The Relationship Between Consistent Early Care and Brain Responses to Emotional Infant Stimuli in Recently Postpartum Mothers: An fMRI Study

by

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A thesis submitted in conformity with the requirements for the degree of Masters of Arts

Department of Psychology

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There is a paucity of research examining the neurobiological functioning of new mothers who have experienced parental loss during development. The current study investigated the relationship between inconsistent (IC) versus consistent (CC) care and brain activity in regions that comprise a putative neurobiological model of mothering. Mothers were shown positive and negative pictures of their own and an unfamiliar infant. Through repeated measures ANOVAs, it was found that BOLD activity was greater for own infant in the nucleus accumbens (NAC) and amygdala (AMY) and that positive pictures elicited greater BOLD response in the NAC, AMY and anterior cingulate cortex. Interestingly, IC mothers show an even greater response own infant in the NAC and left hypothalamus (HYPO). In the left dorsolateral prefrontal cortex, IC mothers showed greater BOLD response to other infant. Thus, functioning of the maternal circuit, which includes areas strongly implicated in reward, may be altered by early experiences.
Early experiences & brain response to infants

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Early experiences & brain response to infants

The Relationship Between Adverse Early Experiences and Brain Responses to Emotional Infant Stimuli in Recently Postpartum Mothers: An fMRI Study

**Mothering: An Overview**

Mothering a child is a responsibility that the majority of human females will undertake at some point in their lives; as of 2008, the average births per woman in Canada alone was 1.6, a rate that is much higher in developing countries (World Bank, World Development Indicators). Although motherhood is something shared by almost the entire global female population, the experiences and practices, while overlapping to a great extent, are still unique, individually varied and shaped by a variety of factors. Cross-cultural similarities in mothering behaviours are many and include nursing, singing, and contingent responding to distress in the infant (Leiderman & Leiderman, 1977; Corter & Fleming, 2002; Bornstein, Tal, & Tamis-LeMonda, 1990; Cote & Bornstein, 2005). Societal and cultural norms, prior experience, level of partner support, personality and age are some of the variables that impact maternal behaviour (Belsky, 1984; Corter & Fleming, 2002; Feldman, 2007; Fleming, 2005; Bornstein, Hendricks, Haynes & Painter, 2007). Bornstein, Hendricks, Haynes and Painter (2007) have identified three domains that are significantly and uniquely related to maternal and child behaviour: contextual factors (i.e., socioeconomic status, maternal employment status, and fathering), parental characteristics (i.e., personality, intelligence), and child characteristics (i.e., gender, age, sociability).

Behaviourally, mothering has been well characterized. Responsiveness and sensitivity are two elements of maternal behaviour in humans from which much variation can be derived. Maternal responsiveness reflects mothers’ reaction to their baby’s behaviour and involves separate factors such as promptness, appropriateness, and contingency (Bornstein & Tamis-LeMonda, 1989). Highly sensitive mothers appropriately and rapidly respond to infant signals (Ainsworth & Wittig, 1969) and beyond this, do so with warmth and affection, providing the highest quality, most optimal care elicited according to the needs of the infant. Research consistently demonstrates that highly sensitive parenting fosters emotionally, cognitively and socially robust infant development (Ainsworth, Blehar, Waters & Wall, 1978; Eshel, Daelmans, de Mello & Martines, 2006; Crockenberg & Leekerke, 2004; Crockenberg, Leekerke & Barrig Jo, 2008; Landry, Swank, Assel, Smith, Vellet, 2001). Recently, Leekerke, Blankson and O’Brien (2009) found that maternal sensitivity may be differentially related to specific types of infant behaviours when they demonstrated that mothers’ sensitive responses to distress, but not nondistress, was related to affect regulation in temperamentally reactive infants.

Infant development is greatly influenced by the quality of maternal care received. For this reason, it is important to understand what regulates mothering itself and what determines individual differences in mothering behavior. With this in mind, the present study explores the relation between 1) mothers’ affective and brain response to infant stimuli that vary in emotion and familiarity, 2) mothers’ own earlier experiences being mothered, 3) their sensitivity towards their own infants during an interaction.

**Early Experience**

Across species, the quality of parenting throughout early childhood and adolescence has consistently been shown to influence normative development. Unfortunately, high quality parenting is not a reliable experience. According to the Canadian Incidence Study of Reported Child Abuse and Neglect (2003) approximately 5% of children aged 1-15 will report some form of maltreatment, a number that has doubled since 1998, and in 82% of cases a parent is the perpetrator. Additionally, in Canada, the divorce rate (before the 30th wedding anniversary) has
been above 35% since at least the 1990s (Lambert, 2009). Since according to Heim, Plotsky and Nemeroff (2004), in humans, the most salient forms of early life adversity are sexual, physical and emotional maltreatment, as well as parental loss, due to death or divorce/separation, the aforementioned statistics are startling and underscore the need for research into the developmental effects of early life adversity, with the potential to inform both early and adult prophylactic and intervention programs.

Numerous empirical studies have examined the experience of early childhood trauma in relation to the course of development of the brain and behaviour. Specifically, early disruptions in family of origin and childhood adversity have been related to alterations in cognitive (executive function), emotional (depression), physiological (HPA axis) and behavioral (parenting) function in adulthood (reviewed in Korosi & Baram, 2009). Many of these functions are highly interrelated. Research with both human and non-human animals provides a window into the effects of early life trauma on adult functioning.

Animals studies, both rodent and primate, provide evidence that the early maternal environment can produce lasting effects on the brain and behaviour, so lasting that they are transmitted across generations (Fleming Kraemer, Gonzalez, Lovic, Rees & Melo, 2002; Maestripieri, Lindell, & Higley, 2007). For example, in rodents, pups of mothers who provide high levels of licking and grooming are more likely to exhibit high levels of licking and grooming themselves to their own offspring, and the reverse is true of low licking and grooming (Francis, Diorio, Liu & Meaney, 1999; Francis, Young Meaney & Insel, 2002). In primates, cross-fostered rhesus macaques, reared by abusive or nonabusive foster mothers, show similar rates of rejection and grooming behaviour during the first 3 months postpartum towards their own young as shown by their foster mothers, however their contact-making behavior remains similar to their biological mothers (Maestripieri, Lindell, & Higley, 2007). This implies that the complex composition of maternal behaviour is guided by both environment and genetics. Thus, it has been suggested that this intergenerational transmission of mothering may occur through developmental, pathophysiological changes that alter neurobiological and neuroendocrinological systems involved in stress and mothering (Fleming, et al., 2002; Maestripieri, Lindell & Higley, 2007; Meaney, 2001).

Using evidence from retrospective ratings of the quality of early care and current behavioural assessments from mother-infant interactions, there is support for the intergenerational transmission of parenting styles in humans as well, which includes factors such as bonding, attachment, and maternal rejection (Belsky, 2005; van Ijzendoorn, 1992; Benoit & Parker, 1994; Miller, Kramer, Warner, Wickramaratne & Weissman, 1997). Further highlighting the importance of studying the early environment, the strength of association between adverse childhood experiences, such as sexual or physical abuse, and adult somatic, psychological and substance abuse problems is comparable to the experience of current abuse in adulthood (McClelland et al., 1997). Moreover, mothers who experience inconsistent care, compared to mothers living with both parents throughout early life, show less affectionate behavior and less contingent ‘sensitive’ responding to their babies in adulthood (Krupa, Coombs, Zinga, Steiner, & Fleming (2005); Gonzalez, Jenkins, Steiner, & Fleming, under revision, Psychoneuroendocrinology). Furthermore, risk for the development of depression, anxiety and other stress-related disorders during adolescence and adulthood is increased in children exposed to early adverse experiences (Rey, 1995; Heim & Nemeroff, 2001; Martin, Bergen, Roeger & Allison, 2004; Halligan, Murray, Martins & Cooper, 2007; McClelland et al., 1997; reviewed in Neigh, Gillespie & Nemeroff, 2009; Heim & Nemeroff, 1999), and then, only in certain individuals, suggesting a role for a genetic predisposition to the effects of early adversity.
Interestingly, Kretchmar and Jacobvitz (2002) examined the relationship between current experiences with one’s mother and compared them to observations of interactions with one’s own infant at various time points. They found that a more balanced current relationship with one’s mother was strongly associated with current positive parenting dynamics, including factors such as sensitivity, intrusiveness and attachment style. This further supports the notion that mothers internalize experiences with their caregiver and emulate them with their own offspring.

**Effects on the Brain**

Although research is scant, as with animal models, the mode of intergenerational transmission of caregiving in humans appears to be through neurobiological alterations to brain areas implicated in mothering and the stress response (Heim, Meinlschmidt, Nemeroff, 2003; Heim, Plotsky & Nemeroff, 2004; Heim et al, 2000; Meaney, 2001). The neurobiological consequences of early life stress include reduced volume of the mid-portion of the corpus callosum and attenuated development of the left neocortex, hippocampus and amygdala, areas that have either delayed postnatal development, a high density of glucocorticoid receptors and/or some measure of neurogenesis (as reviewed in Teicher, Andersen, Polcari, Anderson, Navalta and Kim, 2003). Individuals who experienced early maltreatment report more anhedonia and depressive symptoms and display decreased blood-oxygen-level-dependent (BOLD) activity in the left, but not right, basal ganglia to reward cues compared to non-maltreated counterparts (Dillon, Holmes, Birk, Brooks, Lyons-Ruth & Pizzagalli, 2009). In comparison to those reporting high care, self-reported low quality maternal care in early development is also associated with decreased hippocampal volume compared in mothers (Buss et al., 2007). In another study Kim, Leckman, Mayes, Newman, Feldman and Swain, (2010) found that mothers who reported greater perceived early maternal care had larger grey matter volumes in the superior and middle frontal gyri, orbital gyrus, superior temporal gyrus and fusiform gyrus. As well, mothers who reported higher quality maternal care in childhood also exhibited greater BOLD response in the middle frontal gyrus, superior temporal gyrus and fusiform gyrus in response to infant cries, and mothers who reported lower quality maternal care exhibited increased BOLD response in the hippocampus.

With the exception of these few studies, there is a paucity of research examining the neurobiological processing of new mothers who have experienced parental loss or personal trauma, during early development. In fact, to date, no studies have directly examined the impact specifically of early separation from one or both parents on functional neurobiology in new mothers. The importance of the early maternal environment, in particular one devoid of stress and trauma, in the neurobiological and mental functioning of developing children highlights the need for research in this field.

**Neuroanatomy of Mothering**

In order to understand the rationale behind the choice of brain sites explored in the present study, a brief overview of the neuroanatomy relevant to mothering that constitute the focus of the present study will now be provided.

Mammalian maternal behaviour is governed by a complex set of neural interactions showing established cross species similarity (Numan, Fleming & Levy, 2006). In most mammals the changes to the hormonal milieu associated with parturition trigger a cascade of neurological adaptations that result in typical maternal behaviour. Numan and colleagues have demonstrated that the neurobiology of mothering in rodents relies heavily on downstream projections from the medial preoptic area (mPOA) of the hypothalamus (HYPO) and bed nucleus of the stria terminalis (BNST), as well as afferents from surrounding sensory, limbic and cortical systems (Numan & Insel,
In rodents, the mesocorticalimbic dopaminergic system is thought to act on various psychobiological systems to produce species typical maternal behaviour (Numan & Insel, 2003). Furthermore, parenting-induced neural plasticity extends to brain regions beyond just the HYPO and is, in many cases, long-lasting (Kinsley and Lambert, 2008).

Very recently, neuroimaging research has sought to uncover similar affective, experience-related, hedonic and attention systems comprising typical human maternal behaviour, showing promising early successes (see Swain, Lorberbaum, Kose & Strathearn, 2007). Nitschke, Nelson, Rusch, Fox, Oakes & Davidson (2004) have demonstrated that positive mood ratings are correlated with increased activation in the orbitofrontal cortex (OFC), an area previously implicated in maternal affect, when viewing pictures of one’s own infant. Additionally, Bartels & Zeki (2004) demonstrated increased BOLD response in the striatum, thalamus, OFC, anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) when viewing pictures of one’s own child, however age of the child varied from 9 months to 3.5 years. Leibenluft, Gobbin, Harrison and Haxby (2004) allowed parents to chose pictures of their children (aged 5-12 years) and found greater neural activation in the amygdala (AMY), insula, ACC, and posterior superior temporal sulcus (pSTS). Examining the neural response to infant stimuli of a different modality, women (mothers or not), compared to men, show decreased activity in the ACC in response to infant laughing and crying. Furthermore, activity in the amygdala middle cingulate cortex, insula, ventral PFC, and temporoparietal junction was found to be greater in parents only for infant cry stimuli, whereas it was greater in nonparents for infant laughing stimuli (Seifritz, Esposito, Neuhoff, Luthi, Mustovic, Dammann, von Bardeleben, Radue, Cirillo, Tedeschi & Di Salle, 2003). In another study by Lorberbaum and colleagues (2002), thalamocingulate neural circuitry was engaged to a greater degree when mothers listened to infant cries in comparison to white noise or nothing.

These studies and others demonstrate great potential in identifying distinct maternal circuitry, however, participant populations in each study vary in size, parity, age, and postpartum stage. These studies also differ in the modality of infant cue (cry vs picture), their use of control stimuli, magnet strength, length of time between stimulus acquisition and scan, and random versus fixed effects analyses. The wide methodological variation employed in the small body of literature examining the neural mechanisms of human mothering underscores the need for further research in this field.

*Putative Model of Maternal Neural Circuitry: Regions of Interest*

Recent neuroimaging work suggests that typical human maternal behaviour shares neuroanatomy with other rodents and primates and involves the interaction between maternal-specific and general brain systems that are important in affect, executive functioning, motivation/reward and attention (Numan, Fleming & Levy, 2006). Additionally, Croxon et al. (2005) was able to establish considerable cross-species similarity, between humans and macaques, in connectivity patterns within the prefrontal cortex to subcortical as well as cortical regions. Thus, we have defined various regions of interest derived from a putative model of the functional neuroanatomy of human mothering, which includes regions that overlap with animal models of mothering (from Barrett & Fleming (in press, 2010); see Figure 7a).

**Dorsolateral Prefrontal Cortex**

As defined by Petrides and Pandya (1994; 1999; 2004), the human dorsolateral prefrontal cortex (DLPFC) consists of Brodmann’s areas (BA) 46 and 9 and 9/46 (see Figure 1). BA 46 lies on the middle frontal gyrus...
whereas BA 9 lies on the superior frontal gyrus as well as the middle frontal gyrus (caudal to BA 46). BA 9/46, as first outlined by Petrides and Pandya (1994), was designated as such because of the cytoarchitecture similarity between this portion of regions 46 and 9 (namely a well-developed layer IV) as well as the fact that in the map of the monkey frontal cortex (Walker, 1940) this area was called 46, not 9 as in the human map.

The DLPFC (BA 46, 9 and 9/46) receives input from multimodal areas (the superior temporal sulci) as well as paralimbic areas (the rostral superior temporal gyrus, the anterior and posterior cingulate cortices, and the retrosplenial cortex). Morphological studies have determined that the DLPFC is distinctively connected to the hippocampus via direct axon projections to the retrosplenial cortex (Morris, Petrides & Pandya 1999; Petrides & Pandya, 1999). A distinguishing connectivity feature within the DLPFC is that BA 9 does not receive input from the lateral and media parietal cortex.

From lesion studies conducted with non-human primates, the DLPFC appears to have a general function of actively monitoring, but not necessarily maintaining, multiple sets of stimuli in working memory (Petrides & Pandya, 2004; Petrides, 1991, 1994, 1996, 2005). In other words, although the capacity to hold information online, or to recognize stimuli, does not appear to be disrupted by DLPFC lesions, the ability to monitor the state of information, which involves considering actual, intended, predicted and changing representations of stimuli, is severely disrupted. The unique DLPFC-hippocampal connectivity via the retrosplenial cortex is potentially responsible for the role of the DLPFC in working memory (Petrides, 2005). According to Petrides (2005), this delineates the specialized role of the DLPFC as being responsible for “conscious active control of planned behaviour and cognition”. The complexity and fast behavioural adaptation required of typical maternal behaviour emphasizes the probable requisition of this brain area.

Altered DLPFC metabolism has been found in studies of participants with major depression, in comparison to non-depressed individuals, at baseline (Brody, Barson, Bota & Saxena, 2001). This may be due to the high degree of interconnectivity with paralimbic areas involved in affective processing (George, Ketter & Post, 1994). A recent review by Fitzgerald at colleagues (2006) that attempted to outline a reliable pattern of DLPFC activity in subjects with major depression failed to do so. Instead they found studies that report both increased and decreased activity or blood flow, in both hemispheres and in various sites (i.e., BA 9, 46 or 9/46), underscoring the need for continued research in this area. Due to the higher incidence of major depression perinatally (Dennis, 2004), the DLPFC may be of particular interest when studying maternal behaviour.

**Orbitofrontal Cortex**

The OFC is located on the orbital surface of the prefrontal cortex. While the area is most well defined anatomically in non-human primates as area 14 medially, area 13/25 caudally, areas 11 and 12 laterally, around the inferior convexity, and the ventral part of area 10 toward the frontal pole (Walker, 1940), Petrides and Pandya (1994) have recently attempted to reconcile differences in human and monkey maps. As such, the lateral OFC in humans includes area 47/12 caudally, whereas medially, areas 10 and 25 are the most dorsal and caudal boundaries, respectively (Petrides & Pandya, 1994; Elliot & Deakin, 2005). Ventrally, the OFC includes area 11, which extends medially and laterally. These divisions, however, are still the seat of much debate (see Figure 2; see Ongur, Ferry & Price, 2003 for in depth comparison of architectonic subdivisions using various staining techniques).

OFC connectivity seems to be organized based on functionally distinct roles. The OFC receives inputs from both sensory (taste and olfactory) and visual association areas, somatosensory and temporal cortices, as well as the
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subcortex/striatum where the OFC receives projections from the AMY and mediiodorsal thalamus (Rolls, 1990; Rolls & Baylis, 1994; Barbas, 1995; Morecraft, Geula & Mesulam, 1992; Krettek & Price, 1977; reviewed in Elliot & Deakin, 2005). OFC afferents include the inferior temporal, entorhinal and anterior cingulate cortices, as well as the HYPO, ventral tegmental area and caudate nucleus (Kemp & Powell, 1970; Nauta, 1964). Regionally specific, connections within the anterior OFC are with the granular insula, association cortex, mediiodorsal thalamus, inferior parietal lobule and DLPFC, within the medial OFC are with the cingulate, retrosplenial and entorhinal cortices, as well as the hippocampus, and anterior thalamus, and most caudally within the lateral OFC within the AMY, midline thalamus, noninsocortical insula and temporal pole (Mesulam, Muñson, Levey & Wainer, 1983; Morecraft, Geula & Mesulam, 1992; Vogt & Pandya, 1987; Barbas & De Olmos, 1990; Mesulam & Muñson, 1982; Yeterian & Pandya, 1988; reviewed in Elliot & Deakin, 2005).

The OFC has primarily been implicated in reinforcement processing and inhibitory control (Elliot and Deakin, 2005). More specifically, the OFC is where the brain makes judgments about stimulus value, predictability and behavioural choice. With respect to inhibitory control, the OFC is responsible for prompt adaptation of behaviour in response to changing conditions. OFC lesions or damage disrupt social and emotional behaviour and produce reasoning and judgment deficits (e.g., IOWA gambling task) (Elliot & Deakin, 2005; Bechara, Damasio, Damasio & Anderson, 1994; Damasio, 1994; Rolls, Hornak, Wade & McGrath, 1994). The role of the OFC in behavioural adaptation, positive emotion and social reasoning behaviour makes it important in the context of mothering, which requires behavioural flexibility in response to contextual social cues provided by one’s infant. Furthermore, the OFC has been implicated in deciphering the affective value of a stimulus or event (Rolls, 1999; 2000), a task that normative mothering may require. In fact, as aforementioned, a study by Nitschke et al. (2004) found that OFC activation during viewing of infant pictures was significantly correlated with mothers’ ratings of positive and negative mood.

Anterior Cingulate Cortex

As defined by Brodmann (1909), the ACC extends from the ventral portion of the corpus callosum (BA 33 and BA25) around the genu to include BA24 and 32, terminating in the retrosplenial areas in the caudal isthmus of the posterior cingulate gyrus. This original definition of the ACC has come under much debate as neuroimaging studies find differential patterns of activation within the rostral compared to caudal portions of the ACC (Palomero-Gallagher, Mohlberg, Zilles & Vogt, 2008). A recent cytoarchitectural analysis of the sub- and perigenual cingulate cortices (sACC and pACC, respectively) reveals that they are distinct (Johansen-Berg et al., 2008). Although BA 33, 32 and parts of 24 extend ventral to the genu, most studies focus on BA25 when they refer to the subgenual cingulate, and indeed this area is the only cingulate area located solely subgenially (Palomero-Gallagher, Mohlberg, Zilles & Vogt, 2008; see Figure 3). Relatedly, area 24c is the only area located solely in the perigenual region of the cingulate. Paus and colleagues have identified substantial variation in the sulcal anatomy of the human ACC (Paus et al., 1996a, Paus et al., 1996b), thus a degree of individual specific variation in the cytoarchitectonic boundaries of this region likely exists, making precise delineation difficult.

The ACC is extensively connected to frontal, limbic and viscero motor brain regions (Johansen-Berg et al., 2008). The pACC is connected with the medial prefrontal, anterior midcingulate cortex, nucleus accumbens (NAC) and HYPO. The sACC has connections, many of which are reciprocal, with the NAC/ventral striatum (Kunishio and Haber 1994; Haber, Kushino, Mizobuchi & Lynd-Balta, 1995; Haber, Kim, Mailly & Calzavara, 2006; Ferry,
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Ongur, An & Price (2000), AMY (Freedman et al. 2000), HYPO (Ongur, An & Price, 1998; Freedman, Insel & Smith, 2000; Barbas, Saha, Rempel-Clower & Ghashghaei, 2003), OFC, DLPFC and lateral PFC and the dorsal cingulate cortex (Vogt and Pandya 1987; Carmichael and Price 1996). Despite overlap in the connectivity patterns of the s- and pACC, there are key differences in the strength of these connections that are responsible for the uniqueness of function (Johansen-Berg et al., 2008).

According to Paus (2001), the interaction between regulatory and executive networks through connectivity with the ACC places it at the seat of “willed control of behaviour”. Research examining ACC function seems to converge into three distinct domains: motor control over behaviour, involvement in cognition through connections with the neocortex, and arousal/drive state modulation. Neuromodulators (e.g., dopamine and CRF) act on the ACC to guide the motor-cognitive interface relative to alterations in emotional and motivational states (Paus, 2001). The suggested role of the sACC in affect driven behavioural modulation and the experience of negative mood states has made it the target of deep brain stimulation (DBS) for depression (Mayberg et al., 1999; Mayberg, 2003). As aforementioned, there is an increased incidence of depression in the postpartum period (Dennis, 2004), which makes the ACC a region of particular incidence when studying the neural pattern of response to infant related cues in recently postpartum mothers.

Hypothalamus

The HYPO is located in the ventral portion of the diencephalon, ventral to the thalamus. It is comprised of multiple small nuclei located, with some overlap, in anterior (the medial preoptic, supraoptic, paraventricular, anterior hypothalamic, suprachiasmatic, lateral preoptic and lateral nuclei), tuberal (the dorsomedial hypothalamic, ventromedial, arcuate, lateral and lateral tuberal nuclei) and posterior portions (the mammillary, posterior and lateral nuclei) (Bears, Connors & Paradiso, 2007). The HYPO has numerous reciprocal connections within the central nervous system with areas such as the brainstem, AMY, septum, olfactory bulbs, and frontal cortex, and communication is via neuron connections as well as endocrine hormones (Bears, Connors & Paradiso, 2007).

Of particular interest in the study of maternal behaviour is the mPOA of the rostral HYPO. The mPOA is of central significance in the approach-avoidance model of mothering (Rosenblatt & Mayer, 1995) as it is involved in inhibiting neural systems that promote withdrawal behaviours while jointly stimulating appetitive neural systems that promote attraction towards infant-related stimuli, in rodents (Numan & Insel, 2003). The mPOA contains receptors for prolactin, progesterone and estrogen, where estrogen acts to stimulate oxytocin receptor expression, and studies demonstrate that parturitional hormones act on the mPOA to stimulate maternal behaviour in rodents (Numan & Insel, 2003). It has been proposed that through a combination of parturient hormones and stimulation from pups, maternal responsiveness is initiated and neural circuitry controlling avoidance responses, which are normally active in virgin female rats, are suppressed (Numan & Insel, 2003). Although there is extensive evidence outlining the importance of the mPOA in rodent maternal behaviour, evidence delineating a functionally specific role for the mPOA in typical human maternal behaviour is lacking.

Nucleus Accumbens

The nucleus accumbens is a small cluster of neurons within the striatum located at the junction between the caudate head and putamen that consists of two anatomically and functionally distinct regions, the shell and core. The NAC has mainly GABAergic afferents to the ventral pallidum (VP) which itself projects to the medial dorsal nucleus of the dorsal thalamus, which in turn projects to the prefrontal cortex and striatum. Additional outputs from
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the NAC are to the substantia nigra and reticular formation. NAC efferents include the prefrontal association areas and basolateral amygdala (BLA), both of which are glutamatergic, as well as the ventral tegmental area (VTA), which is dopaminergic (Pennartz, Groenewegen & Lopes Da Silva, 1994).

Neuronal activity within the NAC is thought to be modulated by dopaminergic input from the VTA via the mesolimbic dopamine system. Rewarding stimuli, such asamphetamine, cocaine, sexual behaviour and pups have consistently been associated with robust increases dopamine (DA) activity in the NAC (reviewed in Pecina, Smith & Berridge, 2006). Mogenson & Nielsen, (1983) have proposed that this increase in DA activity in the NAC in response to rewarding stimuli functions to decrease GABAergic output to the VP, which as aforementioned has connections with the thalamus, prefrontal cortex and striatum. In humans, a study by Glocker et al., (2009) found that the NAC was activated by the baby schema, highlighting the potential role of the NAC in human goal-directed maternal behaviour, and potentially memory for infant-like features. This is particularly interesting as the NAC shell, but not core, is involved in long-term retention of pup-driven maternal responsiveness (maternal memory) in rodents as well (Li & Fleming, 2003; Numan, Fleming & Levy, 2006).

**Amygdala**

The amygdala is a mass of grey matter located in the anterior part of the temporal lobe, comprised of two main divisions: the corticobasolateral amygdala (CBL) and the centromedial extended amygdala (EA). The CBL includes the lateral, basolateral, basomedial and cortical nuclei and is primarily glutamatergic (with GABAergic interneurons), whereas the primarily GABAergic EA is comprised of two structurally and functionally discrete regions: the central and medial extended amygdala. According to Price (2003), using evidence from rodent, feline and non-human primate models, there are three main connection systems between the AMY and the rest of the brain: a sensory forebrain system, a brain stem/hypothalamic system and an emotional forebrain system, all of which have mainly reciprocal connections. The sensory forebrain system involves the olfactory cortex, ascending taste/visceral pathways, the posterior thalamus, and sensory cortical associations areas. The brain stem/hypothalamic system (including the HYPO, periaquiductal gray (PAG), reticular formation, ventrolateral medulla and vagal nuclei) appears to be involved regulating visceral responses triggered by emotional stimuli. Finally, the emotional forebrain system shares connections with the orbital and medial prefrontal cortex, the medial thalamus, the ventromedial striatum (including the NAC, caudate and putamen), ventral pallidum, HYPO and PAG.

In general, the AMY guides behaviour in response to motivationally, emotionally and socially relevant stimuli (Adolphs, 2003). Relevant to mothering, in rodents, the medial AMY 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 amygdalar 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,
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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 of the neural correlates of mothering.

Research Aims

Using a region of interest (ROI) approach, the present study sought to investigate the neural underpinnings of human mothers’ response to own and other infant stimuli of varying emotional intensity, and how differences in consistency of care across early development, as well as early adversity, are related to brain activity. By investigating how disruptions to the early rearing environment, in addition to experiencing some form of early trauma, manifest at the neurological level, we will be elucidating one of the variables that influences the uniqueness of the maternal experience. Over the course of the study mothers provided a self-report rating of their early experiences in the family of origin and completed a 30-minute functional magnetic resonance imaging (fMRI) scan where they viewed and rated pictures of their own and an unfamiliar baby that are positive and negative.

We predicted that mothers would show greater BOLD response in all of the ROIs in our maternal neural circuit for own compared to other infant, regardless of the emotional valence of the picture. We also expect that affective valence of the pictures will be related to infant-specific neural activity in brain regions involved in the hedonic quality of stimuli and affective states, and in brain regions that are essential for mothering. A main prediction is that positive infant stimuli will be more rewarding/less aversive than negative pictures. This will be reflected by greater activity in reward-related brain regions (e.g., NAC) for positive pictures, and greater activity in brain regions linked more to negative affect (e.g., pACC) when mothers view negative compared to positive pictures, and whereas, in brain regions integral to the onset of maternal behaviour (e.g., MPOA/anterior hypothalamus) or that are involved in affective processing in general (e.g., AMY) there will be no differences in activity for positive compared to negative pictures. The ‘direction’ of activity may change depending on whether the regions are predominantly excitatory or inhibitory. We eventually hope to discover patterns of brain activity in mothers for emotional baby pictures distinguished by varied patterns of early care and see how this is related to quality of interaction with their infants. Here, we predict that mothers with inconsistent early care will be less sensitive mothers behaviourally, and this will be reflected by less activity, compared to mothers with consistent early care, in our maternal neural circuit when viewing pictures of one’s own infant, regardless of the affective valence. Although, it is of note that, as this is the first study to relate parental separation as a measure of early adversity to brain activity in new mothers in response to infant stimuli, the study is largely exploratory, and as such, specific predictions relating to how early experience will impact these regions' responses are tentative.

Methods

Recruitment Procedures

Twenty (7 primiparous, 13 multiparous) healthy, right-handed, English speaking women aged 25-36 with full-term (38-40 weeks), singleton births were recruited from the maternity ward at St. Joseph’s Hospital in Hamilton, ON (see Table 1 for a summary of demographics). Exclusion criteria for all participants included presenting with serious suicidal, homicidal or infanticidal risk, the infant or mother having a serious medical condition which required treatment, involvement of Children’s Aid Services (CAS), current diagnosis or history of psychiatric disorder or taking medication at the time of the experiment. Research ethics boards at St. Joseph’s Hospital Hamilton and the University of Toronto approved the experiment. Figure 4 displays an overview and
timing of the experimental design. Mothers were compensated $50 for their time and the baby received a small toy. They also received copies of their own infant’s pictures, the videotaped interaction and a picture of their brain.

*Measures*

As part of our multidimensional assessment of maternal factors, we assessed maternal behaviour, maternal responsivity and maternal mood as well as strongly-related or influencing factors such as early life experiences, stress and relationship quality.

**Maternal Affect/Mood**

*The Hamilton Anxiety Scale:* (HAMA), (Hamilton, 1959) is a 14-item clinician-rated tool to assess severity and/or remission of anxiety symptoms. Validation studies have reported reliability and validity scores of .74 and .63 respectively.

*The Edinburgh Postnatal Depression Scale:* (EPDS) (Cox, Holden & Sagovsky, 1987) is a 10-item self-report scale designed to screen for PPD. It has well-established sensitivity (84-100%) and specificity (82-88%; Eberhard-Gran, Eskild, Tambs, Opjordsmoen & Samuelsen, 2001).

*The State-Trait Anxiety Inventory (STAI):* (Spielberger, Gorsuch, & Lushene, 1970; Spielberger, 1996) is a self-report scale consisting of two forms of 20-items each to measure components of state and trait anxiety. The scale has good reliability (.65 to .86) and well-documented sensitivity to change (McDowell & Newell, 1996).  

*The Positive and Negative Affect Scale (PANAS):* (Watson & Clark, 1994) consists of a 60-item scale that measures both positive and negative affect. The two general PANAS scales provide reliable, valid, and largely independent measures of the higher order Positive Affect and Negative Affect dimensions (reliability scores of .83-.90).

*The Montgomery-Asberg Depression Rating Scale (MADRS):* (Montgomery & Asberg, 1979) is a brief tool that will be used to assess severity and/or remission of depressive symptoms. The scale has good psychometric properties (reliability score, .81).

**Early Experience**

The difficulty with measurement in the area of early experience is that accuracy of retrospective report for subjective psychological states and family processes has been found to be low (Henry, Moffit. Caspi, Langley & Silva, 1994) and that current depression has been found to augment these recall biases (Prescott, Bank, Reid, Knutson, Burraston & Eddy, 2000). However, the more concrete the questions, the less biased the retrospective report and measures of early adversity (the Early Experience Questionnaire and Life History Calendar), the stronger the validity. For these instruments retrospective accounts obtained in adulthood agree well with measurement of the family environment made during childhood (Cohn, Campbell, Matias & Hopkins, 1990; Prescott et al., 2000).

*The Life History Calendar (LHC):* (Caspi et al., 1996) is a brief questionnaire to record the history of who the subject lived with while growing up (1-19 years). Reliability ranges from 72% to 92% (Amato, 1994; Henry, Caspi, Moffit & Silva, 1996)

*The Childhood Trauma Questionnaire (CTQ):* (Bernstein et al., 1994; Bernstein, Stein & Newcomb, 2003) is a 28-item brief self-report questionnaire that retrospectively assesses childhood abuse experiences among adolescents and adults. It assesses five types of abuse (physical, emotional and sexual abuse; emotional and physical neglect). It has good test-retest reliability ranging from 0.66 to 0.94 over a 2 to 6 month interval (Paivio and Cramer, 2004; Bernstein et al., 1994) and good convergent validity with therapists’ ratings of childhood abuse (Bernstein et
Behavioural Observations

Videotaped Mother-Infant Interaction: Subjects participated in a 20 minute videotaped non-feeding interaction session. Mothers were asked to interact as they normally would while remaining within the camera's view. Maternal sensitivity was coded using the Ainsworth Maternal Sensitivity Scale (MCS) (Ainsworth & Wittig, 1969). The MCS consists of four nine-point Likert rating scales: acceptance vs. rejection; accessibility vs. ignoring and neglecting; cooperation vs. interference; and sensitivity vs. insensitivity. Higher scores indicate higher quality of maternal interactions (reliability scores of .81; Stiles, 2004).

Early Life Adversity

Early life adversity was assessed with the LHC. Participants were asked if they had lived with both biological parents continuously from the age of 0 to 19 years. Mothers answered either “yes” or “no” and were subsequently categorized into two groupings of consistent care (CC) and inconsistent care (IC), respectively.

Procedure

Mothers completed three visits: a photo shoot, fMRI session and home visit (see Measures and Figure 4). Before visit 1, participants were screened by telephone for scanning eligibility and presence of postpartum depression (using the EPDS). On all three subsequent visits mothers completed the EPDS to assess any change in depressive symptomology. On all visits mothers also completed the HAM-A, MADRS, STAI-S and -T and PANAS.

For visit 1, at approximately 3 months postpartum, mothers were invited to a photo shoot at St. Joseph’s Hospital. Here, a professional photographer obtained a minimum of 20 positive (smiling) and 20 negative (crying) facial expressions of each baby taken on a black background with standard lighting source and levels. Before visit 2, photographs were cropped, resized, adjusted for brightness and masked such that only the infant face was visible. All stimuli were then rated by an independent set of females for intensity of emotion (positive, negative). Ratings were made on a 5-point Likert scale with -2 = very negative and 2 = very positive (see Figure 6 for example of the baby face stimuli). This simple rating scale was chosen because it allows for many stimuli to be rated quickly and it is the same scale the mothers use during the fMRI task. In a pilot study, we found that positive baby faces were consistently rated at a lower intensity that negative baby faces. Thus, for consistency across moms, the 6 faces chosen to comprise the positive and negative stimulus sets must have had a mean emotion rating of approximately 0.67 and -1.95 respectively. For each mother, own baby stimuli to be presented during the fMRI were randomly coupled with an “unfamiliar” baby from our stimulus set (see Figure 6). In addition to mean emotion rating, baby faces were matched for ethnicity.

For visit 2, approximately one week after the photography session and the standardization and preparation of the infant stimuli, mothers completed an Affect Rating Task (ART) during a fMRI session at the Imaging Research Centre in Hamilton, Ontario. For an overview of the fMRI procedure see Figure 9. The ART was presented using E-Prime software (Version 2.0; Psychology Software Tools, Inc., Pittsburgh, PA) on a laptop computer and task timing was coordinated with the acquisition of functional brain images. During each ART run, 4 experimental conditions were presented using a block-design: 1) positive own infant face; 2) negative own infant face; 3) positive unfamiliar infant face; 4) negative unfamiliar infant face. For each 36s condition-block, 6 stimuli were presented; each picture was randomly presented for three seconds, after which mothers had three seconds to rate how the picture made them feel on a 5-point Likert scale with -2 = very negative and 2 = very positive (see
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Experimental blocks were separated by a 32-36s letter-size decision-making distraction task previously used by Barrett and Armony (2006). The purpose of the task is to prevent “carry-over” effects from the previous condition and to attempt to standardize participant behaviour and cognition during the period between experimental conditions. See Figure 5 for a full overview of the procedure. One 5-minute experimental “run” was comprised of the four experimental blocks (followed by a control task) presented in a random order. Three experimental runs were completed for a total session time of 15 minutes.

At visit 3, approximately one week after the fMRI, mothers completed a videotaped interaction with their infants in their homes (see Measures). Following the videotaped interaction, participants were asked to rate the same pictures of own and other infants seen during the fMRI on a number of adjectives presented on a 8-point visual-analog scale the degree to which they feel (in response to the stimulus): sympathetic, alert, distressed, disturbed, irritated, calm, delighted, interested and a need to respond. After the face-rating task, various questionnaires were administered. Finally, mothers were asked to complete the CTQ and LHC.

**MRI Acquisition**

MRI scanning was conducted using a General Electric 3 Tesla whole-body short-bore scanner with 8 parallel-receiver channels (General Electric, Milwaukee, WI). For co-registering functional images with brain structure and later morphometric analysis (see below), a high-resolution T1-weighted (IR-Prep Fast SPGR) scan of detailed anatomy was acquired prior to functional scanning (Prep time = 450; flip angle = 12°; FOV = 24cm; TI(inv) = 450; TE = 2.1; TR system set = 9; Slice thickness = 2.0mm; Frequency matrix = 256; Phase matrix = 256; Frequency direction = A/P. Functional BOLD imaging will be done using an interleaved echo-planar imaging (EPI) sequence with TR=2700ms, TE=35ms, flip angle=90°, 3mm thick (no skip), 42 slices, 64x64 resolution over 24cm FOV).

**Data Analysis**

*Demographic Variables:* Chi-square tests were used to examine differences in mothers with consistent care versus inconsistent care on the following demographic variables: parity, feeding method, type of delivery, income, marital status, education, and age. See Table 1 for a summary of the percentage of women in each category, relative to group (consistent care yes or consistent care no).

*Questionnaire Data:* Univariate analysis of variance (ANOVA) was used to examine potential group differences (based on consistency of care) on the following questionnaire data: EPDS, HAMA-A, MADRS, STAI-S and -T, and PANAS (positive and negative affect scales separately). Please see Table 2 for a summary of means and standard error of the means (SEMs).

*CTQ Scores:* In order to substantiate the measure of consistency of care as a measure of early life adversity, CTQ scores were used. Moderate-severe cutoff values were used to categorize subjects as having experienced abuse (values are 13, 10, 8, 15 and 10 for emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect respectively). These levels were then further collapsed into two categories; mothers who experienced abuse in at least one of the five subscales were classified as having experienced ‘Any Abuse’ and women who reported no abuse on any subscale of the CTQ were classified as having experienced ‘No Abuse’.

*ART:* We used ANOVAs to examine differences in each of the stimulus ratings obtained during and after the fMRI session by infant emotion (positive, negative) and infant type (own versus other).

*fMRI:* Functional MRI data was analyzed using Brain Voyager QX software (Brain Innovation BV,
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Maastricht, Netherlands). Images were pre-processed by performing the following steps: (1) time-correction to account for differences in sampling times for different slices; (2) realignment to the first volume to correct for inter-scan movement; (3) temporal filtering to remove low-frequency drift; (4) spatial normalization the standard space of Talairach and Tournoux (1988) and; (5) smoothing with an isotropic 6-mm FWHM Gaussian kernel. Participants with >3mm of head movement were excluded from analysis (n=0 removed).

For maternal-specific analysis, anatomically defined bilateral ROIs were generated for the sACC (restricted to BA 25), pACC (BA 24/32), DLPFC (BA 9/46), OFC (BA 11), anterior HYPO/mPOA, AMY and NAC (see Figure 7). The pACC and sACC were considered separately as, while they share similarities in terms of cytoarchitecture and connectivity, important differences exist between these regions and collapsing data across these regions seemed ill advised (see Johansen-Berg et al., 2008). Furthermore, the subregion of the pACC that we considered was that which 'hugged' the genu of the corpus callosum, similar to the region described by Johansen-Berg et al., (2008). The DLPFC, also a relatively large and diverse, region, was limited to area 9/46 which has been commonly associated with both executive function and mood (Ko, Monchi, Ptito, Petrides & Strafella, 2008; Paus & Barrett, 2004; Strafella, Paus, Barrett & Dagher, 2001). To define this region of the DLPFC, we placed a 15mm³ box around a previously defined Talairach coordinate centered on area 9/46 (X= 45, Y= 33, Z= -25). The remaining ROIs (sACC (BA 25), OFC (restricted to BA 11), AMY, anterior HYPO/mPOA and NAC) were defined anatomically and in reference to the Talarach atlas using Mango software (Research Imaging Center, University of Texas Health Science Center, San Antonio). For task-specific analyses, anatomically defined bilateral ROIs were generated for the fusiform (FFA) and occipital face areas (OFA). The FFA was defined by placing a 15mm³ box around a region of the FFA (x = 44, y = -54, z= 20) identified in a study by Vuilleumier and colleagues (2001) as being (1) face specific and (2) sensitive to face affect. The OFA was defined by placing a 15mm³ box around OFA coordinates (x = 38, y = -80, z = -7) identified in a face-processing study by Rossion et al., (2003). Primary analyses were conducted in 2 stages. First, for each subject data was analyzed using a general linear model implemented in Brain Voyager, in which events or conditions of interest are modeled by a synthetic haemodynamic response function. The following conditions were entered as predictors in the model: own positive (OP), own negative (ON), unfamiliar positive (UP), unfamiliar negative (UN), fixation prior to distraction (FD) and fixation prior to baby face (BF). Next, for each predictor (OP, ON, UP, UN, FB, FD), average beta weights were extracted from each ROI and entered into SPSS for analysis.

For our primary analysis, in order to examine differences in maternal responsivity to baby stimuli, we performed a Group (CC, IC) by Familiarity (Own, Unfamiliar) by Affect (Positive, Negative) GLM repeated measures ANOVA on extracted beta weights for each ROI. Based on the possibility or suggestion of laterization of function related to emotion, face processing and maternal behaviour (Best, Womer & Queen, 1994; Davidson, 1992; Wager, Phan, Liberzon & Taylor, 2003; Dillon et al., 2009), we viewed each hemisphere of the same ROI as (potentially) functionally separate.

In order to investigate the link between early consistent care and our brain findings we examined group differences in BOLD response in our ROIs between mothers who lived with both biological parents continually from birth to 19 years and mothers who did not (from the LHC) through Consistency X Affect X Familiarity repeated measures ANOVAs, separately for the right and left hemispheres. All significant effects were further investigated using t-tests.
Results

Questionnaire Data

In order to assess the validity of the consistency of care factor as a measure of early life adversity, Group (CC, IC) x CTQ (Any Abuse, No Abuse) Chi-Square test was conducted and revealed a significant difference in the proportion of mothers who lived with both biological parents continually from birth and experienced no abuse and mothers who did not live with both biological parents and experienced some form of abuse ($\chi^2(1, N=20)=6.71, p<0.05$; see Table 4). No significant group differences were found for any of the additional questionnaire data (e.g., PANAS, STAI, HAMA, etc.; see Table 2 for summary of means and SEMs).

Demographic Data

One-way ANOVAs or Chi-Squared statistics for categorical data, with the grouping factor, were performed on all demographic information to ensure no differences between mothers with consistent versus inconsistent care. No significant group differences were observed for age, parity, method of delivery, sex of baby, feeding method, education, income and marital status (see Table 1).

Neuroimaging Data

Repeated measures ANOVAs were used to analyze all of the neuroimaging data, using two within subjects factors: Familiarity (Own, Unfamiliar) and Affect (Positive, Negative), and one between subjects factor, consistency of care (CC, IC). In order to provide a thorough representation of the results, only significant effects at $p<.055$ will be reported.

Main Effects

Familiarity: Significant effects of familiarity were observed in the right and left NAC ($F(1,18)=8.569, p=.009; F(1,18)=16.226, p=.001$; see Figure 8a) and right and left AMY ($F(1,18)=6.522, p=.020; F(1,18)=12.362, p=.002$; see Figure 8a) where BOLD activity was greater in these regions for own compared to other infant, regardless of the baby’s affect state. In no regions was the BOLD response to other infant greater than own infant. ROIs where significant effects were predicted, but not observed, include the HYPO, OFC, ACC, pACC, and DLPFC.

Affect: Analyses revealed greater BOLD response for positive compared to negative pictures in the following brain areas: right and left NAC ($F(1,18)=5.262, p=.034; F(1,18)=5.991, p=.025$; see Figure 9a), right and left AMY ($F(1,18)=5.685, p=.028; F(1,18)=4.920, p=.040$; see Figure 9b), right and left BA25 ($F(1,18)=5.413, p=.032; F(1,18)=4.545, p=.047$; see Figure 9c) and right and left pACC ($F(1,18)=6.291, p=.022; F(1,18)=6.892, p=.017$; see Figure 9d). In no regions was the response to negative pictures greater than to positive pictures. A significant effect of affect was not observed in the follow ROIs: HYPO and OFC, and DLPFC.

Consistency of care: Finally, there was no main effect of consistency of care in any of the ROIs.

Interactions
There was a significant familiarity by consistency of care interaction in the right and left NAC (F(1, 18)=8.717, p=.009; F(1, 18)=6.736, p=.018; see Figure 10) and left HYPO (F(1, 18)=4.209, p=.055; see Figure 11) such that greater BOLD response was observed to pictures of one’s own infant compared to an unfamiliar infant only when mothers received inconsistent care across development. Mothers who received consistent care did not have as variable a BOLD response to own compared to other infant in the aforementioned regions. Interestingly, in the left DLPFC (F(1, 18)=4.448, p=.049; see Figure 12), mothers who reported inconsistent care across development exhibited greater BOLD response to pictures of another infant compared to one’s own infant. No differences in activity were observed in this region for mothers who reported consistent early care. Other ROIs within the maternal neural circuit where an interaction may have been expected, but was not observed, include the AMY, OFC, BA25, pACC and right DLPFC. No significant interactions were found between affect and familiarity in any of our ROIs. Furthermore, there were no significant affect by consistency of care or familiarity by affect by consistency of care interactions in any of our ROIs.

Control Regions

There were no significant main effects of familiarity or affect in our control regions: OFA and FFA. Additionally, no significant interactions were found between affect and familiarity in either ROI. However, there was a significant familiarity by consistency of care interaction in the right OFA (F(1, 18)=4.215, p=.055; see Figure 13), where mothers who reported inconsistent care demonstrate greater BOLD response in this region to pictures of another compared to their own infant, whereas mothers who report consistent care do not differ. There were no significant affect by consistency of care interactions, no significant 3-way interactions and no main effect of consistency of care in any of the control ROIs.

fMRI Ratings

Main Effects

A main effect of affect was observed for the fMRI ratings (F(1, 18)=161.427, p=.000), such that moms reported feeling more positive to positive pictures and more negative to negative pictures. There was no significant main effect of familiarity or consistency of care for the fMRI ratings.

Interactions

There was a familiarity by affect interaction for the ART completed during the fMRI such that mothers rated positive pictures of their own infant higher than positive pictures of another infant and negative pictures of their own infant as more negative than negative pictures of the another infant (F(1, 18)=48.985, p=.000). There were no significant interactions between affect and consistency of care or familiarity and consistency of care for the fMRI ratings. There was a significant 3-way interaction (F(1, 18)=5.214, p=.035; see Figure 14) for the fMRI ratings such that moms who reported consistent early care rated feeling more positive to positive pictures and more negative to negative pictures of their own infant compared to moms with inconsistent early care, who rated positive pictures of
their own infant as more positive than negative, but had no difference in their rating of negative pictures.

Home Visit Ratings

Main Effects
Moms report feeling more alert \((F_{(1, 16)}=6.799, p=.019)\), delighted \((F_{(1, 16)}=21.459, p=.000)\), interested \((F_{(1, 16)}=21.270, p=.000)\) and a greater need to respond \((F_{(1, 16)}=8.514, p=.010)\) to pictures of own compared to other infant (see Figure 15). Significant main effects of familiarity were not found for ratings of distressed, disturbed, irritated or calm. A significant main effect of affect was observed for ratings of sympathetic \((F_{(1, 18)}=25.954, p=.000)\), distressed \((F_{(1, 16)}=35.437, p=.000)\), disturbed \((F_{(1, 16)}=20.495, p=.000)\), irritated \((F_{(1, 16)}=7.490, p=.015)\), calm \((F_{(1, 16)}=46.877, p=.000)\), delighted \((F_{(1, 16)}=140.410, p=.000)\), interested \((F_{(1, 16)}=6.945, p=.018)\) and need to respond \((F_{(1, 16)}=32.611, p=.000)\). Moms reported feeling more sympathetic, distressed, disturbed, and irritated, as well as a greater need to respond to negative compared to positive pictures and more interested, calm and delighted by positive compared to negative pictures (see Figure 16). There was no significant main effect of consistency of care for any of the adjective ratings.

Interactions

A significant familiarity by affect interaction was observed for alert \((F_{(1, 16)}=4.535, p=.049)\), calm \((F_{(1, 16)}=6.923, p=.018)\) and delighted \((F_{(1, 16)}=16.748, p=.001)\) (see Figure 17). Moms report feeling more calm and delighted to pictures of own compared to other infant that are positive, however they report feeling more alert for pictures of own compared to other infant that are negative. There were no significant affect by consistency of care interactions for any of the adjective ratings. There was a significant familiarity by consistency of care interaction where mothers with inconsistent care report feeling more distressed \((F_{(1, 16)}=4.222, p=.057)\) and disturbed \((F_{(1, 16)}=6.328, p=.023)\) for another baby than for their own baby where as mothers with consistent early care report identifying more with each for their own compared to another baby (see Figure 18). There was a significant 3-way interaction for disturbed \((F_{(1, 16)}=5.000, p=.040)\) and irritated \((F_{(1, 16)}=4.886, p=.042)\) such that, mothers with consistent care report feeling more disturbed and irritated by negative pictures of their own infant compared to an unfamiliar infant, whereas mothers with inconsistent care report feeling more disturbed and irritated by negative pictures of an unfamiliar infant (see Figure 19).

Ainsworth Maternal Sensitivity Scale

A univariate ANOVA, with consistency of care (CC, IC) as the between subjects factor, was performed on all subscales as well as the total score for the MCS. Although no significant group differences were observed, the average scores for mothers with consistent care were consistently higher and less variable than for mothers who
Early experiences & brain response to infants

The results of the current study show that emotional infant stimuli can evoke a unique pattern of brain activity specifically elicited by one’s own infant. By comparing BOLD response during viewing of one’s own infant to BOLD response during viewing of another, unfamiliar infant, we observed greater activity in subcortical areas associated with affect and reward processing, specifically, the NAC and AMY. From rodent studies, we know that the shell region of the NAC is important for the initiation of maternal behaviour and for maternal memory (Numan, Fleming & Levy, 2006; Li & Fleming, 2003). DA activity in this area is also increased by a variety of rewarding stimuli (e.g., sex, pups, cocaine) (reviewed in Pecina, Smith & Berridge, 2006). For example, Li & Sinha (2008) provide a review of neuroimaging findings demonstrating that drug seeking behaviour is associated with dysfunctional activity in the NAC. Additionally, Afonso, King, Chatterjee and Fleming (2009) has shown that DA is released in the NAC in new mothers when presented with young, showing a DA profile that is quite different from the profile of DA release to food stimuli. In fact, although DA is released to a variety of stimuli, the animals’ motivational state determines which stimuli are salient and hence, most effective. Finally, our findings are in line with previous literature which has also found greater BOLD response in the NAC for own compared to unfamiliar visual infant stimuli (Bartels & Zeki, 2004; Ranote, Elliott, Abel, Mitchell, Deakin & Appleby, 2004; Strathearn, Li & Montague, 2005, Noriuchi, Kikuchi & Senoo, 2008). It is not surprising, then, that the maternal brain would show more activity to emotional pictures of one’s own infant in this region which has been heavily implicated in the experience of reward/motivation and in maternal memory.

The interpretation of the results for the AMY is less clear. As with the NAC, here we find greater BOLD responses to own over other baby pictures. These results are consistent with some studies, but not others; one neuroimaging study has shown decreased BOLD response in the AMY for pictures of own compared to other infant (Bartels & Zeki, 2004), whereas Leibenluft, Gobbini, Harrison and Haxby (2004) have found the opposite pattern: increased activity in the AMY in response to pictures of own compared to other infant. In humans, the AMY plays a specialized role in judging salience of a reward or punisher of social significance. Relatedly, recent studies by Taylor, Arsalidou, Bayless, Morris, Evans and Barbeau (2009) and Gobbini and Haxby (2007) found greater BOLD response in the AMY for personally familiar compared to unfamiliar adult faces. Thus, it is well established that emotional facial expressions are processed by the AMY, however, variability exists with respect to lateralization of activation, stimulus intensity, stimulus familiarity and the ability of emotional stimuli to even elicit a response in this region (Adolphs, Tranel, Damasio & Damasio, 1994; Phillips, Young & Senior, 1997; Whalen, Raugh, Etcoff, McInerney, Lee, & Jenike, 1998). Recently, Canli, Zhao, Desmond, Kang, Gross & Gabrieli (2001) proposed that individual differences in personality may account for some of the variation in neural activation to emotional stimuli across studies. They examined how extroversion and neuroticism correlate with brain activation to positive and negative pictures and found that highly extroverted individuals exhibit greater activation to positive as compared to negative pictures in the frontal and temporal lobes as well as the caudate, putamen and AMY (as in the current study), suggesting personality influences an individual’s neural response to emotional stimuli. Interestingly, the Canli et al. (2001) study was conducted solely on women, however, since we did not assess personality profiles of our mothers we do not know how this relates to the results of the present study.

Despite the high degree of reciprocal connectivity within our putative neural model of mothering, increased
BOLD activity in response to visual infant stimuli was not observed in cortical ROIs. This may reflect an inability of our highly standardized pictures to engage these higher order areas hypothesized to be involved in more cognitive aspects of mothering, which the current task was not designed to engage. This may also be due to the effect of another variable, such as early adversity.

Beyond familiarity and affect differences, we were able to show for the first time that inconsistent care across formative developmental years, a form of early adversity, can produce changes in the normative pattern of neural response to one’s own infant, as opposed to another infant. Among mothers who had received consistent care there were few differences between responses to own and unfamiliar infants. However, subcortically, in the NAC and left HYPO, mothers with inconsistent care throughout childhood demonstrated greater BOLD response to pictures of their own infant than to pictures of an unfamiliar infant, (whereas mothers who had received consistent care showed no differences). These interactions suggest that the mothers who had received early inconsistent care are the ones who are ‘driving’ the interactions. Similar to our findings, a recent study by Nelson and colleagues (2009) found that peer, as compared to mother, reared rhesus monkeys show enhanced responding to an appetitive stimulus, in the form of aspartame consumption. This demonstrates that early adversity, in the form of maternal deprivation, is associated with enhanced behavioural responses to reward cues, as observed in the current study. Nelson et al. (2009) has suggested that this increased responding to appetitive stimuli may act as a behavioural suppressant for negative emotions, which are often enhanced in animals reared in adverse conditions (Volkow, 2004). We did not observe any differences in self reported mood or anxiety (negative emotions) in the current study, however, it will be interesting to examine a group of mothers with postpartum depression using the same fMRI procedure to see if the effects are augmented.

The ventral striatum, known previously to be important in reward processing, is likely involved in motivation and attention to behavioural responses to events that are salient (both aversive and appetitive) (Berridge and Robinson, 1998; Bindra, 1978; Ikemoto and Panksepp, 1999; Salamone et al., 1997). As aforementioned, various rewarding stimuli elicit DA release in the NAC. Conversely, stress has been shown to enhance mesolimbic dopamine transmission in rodents (Piazza et al., 1989). Low quality early maternal care has also been associated with increased dopamine release in the ventral striatum during a stressful task in otherwise healthy student participants, compared to students with high quality care (Pruessner et al., 2004). Furthermore, Afonso and colleagues have shown that maternal isolation during early rearing is associated with DA dysregulation in the NAC in response to pup stimuli, but not in response to other salient stimuli (e.g., fruit loops). This suggests that the detrimental effects of early maternal deprivation on reward processing in the NAC/ventral striatum may be infant stimuli specific, and not observed for other salient stimuli. Although the own infant stimuli from the current study were conceptualized as intrinsically rewarding, the rewarding value of the pictures was not directly measured. An fMRI task designed to measure how rewarding mothers find pictures of their infants compared to other infants, and potentially other forms of salient stimuli (e.g., money), may tease apart NAC activity due to normal response towards an appetitive versus aversive stimulus.

Although the increased activity for pictures of one’s own infant in mothers with early adversity was only observed in the left HYPO, BOLD response in the right HYPO showed the same effect, but was only marginally significant. The HYPO is an area in rodents that is hypothesized to be involved in approach and avoidance related neural systems. Greater activity in this area for own infant, only in mothers with early adversity, could then reflect
communication with either appetitive or aversive response systems. From home visit ratings, we see that mothers with early adversity fail to distinguish between their own and another infant, rating negative pictures of another infant, but not their own, as more distressing and disturbing. Although, again, it is necessary to measure the rewarding value of positive and negative pictures of one’s own infant directly in future studies, this suggests that mothers with inconsistent care may not find pictures of their own infant uniquely rewarding.

Cortically, rather than subcortically, a different pattern of activity was observed where inconsistent care across early development was associated with greater BOLD response to pictures of another infant. Again, this effect was not seen among mothers who had received consistent care. The DLPFC is involved in dynamic control of intended behaviour and cognition (Petrides, 2005). This suggests that shifts in primary care during childhood may have an effect on the integrity of functioning within the maternal neural circuit, such that higher order cognitive areas (e.g., PFC), known to provide inhibitory feedback to subcortical areas (e.g., AMY), are not operating effectively (Rosenkranz & Grace, 2002). A dysfunction in the connectivity and thus communication between brain regions in mothers with inconsistent care may be responsible for the decreased behavioural responsivity observed in these mothers. To examine this, in a follow-up study we will conduct functional connectivity analyses to examine how activity in the NAC, an area that, from the present study, we have found is robustly activated for own infant stimuli in mothers with early adversity, covaries with activity in other brain regions.

Although we did not predict greater BOLD response to affectively valenced infant cues in mothers with early adversity, as expected, the differential activity we observed was not associated with greater maternal responsiveness. From the ART completed during the fMRI and ratings made at the home visit, we see that mothers who experienced inconsistent care across development are less responsive to their own infant. Thus, BOLD response subcortically, although increased, does not translate into more responsive or sensitive mothering. Although mothers with consistent care do not show greater BOLD response to own infant cues, they do report feeling more distressed, disturbed and irritated by negative pictures of their own infant as well as rate negative pictures of their own infant as more negative overall compared to unfamiliar infant pictures. Mothers with inconsistent care do not rate negative pictures of their own infant as more negative than pictures of another infant. This suggests that mothers with consistent care are behaviourally more responsive to their own infant’s cues, particularly those that signal distress. Responding to infant distress signals, in comparison to nondistress signals, may be proportionally more important as Leerkes, Blankson and O’Brien (2009) have shown that maternal sensitivity is differentially related to responding to distress and affects emotion regulation in the infant. Consistent with this finding, although significance was not reached with the current sample size, mothers with consistent care had higher, less variable scores on all subscales of the Ainsworth and were more responsive to infant distress signals, than mothers with inconsistent care.

In the current study, we found greater activity for positive compared to negative pictures in the NAC, AMY and ACC, never the reverse. The current approach to interpreting activation in multiple regions induced by the same paradigm is to assume that diffuse brain regions briefly organize as neural networks (Horwitz and Braun, 2004), and in fact, each of these highly interconnected regions has been implicated in affective processing, as well as motivation. Consistent with this finding, in a recent meta-analysis of emotional face processing in fMRI, greater activity in the left AMY was found in 149 foci (Fusar-Poli et al., 2009). However, as aforementioned, explaining affective processing at the neural level has met with some degree of inconsistency. For example, the ACC, has been hypothesized to play an essential but nonspecific (attentional) role in stimulus processing, and its precise function
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has not yet fully been elucidated (Deary et al., 2004). Paus, Petrides, Evans, Meyer (1993) proposed that the ACC is involved in both behavioural instigation and inhibition, hence activity in response to positive compared to negative pictures in this region may reflect activation of approach or withdrawal neural systems and further investigation is necessary.

Canli, Amin, Haas, Omura and Constable (2004) have shown that negative current mood state is related to increased activation in the brain response particularly when viewing negative pictures. This suggests that current mood state may be important when interpreting the relationship between brain activation in response to negative emotional pictures. In the current study, there were no significant differences in mood or anxiety levels at scan time, as assessed by the EPDS, STAI-State and PANAS and this may account for the decreased activation to negative pictures.

No significant main effects were observed in our control sites (FFA and OFA) which signifies that the effects we observed in other ROIs were not due to an all over brain effect of familiarity (own over other) or affect (positive over negative). However, there was a significant interaction in the right OFA such that mothers with inconsistent care showed greater BOLD response to pictures of another infant. The right, but not left, OFA is an area that has been implicated in the processing of faces (Kadosh et al., 2010; Ganel, Valyear, Goshen–Gottstein & Goodale, 2005; Maurer, Le Grand & Monchlach, 2002; Pitcher, Walsh, Yovel & Duchaine, 2007; Rotshtein, Vuilleumier, Winston, Driver & Dolan, 2007). The rOFA may function to initially detect as well as receive and reprocess feedback from other brain areas sensitive to face processing, such as the fusiform face area (FFA) (Kadosh et al., 2010; Rotshtein et al., 2007; Schiltz and Rossion, 2006). Thus, the rOFA is implicated in the integrative evaluation of face stimuli (DeGutis, Benton, Robertson & D’Esposito, 2007). The fact that we observe greater BOLD response in mothers with early adversity to pictures of another infant suggests that we understand completely for each brain area the implications of activation versus its absence, or indeed, versus a decrease in activity of a site in relation to baseline. These are issues we would like to further explore.

fMRI measures changes in the regulation of blood flow in the brain during completion of a task. It is now widely accepted that the brain is composed of functionally heterogeneous units that act together to form systems when completing a cognitive task. Measuring the haemodynamic response through BOLD is the mainstay of cognitive neuroscience’s attempt to examine functionally localized sensory, motor and cognitive systems (Logothetis, 2008). Although BOLD has been heavily criticized for being a “surrogate signal” produced by gross functioning of masses of neurons, it is still valuable for its noninvasive nature and high temporal resolution, making it useful for studying neural networks or functional systems. It remains important, however, to recognize that results of fMRI studies are task specific and constrained by the design of the study (Logothetis, 2008). Lastly, it is important to remember that differences in activity do not necessarily reflect excitatory functioning within that region (Logothetis, 2008).

As predicted, consistency of early care, derived from the LHC (Caspi et al., 1996), was related to retrospective reports of childhood trauma, in the form of sexual abuse and/or emotional and physical neglect and abuse. Mothers who did not live with both biological parents continuously from birth to 19 years of age were more likely to experience some form of abuse, as measured by the CTQ. This is consistent with findings from Heim, Plotsky and Nemeroff (2004), who suggest that, in addition to sexual, physical and emotional maltreatment, parental loss is one of the most salient forms of early life adversity. In future studies we hope to achieve more variation in
CTQ scores, potentially using the CTQ to screen for a sample of women who score above the moderate to severe cutoff level in an attempt to strengthen our measure of early adversity.

According to statistics Canada, the Canadian divorce rate is 38% for recently married couples, by their 30th wedding anniversary (Lambert, 2009). Although much of the parent-child separation literature fails to distinguish between loss as a result of death versus divorce, divorce is one of the most common causes of parental ‘loss’ (Canetti et al, 2000). Canetti and colleagues (2000) examined differences in mental health of individuals who experienced parental loss before the age of 15, and distinguished between loss due to separation or death. Consistent with the literature, they found that individuals who experienced parental loss, compared to individuals who did not, demonstrated more psychiatric symptoms, a decreased sense of subjective well-being, reported less support from their family, and felt less cared for and more controlled by their parents. Furthermore, there was an increased risk for psychopathology in children separated from both biological parents due to divorce rather than death. Although our study does not distinguish the cause of parental separation, examining the role of caregiver-child separation, in particular due to divorce, on parenting ability in adulthood is an avenue for future research.

As summarized previously, we understand that experiences early in life shape behavioural, cognitive and emotional responses such that normative infant development is highly dependent on maternal care. Furthermore, we know that individuals who are exposed to early adversity, in the form of maltreatment or parental loss, are more likely to experience psychological illness in adolescence and adulthood. A possible mechanism of transmission of the effects of childhood adversity on later psychosocial and psychosomatic illnesses is through hypothalamic-pituitary-adrenal (HPA) axis dysregulation. Many factors affect HPA axis activity and moderate its relationship with stress, especially during the postpartum period, for example: breastfeeding (Altemus, Deuster, Galliven, Carter and Gold, 1995), parity (Adam & Gunnar, 2001), employment demands (Adam & Gunnar, 2001) and relationship functioning (Adam & Gunnar (2001). The HPA axis exhibits a high degree of interconnectivity with our maternal neural circuit (Sapolsky et al., 2000). Thus, future studies should examine HPA axis functioning in association with brain activity in new mothers to distinguish whether the effects observed in the current study, of early adversity on BOLD response in our maternal circuit, are modulated by changes in HPA axis functioning.

The postpartum period is accompanied by mood fluctuations of varying severity for the majority of mothers. In fact, 10-15% of mothers will experience mood fluctuations so severe as to meet the criteria for a diagnosis of postpartum depression (O’Hara, 2009). The behavioural profile of mothers interacting with their infants has been well established, and this includes that of mothers with extreme mood alterations as seen in those with postpartum depression. However, only a small body of literature exists that examines the neural mechanisms of human mothering and no studies have examined neural activity in mothers with postpartum depression. As we learn more about the normative pattern of neural response to infant stimuli from studies such as the present, future studies should examine whether depressed mothers show differences in neural activation in response to infant pictures of varying affective valence, and determine if brain activity is related to behavioural responsiveness, especially since we know that mothering begets mothering.

Enhancing our understanding of the neural and behavioural responses of mothers to their infants has the potential to greatly inform existing treatment and intervention programs. Further relating the neural and behavioural correlates of mothering to early life experiences will allow for the development of prophylactic programs to optimize mother-infant interaction, and promote positive attitudes, behaviour and infant development in at risk
populations. For example, if distinct adversity conditions associated with aberrant neural activity to infant cues are identified, it may become beneficial to incorporate childhood trauma and consistency of early care screening into regular maternity visits. Thus, a major goal of future endeavors will be to increase awareness and encourage further research on the etiology and treatment of unique maternal experiences.

This project greatly contributed to our current understanding of human maternal neural circuitry and its relation to adverse early childhood experiences, while improving upon currently used methodology. Stringent recruitment, stimulus acquisition and testing procedures were used to bolster methodological strength and generalizability. Acquisition of mother-infant interaction videos will allow for future data analysis to relate mothers’ pattern of response in the magnet to patterns of their interactions with their infants through second-by-second event related coding. Of the only approximately 10 human neuroimaging studies which have been conducted with mothering populations, none have compared mothers to non-mothers in their neural patterns of responsiveness to infant versus non-infant cues, varying in emotional valence. Hence, it is not yet clear whether distinct brain regions mediate maternal behaviour, whether these patterns of activation are only exhibited by mothers, if so, whether they can only be generated in response to one’s own infant. Future studies will address issues of (and vary) stimulus type, stimulus valence, familiarity of stimulus, social significance of stimulus, prior parental experience and parity, and hopefully, will also include dads.
Table 1.

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<td>CC IC</td>
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<td>Mom (years)</td>
<td>31.75±1.24 30.57±1.43</td>
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<td>Baby (months)</td>
<td>4.19±0.30  4.50±0.23</td>
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<tr>
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<td>33 50</td>
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<td>Parity (%)</td>
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<tr>
<td>Income (%)</td>
<td>8.3 14.3</td>
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<th>Married/Common Law CC IC</th>
<th>Other CC IC</th>
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<td>Marital Status (%)</td>
<td>100 100</td>
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<th>At Least High School CC IC</th>
<th>At Least Some College/University CC IC</th>
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<td>Education (%)</td>
<td>100 100</td>
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<th>Vaginal CC IC</th>
<th>Caesarian CC IC</th>
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<td>Delivery Method (%)</td>
<td>66 62.5</td>
<td>33 37.5</td>
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Table 2.

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<td>EPDS</td>
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<td>HAM-A</td>
<td>2.00±0.41</td>
<td>1.50±0.38</td>
<td>1.08±0.38</td>
<td>0.50±0.50</td>
<td>3.08±1.78</td>
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<td>MADRS</td>
<td>1.67±0.56</td>
<td>1.10± 0.44</td>
<td>1.25±0.49</td>
<td>0.37±0.26</td>
<td>1.17±0.34</td>
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<td>STAI-S</td>
<td>24.00±3.49</td>
<td>27.14±1.77</td>
<td>28.11±1.59</td>
<td>25.86±1.50</td>
<td>26.25±1.60</td>
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<td>STAI-T</td>
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<td>28.00±1.79</td>
<td>30.56±1.76</td>
<td>27.29±1.08</td>
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<td>PANAS -Pos</td>
<td>21.42±1.73</td>
<td>18.63±1.13</td>
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<td>21.42±1.64</td>
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<td>PANAS -Neg</td>
<td>14.75±1.25</td>
<td>12.75±0.88</td>
<td>13.25±0.57</td>
<td>12.13±0.99</td>
<td>12.92±0.73</td>
<td>11.43±0.81</td>
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Table 3.

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<tr>
<td>Ainsworth Total</td>
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<td>23.375 ± 2.070</td>
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<tr>
<td>Sensitivity</td>
<td>6.333 ± .310</td>
<td>5.500 ± .655</td>
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<tr>
<td>Acceptance</td>
<td>6.667 ± .256</td>
<td>6.250 ± .726</td>
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<tr>
<td>Availability</td>
<td>6.583 ± .193</td>
<td>6.000 ± .327</td>
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<tr>
<td>Cooperation</td>
<td>5.917 ± .193</td>
<td>5.625 ± .565</td>
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Table 4.

<table>
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<tr>
<th>CTQ (%)</th>
<th>Any Abuse</th>
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<tr>
<td>Consistent Care %</td>
<td>8</td>
<td>92</td>
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<tr>
<td>Inconsistent Care %</td>
<td>62.5</td>
<td>37.5</td>
<td>100</td>
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</table>
Figure 1.
Figure 2.
Figure 3.
Figure 4.

At 3 months postpartum

Assessment 1: Stimulus Acquisition
-EPDS, HAM-A, MADRS, STAI-S/T, PANAS
-Acquisition of own infant stimuli

Assessment 2: fMRI Session
-EPDS, HAM-A, MADRS, STAI-S/T, PANAS
-ART during fMRI

Assessment 3: Home Visit
-EPDS, HAM-A, MADRS, STAI-S/T, PANAS, LHC, CTQ
-20 minute videotaped interaction of mother and infant
Figure 5.

Early experiences & brain response to infants
Figure 6.

Own Positive

Other Positive

Own Negative

Other Negative
Figure 7.

a. 

Yellow = Orbitofrontal cortex (OFC)
Purple = Dorsolateral prefrontal cortex (DLPFC)
Navy = Fusiform face area (FFA)
Light blue = Occipital face area (OFA)
Green = Amygdala (AMY)

b. 

Blue = Subgenual anterior cingulate cortex (sACC)
Red = Perigenual anterior cingulate cortex (pACC)
Brown = Nucleus accumbens (NAC)
Pink = Anterior hypothalamus/medial preoptic area (HYPO)
Figure 8.

a. NAC

b. AMY
Figure 9.

a. NAC

b. AMY
c. BA 25

![Graph showing brain response to infants for BA 25.](image)

- Right BA25
- Left BA25

- Positive
- Negative

---

d. pACC

![Graph showing brain response to infants for pACC.](image)

- Right pACC
- Left pACC

- Positive
- Negative
Figure 10. NAC

a. right

b. left
Figure 11. left HYPO
Figure 12. left DLPFC
Figure 13. right OFA
Figure 14. fMRI

a. Yes

b. No
Figure 15.
Figure 16.

(a) 

(b)
Figure 17.

a. Alert

b. Calm
c. Delighted
a. Distressed

b. Disturbed
Figure 19. Disturbed

a. Positive

b. Negative
Figure 20. Irritated

a. Positive

b. Negative
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References


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