitudes Questionnaire (see Table 3). All analyses revealed significant correlations; Higher EPDS scores were related to higher STAI-Trait Visit 2 scores, CTQ Total scores, PSI Total scores and self-reported Maternal Worry. Higher EPDS scores were also related to poorer quality of care from one’s own mother and poorer overall relationship quality. The EPDS was chosen for analysis as it represents the gold-standard measure of PPD symptomology.

Next, correlations were run across all behavioural measures of mothering outside of the scanner. Once again, due to the high degree of collinearity, correlations are summarized for Ainsworth Total score, MBQS and time spent holding one’s infant from the BEST (see Table 4). All of these analyses revealed significant correlations; Higher Ainsworth score was related to higher MBQS scores and less time spent holding one’s infant during a 20-minute interaction.

Next, we examined the relationship between clinical variables of interest and our measures of maternal behaviour. Higher scores on the EPDS, STAI-T and Parental Distress subscale of the PSI were related to poorer quality maternal behaviour (see Table 5a for summary). Furthermore, higher scores on the EPDS, STAI-T, PSI Total and all subscales (Parental Distress, Parent-Child Difficult Interaction and Difficult Child) were related to more time spent holding one’s infant (Table 5a). It should be noted that, as aforementioned, mothers with PPD were found to spend more time holding their infants, as compared to mothers without PPD (see Figure 9c). On the contrary, higher scores on the Positive Affect factor of the PANAS, as well as higher scores on the Care Mom subscale of the PBI were related to higher quality maternal behaviour, and less time spent holding one’s infant (Table 5a). No other significant relationships were observed among any other clinical variables (subscales and/or total scores).

The relationship between behavioural and attitudinal variables were also explored. Significant negative correlations were found between Maternal Worry, Lability and Need for
Nurturance with various behavioural measures of mothering (see Table 5 for summary; only significant values are displayed). In other words, mothers with lower maternal worry, lower mood labile mood and less self-reported need for nurturance display higher quality maternal care. Significant positive correlations were found between Feel About Children, Interest in Sex and Care Taking with various behavioural measures of mothering (see Table 5 for summary). In other words, mothers who feel more positive about having and caring for children and have higher interest in sex display higher quality maternal care.

3.3 Discussion

In addition to the presence of clinical depression, our sample of PPD mothers displayed markedly elevated levels of current parental distress, general symptoms of anxiety, both trait-based and reactive (state-based), depression, childhood trauma and poorer quality of early maternal care in their own family of origin. They also reported maternal attitudes that reflect more distress on a variety of domains. Interestingly, effect size indicates that differences between PPD and Non-PPD mothers in this sample are most notable for State Anxiety, Parental Distress and symptoms of PPD from questionnaire measures, as well as Maternal Worry, Need for Nurturance, and Care Taking from attitudinal measures. While these analyses were underpowered, it is notable that mood, anxiety and parental distress strongly differentiate PPD from Non-PPD mothers, across measurement modalities (e.g., self-reported behaviours and attitudes).

Stressful recent life events are also a known risk factor for the development of PPD (Dennis, Heaman & Vigo, 2012). Notably, in our sample, PPD mothers do not report that they find their children to be more temperamentally difficult, overall, nor do they perceive their interactions with their children to be more difficult, rather they experience an overall heightened amount of parental distress, namely due to negative evaluations of the impact of parenting roles on their life. They also report greater overall negative affect, state anxiety before and after a mild stressor (e.g., fMRI scan), as well as state anxiety after interacting with their infants. They also demonstrate overall less positive affect than mothers without PPD. Hallmark features of depression include low mood, anhedonia, or a lack of interest or pleasure in previously enjoyable activities, as well as negative self-evaluations. Thus, while this group of PPD mothers report that they experience their lives as more stressful and anxiety provoking than mothers without PPD, it
is difficult to determine whether this is due to the actual presence of increased stressors or an altered perception of their reality due to the presence of depression.

Despite the fact that these measures are designed to reflect discrete constructs of stress, anxiety, mood, trauma, etc., in this sample, in particular, it is apparent that there is a high degree of collinearity among them. Higher scores on the EPDS, a gold-standard measure of PPD symptomatology, were strongly correlated with scores across all other measures. As such, it will be difficult in subsequent analyses (e.g., with neuroimaging data) to determine the degree to which on particular factor may be driving the any observed effects. Thus, rather than examining individual differences on one particular measure, we will categorize mothers as depressed or not based on clinical, diagnostic interview. This approach has been supported by recent work from Pawlby et al. (2008) demonstrating that clinical diagnostic interview was more sensitive in distinguishing the relationship between maternal PPD and child outcomes at 11 years than EPDS cutoff score. For the purposes of our current work, we will use clinical diagnostic status (e.g., PPD vs. Non-PPD) to group our mothers in future analyses with fMRI data.

From a behavioural perspective, the PPD mothers in our study were found to demonstrate less accepting, available, cooperative, and overall sensitive parenting, relative to our Non-PPD sample. The group differences in maternal sensitivity were determined across multiple measures (e.g., MBQS and Ainsworth Maternal Sensitivity scales). The link between PPD and more negative maternal behaviours has been well-established (see Lovejoy, Graczyk, O’Hare & Neurman, 2000 for review). Our findings are also consistent with a recent meta-analysis by Field (2010) that identified decreased maternal sensitivity in mothers with PPD across a variety of cultures and socioeconomic statuses. This work goes on to highlight that specific caregiving behaviours are compromised in mothers with PPD, including breastfeeding and sleep routines. PPD mothers have been found to present with at least two variations of parenting styles, one that may be intrusive, controlling and overstimulating and one that may be withdrawn, passive and under-stimulating (Malphurs et al., 1996). In the current work, we identified that our sample of PPD mothers spend more time holding their babies. This measure of “holding baby” does not speak to the quality of the interaction, per se, and it is possible that this fits with the first profile of intrusiveness. Consistent with this, we also identified that mothers with PPD groom their infants more frequently. Once again, this does not speak to the appropriateness of this form of interaction; whether infants of depressed mothers are in higher need of grooming behaviours is
not something that was investigated in the current work. It is possible that this increased grooming behavior represents a form of controlling, over-engagement in instrumental care activities on the part of the depressed mother. We also identified that PPD mothers try to engage their infants in play with toys less frequently, and that their infants in turn spend less time playing with toys. These measures may be capturing the other end of the spectrum, where PPD mothers sometimes present as passive or under-stimulating. This is consistent with work by Paulson, Dauber & Leiferman (2006) that identified that mothers with PPD engage in less enrichment activities with their infants (e.g., reading, singing songs, telling stories and playing peekaboo). Furthermore, we observed that PPD mothers smile and laugh with their infants less frequently than Non-PPD mothers, suggesting the overall quality of their interactive style may lack warmth and affection.

The aforementioned behavioural measures are coded by independent observers blind to the group (PPD vs. Non-PPD), and thus represent an unbiased account of maternal sensitivity and responsiveness. However, mothers in our study were also asked to evaluate their own attitudes related to parenting on a self-report questionnaire. Here, we observed that new mothers with PPD report greater levels of maternal worry and more labile affect. They also report that they require more nurturance than they are currently receiving, day-to-day (e.g., “I need someone to pay more attention to my needs than they are currently”) and they report less enjoyment in their overall care taking duties as a parent. They also report poorer overall self-image, poorer self-confidence as a mothers and reduced confidence in social situations since becoming a parent (e.g., “having a baby has made me less open to other people”). They also report reduced desire to be in situations involving other children. They also report poorer overall quality of relationship with their own father. Finally, they report reduced desire for sex. As such, in addition to being distinguishable behaviourally, this group of PPD mothers characterizes themselves as experiencing a variety of difficulties related to parenting, social support and self-confidence. Furthermore, many of these attitudinal variables are related, in ways that one would expect, to the various measures of maternal behaviour/sensitivity.

In the current Study, we found that the PPD mothers in our sample carry an overall greater burden of distress, across a variety of measures, than the Non-PPD mothers. In particular, they report greater parental distress, symptoms of depression and trait anxiety, while also feeling a greater need for nurturance, maternal worry and reduced enjoyment of the daily caretaking
duties for their child. Furthermore, we found that these symptoms of anxiety, depression, and parental distress as well as maternal worry, need for nurturance and reduced enjoyment of caretaking were associated with poorer quality of observed maternal care. Due to the cross-sectional nature of this study, it is difficult to determine whether the elevations across these measures preceded the development of maternal depression and behavioural differences in mother-infant interactions, or vice versa (e.g., with current parenting stress and maternal attitudes reflective of greater distress). Though we did not measure this directly, it is possible that the experience of childhood trauma and poorer quality of parental care during their own development predisposed these mothers to PPD and/or behavioural profiles that are less sensitive. Future studies should seek to better understand this relationship. It is also difficult to distinguish whether the behavioural and attitudinal difficulties reviewed here are derived from symptoms of the depression itself (e.g., anhedonia, low mood, lack of energy) or whether they represent actual difficulties in parenting behaviours experienced by these mothers, due potentially to lack of experience, reduced confidence in one’s parenting ability, etc. Future work should follow women with and without PPD longitudinally, to determine whether differences in parenting ability persist even after the mother’s depression has remitted. If they do persist, intervention programs can be developed to target training of specific aspects of mother-infant/child interactions (e.g., feeding, sleep routines, dressing, etc.).

4 Study 2: Postpartum Depression and Brain Response to Infants: Differential Amygdala Response and Connectivity

Postpartum depression (PPD) is the most common maternal birth complication (Ross et al., 2005). For approximately 15% of mothers this time period is accompanied by severe mood disturbance that meets the criteria for depression and includes symptoms such as irritability, uncontrollable crying, extreme sadness/hopelessness and sometimes thoughts of harm to self and to the baby (Cox et al., 1993; O'Hara & Swain, 1996; Beck, 2001; Halbreich & Karkun, 2006; Dennis et al., 2012; American Psychiatric Association, 2000). Despite its prevalence and pervasive impact on the developing infant (Halligan, et al., 2007; Murray, 1992; Pawlby et al. 2008), our understanding of the neural bases of PPD relies on only a few recent studies (Moses-
Kolko et al., 2010; Moses-Kolko et al., 2011; Silverman et al., 2007; Silverman et al., 2011; Moses-Kolko et al., 2012; Chase et al., 2013; Laurent & Ablow, 2013; Laurent & Ablow, 2012; see Barrett & Fleming, 2011; Swain et al., 2014; Moses-Kolko et al., 2014 for reviews). These studies have identified an inverse relation between PPD symptom severity and amygdala (AMY) response (Moses-Kolko et al., 2010; Silverman et al., 2011), and suggest that this AMY hyporesponsiveness may be pathognomonic for PPD.

With a known role in the processing of motivationally, emotionally and socially relevant stimuli (Adolphs, 2003; Adolphs et al., 2002; Cunningham & Brosch, 2012; Pessoa, 2010), it is not surprising that the AMY may play an important role in PPD and mothering, in general. Previous work in women without clinical depression has found that the AMY responds preferentially, or selectively, when mothers view their own compared to an unfamiliar infant (Leibenluft et al., 2004; Seifritz et al., 2003; Ranote et al., 2004; Barrett et al., 2012; Strathearn & Kim, 2013). As such, it appears that healthy mothers have an AMY that responds selectively to their own baby. Thus, it is possible that an AMY response which deviates from this pattern of response especially to images of infants, may be problematic for childrearing. In fact, work with other mammals suggests that species-typical maternal behavior is dependent upon normative AMY functioning (Fleming et al., 1980; Numan et al., 1993). Furthermore, work from our lab (Barrett et al., 2012) has demonstrated that infant-related AMY function is related to maternal anxiety, levels of distress during parenting, and individual differences in attitudes towards mothering. Conceivably, it is important to characterize whether and how infant-related AMY functioning differs in human mothers with PPD as compared to non-depressed mothers, and whether in PPD mothers, the AMY is differentially engaged with other brain regions during the processing of infant cues.

To date, negative non-infant stimuli have primarily been used to examine the neural correlates of PPD (e.g., Moses-Kolko et al., 2010; Moses-Kolko et al., 2011; Silverman et al., 2007; Silverman et al., 2011). Laurent & Ablow (2012) used negative infant stimuli for the first time, choosing to examine the brain response in mothers with depressive symptomology in the late postpartum stage (15-18 months) to infant cries. Although this work provides important first insights, for most mothers, infants represent motivationally relevant, positive stimuli. Relatedly, PPD is characterized by an altered emotional, cognitive and behavioral response towards a stimulus that is typically interpreted as rewarding (e.g., one’s own infant). The impact that this
disorder has on mothering abilities highlights the need to understand the neural response of mothers with PPD to positive infant stimuli, specifically, in comparison to other positive non-infant stimuli. It is also important to understand whether the pattern of brain response is specific to their own, or generalizable to all infants. Examining this may have implications for the treatment of PPD.

One recent study (Laurent & Ablow, 2013) examined the brain response in mothers with late postpartum stage depression (15-18 months) to positive pictures of their own infant as compared to positive pictures of an unfamiliar infant. They identified no group differences (PPD vs. Non-PPD). Numerous factors may explain these unexpected results. For example, PPD has a high rate of onset in the early postpartum period (Cox, Murray & Chapman, 1993) and depressive symptoms tend to remain elevated throughout the first postpartum year (Dennis et al., 2012). It is possible that brain differences in mothers with PPD may change across the postpartum period and that the authors may have failed to capture these mothers at their most vulnerable stage. Furthermore, the authors used a whole-brain approach to data analysis rather than an a priori hypothesis driven region-of-interest analysis. As much of the existing research indicates that there may be altered brain response in PPD in relatively small brain regions (e.g., the AMY), some of their results may have been masked due to the stringent corrections for multiple comparisons inherent to whole-brain analyses.

In contrast to the paucity of brain-related research on PPD, brain response differences in individuals with major depressive disorder (MDD) have been relatively well characterized. For instance, MDD is associated with negative biases in processing facial expressions and altered activity in emotion-related brain regions in response to emotional facial expressions (Gil et al., 2011; Arteche et al., 2011; Anand et al., 2005; Dannlowski et al., 2009), especially in limbic structures. More specifically, there is greater AMY response to emotional faces in individuals with MDD, and this AMY hyperresponsiveness is primarily for negative stimuli (Hamilton et al., 2012; Suslow et al., 2010; Victor et al., 2010). Thus, although both MDD and PPD are classified as depression, there appears to be a stark contrast between the AMY hyper-responsiveness to negative stimuli in studies of MDD and the hypo-responsiveness to negative stimuli observed in existing studies of PPD (Moses-Kolko et al., 2010; Silverman et al., 2011). As of yet, we do not know whether this paradox in brain response to negative stimuli (e.g., decreased in PPD and increased in MDD) will carry over into research with positive stimuli (e.g., increased in PPD and
decreased in MDD). Relative to MDD our understanding of the neurobiology of PPD is still in its ‘infancy’ and continued research into this contradictory AMY response is important given that the symptoms of the disorders overlap to such a large degree.

While previous work with nonclinical samples has suggested that the AMY may play a unique role in the processing of negative- or threat-related stimuli (see Phelps & LeDeoux, 2005), more recent work supports the notion that the AMY is also responsive to uncertainty (e.g., Whalen, 2007) and novelty (e.g., Balderston, Schultz & Helmstetter, 2011), regardless of the emotional valence of the stimuli. Thus, the AMY may play a role in relevance detection (Sander et al., 2003) based on the particular motivational state, goals and/or needs of the observer (see also Cunningham & Brosch, 2012). Throughout pregnancy, the postpartum period and continued motherhood, women are placed in a particularly unique motivational state to which infants and children serve as stimuli worthy of detection, sine qua non. Thus, we believe this proposed role for the AMY forms a particularly relevant foundation for reconciling the growing literature examining the brain response to various stimuli, infant and non-infant, positive and negative, in mothers with and without mood changes.

In addition to differences in mean level AMY responsivity, it is becoming increasingly clear that brain networks underlie many cognitive processes, and differential connectivity are associated with many forms of psychopathology. For instance, resting-state connectivity between the prefrontal cortex and AMY is reduced in depression (Chase et al., 2013; Zhang et al., 2014; Tang et al., 2013). Only one study has examined task-dependent (during viewing of negative adult faces) functional connectivity of mothers with PPD in the immediate postpartum period (Moses-Kolko et al., 2010). This study found decreased top-down dorsomedial prefrontal cortex-AMY effective connectivity in mothers with PPD. Although functional connectivity has been examined with mothers who vary in maternal responsiveness (Atzil et al., 2011), we do not yet understand, however, how task-dependent functional brain networks that covary with the AMY (Mayberg, 2003; Shafi et al., 2012) may be altered in mothers with PPD when they are viewing infant faces.

To address the above concerns, through fMRI, our study will be the first to examine 1) AMY response to positively valenced infant stimuli of varying familiarity, and to positively valenced non-infant stimuli; 2) functional connectivity using the AMY as a seed of interest, during the
viewing of infants and non-infant stimuli, in mothers with and without clinically determined PPD. First, in line with recent views that the normative functional role of the AMY includes assisting with both the identification of a salient stimulus and the convening of necessary resources for an adaptive response to said stimulus (Cunningham & Brosch, 2012), we hope to replicate the existing work from our lab (Barrett et al., 2012), as well as others (Leibenluft et al., 2004; Seifritz et al., 2003; Ranote et al., 2004; Strathearn & Kim, 2013) that shows that Non-PPD mothers show a preferential BOLD response in the AMY for their own, as opposed to another infant. Second, we predict that this preferential blood-oxygen-level dependent (BOLD) response for one’s own baby in the AMY in Non-PPD mothers will be blunted in mothers with PPD; This may be due to overall higher responsiveness to an unfamiliar infant, or to blunted responsiveness to one’s own infant. We also expect to see an altered pattern of task-based cortico-limbic connectivity in PPD compared to Non-PPD mothers. For example, it is possible that we will see decreased connectivity between the AMY and other brain regions important in affective processing or reward in mothers with PPD, compared to Non-PPD mothers. As work with other species demonstrates that parity or maternal experience is known to influence many aspects of mothering, including brain response (Featherstone, Fleming & Ivy, 2000; Scanlan, Byrnes & Bridges, 2006; Anderson, Grattan, van den Ancker & Bridges, 2006; Love et al., 2005), we will include this as a predictor in our analyses. For example, it is possible that multiparity, as compared to primiparity, will be associated with decreased AMY response (due to its proposed role in uncertainty detection), but overall enhanced connectivity between the AMY and other brain regions known to be important in affective or reward processing during the viewing of infant cues, as these connections may be strengthened with greater maternal experience.

4.1 Abbreviated Methods

Our study population consisted of mothers, 2-5 months postpartum, with (n=28) and without (n=17) PPD, as determined by diagnostic interview (CIDI-V), who are 20-40 years of age, with singleton, full-term babies. Using fMRI (GE 3-T scanner), all mothers viewed smiling pictures of infants in a block design (3 conditions: Own, Other and Non-Infant; see Figure 3 for summary). We first used an ROI approach, examining only the AMY, followed by psychophysiological interaction (O’Reilly et al., 2012) using the AMY as a seed for all connectivity analyses during the viewing of Own-Other infant stimuli. We then correlated
connectivity parameters with measures of mood (EPDS score) and trait anxiety (STAI-T). We also examined the potential mediating factor of maternal experience, or parity.

4.2 Results

4.2.1 Subject Characteristics

Fifty-four mothers completed the study, however 9 mothers were excluded from analyses due to high movement during the fMRI (>2mm); the current results represent data from 17 Non-PPD mothers and 28 PPD mothers. Maternal age and education, as well as delivery method, parity, and breastfeeding status were not significantly different across Non-PPD and PPD mothers (see Table 2). Other than parity (discussed subsequently), these variables did not contribute to the models discussed below, and were thus excluded from analyses. From a multivariate ANOVA PPD mothers reported significantly higher depressive symptomology (EPDS $F(1, 43) = 14.403, p = .001$) and trait anxiety (STAI-T$F(1, 43) = 45.952, p = .001$; Table 2). Although eleven PPD mothers were taking SSRI medication, EPDS and STAI-T scores for PPD mothers did not differ based on medication status (SSRI vs. no medication; EPDS $F(1, 26) = 1.180, p = .287$ and STAI-T $F(1, 26) = .758, p = .392$).

4.2.2 ART

During the ART, all mothers reported that they feel more positive when they are viewing their Own compared to Other infants or Non-Infant pictures ($F(1, 43) = 75.405, p = .001$). There were no group differences in this self-reported experience of positivity across conditions ($F(1, 43) = .733, p = .397$; Figure 10); PPD mothers and Non-PPD mothers all report experiencing the same degree of positive affect when they view pictures of Own, Other and Non-Infant stimuli.

4.2.3 ROI Analysis

**Non-PPD Mothers.** As shown in Figure 11a, average BOLD response in the bilateral AMY in mothers without PPD was greater for OwnView-OtherView (right AMY: 190 voxels, $p = 0.00473, z = 3.65$, peak $x = 24, y = -2, z = -14$; left AMY: 63 voxels, $p = 0.039, z = 3.12$, peak $x = -24, y = -4, z = -12$). There were no differences in AMY response to OtherView-NonInfantView.
PPD Mothers. Average BOLD response in PPD mothers was greater for OwnView-OtherView only in the right AMY (87 voxels, $p = 0.0246$, $z = 3.76$, peak $x = 26$, $y = 0$, $z = -12$; see Figure 11b). There were no differences in AMY response to OtherView-NonInfantView.

Group-Level. No group differences (e.g., both PPD>Non-PPD and/or Non-PPD>PPD) were observed for our contrasts of interest: OwnView-OtherView or OtherView-NonInfantView. With respect to condition-level differences, there were no group differences in average BOLD response for OwnView in Non-PPD compared to PPD mothers. However, in comparison to Non-PPD mothers, PPD mothers demonstrate increased BOLD response to OtherView (105 voxels, $p = 0.0173$, $z = 3.06$, peak $x = 24$, $y = -8$, $z = -18$; see Figure 12a) and to NonInfantView (54 voxels, $p = 0.0472$, $z = 3.24$, peak $x = 26$, $y = 0$, $z = -14$; see Figure 12b) in the right AMY. Thus, when BOLD response is collapsed across all conditions (OwnView, OtherView and NonInfantView), PPD mothers show an overall increased response in the right AMY (78 voxels, $p = 0.0291$, $z = 3.44$, peak $x = 28$, $y = -2$, $z = -12$; see Figure 12c). Medication status was used as a covariate in the model.

Parity. There was a marginal Parity x Group interaction for bilateral AMY response to OwnView (right AMY: $F(1, 41) = 3.72$, $p = .061$; left AMY: $F(1, 41) = 3.315$, $p = .076$; see Figure 13). While there was no group difference in AMY response in primiparous mothers, multiparous PPD mothers had greater bilateral AMY response than Non-PPD multiparous mothers. In other words, AMY response appears to decrease with experience in Non-PPD mothers, but increase with experience in PPD mothers. There were no group differences in AMY response to OtherView or NonInfantView by maternal experience. These findings should be considered exploratory, as they are derived from a small sample of multiparous (Non-PPD n = 5, PPD n = 10) relative to primiparous (Non-PPD n = 12, PPD n = 18) women, in the Non-PPD sample, in particular.

4.2.4 PPI Analysis

Group-Level. Although we observed group-level ROI differences in the right AMY, but not the left AMY, BOLD response differences do not always predict connectivity differences. Furthermore, our a priori hypothesis did not predict this laterality effect. As such, we proceeded to examine both right and left AMY connectivity differences with PPI. During OwnView-OtherView, at cluster corrected $p < .05$ ($z = 2.3$), controlling for medication status, Non-PPD
mothers showed *increased* connectivity between the bilateral AMY and the right insular cortex (IC), whereas PPD mothers show *decreased* AMY-IC connectivity (right AMY-right IC: 933 voxels, \( p = 0.000244, z = 3.83, \) peak \( x = 54, y = -10, z = 4 \); left AMY-right IC: 534 voxels, \( p = 0.0239, z = 3.29, \) peak \( x = 34, y = 8, z = 14 \); see Figure 14). There were no group differences in connectivity with the left or right AMY during OtherView-NonInfantView.

**Parity.** From a repeated measures ANOVA with group (Non-PPD vs. PPD) and parity (primiparous vs. multiparous) between subjects factors and bilateral AMY to IC connectivity within subjects factors, an interaction between group and parity is observed \( (F(1, 41) = 5.617, p = 0.023) \). Although AMY-IC connectivity is low in PPD mothers, regardless of the amount of parenting experience they have (e.g., low in both primiparous and multiparous mothers), in Non-PPD mothers, AMY-IC connectivity increases with maternal experience (e.g., multiparous > primiparous; see Figure 15). These findings should be considered exploratory, as they are derived from a small sample of multiparous (Non-PD n = 5, PPD n = 10) relative to primiparous (Non-PPD n = 12, PPD n = 18) women, in the Non-PPD sample, in particular.

### 4.2.5 Correlations

**Non-PPD Mothers.** As can be seen in Table 6, EPDS scores were negatively correlated with left AMY response to OtherView-NonInfantView \( (r = -.59, p = .013) \) and positively correlated with left AMY response to NonInfantView \( (r = .71, p = .001) \). STAI-T scores were also negatively correlated with left AMY response to OtherView-NonInfantView \( (r = -.59, p = .013) \). In other words, more anxious mothers within the non-PPD group tended to show reduced Other Infant-NonInfant differences in BOLD response in left AMY. We also observed a negative correlation between STAI-Trait and left AMY response for OwnView \( (r = -.54, p = .026) \) and OtherView \( (r = -.50, p = .039) \). Hence, greater trait anxiety is associated with reduced left AMY response to babies (both own and other) in Non-PPD mothers. There were no significant correlations between right AMY response to our conditions of interest and EPDS or STAI-T.

ART ratings made by Non-PPD mothers during the fMRI for their own infant were not significantly correlated with bilateral AMY response to OwnView or OwnView-OtherView. However, ART ratings for other infants were positively related to bilateral AMY response for the contrast OwnView-OtherView \( (r = .49, p = .046) \). This suggests that mothers who show a larger
differential AMY response to their own infant (e.g., greater own-other difference in the AMY) report higher positivity ratings for ‘other’ infants.

**PPD Mothers.** As shown in Table 6, EPDS scores were positively correlated with left AMY response to NonInfantView (r = .39, p = .043). There were no other significant correlations between EPDS or STAI-T and bilateral AMY response to our contrasts or conditions of interest. There were no significant correlations between ART ratings to Own or Other infants and AMY response in mothers with PPD.

**All Mothers.** EPDS scores were positively correlated with right AMY (r = .45, p = .002) and left AMY (r = .49, p = .001) response to NonInfantView. We also observed a positive correlation between STAI-T scores and right AMY response to OtherView (r = .3, p = .045). There were no significant correlations between ART ratings to Own or Other infants and AMY response in mothers with PPD.

**Connectivity Analysis.** AMY-right IC connectivity parameters were negatively correlated with both EPDS (right AMY-right IC: r = -.339, p = .023; left AMY-right IC: r = -.411, p = .005; Figure 16) and STAI-T (right AMY-right IC: r = -.501, p = .001; left AMY-right IC: STAI-T r = -.548, p = .001; Figure 16). This suggests that increasing depressive symptomology and trait anxiety are related to decreasing AMY-right IC connectivity. AMY-right IC connectivity was not correlated with ART scores.

### 4.3 Discussion

The first goal of the current study was to replicate our and others’ previous work showing preferential AMY responsiveness to one’s own as compared to another infant’s face (Leibenluft et al., 2004; Seifritz et al., 2003; Ranote et al., 2004; Barrett et al., 2012; Strathern & Kim, 2013). Indeed, we identified enhanced bilateral AMY response when Non-PPD mothers view their own versus other infants. This effect has been replicated in similar studies that demonstrate enhanced AMY response to personally relevant faces (e.g., partner faces (Taylor et al., 2009)). The AMY is a brain region known to play a critical role in socioemotional processing (Adolphs, 2003; Adolphs et al., 2002; Pessoa, 2010) and maternal behavior (Fleming et al., 1980; Barrett & Fleming, 2011). Recently, Cunningham and Brosch (2012) have conceptualized the AMY as an early part of an affective system responsible for identifying important environmental stimuli and
facilitating appropriate responding to said stimuli. One’s own infant represents a particularly salient environmental stimulus for the recently postpartum mother. This saliency appears to be manifest at the neural level through enhanced AMY response.

Next, we sought to examine whether this specificity effect is conserved in mothers with PPD. For the first time, we found that PPD mothers do, in fact, show a preferential response in the right AMY to their own as compared to an unfamiliar infant. As such, all mothers, regardless of depression status, show greater BOLD response in the AMY for their own infant compared to an unfamiliar infant. This increased BOLD response for one’s own infant in the AMY is interesting in the context of findings by Kim et al. (2010) which identified increased AMY volume across the early postpartum period as associated with enhanced positive perception of one’s baby. Although these findings may appear contrary to existing fMRI studies that find blunted activation in the AMY in PPD mothers (Moses-Kolko et al., 2010; Silverman et al., 2011), the current study differs in a notable way. Rather than using negative stimuli (e.g., words, adult faces), we utilized stimuli that are positively salient and specific to the motivational state of the observer: positive pictures of babies - specifically, one’s own baby. Facial expressions are a primary means of communicating emotion for a developing infant and they are known to elicit infant-directed gaze from the mother (Klaus et al., 1975; Yale et al., 2003; Colonnesi et al., 2012). This relationship indicates that infant visual stimuli elicit maternal arousal and may reflect maternal motivation. In line with recent theories of AMY functioning as being involved in novelty (Balderston, Schultz & Helmstetter, 2011), uncertainty (Whalen, 2007) and relevance detection based on the particular motivational state, goals and/or needs of the observer (Cunningham & Brosch, 2012) it is possible then, that negative stimuli are not motivationally salient enough to engage the AMY in a PPD population.

Interestingly, from group analyses, while we observe no differences between PPD and Non-PPD mothers in their AMY BOLD response to their own infant, we do see an overall enhanced response to both other as well as non-infant stimuli in the right AMY in PPD mothers. In other words, while the unique response to own infant is preserved in mothers with PPD, they show a ramping up of AMY response to all other positive stimuli, both infant and non-infant. It is possible that the enhanced right AMY response we observed in mothers with PPD to all stimuli represents a generally enhanced or even dysregulated arousal/vigilance for salient stimuli. Although this study was designed to examine differences between clinical and non-clinical
depression, anxiety is also a prominent feature of PPD. Importantly, in addition to depressive symptomology, the mothers in our PPD group also reported elevated trait anxiety, as compared to Non-PPD mothers. Future studies should seek to tease apart the degree to which these findings may be related to symptoms of depression, anxiety or both.

During the fMRI, mothers in the current study were instructed to think about and rate how they felt when viewing pictures of infants and other positive stimuli. All mothers, regardless of depression status, reported feeling most positive when viewing their own infant. Thus, the increased AMY we observed in the current study occurred in the absence of self-reported differences during the rating task. Notably, BOLD response does not necessarily map onto behavioural response; we cannot assume that increased signal in a particular brain region will be associated with behavioural changes. In fact, from our ART results, we did not observe a correlation between ratings in the scanner and BOLD response in the AMY. Rather, we observe the opposite in Non-PPD mothers: the more positive they rate pictures of other babies, the more preferential their BOLD response is for their own baby in the left AMY. Thus, in Non-PPD mothers, the specificity of the response (high for own baby, low for other baby), rather than the average activation, appears to relate to self-reported positive affectivity when viewing the pictures. This relationship was absent in PPD mothers. Further studies should seek to clarify whether the increased BOLD response to all positively salient stimuli in PPD mothers is reflected in other behavioural measures, such as those obtained from mother-infant interactions. Knowing how a depressed mother’s brain responds to infant stimuli is critical as the symptoms of PPD impact the mother-infant dyad and often involve excessive worry or guilt surrounding parenting abilities (Ross et al., 2005). Relatedly, mothers with PPD typically display an altered pattern of behavioural interaction with their infants (e.g., more intrusive and irritated and less sensitive and contingent (Murray et al., 1996; Cohn et al., 1990; Stanley, Murray & Stein, 2004; Fleming et al., 1988)). Knowing this, it will be important for future studies to investigate how these differences relate to brain response to infants in mothers with and without PPD.

The second major goal of the current study was to investigate whether the pattern of connectivity between the AMY and other brain regions is altered in mothers with PPD.

Using task-based AMY connectivity in PPD and Non-PPD mothers we found that AMY-right IC functional connectivity, brain regions with strong reciprocal anatomical connections, is enhanced
when Non-PPD mothers are viewing their own compared to another infant, but decreased in PPD mothers. Furthermore, this connectivity pattern is positively correlated with both depressive symptomology and trait anxiety. The dorsal posterior IC has been conceptualized as the primary interoceptive cortex, responsible for representing the physiological sense of one’s body (Craig, 2002). The right anterior IC is important for representing one’s internal state (Craig, 2009) and is activated in tasks that measure subjective emotional awareness, in particular, studies that assess recall of sadness (Mayberg et al., 1999), anger (Damasio et al., 2000), anxiety (Benkelfat, et al., 1995), pain (Ploghaus et al., 1999) disgust (Phillips et al., 1997) and other aspects of emotional awareness (see Craig, 2002 for summary). Researchers have proposed that the representation of the physiological condition of the body in the insular cortex serves as the neural substrate for these subjective feelings and emotions (Craig, 2002; Craig, 2009). This role of the IC is of particular relevance to PPD as self-perceived maternal health was recently identified as the strongest risk factor for persistent PPD (Dennis et al., 2012), and anxiety and parenting stress are common postpartum (Miller et al., 2006). It is also interesting in the context of the current study instructions ('think about how you feel when viewing these pictures'). Non-postpartum mood disorders have been associated with decreased anterior IC volume (Takahashi et al., 2010), decreased IC activity during interoception (Avery et al., 2014) and altered IC BOLD response following a variety of treatments (see McGrath et al., 2013). Additionally, altered connectivity between the IC and limbic structures important for fast processing of emotional stimuli, such as the AMY (Ramasubbu et al., 2014; Manoliu et al., 2014), and more prefrontal regions thought to be important in guiding motivated actions, such as the anterior cingulate cortex (Connolly et al., 2013) has been identified in individuals with major depressive disorder (see Drevets, Price & Furey, 2008 for review).

The insular cortex has been proposed as a brain region involved in the physiological pathway underlying the negative or overly catastrophic evaluations of the sensations in one’s body often observed in anxiety disorders (Paulus & Stein, 2006). More specifically, Paulus and Stein (2006) propose that there may be a mismatch between observed and expected body states in individuals with anxiety disorders, which can result in cognitive and behavioural compensatory mechanisms (e.g., worrying and avoidance, respectively), and that this process may be related to IC functioning. As aforementioned, while the goal of this study was to examine clinical depression, anxiety is also common in the postpartum period and is a prominent feature
of PPD. Furthermore, the PPD and Non-PPD mothers in this study report significant differences in levels of trait anxiety. Preliminary analyses (Wonch et al., in prep) indicate that a similar pattern of findings are observed if individual differences in anxiety are used to predict connectivity, rather than PPD diagnostic grouping. Given the striking differences in AMY-right IC connectivity observed here in the context of increased self-reported trait anxiety, future studies should seek to clarify the unique influence of both depression as well as anxiety.

Interestingly, we also found that AMY-right IC connectivity increased with maternal experience in Non-PPD mothers, a pattern that was not observed in PPD mothers. Although this finding was not anticipated, it is consistent with our conceptualization of AMY-IC functionality. If the AMY is thought to play a role in rallying together appropriate recourses to respond to emotionally salient or intense environmental stimuli (Cunningham & Brosch, 2012), one could hypothesize that increasing connectivity between this brain region and the IC, important for representing the physiological state of the body to guide subjective emotional experience (Craig, 2002), would increase with parental experience. Interestingly, we observed this in the context of a marginal difference based on parity in overall BOLD response in the AMY; while there was no group difference in AMY response in first time mothers, multiparous PPD mothers had marginally greater bilateral AMY response as compared to multiparous Non-PPD mothers. In other words, despite increased overall BOLD response in the AMY in multiparous PPD mothers, they do not show increased AMY-right IC connectivity. To our knowledge, this is the first report of altered response and functional connectivity in mothers as a function of their parity status. However, it is important to note that the current study was not designed to test this hypothesis directly. Further studies should continue to investigate the role of the AMY in maternal experience in mothers with and without PPD. For example, by examining unique contributions of AMY subregions (see for example with anxiety, Etkin et al., 2009).

As research with MDD indicates that AMY hyperresponsivity to negative stimuli may be a trait-like characteristic of the disorder (Price & Drevets, 2010), studies with PPD postulate that AMY hyperresponsiveness to negative stimuli may be pathognomonic of PPD (Silverman et al., 2011). Although, this is the first study to examine AMY response to positive stimuli in PPD, recent studies with MDD suggest that AMY response is decreased in response to positive stimuli (Stuhrmann et al., 2013). It is interesting, then, that we again find the opposite pattern of AMY responsivity in PPD (increased to positive stimuli in the right AMY rather than decreased,
similar to what is seen with MDD). The present findings add to the literature examining the brain response of PPD mothers to emotional stimuli. They also support the notion that PPD may be phenotypically distinct from MDD. Future research should seek to compare directly how the AMY and other brain regions important in monitoring affective stimuli (e.g., the salience network and/or affective network (Menon & Uddin, 2010; Price & Drevets, 2010), respond to both positive as well as negative stimuli, infant and non-infant, in mothers with PPD.

Depression is not the only mental health concern faced by mothers during pregnancy and/or the postpartum period; many mothers also experience clinically relevant symptoms of anxiety, substance abuse and/or trauma (see Moses-Kolko et al., 2014 for review). Studies that examine the pattern of brain activity in mothers with other forms of maternal psychopathology have also identified altered AMY responsivity. For example, Kim, Fonagy, Allen & Strathearn (2014) identified decreased AMY response to infant distress cues in mothers with unresolved trauma. Important future insights may come from studies that measure overlapping symptomology of these disorders and examining how these relate to brain function in regions known to be important for regulating affect, reward and even memory.

Top-down effective connectivity between the prefrontal cortex and AMY during the viewing of negative adult faces has been shown to be decreased in PPD mothers (Moses-Kolko et al., 2010). Thus, it is interesting that we also observed decreased functional connectivity between the IC, a region so strongly implicated in interoception and subjective emotional awareness (Craig, 2002), and the AMY specifically when PPD mothers view pictures of their own infant. Given this, together with previous reports of decreased AMY response to threatening words (Silverman et al., 2007), future research should examine how the brains of mothers with PPD process both threatening and rewarding infant and non-infant stimuli, and relate this to actual mothering behavior. Future studies should also seek to clarify whether the decreased AMY-IC connectivity observed here in PPD mothers reflects increased or dysregulated bottom-up influence of the AMY on the IC. The frequency with which PPD occurs as well as the potential for negative consequences for the developing infant underscore the need for continued research into its neurobiological substrates.
5 Study 3: Amygdala Subregion Response and Connectivity in Mothers With and Without Postpartum Depression

Consistent with rodent studies demonstrating that amygdala (AMY) lesions can affect the expression and/or quality of maternal behavior (Fleming et al., 1980; Numan et al., 1993; see Numan, 2006; Olazabal et al., 2013 for reviews of the neurobiology of rodent maternal behaviour), a growing body of research has identified a role for the AMY in affective features of human mothering, specifically, while processing infant stimuli. Amygdala activation to infant cues has frequently been demonstrated using passive viewing paradigms in fMRI where new mothers view pictures or videos of their own, familiar or unfamiliar infants (Barrett et al., 2012; Leibenluft et al., 2004; Ranote et al., 2004; Strathearn & Kim, 2013; Wonch et al., 2016). Typically in this work, the human AMY shows increased BOLD response for one’s own as compared to an age matched unfamiliar infant. This differential AMY responsiveness to one’s own infant has also been related to measures of trait anxiety, parental distress and self-reported maternal attachment (Barrett et al., 2012). Together, this suggests that the human AMY may play a vital role in maternal mood and in the motivation to mother.

Many new mothers experience mood changes postpartum. For approximately 15% of new mothers, these mood changes persist for at least two weeks and include low mood, anhedonia, feelings of guilt surrounding one’s ability to parent a new child and more, meeting the criteria for postpartum depression (PPD; Ross et al., 2005; Cox et al., 1993; O'Hara & Swain, 1996; Beck, 2001; Halbreich & Karkun, 2006; Dennis et al., 2012; American Psychiatric Association, 2000). While common, PPD is still understudied from a neurobiological perspective. Recent work from our laboratory has shown that mothers with PPD display the same differential responsiveness in the AMY (specifically, the right AMY) when they view their own versus an unfamiliar infant that, as aforementioned, has been well-documented in non-depressed mothers (Wonch et al., 2016). PPD mothers also appear to demonstrate an overall enhanced AMY response to all positive stimuli (e.g., familiar and unfamiliar infants as well as non-infant stimuli; Wonch et al., 2016) but an overall blunted AMY response to negative stimuli (e.g., words (Silverman et al., 2007; Silverman et al., 2011) or faces (Moses-Kolko et al., 2010)).
Despite this overall increased right AMY response in PPD relative to Non-PPD mothers to positive stimuli, we also found that PPD mothers showed decreased AMY to right insular cortex connectivity during the viewing of their own versus an unfamiliar infant (Wonch et al., 2016). Furthermore, AMY to right insular connectivity was negatively correlated with measures of trait anxiety and postpartum depressive symptomology, where enhanced symptoms of anxiety and depression were related to reduced connectivity (Wonch et al., 2016). This work is particularly unique, as it investigated task-related connectivity in the human AMY in new mothers using stimuli that was specific to the motivational-state of the subject (e.g., infants). As such, these findings represent important first insights into how the AMY, known for its role in the processing of socially salient stimuli, may interact with other brain regions important in processing socially/emotionally salient cues (e.g., the insula), when new mothers who experience mood changes postpartum.

Until recently, due to limitations in statistics and spatial resolution, the human AMY has typically been discussed as a unified, homogeneous structure in the human fMRI literature. However, the AMY is, in fact, a heterogeneous structure, comprised of various subnuclei. Animal work shows quite clearly that different components or nuclear groups within the amygdala are affecting mothering in different ways (Numan et al., 2010; Morgan et al., 1999; Numan, Numan & English, 1993). At least three anatomically and functionally distinct sub regions have been most frequently investigated in humans: the basolateral (BL), centromedial (CM) and superficial (SF) amygdala. A recent, comprehensive review utilized meta-analytic connectivity-based parcellation mapping to investigate the role of the BLA, CMA and SFA in the existing human neuroimaging literature (Bzdok et al., 2013). They found that they BLA tends to be associated with coordinating higher-level sensory input and significance detection, the CMA is associated with mediating attentional, vegetative and motor responses and the SFA is associated with olfactory and social information processing. These subnuclei have also been shown to be differentially involved in the processing of emotional face stimuli in anxious individuals (Etkin et al., 2004; Etkin et al., 2009).

In rodents, two subregions, the BLA and CMA, have primarily been investigated. These subregions have been shown to play unique roles in species-typical maternal behavior. For example, the BLA is believed to play an excitatory role in maternal behaviour. Recent research by Numan and colleagues hypothesizes that the BLA influences appetitive, but not
consummatory aspects of mothering by relaying pup-related sensory inputs to the nucleus accumbens/ventral pallidum reward circuitry. They demonstrated that disrupting activity of the BLA reduces goal-directed maternal responses (e.g., retrieval behavior), but not consummatory maternal responses (e.g., nursing) (Numan et al., 2010). Lee, Clancy, & Fleming, (2000) found BLA lesions disrupted not only pup retrieval, but also licking, as well as operant responses to gain access to pups. CMA, on the other hand, is thought to play an inhibitory role in maternal behavior. Virgin rodents, animals who have never been mothers, are typically neophobic; pup-related stimuli initiate avoidance responses in these animals. Fleming and colleagues have demonstrated that lesions to the CMA encourage the onset of maternal behaviour in virgin animals (Fleming, Vaccarino, & Luebke, 1980; Fleming, Miceli, & Moretto, 1983; Oxley & Fleming, 2000). Furthermore, they demonstrate that, in animals that have maternal experience, lesions to the CMA do not disrupt the typical repertoire of maternal behaviour (Akbari et al., 2007).

In the current study, using fMRI, we will investigate, for the first time, whether the BLA, CMA and/or SFA respond differentially in new mothers to positive pictures of their own as compared to an unfamiliar infant. While this work is exploratory, the following predictions have been made, given our understanding of the unique roles of each of these subregions from both human and non-human studies. With respect to the BLA, we predict that our results will mimic this region’s proposed excitatory role in rodent maternal behavior. In other words, we expect to see greater BOLD response in the BLA when mothers view their own as compared to an unfamiliar infant. Given the proposed role for the SFA in social processing (Bzdok et al., 2013), we may once again observe greater BOLD response in the SFA when mothers view positive pictures of their own, as compared to an unfamiliar infant. The behaviour of the CMA is somewhat less predictable. Rodent work suggests that the CMA plays an inhibitory role in maternal behavior, and as such, we may observe greater BOLD response for an unfamiliar infant as compared to one’s own infant. We may also observe a blunted differential responsiveness for one’s as compared to an unfamiliar infant. Alternatively, we may observe a greater BOLD response in the CMA for own as compared to other infants, due to its role in guiding attentional and motor responses (see Bzdok et al., 2013 for review). We will also examine whether the aforementioned predicted effects in mothers without PPD are mirrored in mothers with PPD. As previous studies have found similar AMY response in mothers with and without PPD, with
overall enhanced AMY response to all stimuli in PPD mothers (Wonch et al., 2016), we predict that we will not observe strong group differences at the region-of-interest (ROI) level.

Nevertheless, from our previous work (Wonch et al., 2016), we understand ROI-level differences do not always predict connectivity-level differences. As such, we will also investigate task-based connectivity differences in mothers with and without PPD when they are viewing infant stimuli, using the three AMY subregions as seeds. Here, we predict that mothers without PPD will show overall greater connectivity between the AMY subregions and a network of brain regions important in affective and reward processing, as compared to mothers with PPD. We expect to observe both overlapping and distinct connectivity patterns between the three subregions. For example, we may observe blunted connectivity in mothers with PPD when they view their own compared to another infant between these AMY subregions in other brain regions involved in interpreting the hedonic quality of stimuli and affective states (e.g., orbitalfrontal cortex (OFC), pregenual and posterior cingulate, temporal and striatal regions; Fitzgerald et al., 2008) and the strength of connectivity may vary by subregion. We expect to observe overlapping connectivity in the insular cortex, specifically, as this was observed in our previous work that examined the Amy as a whole (Wonch et al., 2016).

As with Wonch et al. (2016), in order to determine specificity of the response, BOLD response to other positive, non-infant stimuli was also examined. AMY response to these other, non-infant stimuli will then be contrasted with BOLD response to unfamiliar, positive infant stimuli. With respect to stimulus type, rather than familiarity, we might expect regions in the medial temporal lobe to be differentially connected to these amygdala subregions in response to infant, but not non-infant stimuli, as the medial temporal lobe is known to differentially respond to faces compared to objects (Barense, Henson and Graham, 2011). We may also expect to see differences in brain regions typically involved in processing meaningful stimuli, such as the perirhinal cortex, hippocampus and fusiform face area (e.g., Barense, Henson and Graham, 2011; Van Bavel, Packer & Cunningham, 2011).

5.1 Abbreviated Methods

Our study population consisted of mothers, 2-5 months postpartum, with (n=28) and without (n=17) PPD, as determined by diagnostic interview (CIDI-V), who are 20-40 years of age, with singleton, full-term babies. Using fMRI (GE 3-T scanner), all mothers viewed smiling
pictures of infants in a block design (2 conditions of current interest: OwnView and OtherView; see Figure 3 for summary). The human AMY is comprised of three functionally distinct subregions: basolateral (BLA, sensory integration), centromedial (CMA, attentional reallocation) and superficial (SFA, socially-relevant processing). We predict that there will be subregion-level differences in AMY connectivity between PPD and Non-PPD mothers. We first used an ROI approach, examining only the three AMY subregions (BLA, CMA and SFA), followed by three separate psychophysiological interaction (O’Reilly et al., 2012) analyses using the AMY subregions as seeds, during the viewing of Own-Other infant stimuli. We also examined the potential mediating factor of maternal experience, or parity.

5.2 Results

5.2.1 Subject Characteristics

Fifty-four mothers completed the study, however 9 mothers were excluded from analyses due to high movement during the fMRI (>2mm); the current results represent data from 17 Non-PPD mothers and 28 PPD mothers. Maternal age and education, as well as delivery method, parity, and breastfeeding status were not significantly different across Non-PPD and PPD mothers (see Table 2). From a multivariate ANOVA PPD mothers reported significantly higher depressive symptomology (EPDS ($F(1, 43) = 14.403, p = .001$)) and trait anxiety (STAI-T ($F(1, 43) = 45.952, p = .001$); Table 2). Although eleven PPD mothers were taking SSRI medication, EPDS and STAI-T scores for PPD mothers did not differ based on medication status (SSRI vs. no medication; EPDS $F(1, 26) = 1.180, p = .287$ and STAI-T $F(1, 26) = .758, p = .392$).

5.2.2 ROI Analysis

As with Study 2, a region-of-interest approach was first used to examine the potential for subregion differences in the pattern of AMY response to the viewing of one’s own and other infant. Each of the three AMY subregions (BLA, CMA and SFA) were first examined independently for the following two contrasts: OwnView-OtherView and OtherView-NonInfantView. Next, separate repeated measures ANOVAs were conducted to investigate potential differences in the Left and Right AMY subregion BOLD response for our contrasts of interest (e.g., OwnView-OtherView and OtherView-NonInfantView) in mothers with and without PPD. Subregion (BLA, CMA and SFA) served as the within subjects factor and Group
(Non-PPD and PPD) served as the between subjects factor for each ANOVA (Left OwnView-OtherView, Right OwnView-OtherView, Left OtherView-NonInfantView and Right OtherView-NonInfantView). As aforementioned, ROIs were determined using the Amunts et al. (2005) subregions. Medication status was controlled for in all analyses.

In order to demonstrate that the BLA, CMA and SFA ROIs are indeed measuring unique, subregion specific BOLD signal, average BOLD response during all conditions combined (OwnView, OtherView and NonInfantView) for each subregion, bilaterally, was extracted and means were compared using paired sample t-tests in SPSS. Average BLA response for all conditions \( (M = 11.805, \ SD = 15.916) \) was marginally different from average CMA response for all conditions \( (M = 7.972, \ SD = 8.658; \ t(44) = 1.845, \ p = .072) \). Average BLA response for all conditions was significantly different from average SFA response for all conditions \( (M = 16.657, \ SD = 18.181; \ t(44) = -3.025, \ p = .04) \). Average CMA response for all conditions was significantly different from average SFA response for all conditions \( (t(44) = -4.234, \ p = .001) \). While the difference between BLA and SFA must be interpreted with some caution, as the effect was only marginal, it was assumed that the BLA, CMA, and SFA were, indeed, measuring unique, subregion specific BOLD response.

**Non-PPD Mothers.** As shown in Figure 17, average BOLD response in the bilateral BLA is greater for OwnView than OtherView for both right \( (p = 0.00345) \) and left \( (p = 0.0455) \) BLA right \( (p = 0.00885) \) and left \( (p = 0.0217) \) CMA and right \( (p = 0.01) \) and left \( (p = 0.0254) \) SFA. There were no subregion differences (e.g., BLA, CMA and SFA) in the BOLD response for the contrast OwnView-OtherView. Average BOLD response within the BLA, CMA or SFA was not different for OtherView as compared to NonInfantView, nor were there any differences between subregions. Depicted in Figure 18a and Figure 18b are peak activation differences for visualization, only.

**PPD Mothers.** There were no differences in average BOLD response in the bilateral BLA for OwnView as compared to OtherView. However, the average BOLD response in the bilateral CMA (right \( p = 0.0217 \); left \( p = 0.0121 \)) and bilateral SFA (right \( p = 0.0135 \); left \( p = 0.0413 \)) are greater for OwnView than OtherView (see Figure 18). There were no differences between subregions (e.g., BLA, CMA and SFA) in the BOLD response for OwnView as
compared to OtherView. There are no differences in the average BOLD response for OtherView as compared to NonInfantView in the bilateral BLA, CMA or SFA.

**Group Level.** There were no group differences (Non-PPD vs. PPD) in BOLD response for OwnView-OtherView or OtherView-NoninfantView in the BLA, CMA and/or SFA. Furthermore, there no significant interactions between Subregion and Group, bilaterally, for either contrast of interest.

**Parity.** From a repeated measures ANOVA, with predictors and outcomes as described above, parity was entered as a covariate. There was no effect of parity on the model.

### 5.2.3 PPI Analysis

**Group-Level.** In order to further examine the impact of motion on the group differences, discussed subsequently, group differences (PPD vs. Non-PPD) in both absolute and relative total motion were examined using separate univariate ANOVAs in SPSS. No significant group differences in absolute or relative motion were found.

Although we observed no significant group (Non-PPD vs. PPD) differences or interactions between subregion and group at the ROI level, as we have recently demonstrated (Wonch et al., 2016), ROI differences do not always predict connectivity differences. As such, we proceeded to investigate connectivity-level effects in the right and left BLA, CMA and SFA using PPI (see general methods). The results are summarized subsequently, as well as in Table 7 and Figure 19. Please note that depicted in Figure 19a-e are average parameter estimates for the clusters showing a significant group difference in connectivity with each AMY subregion. All effects are cluster corrected $p < .05$ ($z=2.3$), controlling for medication status. **BLA.** During OwnView-OtherView, Non-PPD mothers, as compared to PPD mothers, showed increased connectivity between the right BLA and regions of the bilateral insula/superior temporal gyrus, precuneus/posterior parietal lobe, temporal/parietal junction and the ventral striatum (extending to right orbitofrontal cortex; Figure 19a.). Non-PPD mothers also showed increased connectivity between the left BLA and regions of the bilateral insula/superior temporal gyrus extending posterior to the superior parietal lobule (Figure 19b). In contrast, no brain regions showed increased connectivity with the bilateral BLA in PPD mothers, as compared to Non-PPD mothers. Furthermore, no brain regions showed group differences in connectivity with the
bilateral BLA during the contrast OtherView-NonInfantView. **CMA.** During OwnView-OtherView, Non-PPD mothers, as compared to PPD mothers, showed increased connectivity between the right CMA and regions of the right insula/superior temporal gyrus and precuneus/posterior parietal lobe (Figure 19c). There were no group connectivity differences observed for the left CMA. In contrast, no brain regions showed increased connectivity with the bilateral CMA in PPD mothers, as compared to Non-PPD mothers. Furthermore, no brain regions showed group differences in connectivity with the bilateral CMA during the contrast OtherView-NonInfantView. **SFA.** During OwnView-OtherView, Non-PPD mothers, as compared to PPD mothers, showed increased connectivity between the right SFA and regions of the bilateral insula extending to the temporal/parietal junction, as well as the precuneus/posterior cingulate cortex (Figure 19d). Non-PPD mothers also showed increased connectivity between the left SFA and regions of the bilateral insula/superior temporal gyrus extending to the inferior parietal lobule (Figure 19e). In contrast, no brain regions showed increased connectivity with the bilateral SFA in PPD mothers, as compared to Non-PPD mothers. Furthermore, no brain regions showed group differences in connectivity with the bilateral SFA during the contrast OtherView-NonInfantView.

**Parity.** Univariate ANOVAs were conducted to investigate whether group differences in subregion connectivity differed by parity. Group (Non-PPD vs. PPD) and parity (primiparous vs. multiparous) served as between subjects factors and connectivity parameter estimates from the PPI analysis served as the dependent variables. An interaction between group and parity was observed for bilateral BLA and SFA to bilateral IC connectivity. More specifically, across subregions, Non-PPD mothers show greater connectivity with the IC if they were multiparous, whereas multiparous mothers with PPD showed decreased subregion to IC connectivity (see Table 8 and Figure 20 for full summary of effects). Parity x Group interactions were not observed for CMA to insula connectivity. Furthermore, Parity x Group interactions were not observed for BLA, CMA or SFA subregion to other brain region connectivity (e.g., ventral striatum, precuneus, etc.).

### 5.2.4 Correlations

At the ROI level, there were no significant correlations between the BOLD response for OwnView-OtherView or OtherView-NonInfantView with EPDS or STAI-T from Visit 2.
At the connectivity level, parameter estimates from almost all clusters showing group differences in connectivity with the BLA, CMA and SFA show significant negative correlations with EPDS and STAI-T from Visit 2. Please see Table 9 for a summary of the significant correlations.

5.3 Discussion

Consistent with previous research (Leibenluft et al., 2004; Seifritz et al., 2003; Ranote et al., 2004; Barrett et al., 2012; Strathearn & Kim, 2013), we recently demonstrated that the AMY responds differentially to positive pictures of one’s own infant as compared to an unfamiliar infant (Wonch et al., 2016). We also demonstrated that this differential AMY responsiveness to one’s own infant is preserved in mothers with PPD. Understanding that the human AMY is comprised of at least three structurally and functionally distinct subregions, in the current work, we sought to examine whether the BLA, CMA and SFA responded differentially to familiar (one’s own) and unfamiliar infant stimuli in mothers with and without PPD.

In Non-PPD mothers, we found that all three of the AMY subregions show a preferential response for one’s own compared to an unfamiliar infant. However, in PPD mothers, we found that only the CMA and SFA respond preferentially to one’s own compared to an unfamiliar infant. Notably, while these effects were present in each group individually, we did not observe significant group differences (Non-PPD vs. PPD) in the degree of this differential responsiveness to Own and Other infants in the BLA, CMA or SFA. Thus, while PPD mothers do not demonstrate a robustly unique response to their own infant in the BLA, the degree of this differential responsiveness is not statistically different from that of Non-PPD mothers.

Next, we examined whether there were differences between the BLA, CMA and SFA in the degree of differential responsiveness for one’s own infant. Here, we did not observe differences between subregions in responsiveness for Own as compared to Other infant. This suggests that, at the ROI-level, each of the amygdala subregions are involved to the same degree in the processing of infant facial cues, namely cues that relate to one’s own infant.

We also sought to examine whether this effect was unique to infants, or was generalizable to all positive stimuli. Here, we identified that, while each of the AMY subregions respond more for positive pictures of one’s own infant as compared to positive unfamiliar infant
pictures, there are no differences in the responsiveness to positive pictures of an unfamiliar infant compared to non-infant pictures. Thus, in both Non-PPD and PPD mothers, AMY subregions respond more to positive pictures of one’s own infant as compared to both positive pictures of other infants and non-infant stimuli. This finding was expected for the BLA and SFA, due to their proposed excitatory roles in mothering and social processing, respectively. However, this finding was somewhat unexpected for the CMA; the CMA has a proposed inhibitory role in maternal behaviour from rodent work (e.g., Fleming, Vaccarino & Luebke, 1980), however, a recent review by Bzdok and colleagues (2013) highlights the proposed role of the CMA in guiding attentional and motor responses, which may explain the increased responsiveness to own versus other infants. We have shown with our previous work that the AMY as a whole responds more to positive pictures of one’s own infant as compared to an unfamiliar infant, regardless of depression status (see Wonch et al., 2016). Once again, we observed no between subregion differences in the degree of responsiveness to an unfamiliar infant as compared to other positive non-infant stimuli. We also observed no differences between Non-PPD and PPD mothers in the brain response to Other infants compared to Non-Infant stimuli.

After obtaining overlapping results at the ROI level, we sought to investigate whether there may also be overlapping and/or unique patterns of connectivity between each of the AMY subregions and other brain regions while mothers with and without PPD viewed pictures of their own infant as compared to another infant. Our previous work that examined AMY connectivity as a whole during this same paradigm suggested that mothers without PPD show stronger AMY to right insular cortex connectivity, as compared to mothers with PPD for the contrast own versus other infant. As such, we anticipated that we would observe overlapping connectivity amongst each of the three AMY subregions with the insula. Indeed, this is what we observed; the BLA, CMA and SFA all show striking group differences (Non-PPD greater than PPD) in connectivity with the insular cortex when mothers view their own compared to an unfamiliar infant. As discussed in Wonch et al. (under revision), the insular cortex plays an important role in interoceptive processing or the representation of one’s internal physiological state in relation to emotion (Craig, 2009). More specifically, the anterior insular cortex is active by a variety of emotional awareness tasks (e.g., sadness, anger, anxiety, pain and disgust (Mayberg et al., 1999; Damasio et al., 2000; Benkelfat, et al., 1995; Ploghaus et al., 1999; Phillips et al., 1997)). Craig (2009) suggests that the insular cortex may be involved in the processing of subjective feelings...
and emotions. Conceivably then, the negative connectivity between each subregion of the AMY and the IC that was observed in mothers with PPD may be detrimental to their ability to respond sensitively to a developing infant. While the current study did not assess the relationship between AMY to IC connectivity and maternal sensitivity, directly, future studies should seek to do so.

We also observed overlapping patterns of connectivity between the BLA, CMA and SFA with the precuneus/posterior parietal lobe. Here, once again, mothers without PPD showed stronger connectivity during the viewing of their own versus and unfamiliar infant, as compared to mothers with PPD. This area is understood to be a central node in the default control network (DCN), where increasing task difficulty is typically thought to lead to decreased connectivity between this node and the DCN (Fox, Snyder Vincent, Corbetta, Van Essen & Raichle, 2005). However, other studies have shown that the precuneus is engaged during a variety of tasks (e.g., episodic memory retrieval; Maddock, Garrett & Buonocore, 2001). This has lead to the supposition that the precuneus may play an important role in the regulation of attention and cognition (Pearson et al., 2011; Leech and Sharp, 2013). Rather than being anticorrelated with task-based networks, as previously believed, recent evidence suggests that connectivity between the precuneus and frontoparietal attention networks may increase during task performance, whereas connectivity between the precuneus and the DCN may decrease during task performance (Utevsky, Smith & Huettel, 2014). Depression often involves diminished concentration and indecisiveness (American Psychiatric Association, 2000a). Knowing this, it is not surprising that each of the AMY subregions are more strongly connected to a brain region important for attention in mothers without PPD, as compared to mothers with PPD. Recently, meta-analytic connectivity modeling was used to suggest that the bilateral AMY is functionally connected to the precuneus/posterior parietal lobe during resting state (Robinson, Laird, Glahn, Lovallo & Fox, 2010). While network connectivity was not tested directly in our analysis, future studies could examine whether the precuneus may act as a convergence region between early representations of emotion, involving the AMY, and higher order cognitive processes subserved by attention and default networks.

In both the BLA and SFA, the clusters showing group differences in task-based connectivity included the right and left TPJ. There is ongoing debate regarding the functional significance of the TPJ. Some researchers suggest it plays a role in domain-general attentional processes (e.g., Mitchell, 2008) whereas others point to involvement in more specific processes
such as representing others’ mental states (e.g., Saxe and Kanwisher, 2003; Saxe and Powell, 2006). Further recent work has suggested that components of the TPJ may be involved in behavioural imitation, specifically, though connectivity with the medial prefrontal cortex, switching between representation of self and other to facilitate or inhibit imitative actions (e.g., Santiesteban et al., 2012; Cook 2014). In particular, Cook (2014) review the perspective that more ventral regions of the TPJ may be involved in domain-general attentional control, regardless of whether or not the information is self- or other-relevant, whereas more dorsal regions may be involved in switching attentional control to facilitate imitative action when task-relevant information is self- or other-relevant. It is interesting that the CMA, with proposed role in attending to salient environmental cues and influencing autonomic and motor responding to said cues (Bzdok et al., 2013), did not show group differences in connectivity with these regions. This suggests that the CMA, which is thought to play an inhibitory role in maternal behaviour from rodent work (Numan et al., 2010; Oxley & Fleming, 2000), is similarly engaged with the TPJ in mothers with and without PPD when they view their own infants. Rather, regions of the AMY that are more strongly related to learning of stimulus-value associations and processing of social information (e.g., BLA and SFA), which play an excitatory role in maternal behaviour from rodent work, show stronger connectivity with this region in mothers who are not depressed.

Uniquely, the right BLA is the only AMY subregion to show stronger connectivity with a region in the ventral striatum (extending to the right OFC). As reviewed in Bzdok et al. (2013), the human BLA is thought to be involved in integrating visual, auditory, gustatory and somatosensory environmental information, and relaying this information to higher level cortical areas for further reward-related processing. It has also been linked to the default mode network, which includes brain regions such as the medical PFC, inferior parietal cortex and posterior cingulate cortex (as aforementioned), known to play a role in self-reflection, associative processing of environmental information and integration with self-relevant cognition, as well as significance detection and associative learning. Importantly, Numan and colleagues have recently suggested that, in particular, appetitive aspects of maternal behaviour in the rodent may be disrupted through BLA lesions. A putative pathway for this altered behavior is through decreased connectivity with the nucleus accumbens/ventral pallidum reward circuitry (Numan et al., 2010). Further research should seek to investigate, a priori, this BLA to ventral striatum
connectivity in human mothers, to examine whether altered functioning along this pathway may mediate the passive, anhedonic, withdrawn behaviours observed in some mothers with PPD.

Importantly, evidence from non-human animals suggests that the BLA is also thought to detect and integrate salient somatosensory information and relay this directly to the CMA, which is then involved in mounting a response to these cues through connections to brain systems involved in autonomic and motor responsiveness and attentional reallocation (see Pessoa & Adolphs, 2010 for review). Less understood about the role of the SFA. Although we observed overlapping and unique patterns of connectivity among each of the subregions, we did not identify differences in BOLD response between the three subregions in the current study. We may have missed these subtle differences, or overlooked subregion to subregion connectivity, due to the nature of our paradigm being block design rather than event-related; perhaps we would have observed subregion differences if we were not forced to average across 4-second trials in our 20-second blocks. Future studies could tailor their task to further examine the potential for subregion differences.

In summary, the current work demonstrated, for the first time, that the three AMY subregions respond similarly to positive infant pictures (e.g., greater for own versus other infants). Furthermore, they respond more for own versus other infants, regardless of depression status. Similar to our previous work (wonch et al., 2016), while we did not observe group differences (PPS vs. Non-PPD) at the ROI level, we did when we examined AMY to brain connectivity using PPI. While we found overlapping patterns of connectivity among the BLA, CMA and SFA with the insula and the precuneus/posterior cingulate, the BLA, uniquely, showed stronger task-based connectivity with the ventral striatum in Non-PPD mothers, as compared to PPD mothers.

6 Study 4: Amygdala Response and Connectivity in Relation to Maternal Behaviour in Mothers With and Without Postpartum Depression

Motherhood is a transformative experience; Physiologically, neurologically, attitudinally, and behaviourally, mothers undergo a host of changes that unify and distinguish them from non-
mothers. For example, behaviourally, most mothers provide instrumental care for their babies (such as feeding, changing, or clothing them), they may also sing to their babies, carry them, and respond to their distress cues. However, amongst themselves, mothers are also unique; they have highly individually varied experiences and practices while parenting an infant (see Barrett & Fleming, 201; Lonstein, Levy, & Fleming, 2015; see also Special Issue on Parenting, Hormones & Behavior, 2015). One such behavioural dimension along which mothering practices may vary is maternal sensitivity (Ainsworth & Wittig, 1969). Maternal sensitivity involves warm, appropriate, contingent and rapid response to infant bids from proximity or contact. Thus, highly sensitive mothers not only respond to their infants’ cues, they do so in a way that acknowledges the immediate and individual signals or needs of the infant, paying close attention to their most subtle cues and using them to guide their behaviour. Decades of research has now accumulated to highlight the positive relationship between sensitive maternal responding and the development of secure infant attachment behavior (for example, Ainsworth & Wittig, 1969; de Wolff & van IJzendoorn, 1997).

We know now that the experiences one has early in development can produce lasting effects on the brain, physiology and behavior (Lomanowska, Boivin, Hertzman, & Fleming, 2015; Brett, Humphreys, Fleming, et al., 2015). Children’s brains are highly plastic and susceptible to social influence, the earliest form of which is generated by parents (Ermisch, Jantti & Smeeding, 2012; Boivin and Bierman, 2013). Language abilities, emotion regulation, interpersonal skills and cognition are shaped in the family of origin. Unfortunately, sensitive, nurturing early parenting is not a universal experience. Studies examining the developmental outcomes of children living in almost or complete social isolation, without access to adequate caregiving have identified marked adverse cognitive effects that persisted to age 11, if the deprivation persists for the first 6-months of life (Beckett et al., 2006). However, longer institutionalization (e.g., to 42-months) does not worsen cognitive outcomes. Studies of normal variations in parenting of children not reared in an institutional setting also outline the importance of early experiences in shaping developmental trajectories. For example, Crockenberg and Leerkes (2006) found that, in 6-month old infants, high reactivity to novelty, as well as withdrawal behaviour predicts anxious behaviour at 2.5 years of age, only when mothers are less sensitive. Sensitive periods in development are conceptualized as times when the child’s developing brain is more susceptible to environmental influence (see Brett, et al., 2015). As
such, the first 6 months of life may represent one such “sensitive period” in child development, where nurturing maternal influence is vital. Knowledge of the enduring developmental impact of mother-infant interactions during the first months of life underscores the need to study the neural correlates of maternal behavior during this time period, in particular.

Mood changes are common in the postpartum period. For approximately 15% of new mothers, these mood changes persist for at least two weeks and include heightened low mood, anhedonia, feelings of guilt surrounding one’s ability to parent a new child and more, meeting the criteria for postpartum depression (PPD; Ross et al., 2005; Cox et al., 1993; O'Hara & Swain, 1996; Beck, 2001; Halbreich & Karkun, 2006; Dennis et al., 2012; American Psychiatric Association, 2000). Mothers with PPD demonstrate an altered repertoire of parenting abilities relative to mothers without PPD. For example, they tend to be more intrusive, irritated, and negative in their interactions with their infants (Murray et al., 1996; Cohn et al., 1990), they also tend to interpret their infant’s behaviour more negatively (Field et al., 1993). Additionally, they are less affectionate with their infants (Fleming et al., 1988; Stanley et al., 2004) and respond less sensitively and contingently to their infants (Murray et al., 1996; Fleming et al., 1988; Stanley et al., 2004). They also demonstrate less positively synchronous interactions with their babies compared to mothers without PPD (Field et al., 1990). Interestingly, a recent study found that mothers with PPD were less likely to accurately identify happy infant faces in a morphed emotion labeling task (Arteche et al., 2011). Whether this decreased ability to detect positive emotions from infant faces at lower intensity translates into reduced maternal responsiveness to positive affect at the behavioral level remains to be investigated.

Given what we now understand about the relation between parenting and child development, it is not surprising to see that children of mothers with PPD tend to fare more negatively from a social, emotional, cognitive, behavioural, and developmental perspective, than children reared by mothers who are not depressed. For example, children of mothers who were depressed postpartum show overall poor cognitive outcome at 18 months, more difficulties in social interactions with their peers at 5 years of age, higher rates of mood and anxiety disorders at 13 years, and higher rates of mood disorders at 16 years (Murray et al., 1996; Halligan et al., 2007; Murray et al., 2011). This work highlights the importance of studying neural and behavioral mechanisms of both maternal behavior and mood and the impact on them of infants and their cues.
Despite its prevalence, the neurobiological substrates of PPD are still understudied. In a sample of healthy women, Barrett et al. (2012) identified that the amygdala (AMY) response to own, as compared to an unfamiliar infant, is positively related to maternal anxiety and parental distress. Follow-up work from our laboratory has demonstrated that mothers with and without PPD show differential responsiveness in the AMY (specifically, the right AMY) when they view their own versus an unfamiliar infant (Wonch et al., 2016). Mothers with PPD also appear to demonstrate an overall enhanced AMY response to all positive stimuli (e.g., familiar and unfamiliar infants as well as non-infant stimuli; Wonch et al., 2016) and overall blunted AMY response to negative stimuli (e.g., words (Silverman et al., 2007; Silverman et al., 2011) or faces (Moses-Kolko et al., 2010)). Most notably, mothers with PPD, as compared to mothers without, demonstrate decreased connectivity between the AMY and the insular cortex, a region known for its role in interoception (Wonch et al., 2016). These differences suggest that, while mothers with PPD may be well-tuned to the salient environmental cues generated by their own infants (e.g., positive facial expressions), as evidenced by increased AMY activity, an altered pattern of connectivity with brain regions important for guiding ones subjective awareness of their emotions and the physiological state of the body may impact how a depressed mother is able to interpret and respond to their infant’s cues.

Recently, attention has turned towards uncovering the link between neural responses and behavioural responsivity to infants. For instance, there is a significant positive correlation between BOLD responses attained at 3-4 weeks in response to infant cries and maternal sensitivity at 3-4 months postpartum in the right superior frontal gyrus and right lateral globus pallidus/AMY region (Musser et al., 2012). Additionally, increased response to infant cries in the right superior frontal gyrus and AMY at one month postpartum are associated with greater maternal sensitivity at 3–4 months postpartum (Kim et al., 2011). Rather than look at the construct of maternal sensitivity, Atzil et al. (2011) chose to examine mothers who interact in synchronous and intrusive ways with their infants, and compare their brain response to video clips of dyadic interactions between themselves and their infants, as well as dyadic interactions of other mother-infant pairs. They found that mothers who display greater synchrony in their interactions show higher response in the left nucleus accumbens, whereas mothers who display greater intrusiveness show greater response in the right AMY. Additionally, the pattern of brain connectivity when viewing these video clips to emotion modulation, theory-of-mind, and
empathy networks and pro-action areas was different among synchronous and intrusive mothers. It should be noted that they utilized a composite measure of sensitivity, harmony and synchrony (Atzil et al., 2011). Examining these domains separately would allow greater specificity when relating behaviour to brain response.

The current study will examine the relation between brain response and connectivity to infant cues in mothers with and without PPD and maternal sensitivity, as measured behaviourally. To do this, we will first examine maternal behavior in association with brain activity in the AMY. There are many ways of assessing maternal behavior (e.g., maternal sensitivity, vocalization frequency, maternal intrusiveness, etc.). Although each of these may relate uniquely to different components of known brain networks (e.g., executive, salience, default mode, etc.), we will focus on one region, the AMY, and its task-based connectivity (e.g., during viewing of infant stimuli) with other brain regions. Maternal sensitivity is the ability to appropriately and rapidly respond to infant signals with warmth and affection, providing the highest quality care elicited according to the needs of the infant (Ainsworth & Wittig, 1969). We predict that this characteristic, in particular, will be dependent upon normative AMY functioning, as the AMY plays a role in both socioemotional processing (Adolphs, 2001; Adolphs, Baron-Cohen and Tranel, 2002; Pessoa, 2010) and maternal behavior (see for example Fleming, Vaccarino, and Luebke, 1980; Barrett and Fleming, 2010; Numan et al., 2010; Lonstein, Levy, & Fleming, 2015). Although no study has related maternal sensitivity to the mother’s brain response to positive infant stimuli, one study has used infant cry stimuli (Musser, et al., 2012). Similar to their results, we expect to observe a correlation between maternal sensitivity and brain response to infant cues in the AMY. However, the direction of this relation may change, as we will be using positive rather than negatively valenced stimuli presented in a different modality (visual).

Recent work by Wonch et al., (in prep) found the the basolateral amygdala (BLA), centromedial amygdala (CMA) and superficial amygdala (SFA) have both overlapping and distinct patterns of task-based connectivity (during the viewing of own and other infants) with the rest of the brain. In particular, the BLA, CMA and SFA all show striking group differences (Non-PPD greater than PPD) in connectivity with the insular cortex and precuneus/posterior parietal cortex when mothers view their own compared to an unfamiliar infant. Furthermore, both the BLA and SFA, show group differences (Non-PPD vs. PPD) in task-based connectivity
with the right and left temporoparietal junction (TPJ). However, the BLA is the only AMY subregion to show stronger connectivity with a region in the ventral striatum (extending to the right OFC) in Non-PPD vs PPD mothers; the CMA and SFA did not show this group difference. Understanding that there are both overlapping and unique patterns of task-based connectivity between each of the AMY subregions and the rest of the brain, the current study will examine the relationship between maternal behavior, outside of the scanner and the connectivity parameters for the entire AMY (obtained from Wonch et al., 2016), as well as each of the individual subregions (obtained from Wonch et al., in prep; Study 3) during the viewing of own vs. unfamiliar infant stimuli.

6.1 Abbreviated Methods

Our study population consisted of mothers, 2-5 months postpartum, with (n=28) and without (n=17) PPD, as determined by diagnostic interview (CIDI-V), who are 20-40 years of age, with singleton, full-term babies. Using fMRI (GE 3-T scanner), all mothers viewed smiling pictures of infants in a block design (2 conditions of current interest: Own and Other; see Figure 3 for summary). We examined whether entire AMY, as well as subregion-level differences in AMY response and connectivity between PPD and Non-PPD mothers was related to various measures of maternal behaviour (e.g., Ainsworth Maternal Sensitivity Scale and MBQS). We utilized data from Study 2 and Study 3 obtained first using ROI and psychophysiological interaction (O’Reilly et al., 2012) analyses using the entire AMY, as well as its subregions, as seeds, during the viewing of Own-Other infant stimuli. Spearman (and Pearson partial correlations, where necessary) were used to examine the relationship between measures of maternal behavior (MBQS and Ainsworth/subscales) with our fMRI conditions (OwnView), contrasts (OwnView-OtherView) and connectivity parameters.

6.2 Results

6.2.1 Subject Characteristics

Fifty-four mothers completed the study, however 9 mothers were excluded from analyses due to high movement during the fMRI (>2mm); the current results represent data from 17 Non-PPD mothers and 28 PPD mothers. Demographic (e.g., maternal and infant age, sex, education), and clinical variables (e.g., EPDS, STAI-S/T) were analyzed with SPSS using a univariate
ANOVA or chi-square test, where appropriate. Maternal age and education, as well as delivery method, parity, and breastfeeding status were not significantly different across Non-PPD and PPD mothers (see Table 2). Although our subsequent work has indicated that parity contributed to the relationship between AMY-IC connectivity and depression status, partial correlations relating AMY-IC connectivity and behavior, with demographics included as ‘covariates’ or partialled out, indicated that none of the above-mentioned variables, including parity, contributed to the models discussed below, and were thus excluded from analyses. From a multivariate ANOVA PPD mothers reported significantly higher depressive symptomology (EPDS ($F(1, 43) = 14.403, p = .001$) and trait anxiety (STAI-T ($F(1, 43) = 45.952, p = .001$); Table 2). Although eleven PPD mothers were taking SSRI medication, EPDS and STAI-T scores for PPD mothers did not differ based on medication status (SSRI vs. no medication; EPDS $F(1, 26) = 1.180, p = .287$ and STAI-T $F(1, 26) = .758, p = .392$). Medication status (SSRI vs. None) was not a significant predictor in any model and, thus, was not included in subsequent analyses.

6.2.2 Group Differences in Behaviour

As compared to Non-PPD mothers, mothers with PPD show less overall sensitivity to their infants, reflected both in their total Ainsworth scores ($F(1, 42) = 7.298, p = .010$; see Figure 9a) and in their MBQS scores ($F(1, 42) = 5.151, p = .028$; see Figure 9b). The reduced Maternal Sensitivity reflects reduced scores on each of the 4 component factors (acceptance ($F(1,42) = 8.071, p = .007$; see Figure 9a), availability ($F(1, 42) = 5.194, p = .028$; see Figure 9a), cooperativeness ($F(1, 42) = 4.949, p = .032$; see Figure 9a) and sensitivity ($F(1, 42) = 6.963, p = .012$; see Figure 9a).

6.2.3 Correlations between Behaviour and AMY

In these analyses correlations were undertaken between mothers differential responses to own infant vs. another infant (as a contrast) and measures of Maternal Sensitivity. In no case were there significant correlations between mothers’ BOLD responses to the individual condition response to own baby and behavior.

Non-PPD Only. BOLD response in the left, but not the right, AMY for the contrast OwnView-OtherView, was significantly correlated with Ainsworth Total ($r = .518, p = .040$; see Figure 21a) and especially with the factors of acceptance ($r = .566, p = .022$), and cooperation (r
= .502, p = .048). There are no other correlations between left or right AMY connectivity with the right insula and any measures of maternal behaviour. There are no correlations between the ART ratings for own baby and any measures of maternal behaviour.

**PPD Only.** BOLD response in the left and right AMY for the contrast OwnView-OtherView, was significantly correlated with Ainsworth Total (L: r = .401, p = .034, Figure 21a; R: r = .460, p = .014, Figure 21b) and MBQS (L: r = .383, p = .044, Figure 22a; R: r = .419, p = .026, Figure 22b). The Ainsworth Total effects were based primarily on effects of factors: cooperation (L: r = .460, p = .014; R: r = .574, p = .001) and sensitivity (L: r = .385, p = .043; R: r = .415, p = .028). There are no correlations between left or right AMY connectivity with the right insula (obtained from Wonch et al., 2016) and any measures of maternal behaviour. There are no correlations between the ART ratings for own baby and any measures of maternal behaviour.

**All Subjects.** BOLD response in the bilateral AMY for the contrast OwnView-OtherView, was significantly correlated with Ainsworth Total (L: r = .402, p = .007; R: r = .418, p = .005) and MBQS (L: r = .370, p = .013; R: r = .342, p = .023). The Ainsworth effects derive from component factors (acceptance (L: r = .368, p = .014; R: r = .331, p = .028), availability (L: r = .292, p = .055 (marginal); R: r = .369, p = .014), cooperation (L: r = .454, p = .002; R: r = .496, p = .001), and sensitivity (L: r = .353, p = .019; R: r = .332, p = .028). To demonstrate that there are no group differences in these relationships, the individual effects for Non-PPD and PPD mothers have been plotted separately on the same graph. There are no correlations between left or right AMY connectivity with the right insula and any measures of maternal behaviour. There are no correlations between the ART ratings for own baby and any measures of maternal behaviour.

### 6.2.4 Correlations between Behaviour and Subregions

**Non-PPD Only.** BOLD response in the left, but not the right, BLA for the contrast OwnView-OtherView was significantly correlated with Ainsworth Total (r = .527, p = .036) and with component factors of acceptance (r = .581, p = .018) and cooperation (r = .508, p = .045). There were no significant correlations between bilateral CMA or bilateral SFA BOLD for OwnView-OtherView and any behavioural measures of mothering. With respect to connectivity, there were also no correlations between left or right AMY subregion connectivity with any
measures of maternal behaviour. There are no correlations between the ART ratings for own baby and any measures of maternal behaviour.

**PPD Only.** BOLD response in the bilateral BLA for the contrast OwnView-OtherView, was significantly correlated with Ainsworth Total (L: r = .379, p = .046; R: r = .395, p = .037) (and with acceptance (left r = .475, p = .011; right r = .522, p = .004) and cooperation (r = .508, p = .045)). There were no significant correlations between bilateral CMA or bilateral SFA BOLD for OwnView-OtherView and any behavioural measures of mothering. With respect to connectivity, there were also no correlations between left or right AMY subregion connectivity (obtained from Wonch et al., in prep) with any measures of maternal behaviour. There are no correlations between the ART ratings for own baby and any measures of maternal behaviour.

**All Subjects.** When all subjects are included in the analyses, we find that left and right BLA BOLD response for OwnView-OtherView are positively correlated with Ainsworth total (L: r = .373, p = .013; R: r = .408, p = .006). These results are based on a significant effect for the component factors acceptance (L: r = .329, p = .029; R: r = .337, p = .02) and sensitivity (L: r = .314, p = .038; R: r = .336, p = .026). For right BLA, effects were also found for availability (r = .340, p = .024) and cooperation (r = .486, p = .001), but not Total score. In the right BLA only, a significant relationship was also observed between BOLD response and MBQS (r = .343, p = .022). Left SFA BOLD response for OwnView-OtherView was also positively correlated with Ainsworth Total (r = .307, p = .043). There were no significant correlations between CMA BOLD response with any measures of maternal behavior.

Bilateral BLA connectivity with the left insula was marginally related to Total Ainsworth (L: r = .279, p = .067, R: r = .275, p = .071) and MBQS (L: r = .279, p = .066, R: r = .292, p = .054) and significantly correlated with factors of acceptance (L: r = .324, p = .032, Figure 23a; R: r = .300, p = .048, Figure 23b) and sensitivity (L: r = .312, p = .039, Figure 24a; R: r = .305, p = .044, Figure 24b). There were no significant correlations between SFA or CMA connectivity with any measures of maternal behavior. Notably, when depression status (Non-PPD vs. PPD) is controlled for using Pearson partial correlation, the relationship between bilateral BLA to left IC connectivity and maternal sensitivity and acceptance disappears. Thus, for visualization purposes, the relationship between BLA to IC connectivity and maternal sensitivity and acceptance has been plotted separately for Non-PPD and PPD mothers.
6.3 Discussion

There is a growing body of work suggesting that the human AMY responds preferentially to facial expressions from one’s own infant, as compared to another infant (Leibenluft et al., 2004; Seifritz et al., 2003; Ranote et al., 2004; Barrett et al., 2012; Strathearn & Kim, 2013; Wonch et al., 2016). Furthermore, recent work suggests that this preferential responsiveness may be preserved, at least in the right AMY, in mothers with postpartum depression (Wonch et al., 2016). Nevertheless, our earlier work showed that mothers with PPD do not appear to show a completely normative profile of brain response and connectivity, as compared to mothers without PPD (Wonch et al., 2016). Namely, they display overall enhanced responsiveness in the AMY to infant stimuli, both own and other, as well as an altered pattern of task-based connectivity (e.g., viewing own vs. unfamiliar infant) between the AMY and the right insular cortex. The current study sought to explore the relationship between brain response to infants, in mothers with and without PPD, and real-time measures of maternal behavior obtained outside of the scanner. Thus far, seemingly conflicting results have suggested that there is a positive correlation between AMY response to infant cries and maternal sensitivity (Musser et al., 2012), while another study has identified a positive correlation between AMY response to videotaped mother-infant interactions and maternal intrusiveness. This study sought to extend these findings by examining brain response to standardized, positive infant pictures, by exploring subnuclei within the amygdala and by undertaking connectivity analyses between those subnuclei and other brain sites. We also based our behavioral measures on well-documented and validated measures of Maternal Sensitivity,

With respect to maternal behaviour (e.g., MBQS, Total Ainsworth), mothers with PPD compared to those without PPD, show reduced overall quality of maternal sensitivity. Interestingly, in the current study, no relationship was identified between brain response solely to own infant and any measure of maternal behaviour. However, when we examined the relationship between measures of maternal behaviour and brain response to mothers’ own infant in contrast to an unfamiliar infant (e.g., OwnView-OtherView), we found that, regardless of depression status, higher AMY responsiveness was associated with higher scores on the MBQS and most or all of the subscales of the Ainsworth Maternal Sensitivity Scale. In other words, mothers who showed a more “unique” brain response to their own infant demonstrated higher quality maternal behavior, overall. This relationship was observed across all mothers, regardless
of their depression status. As indicated in Wonch et al. (2016) mothers with PPD demonstrate an overall enhanced AMY response to “other” babies, as compared to non-depressed mothers. Thus, although mothers with PPD still show a unique response to own vs. other infant, they do so to a lesser extent than do Non-PPD mothers. The current study indicates that, while depressed mothers tend to show reduced differential brain response to their own infant in contrast to another infant, as well as poorer quality maternal behavior, mothers with higher brain response to own vs. other infant, overall, shower greater quality of mothering.

Research suggests that the AMY may respond to uncertainty (e.g., Whalen, 2007) and novelty (e.g., Balderston, Schultz & Helmstetter, 2011). It is interesting, then, that all mothers display an overall increased AMY response to images of their own infant, with whom they have had the opportunity to interact with daily for the past 2-5 months, as compared to images of a completely novel, unfamiliar infant. Studies also suggest that the AMY may have a more specialized role in relevance detection (Sander et al., 2003), which will depend on an individual’s particular motivational state, goals and/or needs (see also Cunningham & Brosch, 2012). As such, it is also interesting that mothers with PPD display an overall enhanced AMY response to all babies. It may be that for PPD mothers, all babies are relevant, but they may represent stimuli of differing value (e.g., they trigger alarm), whereas for mothers who are no depressed, their own baby hold more value than “other” babies, and these babies may be less alarming. In our previous work (Wonch et al., 2016), we discuss how, when asked to rate how they feel when looking at pictures of their own and other babies, PPD mothers do not differ from Non-PPD mothers; they all rate feeling more positive for their own than an unfamiliar baby, to the same degree. Nevertheless, this line of thinking requires further investigation; future studies should seek to further disentangle the meaning behind the unique responsiveness of the AMY in Non-PPD mothers to pictures of their own babies.

Most importantly, the current work identified a relation between brain response to own vs an unfamiliar infant and various well-validated measures of maternal behavior obtained from videotaped interactions outside of the scanner. As mentioned, AMY is important for detecting relevant, salient, social stimuli, and orchestrating the appropriate cascade of responding to said stimuli. We have identified previously that PPD mothers spend more time holding their infant, however they respond less sensitively in behavioural interactions with their infants (Wonch et al., in prep (Study 1). As such, PPD mothers may engage with their infants as much as, if not
more, that Non-PPD mothers, behavior which could conceivably involve the AMY detecting their infant as a “relevant” or important cue which requires responding, however, they may do so in a less accepting, sensitive way than mothers without depression. As such, the current results may suggest that mothers who do not detect their own baby as more “relevant” than an unfamiliar baby respond to them with less sensitivity outside of the scanner. However, these results require replication.

In our previous work (Wonch et al., 2016), we identified a significant group difference (Non-PPD > PPD) in AMY to right IC connectivity when new mothers view their own vs other infants. Interestingly, in the current work, we did not observe any correlation between our measures of maternal behaviour and these AMY-right IC connectivity parameters. Nevertheless, we know that the AMY is comprised of at least three functionally distinct subregions: the BLA, CMA and SFA. Animal work has identified distinct roles for at least two subregions or subnuclear groups with respect to species-typical maternal behaviour (Numan et al., 2010; Morgan et al., 1999; Numan, Numan & English, 1993). For example, Numan and colleagues suggest that the BLA influences appetitive, but not consummatory aspects of mothering (Numan et al., 2010). The CMA, on the other hand, is thought to play an inhibitory role in maternal behavior, where Fleming and colleagues have demonstrated that lesions to the CMA encourage the onset of maternal behaviour in nulliparous animals (Fleming, Vaccarino, & Leubke, 1980; Fleming, Miceli, & Moretto, 1983; Oxley & Fleming, 2000). Human work suggests that the BLA tends to be associated with coordinating higher-level sensory input and significance detection, the CMA is associated with mediating attentional, vegetative and motor responses and the SFA is associated with olfactory and social information processing (see Bzdok et al., 2013 for review). While we have previously identified overlapping patterns of connectivity between each of these subnuclei and other brain regions during the viewing of own vs other infant stimuli (see Wonch et al., in prep), there are also distinct, subregion specific patterns of connectivity. As such, we predicted that we may also observe subregion-level differences in the relationship between brain response to infants and measures of maternal behavior. Indeed, we found that, at the region-of-interest level, all mothers, regardless of depression status, show a positive correlation between the bilateral BLA and SFA for some measures of maternal behaviour. However, we did not see any significant correlations between maternal behavior and brain response in the CMA to own vs. an unfamiliar infant. These results are consistent with the
proposed excitatory role in mothering of the BLA, from rodent work, as well as the proposed roles of the BLA and SFA in significance detection and social information processing, respectively, from human studies.

We next sought to examine whether our measures of maternal behavior were correlated with the various connectivity parameters between each AMY subnuclei and other brain regions, obtained from Wonch et al., (in prep). Here, we identified a positive correlation between some components of maternal behaviour (specifically sensitivity and acceptance) and connectivity parameters for the bilateral BLA to the left insular cortex. We did not observe any correlation between our measures of mothering and the connectivity parameters for the BLA and other brain regions (e.g., the precuneus/posterior parietal cortex, TPJ or nucleus accumbens). Furthermore, this relationship between BLA-IC connectivity and maternal behavior was subregion specific; we did not observe this relationship for the SFA-IC or CMA-IC connectivity parameters. Thus, despite the BLA, CMA and SFA having overlapping patterns of connectivity with the IC, only the BLA to IC connectivity was related to mothering, specifically sensitivity and acceptance. It may be notable that, of the three subregions, the BLA had the most diffuse pattern of connectivity with other brain regions during the viewing of own vs other infants. In other words, the BLA was coupled with a more diffuse pattern of brain regions, including, uniquely, the ventral striatum, than the CMA and SFA (see Wonch et al., in prep; Study 3). The BLA is thought to play an excitatory role in maternal behaviour, influencing appetitive aspects of mothering via sensory input to the nucleus accumbens/ventral pallidum reward circuitry (Lee, Clancy & Fleming, 2000; Numan et al., 2010).

As mentioned previously, the relationship between AMY response, as well as connectivity with the IC, and measures of maternal behavior were consistent across all mothers, regardless of depression status. At the ROI level, these effects remained, even when depression status was controlled for; mothers with higher scores on the Ainsworth and MBQS also demonstrate higher AMY responsiveness to their own vs an unfamiliar infant, regardless of whether they are depressed or not. However, the relationship between bilateral BLA to left IC connectivity parameters and maternal sensitivity and acceptance did not remain significant when depression status was controlled for. When Non-PPD and PPD mothers were examined separately, there was no correlation between maternal behavior and connectivity; this relationship was only observed when we looked at all mothers. Nevertheless, it appears as
though depression status does indeed impact this relationship; when graphed separately for visualization purposes, it is clear that there is no relationship between connectivity and behavior in each group. Despite PPD mothers showing significantly reduced maternal sensitivity, overall, it is only when combined that we see the effect. With a larger sample size, we may observe the effect in the individual groups.

Sensitivity is a broad construct. More specifically, a sensitive mother must not only notice her infants cues (e.g., be present and attentive), she must also have the cognitive and physical capacity to deliver on the infants’ needs, and she should do so in a prompt and kind manner. Relatedly, other researchers have defined additional unique and overlapping constructs such as mutuality (e.g., positive mother-infant exchanges), synchrony (e.g., appropriate fit of mother and infant behaviour fostering a state of social harmony), positive attitude, emotional support, stimulation, mind-mindedness (de Wolff & van IJzendoorn, 1997) as being relevant when studying the relationship between mothering and infant behavior/outcomes. For example, synchronous behavior has been related to secure infant attachment, maternal intrusiveness and overstimulation has been related to avoidant attachment styles, and inconsistent or under-involved parenting styles have been related to resistant infant attachment (see Isabella & Belsky, 1991). Future work should seek to examine the relationship between brain response and various other dimensional aspects of maternal behavior to determine whether the effects are specific to sensitivity. Furthermore, it may be also be important to consider the possible bi-directional relationship maternal behavior and child temperament when considering the relationship between mothering and behavior. For example, mothers of children with more difficult attachment styles have been shown to be less sensitive (Pederson et al., 1990). Addressing child temperament and/or attachment style may be an avenue of future research. Additionally, our study did not examine the impact of parenting behaviours on the infant. Future longitudinal studies are needed to characterize the effects of maternal behavior on offspring development in association with brain response to examine whether this changes across the postpartum period.

Although little research has been conducted that examined the relationship between AMY response and behavior, our findings are consistent with work by Musser et al., 2012 that identified a positive correlation between AMY response to infant cries and maternal sensitivity. Aztil et al. (2011) identified contradictory findings; they found that mothers who display greater intrusiveness show greater response in the right AMY. However, in the Aztil et al. (2011) study,
mothers were videotaped interacting with their infants, just as they normally would, and these videos were then coded for maternal synchrony as well as intrusiveness. Mothers were then shown these same videos while in the fMRI scanner. Thus, mothers essentially watched videos of themselves, with varying degrees of individual intrusiveness. It is possible that mothers’ brains respond differently when they are watching more intrusive behavior, and that this is what drove the group differences in brain response reported in this study.

A limitation of the current work is the effect of laterality. More specifically, in Wonch et al. (2016), we observed group differences in the connectivity between the bilateral AMY and the right IC. In the current study, we did not identify a relationship between these connectivity parameters and any measure of maternal behavior. In the current study, when we examined a relationship between sensitivity and acceptance with the connectivity parameters obtained between the bilateral BLA and the left IC obtained from Wonch et al., (in prep), we observed a significant positive relationship. It is possible that with a greater sample size we would have also observed group differences in connectivity between the bilateral AMY and the left IC, however this was not the case in Wonch et al., (2016). As such, we were not able to correlate measures of maternal behavior with connectivity between the entire AMY and the left IC, only with the three AMY subregions and the left IC. Regardless, these laterality effects require further investigation in future studies examining maternal behavior and brain response to infants.

7 General Conclusions

This series of studies attempted to elucidate the relation between mood, behaviour and brain response to infants in new mothers. More specifically, they were designed to: 1) characterize maternal attitudes, behavior, as well as other variables such as mood, early experiences and stress, in a group of mothers with and without PPD, confirming that our sample of PPD women conform to previously understood characteristics of depressed mothers (e.g., less sensitive in interactions with infants, greater parenting stress, etc.) 2) examine neural circuits known to be involved in depression and mothering from rodent and other human imaging work (namely, the AMY), 3) examine more specifically whether there are regional response or connectivity differences between each of the subnuclei of the AMY during the viewing of infant stimuli, 4) relate AMY response and connectivity to measures of maternal behavior thought to differ between mothers with and without PPD (from Study 1).
Interestingly, we found that while mothers with PPD may spend more time holding their infants, overall, they engage with their infants in a less sensitive, accepting, available and cooperative way. At the level of the brain, mothers with PPD show an increased AMY response to own vs. unfamiliar infant, just as mothers without PPD do. However, mothers with PPD also demonstrate an overall enhanced AMY response to “other” infants, showing a less differential AMY response to their own baby. Furthermore, mothers with PPD show a negative coupling between the AMY and the right IC during the viewing of their own as compared to an unfamiliar infant, whereas mothers without PPD show a positive coupling. The AMY and IC are two brain regions thought to be important for the experience of subjective emotion, in particular anxiety and distress (Craig, 2002; Craig, 2009; Phelps & Ledoux, 2005). As poor self-perceived maternal health is a strong risk factor for PPD (Dennis et al., 2012) and anxiety and stress are common postpartum (Miller et al., 2006), it makes sense that this perturbations in AMY-IC connectivity may be involved in the pathophysiology of PPD. All three AMY subregions, the BLA, CMA and SFA, show group differences (PPD<Non-PPD) in task-based connectivity with the IC and precuneus/posterior parietal cortex, however, the BLA, specifically demonstrates unique task-based connectivity with nucleus accumbens/ventral striatum. Although each subregion shows task-based connectivity with the IC, it is the connectivity between the bilateral BLA, in particular, with the left IC that is associated with maternal sensitivity and acceptance.

As we observed throughout this work, ROI-level differences do not always translate into connectivity-level differences. For example, in Study 2, while we observed no significant difference between mothers with and without PPD in the degree of AMY responsiveness to own vs. unfamiliar, we did observe differences in connectivity between the AMY and the right IC. An elegant paper by Whalen (2007) suggests that the function of the AMY may be vigilance in the face of threatening (or perhaps, “salient” or “relevant”) stimuli. More specifically, he highlights work demonstrating that anxious and non-anxious individuals can have similar AMY responsiveness to unpredictability. He then speculates whether the function of higher-order brain areas (e.g., the prefrontal cortex, or in our case the insular cortex) may serve to override this AMY hyperresponsiveness in non-anxious subjects. This interpretation of AMY function fits well with our current work, where both healthy and depressed new mothers show similar brain response to their own babies, however, the IC may handle the calculation of the “need for responsiveness” differently. It will be important to continue to investigate whether variations in
the responsiveness of particular nodes result in perturbations to known brain networks that subserve the various aspects of mothering, or whether connectivity differences among these nodes relates to individual differences in mothering.

7.1 Limitations

There are a few potential limitations that cannot be addressed by the current study. For example, disturbances to the sleep-wake cycle are hallmark symptoms of MDD (American Psychiatric Association, 2000). However, under normal circumstances, the postpartum period is characterized by disrupted sleep and in some cases, extreme sleep disturbances, leading some researchers to postulate that disrupted circadian rhythms, which we did not measure, may be part of the pathogenesis of PPD in vulnerable women (Ross et al., 2005; Park et al., 2013). Additionally, PPD is a heterogeneous condition with wide variations in time of onset (e.g., pregnancy (which trimester?) vs. postpartum) and previous history of MDD or PPD. Some suggest that there may be phenotypic variation in uniquely ‘postnatal’ depression, rather than antenatal (Cooper & Murray, 1995; Phillips et al., 2010). Although there are benefits to having strict inclusion criteria, the wide variations in symptomology, onset, history and course of PPD are often not captured by such rigidity. Our study did not attempt to impose such criteria, thereby enhancing the ecological validity and generalizability of our findings to the greater population of women with PPD. A variety of other factors may influence how the brains of new mothers respond to their infants. For example, an association was identified between BDNF Met66 carrier status and development of PPD symptoms, only when mothers delivered during autumn/winter (Comasco et al., 2011). Ideally, future studies should adopt a multidimensional approach when assessing maternal behavior in relation to brain response in PPD mothers.

Despite neuroimaging evidence that brain regions showing decreased activation in individuals with MDD show increased activation following treatment with SSRIs, and vice versa (Fitzgerald et al., 2008; Price & Drevets, 2010), as noted, we did not see differences in AMY response with SSRI use in PPD mothers. It is possible that with stronger controls (e.g., specific type of SSRI, duration of use, dose, etc.) and a study designed specifically to target this relationship, we may see an association between brain response in PPD mothers and medication use. Future studies should do this, as controversy surrounding medication use during pregnancy and during breastfeeding still exists (Nulman et al., 2012; Steiner, 2012; Weissman et al., 2004).
In our study, the average EPDS scores for the mothers in our PPD group were not above the widely cited cutoff score of 12 at the time of the scan (Cox et al., 1987). While we recognize that this is below standard clinical cutoffs on this measure, due to both the repeat nature of our testing (e.g., clinical interview conducted approximately one week before fMRI scan) and the potentially fluctuating nature of PPD symptomology, we are not surprised that scores on this measure varied within mothers; it is possible that some women may have begun to compensate for their depressive symptomology by the time of the scan. Interestingly, a recent meta-analysis identified wide variation in the sensitivity and specificity of the EPDS as a screening measure for PPD (Gibson et al., 2009). In another study, using EPDS cutoff scores to classify mothers with or without a history of PPD failed to identify a relationship between child outcomes at 11 years and PPD, yet when they examined group differences based on diagnostic criteria from a standardized clinical interview, they identified significant differences (Pawlby et al., 2008). This indicates that EPDS may not adequately distinguish mothers with and without PPD, when compared to a diagnostic interview. Thus, the design of our current study is preferred, where mothers were grouped by diagnostic criteria rather than scores on a non-diagnostic mood measure.

Some studies suggest that antenatal depression may be as common as postpartum depression and include shared risk factors (Milgrom et al., 2008), highlighting the need for early identification and intervention. While the tendency has been to focus on depression in the postpartum period, a recent study suggests that by doing so we may be overlooking a subgroup of women who experience perinatal distress and anxiety, but do not identify as “depressed” (Miller et al., 2006). As such, by examining broad indicators of distress in the antenatal and postpartum period, we may better capture the various difficulties experienced by new mothers.

7.2 Future Directions

While this series of studies aimed to examine a group of women with the primary diagnosis of depression, however, as evidenced by high STAI-S and STAI-T scores (see Figure 5b and 5c), this group of women also presented with high symptoms of anxiety. This is not unusual; depression and anxiety are highly comorbid (Brown, Campbell, Lehman, Grisham & Mancill, 2001), especially in women (Kravitz et al., 2014) and in the postpartum period (Falah-Hassani, Shiri & Dennis, 2016). Cognitive behavioural therapy is the current gold standard of non-psychopharmacological treatment for both anxiety and depression. Treatment outcome
studies have found that successful treatment response to CBT for anxiety often results in reductions in depression symptoms in individuals with comorbid depression (Dear et al., 2016). This leads one to speculate on the potential for shared neural substrates of these two common illnesses. If indeed they do share a common neural mechanism, future studies may do well to examine individual differences in various depressive or anxious symptom traits (e.g., “an unpleasant thought enters my mind and I cannot get rid of it”) rather than grouping women into diagnostic categories. This may allow for more precise delineation of the roles of various neural substrates in particular and shared aspects of both depression and anxiety.

For the current work, we chose to focus mainly on one brain region, the AMY, and how it relates to maternal mood and behaviour. Existing work has found very interesting relationships between other maternal factors, such as type of delivery (c-section vs. vaginal; Swain et al., 2008) and feeding method (breastfeeding vs. bottle feeding; Kim et al., 2011), as well as other constructs such as quality of care in one’s own early life and brain response in regions outside of the AMY (Kim et al., 2010). Future work should seek to replicate and expand this work by examining how these factors also relate to measures of observed maternal behaviour.

This work examines the neural correlates of maternal behaviour. To date, little research has examined the neural changes that accompany the transition to fatherhood (see Swain et al., 2014), despite the fact that fathers are playing an ever increasing role in child care and development, as evidenced by the rise in use of paternal leave (see Marshall, 2006). In one recent study that compared fathers to non-fathers, the authors identified a higher response in brain regions important for face emotion processing (e.g., caudal middle frontal gyrus), mentalizing (e.g., TPJ) and reward processing (e.g., medial OFC) in response to pictures of children (Mascaro, Hackett & Rilling, 2014) in fathers. Furthermore, they identified a negative correlation between testosterone levels (lower in fathers than non-fathers) and middle frontal gyrus response to child stimuli. They suggest this decline in testosterone, associated with greater prefrontal cortex response to children, may prime fathers to respond to their children with greater emotional control/empathy (Mascaro, Hackett & Rilling, 2014). Further research has identified that fathers of children aged 1-2 years old who show a medium, rather than low or high, amount of brain activation in the anterior IC in response to cries were the most engaged caregivers (Mascaro, Hackett, Gouzoules, Lori & Rilling, 2014). With respect to brain-behaviour correlations, a recent study that brain response to own versus other infant stimuli were linked with paternal sensitivity,
paternal reciprocity, and testosterone (Kuo, Carp, Light & Grewen, 2012). As these studies demonstrate, similar methodology can be used to compare, directly, the differences and similarities between the neural correlates of parenting in both mothers and fathers.

Thus far, fMRI paradigms that examine the neural correlates of mothering have typically been passive viewing/listening paradigms, where they require mothers to view photos, videos or auditory clips. Sometimes, as with our current design, the mothers are then asked to make some sort of indication as to the valence of the clips/videos/photos or of their own emotions while viewing/listening to them. Recently, as with the current work, there has been a trend towards relating brain response to measures of maternal behavior obtained outside of the scanner. As this trend continues, future work should seek to target specific brain systems thought to play a role in various aspects of maternal behavior. For example, it may be useful to design paradigms that engage attention or executive networks (e.g., using traditional n-back tasks, adapted to be “mother-baby” specific) to examine more of the cognitive effects of mothering and/or postpartum mood changes. This approach, coupled with that mentioned above, where researchers may adapt an individual differences approach by examining specific symptom traits of anxiety, PPD or attitudes towards mothering, may allow for researchers to target specific brain networks thought to underlie mothering (e.g., examine symptoms of decreased motivation with reward-based or gambling tasks, or symptoms of inattention/decreased concentration with tasks that assess fronto-parietal attention networks, etc.). We know much about these brain networks from the “non-mothering” literature. For example, we know that there are various discrete and interacting brain systems involved in attention, including the dorsal (intraparietal sulcus, superior parietal lobule, dorsal frontal cortex (precentral sulcus/frontal eye fields)) and ventral (temporoparietal junction, ventral supramarginal gyrus, and ventral frontal cortex (middle frontal gyrus, inferior frontal gyrus, frontal operculum, and anterior insula)) attentional networks, as well as other brain stem regions with a known role in attentional orienting (e.g., superior colliculus) (Corbetta, Patel, and Shulman, 2008; Corbetta and Shulman, 2002). The dorsal attentional orienting network appears to be involved in exogenous as well as goal-driven (or endogenous) reorienting, whereas both the dorsal and ventral attentional orienting networks are thought to play a role in stimulus-driven reorienting to salient stimuli (Corbetta, Patel, and Shulman, 2008). Mothering a child requires a huge amount of attentional control. Furthermore, decreased concentration and attentional disturbances are hallmark symptoms of depression,
including that which occurs postpartum. It will be crucial to utilize this knowledge in designing future fMRI paradigms that examine the neural correlates of mothering.

Unlike the Atzil et al. (2011) study that used a composite measure to identify mothers as synchronous or intrusive, it is also important to relate moment by moment behavioural responding (e.g., time spent vocalizing, touching or gazing at infant) to brain response to infants. For example, orienting, or the ability to distinguish relevant information from multiple sensory stimuli, is necessary for maternal sensitivity. It is possible that moment-by-moment time-dependent components of mothering behavior (e.g., contingent responding, monitoring one’s surroundings, monitoring infant facial expressions, being able to identify only the most relevant infant cues, etc.) required for sensitive parenting, as well as selectively attending to one’s infant in the face of other conflicting sensory stimulation, will be related to functional adequacy of the dorsal and ventral attentional brain systems. For example, in the more goal-oriented or endogenous orienting system, the dorsal stream, may be more engaged in mothers who selectively attend to their infants in the face of distractions. The ventral stream may be disengaged during these types of tasks. Recent work from our lab demonstrated that mothers with fewer extra-dimensional shift errors on the Cambridge Neuropsychological Test Automated Battery, a proxy for better attentional set maintenance, in the early postpartum period are more sensitive in their interactions with their infants (Gonzalez, Jenkins, Steiner & Fleming, 2012). As a result, it is possible that mothers who demonstrate more maternal sensitivity to have enhanced connectivity among the dorsal orienting network. We also know that depressive symptom severity is negatively correlated with maternal sensitivity (Gonzalez, Jenkins, Steiner & Fleming, 2012). To our knowledge there are no studies that examine directly how maternal sensitivity relates to the integrity of attentional control neural networks in mothers with PPD. There is, however, a growing body of literature suggesting that individuals with MDD exhibit deficits in executive functioning on standardized neuropsychological tasks that may affect attentional control (Snyder, 2013) and differential responsiveness in prefrontal regions of attentional brain networks (Kerestes et al., 2012). Thus, PPD mothers may also show decreased connectivity with dorsal and ventral prefrontal components of the attentional orienting networks.

Face processing is another aspect of social behavior that has been investigated at length at the level of the brain. In general, studies show that when humans view faces a distributed cortical
network is engaged (reviewed in Ishai, 2008). Two pathways have been proposed, one for the processing of invariant features which consists of occipitotemporal regions in extrastriate visual cortex (including the fusiform gyrus) or ‘core’ regions and one for the processing of variant features which consists of limbic and prefrontal (including the superior temporal sulcus) or ‘extended’ regions which are used to obtain meaning from faces (Haxby, Hoffman and Gobbini, 2000; Ishai, 2008). Connectivity analysis converges on the lateral fusiform gyrus as the primary entry node in facial processing system, an area that shows greater response to faces than other objects (Fairhall and Ishai, 2007; Kanwisher et al., 1997). Activation within visual, limbic and prefrontal face-responsive regions is stimulus (e.g., unfamiliar, famous, neutral and emotional faces) and task (e.g., passive viewing, attractiveness rating) independent (Ishai et al., 2005; Kranz and Ishai, 2006). The perirhinal cortex and hippocampus appear to be activated when an individual is discriminating meaningful from novel faces and objects. In the temporal pole, however, there also appears to be greater activity for meaningful faces, but not for objects, suggesting that the medial temporal lobe is important for perceptual discrimination of meaningful faces (Barense, Henson and Graham, 2011). Furthermore, the fusiform face area is activated in response to faces from an in-group, but not and out-group (Van Bavel, Packer & Cunningham, 2011). Relatedly, network studies find increased connectivity between the fusiform gyrus and the amygdala when individuals are viewing emotional faces, and increased connectivity between the fusiform gyrus and the orbitofrontal cortex when individuals are viewing famous faces (Ishai, 2008). Infants use facial expressions as a primary means of communicating with their caregivers. As such, it is crucial that caregivers be able to adequately read and interpret these infant facial expressions. Future research examining the neural correlates of mothering should specifically examine the face processing system.

Because faces are inherently similar in composition, whereas other objects and scenes are not, choosing appropriate non-infant control stimuli is particularly difficult. For example, one might expect to observe a more homogeneous neural activation pattern for faces rather than scenes, which may be more distributed. In fact, a recent meta-analysis by Sabatinelli et al. (2011) found that there are brain areas that are specialized for processing emotional faces and emotional scenes, as well as unique brain regions that respond to the increased perceptual heterogeneity of scenes, objects, etc. As such, any non-infant control stimuli should be interpreted with caution.
7.3 Implications

Knowing how a depressed mother’s brain responds to her own and other infants is critical as many of the symptoms of PPD focus on the mother-infant dyad and involve excessive worry or guilt surrounding parenting abilities (Ross et al., 2005). The current work adds to the existing literature outlining the altered repertoire of mothering observed in mothers with PPD, specifically decreased sensitive responding. The current work identified that maternal sensitivity is associated with increased basolateral AMY to IC connectivity, which is also associated with mood. As such, it is possible the interventions aimed at increasing sensitivity, may indirectly target the underlying neural circuitry of maternal depression, as we have identified that both depression and maternal sensitivity share neural substrates. Future studies should attempt to better elucidate this connection between brain, behavior and mood in new mothers.

Finally, we now understand that mothers with PPD show an overall enhanced AMY response to all babies, whereas mothers without PPD show a more differential AMY response to their own infant. This differential responsiveness to own vs. other baby in mothers with PPD is then related to an altered pattern of connectivity between the AMY and the IC, a brain region thought to be important for registering the subjective sense of emotion. Variations of mindfulness meditation (e.g., mindfulness-based stress reduction, integrative body-mind training, etc.) have been associated with benefits to emotional wellbeing, such as reduced depressive and anxious symptomology (e.g., Santarnecchi et al., 2014; Marchand, 2013; Marchand, 2012; Fjorback et al., 2011) as well as neurological changes in the brain circuits outlines in the current series of studies, including increased cerebral blood flow to the insular cortex (Tang, Lu, Feng, Tang & Posner, 2015) and increased cortical thickness of the insular cortex (Lazar et al., 2005; Santarnecchi et al., 2014), as well as increased activation of the insula and connectivity with the medial prefrontal cortex (Farb et al., 2007; Farb et al., 2010). Furthermore, reductions in perceived stress following mindfulness training have been associated with decreased right basolateral amygdala gray matter density (Holzel et al., 2010). The AMY and IC, as well as their task-based connectivity, appear to be important neural substrates in maternal depression as well as maternally sensitive responding. Recent work suggesting that mindfulness training may alter these neural circuits provides important insights into the potential for novel interventions for PPD.
Table 1.

<table>
<thead>
<tr>
<th>Article</th>
<th>Postpartum Stage</th>
<th>Stimulus Type</th>
<th>Condition</th>
<th>Results</th>
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<tbody>
<tr>
<td>Bartels &amp; Zeki, 2004</td>
<td>9 months-6 years</td>
<td>own and familiar infant faces; best friend and familiar adult faces; romantic partner</td>
<td>own infant-romantic partner</td>
<td>PAG, lateral OFC, hCa, Th, STG, TP, St, SFG</td>
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<td>Leibenluft, Gobbini, Herrison &amp; Haxby, 2004</td>
<td>5-12 years postpartum</td>
<td>own, familiar and unfamiliar childrens’ faces; unfamiliar adult faces</td>
<td>own-familiar</td>
<td>right AMY, left In, ACC, DLPFC, left FFG, left STS, right Pr</td>
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<td>familiar-unfamiliar</td>
<td>right ACC, left In, left STS, PCC/Pr</td>
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<td>unfamiliar child-unfamiliar adult</td>
<td>FFG, IPS, Pr, posterior STS</td>
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<tr>
<td>Nitschke et al., 2004</td>
<td>2-4 months; primiparous</td>
<td>own and other infant faces</td>
<td>own-other</td>
<td>OFC; positive correlation with pleasant mood</td>
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<td>Strathearn, Li, Fonagy &amp; Montague, 2008</td>
<td>5-10 months; primiparous</td>
<td>own and other happy, neutral and sad infant faces</td>
<td>own-other</td>
<td>mPFC, ACC, In, DLPFC, PMA, vSt, hCa, Pu, VTA, SN, S/M/ITG, AMY, Th, HYPO</td>
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<td>own happy-other happy</td>
<td>Pu, left SN, Th, left superior AMY</td>
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<td>own happy&gt;own neutral&gt;own sad</td>
<td>graded response in vSt</td>
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<td>Stratheran &amp; Kim (2013)</td>
<td>11 months; primiparous</td>
<td>own and other happy, neutral and sad infant faces</td>
<td>own and other</td>
<td>AMY</td>
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<td>own happy-own sad</td>
<td>AMY</td>
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<td>other sad-other happy</td>
<td>AMY</td>
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<td>Swain, et al. 2008</td>
<td>2-4 weeks; vaginal vs. caesarian delivery</td>
<td>own and other infant cry; white noise</td>
<td>own-other contrast, vaginal&gt;caesarian</td>
<td>HYPO, SP, STG, pons, cerebellum, Ca, Pu, Th</td>
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<tr>
<td>Kim et al., 2010</td>
<td>2-4 weeks</td>
<td>structural (VBM) and quality of maternal care; other infant cries; white noise</td>
<td>high maternal care, increased grey matter</td>
<td>SFG, MFG, OG, STG, FFG</td>
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<td>other, higher-lower maternal care</td>
<td>MFG, STG, FFG</td>
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<td>Kim et al., 2010</td>
<td>2-4 weeks and 3-4 months</td>
<td>structural change (VBM) across time</td>
<td>increased grey matter</td>
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<td>correlated with positive perception of baby</td>
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<td>HIP</td>
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<tr>
<td>Kim et al., 2011</td>
<td>2-4 weeks; breast- vs. bottle-feeding</td>
<td>own and other cry; maternal sensitivity</td>
<td>own-other, breastfeeding mothers</td>
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<td>S/IFG, right FFG, left S/MTG, In, Pr, St, AMY</td>
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<td>own-other, high maternal sensitivity @ 4 months</td>
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<td>right SFG, AMY</td>
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<td>Seifritz et al., 2003</td>
<td>parents (under 3yrs old) vs. non-parents</td>
<td>other infant cries and laughs</td>
<td>crying-control + laughing-control, women</td>
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<td>right AMY, pACC, left vPFC, In, left TPJ</td>
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<td>laughing-crying, non-parents</td>
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<td>Noriuchi, Kikuchi &amp; Senoo, 2008</td>
<td>16 months</td>
<td>own and other playing or distressed infants (dynamic video)</td>
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<td>dorsal OFC, Ca, right IFG, DMPFC, ACC, PCC, Th, SN, posterior STS</td>
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<td>Rantoe et al., 2004</td>
<td>4-8 months</td>
<td>own and other infant (dynamic video); neutral video (traffic)</td>
<td>infant-neutral video</td>
<td>visual processing regions, postcentral gyri</td>
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<td>visual processing regions, right DLPFC, right mPFC, left FP, OFC, left PCG, HIP, cerebellum</td>
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<td>Lorberbaum et al., 4-8 weeks</td>
<td>other infant cries; white</td>
<td>cries-noise and cries only</td>
<td>medial Th, mPFC, right OFC, midbrain,</td>
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<td>Study Details</td>
<td>Condition Details</td>
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<td>2002</td>
<td>Atzil, Hendler &amp; Feldman, 2011</td>
<td>4-6 months, synchronous vs. intrusive parenting</td>
<td>mother-infant interaction videos (own and other infants); plasma OXT</td>
<td>HYPO, St, lateral septal area</td>
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<td>cries-noise, not cries only</td>
<td>ACC, PCC</td>
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<td>synchronous mothers</td>
<td>left NAC</td>
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<td>mPFC</td>
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<td>synchronous mothers, right AMY correlations</td>
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<td>own-other</td>
<td>right IPL, ITG, PCG, claustrum, PR, hCa, NAC, S/MFG, ACC, postCG, body Ca, IOG, Th, In, SMG (AMY, uncorrected)</td>
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<td>2011</td>
<td>Barrett et al., 2011</td>
<td>3 months</td>
<td>own and other positive and negative infant faces</td>
<td>AMY, Th, S/MTG, cerebellum</td>
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<td>own positive-other positive</td>
<td>postCG, subgenual ACC, ventral Pu, STG</td>
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<td>own negative-other negative</td>
<td>parietal cortex, In, striatum, S/MTG, MFG</td>
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<td>positive-negative</td>
<td>lower trait anxiety, EPDS, and parental distress; higher positive affect</td>
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<td>own-other AMY, positive correlation</td>
<td>greater own cry-control noise in PAG, right In, OFC, ACC, mPFC correlated with ess HPA reactivity</td>
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<tr>
<td>2011</td>
<td>Laurent, Stevens &amp; Ablow, 2011</td>
<td>18 months</td>
<td>own and other infant cry; control noise; HPA reactivity to strange situation</td>
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* FP, frontal pole; OFC, orbitofrontal cortex; OG, orbital gyrus; mPFC, medial prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; MGF, middle frontal gyrus; SGF, superior frontal gyrus; PMA, primary motor area; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; In, insula; TP, temporal pole; AMY, amygdala; HIP, hippocampus; ITG, inferior temporal gyrus; MTG, medial temporal gyrus; STG, superior temporal gyrus; STS, superior temporal sulcus; postCG, postcentral gyrus; PCG, precentral gyrus; SMG, supramarginal gyrus; IPL, inferior parietal lobule; SP, superior parietal; IPS, intraparietal sulcus; TPJ, temporoparietal junction; Pr, precuneus; FFG, fusiform gyrus; IOG, inferior occipital gyrus; Th, thalamus; HYPO, hypothalamus; hCa, head caudate; Pu, putamen; NAC, nucleus accumbens; vSt, ventral striatum; VTA, ventral tegmental area; SN, substantia nigra; PAG, periacuicular grey;
Table 2.

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<tr>
<th>Demographic Measures</th>
<th>Non-PPD Mothers (n=17)</th>
<th>PPD Mothers (n=28)</th>
<th>Statistical Analysis</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>29.18 ± 1.19</td>
<td>30.64 ± 0.93</td>
<td>F(1,43) 1.02</td>
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<td>Education (% High School)</td>
<td>5.88%</td>
<td>14.29%</td>
<td>χ²=0.76</td>
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<tr>
<td>Delivery Method (Vaginal:Caesarian)</td>
<td>70.59%</td>
<td>75.00%</td>
<td>χ²=1.05</td>
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<td>Parity (Primiparous:Multiparous)</td>
<td>70.59%</td>
<td>64.43%</td>
<td>χ²=0.19</td>
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<tr>
<td>Feeding Method (Breast:Bottle)</td>
<td>70.59%</td>
<td>57.14%</td>
<td>χ²=0.81</td>
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<td>Clinical Measures</td>
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<tr>
<td>Edinburgh Postnatal Depression Scale</td>
<td>3.12 ± 1.07</td>
<td>8.29 ± 0.84</td>
<td>14.40</td>
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<tr>
<td>State-Trait Anxiety Inventory (Trait Version)</td>
<td>27.82 ± 1.98</td>
<td>44.86 ± 1.54</td>
<td>45.95</td>
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Chi-square test (df=1); PPD=Postpartum Depression, *indicates significant group difference at p<.05
**Table 3.**

<table>
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<tr>
<th>EPDS Visit 2</th>
<th>STAI-Trait Visit 2</th>
<th>CTQ Total</th>
<th>PSI Total</th>
<th>Care Mom</th>
<th>Intimate Relationship Quality</th>
<th>Maternal Worry</th>
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<td>Correlation Coefficient</td>
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<td>0.001</td>
<td>0.001</td>
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<tr>
<td>Ainsworth Total</td>
<td>MBQS</td>
<td>Duration of Holding</td>
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<td>0.961</td>
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Table 4.
Table 5.

5a.

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<th>MBQS</th>
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<th>EPDS Visit 2</th>
<th>STAI-Trait Visit 2</th>
<th>PSI Total</th>
<th>Parental Distress</th>
<th>Parent-Child Difficult Interaction</th>
<th>Difficult Child</th>
<th>Positive Affect</th>
<th>Care Mom</th>
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<td>-.250</td>
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Table 6.

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<th>Non-PPD Mothers (n=17)</th>
<th>PPD Mothers (n=28)</th>
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<td>p-value</td>
<td>r-value</td>
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<td>.046*</td>
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*indicates significant correlation (p<.05)
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**Side: L=Left hemisphere, R=right hemisphere; cluster size is in voxels; Z=peak Z-statistic for BOLD signal in cluster; x,y,z=3D coordinates in MNI space**
Table 8.

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<table>
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<td>Left Insula to TPJ</td>
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</table>
Figure 1.
Figure 2.

At 2-5 months postpartum:

Visit 1
- CIDI-V
- Edinburgh Postnatal Depression Scale
- STAI-T
- PANAS
- MADRS

Visit 2
- Edinburgh Postnatal Depression Scale
- STAI-T
- STAI-S (pre/post)
- MADRS
- Saliva

Visit 3
- Edinburgh Postnatal Depression Scale
- STAI-T
- STAI-S
- PANAS
- MADRS
- Childhood Trauma Questionnaire
- Life History Calendar
- Parental Stress Index
- Parental Bonding Instrument
- Maternal Attitudes Questionnaire
- Dyadic Adjustment Scale
- Life Events Calendar
- Interaction Video
- Saliva

Visit 1

1 week

Visit 2

1 week

Visit 3
Figure 3.
Figure 4.
Figure 5.

5a.

![EPDS Score](chart1.png)

5b.

![STAI-Trait Score](chart2.png)

5c.

![PANAS Score](chart3.png)
Figure 6.
Figure 7.
Figure 8.

8a.

[Bar chart showing maternal worry, negative self-image, lability, and need for nurturance factor scores (M +/- SEM) for Control and PPD groups.]

8b.

[Bar chart showing maternal self-confidence, relationship with father, feelings about children, information seeking, care-taking, and social confidence factor scores (M +/- SEM) for Control and PPD groups.]
Figure 9.

9a. [Bar graph showing Ainsworth Maternal Sensitivity Scale Score (M +/- SEM) for Control and PPD groups across categories: Acceptance, Availability, Cooperation, Sensitivity, and Ainsworth.Total.]

9b. [Bar graph showing MBQS Scores M +/- SEM for Control and PPD groups.]

9c. [Bar graph showing Time Spent Holding Infant (M +/- SEM) for Control and PPD groups.]
$9d.$
Figure 10.

Affect Rating Task Score (M ± SEM)

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<thead>
<tr>
<th>Category</th>
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<th>PPD</th>
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<td>Own</td>
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<tr>
<td>Other</td>
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<tr>
<td>Non-Infant</td>
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* Significant difference
Figure 11.

11a. Non-PPD Mothers

11b. PPD Mothers
Figure 12.

12a.

12b.

12c.
Figure 13.
Figure 14.
Figure 15.
Figure 16.

**STAI-T**

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- Left AMY-Right IC

**EPDS**

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- Left AMY-Right IC
- Right AMY-Right IC
Figure 17.
Figure 18.
Figure 19.

19a.

19b.
19c.

19d.
19e.
Figure 20.

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<td>0.4</td>
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<td>0.8</td>
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<td>-0.2</td>
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<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
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- Control
- PPD
Figure 21.

21a.

21b.
Figure 22.

22a.

[Graph showing the relationship between MBQS Score and Average Left AMY BOLD Response for OwnView-OtherView for Non-PPD and PPD groups.]

22b.

[Graph showing the relationship between MBQS Score and Average Right AMY BOLD Response for OwnView-OtherView for Non-PPD and PPD groups.]
Figure 23.

23a.

23b.
Figure 24.

24a. 

![Graph 1: Non-PPD vs. Ainsworth Maternal Sensivity Score for Left BLA-Left IC Parameter](chart1.png)

24b. 

![Graph 2: Non-PPD vs. PPD vs. Ainsworth Maternal Sensitivity Score for Right BLA-Left IC Parameter](chart2.png)
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