The Brain Basis of Maternal Responsiveness:

Systematic review and meta-analysis of neural pathways

A thesis submitted to the University of Manchester for the degree of MPhil in the Faculty of Medical and Human Sciences

2012

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Abstract:

The Brain Basis of Maternal Responsiveness: Systematic review and meta-analysis of neural pathways

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Several studies have used fMRI in an attempt to establish whether there is a neural network specific to maternal responsiveness, but their sample size has generally been small to moderate, and data have never been synthesised quantitatively.

Here, a systematic review and meta-analysis of existing data was carried out. The analysis revealed that there is neural activation associated with healthy mothers' exposure to children, which is stronger in response to own versus other children. This includes areas associated with visual processing, attention, executive functioning, emotion processing, obsession and reward. The activation of many of the brain areas associated with reward and obsession, as well as the deactivation of areas associated with negative emotions, was specific to exposure to mothers' own children. These findings are to a large degree in line with Swain's (2008) model of parental responsiveness, although some alterations to the model, such as clarification and delineation of the role of the cerebellum and reconsideration of the role of the hippocampus, are necessary.

There is a lack of evidence concerning the specificity of the identified neural activation to maternal responsiveness, but the identified brain network may nevertheless serve as a biomarker of healthy maternal responsiveness for future research and may be used in the development of novel parenting interventions.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright Statement

Acknowledgements

First of all I would like to thank Professor Kathryn Abel for all her continued help and support. I would also like to thank Dr Richard Drake, Dr Rebecca Elliott, Dr Ian Ellison-Wright, Dr Darragh Downey, Professor Steve Williams, Dr Wendy MacDonald, and Dr Vanessa May for their input and support, and for always lending me a helping hand. Finally, a big thank you to my parents, who are always there for me.

1. Introduction

1.1. Study rationale

Squire and Stein (2003) have argued that functional Magnetic Resonance Imaging (fMRI) is an underexploited tool that can strengthen current understanding of maternal behaviour. Although it has a relatively poor temporal resolution, it has a very good spatial resolution (~1mm; Huettel et al., 2009) and can therefore provide much insight into the brain basis of maternal responsiveness. Developing evidence for the neurology underpinning maternal responsiveness has two potentially important clinical implications: First, if it is possible to establish particular neural responses associated with maternal responsiveness, these may be used as biomarkers for healthy maternal responsiveness in the assessment of patients who may be at risk of displaying poor parenting skills, such as patients with depression or schizophrenia (O'Connor & Scott, 2006); second, they may be used as biomarkers in studies evaluating the efficacy of interventions to enhance maternal responsiveness, for example the 'bonding hormone' oxytocin, which has been investigated by recent research (e.g. Riem et al., 2012; Riem, 2012).

Swain (2008) proposed a model of parental responsiveness involving subcortical regions including the amygdala, hypothalamus, and thalamus, and cortical regions, including orbitofrontal cortex, insula, and cingulate. Although this model has not formally been tested, several studies have used fMRI in an attempt to identify brain regions associated with human maternal responsiveness. Past studies either compared maternal responses to generic child stimuli versus control stimuli, or own child versus generic child stimuli. Studies generally used a small to moderate number of participants, and to date these studies have not been synthesised quantitatively. Given the potential for conflicting results from the functional imaging literature on maternal responsiveness, meta-analysis may be the most appropriate way to establish which brain areas are most likely to represent a dedicated neural network of maternal responsiveness as per Swain's (2008) model. Wright et al. (2007) argue

that systematic review and meta-analysis of appropriate studies can be the best form of evidence available to researchers and clinicians. Similarly, Lieberman and Cunningham (2009) recommended greater focus on meta-analysis in fMRI research, as this has the potential to provide very reliable results: It reduces Type II errors (i.e. missing true effects), and this allows for more lenient thresholding and hence avoidance of Type I errors (i.e. false alarms).

1.2. Aims

1) The main aim of this study is to determine whether there is a dedicated neural network associated with maternal responsiveness, and if so, where this is located in the brain.
    - In order to do so, previous fMRI evidence will be synthesised and meta-analysed using the software GingerALE (Eickhoff et al., 2009).
    - The current study will be the first study formally to use meta-analysis to provide a more accurate appraisal of the neural basis of maternal responsiveness.

- The following contrasts will be examined:
    a) Maternal neural responses to children (own and other) versus control stimuli
    b) Maternal neural responses to own versus other children

    - These contrasts were chosen because they provide evidence for a specific neuronal response associated with mothers' exposure to children, and about whether or not brain activation is specific or stronger to exposure to own versus other children.
    - Both contrasts will allow us to determine imaging patterns which may become a biomarker for subsequent studies of the effects of novel parenting interventions. Neural activity associated with contrast a) could be used as a biomarker in research involving non-mothers or preterm mothers, and

neural activity associated with contrast b) in research involving mothers.

2) The second aim of the study is to assess the model of parental responsiveness as proposed by Swain (2008).

1.3. Mothering as a public health concern

The relationship between an infant and her or his caregiver is critical for the survival and the social, emotional, and cognitive development of the infant (Insel and Young, 2001; Sroufe et al, 2005). In the majority of cases, it is the mother who is a child's main caretaker (Shable et al., 1995) - most women will bear and care for a child at some point in their life (Kirkley, 2000).

There are considerable individual differences in women's adjustment to parenthood (Twenge et al., 2003). 10% to 15% of new mothers suffer from postnatal depression (Mallikarjun & Oyebode, 2005) and as many as 43% may suffer from postnatal anxiety (Glasheen et al., 2010). These difficulties may lead to problematic parenting and insecure attachment patterns between mother and child (O'Connor & Scott, 2006).

Warm and nurturing mothering in a safe environment is associated with the development of self-esteem, happiness and a lower risk of psychopathology in offspring (Cheng & Furnham, 2004; DeHart et al., 2006; Mikulincer & Shaver, 2004); in contrast, situations in which there is a lack of secure attachment between infant and mother are associated with various mental health conditions and behavioural problems in the child, including depression (Bifulco et al., 1998), conduct disorder (Hutchings & Lane, 2005), antisocial behaviour (Sutton et al., 2004, Trembley et al., 2004), and delayed language acquisition (Glascoe & Leew, 2010).

In the U.K. approximately 10% of children suffer from diagnosable behavioural and emotional problems (Green et al., 2004). Children who go on to develop behavioural problems cost society, as well as themselves

and their families, dearly. For example, an empirical follow-up study showed that by age 27, children in England with oppositional and conduct disorders at age 10 had each cost the public around £200,000 – ten times more than controls (Scott et al., 2001). In addition, problematic parenting has been found to be transmitted across generations (Belsky et al., 2005), creating a vicious circle of poor mental health. A better understanding of what constitutes healthy maternal neuronal responsiveness is important for the development of novel parenting interventions, which may improve children's and mothers' wellbeing, and reduce the financial and social burden to society.

1.4. The transition to maternity

1.4.1. Maternal emotions and the establishment of the maternal bond

New motherhood is associated with a set of specific feelings and behaviours, which may suggest the existence of a neural network specific to motherhood. Mothers report experiencing joy about being 'at one' with their new infant, but also intrusive worries that something bad could happen to the child or their relationship. Feelings of intimacy and 'being at one' with the infant relate to breastfeeding in particular, but also cleaning, grooming, play and dressing behaviours (Leckman et al., 1999).

Many mothers describe their feelings towards their child as akin to being 'in love' and experience their child as 'perfect', an experience which increases during the postpartum period, reaching its peak when the infant is three months old, at which point more than 70% of mothers may endorse this experience (Swain et al., 2005). Mothers also frequently feel compelled to shape their behaviour to the perceived needs of their child (Leckman et al., 1999), resulting in a heightened sense of responsibility, behaviours aimed at ensuring the safety of the child, and increased sensation of reward (Leckman et al., 2004).

These experiences and feelings may be specific to new mothers, and may relate to their own, but to some extent also to other children. Giardino et al. (2008) found that teen mothers reported more sympathy and alertness

in response to cries of unknown infants compared to nulliparous teens. In addition, adult mothers, but not nulliparous teens (or teen mothers), showed an ‘alerted’ pattern of heart rate and cortisol levels in response to cries of unknown infants.

Differences have also been observed between maternal and paternal behaviour. Swain et al. (2004) conducted interviews with American mothers and fathers, and found that mothers were significantly more likely to be preoccupied with their infant's safety and their unimpeded access to their child than fathers, and that there was a positive correlation between parental preoccupations and depression. Such preoccupations may be especially common in relation to a mother's first child (Swain et al., 2004). The authors also suggested that mothers' greater level of preoccupation with their infants may result in greater amygdala and basal ganglia activation. Gordon et al. (2010) reported that mothers and fathers showed similar amounts of infant contact, but mothers were more likely to engage in affectionate contact, whereas fathers were more likely to engage in stimulatory contact.

Several research groups have attempted to assess predictors of maternal responsiveness using behavioural and physiological methods, but these provide low reliability. Frodi and Lamb (1980) reported that for mothers who maltreat their children, audiovisual infant stimuli elicit exaggerated physiological responses. Soltis (2004) reported that parents' failure to regulate their arousal and maintain a caring stance in response to infant crying is an important risk factor for such maltreatment, as well as infanticide. In addition, mothers who report stress or depression may be more likely to display inappropriate parenting behaviours.

There are also differences in maternal behaviour relating to age. Thus, compared to teen mothers, older mothers display more affectionate behaviours towards their infants, whereas teen mothers display more instrumental behaviour, with breastfeeding teen mothers also displaying higher levels of the 'stress hormone' cortisol. Similarly, mothers who

received less maternal care in childhood have been found to be more likely to display more instrumental behaviour and less affectionate behaviour towards their children (Krpan et al., 2005).

1.4.2. Reproduction-induced neurological changes in the maternal brain

There is a wealth of evidence suggesting that hormone-induced changes occur during and after pregnancy in the mammalian female brain which mimic changes seen following any form of training stimuli, for example learning to juggle (Draganski et al., 2004) or studying (Draganski et al., 2006) over a few months. Pregnancy hormones progesterone and oestrogen among others interact with exposure to offspring, which represents 'an enriched environment', and alter the properties of neurons in specific brain regions, improve learning ability, mitigate anxiety and stress responsiveness, and enhance problem solving in novel contexts (Kinsley & Lambert, 2008). Changes include the development of new connections through dendritic growth and arborisation that create a mechanism for plasticity and new learning in somatosensory cortex (Xerri et al., 1994), hippocampus (Woolley & McEwan, 1993), and amygdala (Rasia-Filho et al., 2004).

Through pregnancy, parturition and lactation, significant changes occur in the system of the neurotransmitter oxytocin, which is synthesised in the supraoptic and paraventricular nuclei of the hypothalamus and projects to the basal ganglia and amygdala, and is involved in bonding and social skills (e.g. Gordon et al., 2010; Feldman et al., 2010). Rodent studies suggest particularly high oxytocin receptor concentration in new mothers in the medial nucleus of the amygdala and associated areas (Young et al., 1997; Terenzi & Ingram, 2005), and a smaller proportion of oxytocin-responsive neurons in the central nucleus of the amygdala (Terenzi & Ingram, 2005).

In human new mothers, Kim et al. (2010) examined grey matter changes associated with maternity using voxel-based morphometry on high

resolution magnetic resonance images of mothers' brains at two time points: two to four weeks postpartum and three to four months postpartum. They found increases between the time points in grey matter volume of the prefrontal cortex, parietal lobes and midbrain areas. Increased grey matter volume in the midbrain, hypothalamus, substantia nigra and amygdala positively correlated with positive maternal perception of her child.

Pearson et al. (2009) found that women develop higher accuracy scores to encode adult emotional expressions of anger, fear, sadness and disgust between early and later pregnancy. They theorised that this is due to effects on the brain of the raised oestrogen and progesterone levels that accompany pregnancy, specifically dentritic spine growth and increased activity in hippocampus and amygdala (Kinsley et al., 2006; Goldstein et al., 2005; Jasnow et al., 2006), and increased activity in prefrontal cortex (Keenan et al., 2001).

1.4.3. The role of neurotransmitters in the transition to maternity

1.4.3.1. Animal studies

Oxytocin (OT) regulates the onset of mammalian maternal behaviour as shown when injected into the cerebral ventricles of a virgin rat to produce nurturing behaviour towards young ones where she otherwise would avoid or attack the pups ('pup avoidance'; Murphy et al., 1987; Jin et al., 2007). Similarly, OT antagonists block the onset of maternal behaviour in new rat mothers (van Leengoed et al., 1987). Knockout mice lacking either the OT receptor or the hormone itself display decreased pup retrieval, licking and grooming (Pedersen et al., 2006), and are more likely to display infanticidal behaviour (Ragnauth et al., 2005). Similar effects have been found in a number of other mammalian species: OT receptor density in prairie voles correlates positively with maternal behaviour (Olazabal & Young, 2006), and OT infusion in sheep induces nurturing behaviour (Kendrick et al., 1987).

Suckling, audiovisual and olfactory stimuli have all been found to stimulate maternal care in rats at least partially through increased expression of oxytocin receptors in specific brain areas, including bed nucleus of the stria terminalis, hypothalamic paraventricular nuclei, ventral tegmental area, medial preoptic area, lateral septum, and central nucleus of the amygdala (Francis et al., 1999; Francis, Champagne & Meaney, 2000).

Density of oxytocin receptors in the amygdala and associated areas varies with levels of gonadal steroids, particularly oestrogen (Patchev et al., 1993; Krémarik et al., 1995), and with the reproductive state of the animal, with mothers revealing higher OT receptor density (Young et al., 1997). Terenzi and Ingram (2005) found that, compared with virgin or pregnant female rats, lactating rats exhibited a larger proportion of OT-responsive neurons in the medial nucleus of the amygdala, but a smaller proportion in the central nucleus of the amygdala. In addition, repeated oxytocin administration induced sensitisation in the central, but not medial, nucleus of the amygdala, suggesting that different neuronal populations in the amygdala have separate functional capacity.

Rodent knock-out studies also confirm the role of prolactin, vasopressin, oestrogen and dopamine in maternal behaviours (Leckman & Herman, 2002). Dopamine is involved in motivational and rewards systems (Schultz, 2006), and directly modulates oxytonergic systems in the female prairie vole's nucleus accumbens, which is critical for the formation of social attachment (Liu & Wang, 2003). Social attachment therefore appears to be the result of activation of bonding and motivational systems.

1.4.3.2. Human studies

Evidence for a role of OT in the transition to maternity and in maternal behaviour in women is also emerging. Feldman et al. (2007) reported that OT plasma levels at early pregnancy and the postpartum period significantly and positively correlate with maternal bonding behaviours such as gaze, vocalisations, positive affect and touch, attachment-related thoughts and frequent checking of the infant. Other studies report that

maternal OT plasma levels are associated with affectionate parenting behaviours, including use of ‘motherese’ vocalisations, the expression of positive affect, and affectionate touch (Gordon et al., 2010; Feldman et al., 2010).

Tops et al. (2007) described an association between plasma OT levels in new mothers and strength of attachment. This has tentatively been associated with a gene polymorphism in the oxytonergic system, such that mothers with a less 'efficient' variant of a particular gene associated with the oxytonergic system display lower levels of sensitive responsiveness to their toddlers (Bakermans-Kranenburg & van Ijzendoorn, 2008). Strathearn et al. (2009) found OT release in response to infants was higher if mothers were assessed as securely rather than insecurely attached to their child. In addition, mothers who gave birth vaginally rather than by caesarean section may be more sensitive to their baby’s cry two to four weeks postpartum - the varying levels of OT during delivery are thought to play a contributory and causal role (Swain et al., 2008).

Bick and Dozier (2009) describe OT levels in mothers to be higher after interaction with children, no matter whether these are their own or unknown children. In fact, OT levels were higher if the child was unknown compared to when the child was their own. The authors suggested this may be due to OT playing a role in the onset, rather than maintenance, of maternal behaviour. They also noted that exposure to unknown children represented greater stress and pointed to the anxiolytic function of OT (Heinrichs et al., 2003).

Riem at al (2011) reported that intranasal administration of oxytocin reduced amygdala activation and increased activation of the insula and the inferior frontal gyrus in response to baby cries. They argued that OT functioned by reducing activation of the neural systems associated with anxiety and aversion, and by increasing activation in areas associated with empathy. Strathearn (2011) has argued that, at least in humans,

oxytocin may affect maternal responsiveness by activating dopaminergic reward pathways in response to socially salient cues.

Bos et al. (2010) reported that testosterone administration in young women heightened activation in thalamocingulate regions, insula and cerebellum in response to infant cries, and suggested that this may be caused via its metabolite oestradiol, which is the predominant oestrogen throughout women's reproductive years.

1.5. The brain basis of maternal responsiveness

1.5.1. Animal Studies

As can be seen in Table 1, several behavioural elements of maternal care are common across mammalian species, including humans. We might therefore assume that some basic brain processes, including the rewarding aspects of the maternal bond, are common to mammals. Three clusters of brain regions have been found to be involved in the regulation of maternal behaviour in mammals: Motivational systems of the basal forebrain and midbrain; limbic circuits processing emotional stimuli and responses, including the amygdala and septal regions; and sensation-driven thalamocingulate circuits.

Table 1: Common behavioural elements of maternal care across mammalian species

Feature
- Nest building and maintenance (place preference)
- Perceptual exploration (identification of nest and/or offspring)
- Retrieval (reciprocal calls)
- Grooming and kissing or licking
- Crouching or preferred nursing positions
- Nursing and lactation and/or feeding
- Prolonged physical contact/sleeping together
- Aggressive behaviour in response to perceived threats to their offspring

Source: Swain et al. (2007); used with permission of the author

Motivational systems of the basal forebrain and midbrain. There is convincing evidence for a central role of the medial preoptic area (MPOA) and nearby ventral part of the bed nucleus of the stria terminalis (VBNST) in mammalian maternal behaviour (Numan, 1994). These are small basal forebrain structures lying just anterior to the optic chiasm and hormone regulatory system of the hypothalamus. Lesions of the area of the MPOA and VBNST or its lateral efferent connections disrupt maternal behaviour in the rat (Numan et al., 1985; Numan et al., 1990; Numan & Numan, 1996), and oestradiol injections into this area facilitate such behaviour (Numan et al., 1977). There are neural projections from the MPOA and VBNST into the ventral tegmental area (VTA) and the substantia nigra, which are rich in dopamine and have been found to play a key role in motivated approach behaviour (Mirenowics & Schultz, 1996) such as approaching pups (Numan et al., 1985). The VTA and substantia nigra project along dopaminergic pathways to the midbrain, striatum, anterior cingulate and prefrontal cortex (Mello & Villares, 1997), and lesions along these pathways interfere with maternal behaviour (Hansen, 1994; Numan & Numan, 1997).

Limbic emotion control circuits involving septal regions and the amygdala. Limbic circuits, such as septal regions and the amygdala, are connected to the MPOA and are important for mammalian parenting. Rodents with septal lesions are more likely to commit infanticide (Slotnick & Nigrosh, 1975; Flannelly et al., 1986; Novakova et al., 1993). Such lesions also inhibit nest building, and cause pup retrieval to become disorganised, meaning mothers often drop their young and leave them outside the nest (Slotnick & Nigrosh, 1975). The amygdala has been found to be involved in both facilitating and inhibiting parental behaviour. On the one hand, amygdala lesions have been found to inhibit maternal affiliation in non-human primates (Kling & Steklis, 1976), suggesting a facilitative role, whereas such lesions have also been found to reverse the avoidance behaviour displayed by nulliparous rat females in response to pup smells, suggesting an inhibitory role, at least in nulliparous female rats (Fleming et al., 1983; Numan et al., 1993). Swain et al. (2007) suggested that these

findings may point to certain sub-regions of the amygdala being involved in facilitating maternal behaviour, while other sub-regions are involved in its inhibition. This is supported by the existence of two distinct neuronal populations within the amygdala (Huber et al., 2005), which may have opposing effects on parental behaviour.

Sensation-driven thalamocingulate circuits. Several animal studies suggest that the cingulate gyrus and its connected thalamic nuclei, including the dorsomedial, medial pulvinar, midline, and anterior thalamic nuclei (dopaminergic structures involved in selective attention), play an important part in mammalian maternal bonding and behaviour (Mesulam, 2000). In rats and hamsters, cingulate lesions, which cause retrograde degeneration of medial thalamic nuclei, have been found to impair maternal behaviour, including pup retrieval, actively allowing pups to nurse, and nest building, although the motivation to care for pups remains intact (Maclean, 1990; Murphy et al., 1981; Slotnick, 1967; Stamm, 1955). The degree of impairment strongly correlates with the degree of anterior thalamic nuclei degeneration (Slotnick, 1967; Slotnick & Nigrosh, 1975). In addition, Swain et al. (2007) have argued that the fact that the anterior cingulate is rich in opioid receptors (Wise & Herkenham, 1982) provides further evidence for its role in maternal bonding and care taking behaviour, as opioids influence maternal retrieval of separated young in several species (Panksepp et al., 1994). Some studies have failed to demonstrate altered maternal behaviour with cingulate lesions in mice (Slotnick & Nigrosh, 1975), or to associate cingulate activity with maternal behaviour in rats (Lonstein et al., 1998). Swain et al. (2007) argued that the cingulate might not be essential for parenting, but might be involved in the organisation of a range of complex behaviours, including parenting.

Bick and Dozier (2009) pointed out that the generalisations from such research to humans is limited because humans do not exhibit the same obvious transition from avoidance or aversion of young to maternal behaviour that is seen in rats. Similarly, Kentner et al. (2010) pointed out that there are significant differences in parental responses between

humans and other mammals, and warned about generalising too readily from animal studies. Some have argued that it might be more informative to concentrate on experiments involving human parents (e.g. Knight et al., 2010). In this context, fMRI studies of maternal responsiveness are likely to be particularly useful (Squire & Stein, 2003).

1.5.2. Human brain responses relevant to maternal responsiveness

In recent years there has been a wealth of research examining human brain responses to people in general, to attachment figures and to children, most of which used fMRI. These studies may provide clues to the brain basis of maternal responsiveness.

1.5.2.1. Human brain responses associated with social interaction

Several cognitive abilities are likely to play a part in maternal responsiveness. For instance, mothers need to be able to empathise in order to interpret their child's non-verbal communication. Singer et al. (2004) reported that anterior cingulate, insula, brain stem and cerebellum were activated when participants received physical pain, and also when it was implied that a loved one was receiving pain. In the latter case, this activation was associated with participants' scores on measures of empathy. The activation of prefrontal and temporal cortex has also been associated with the ability to empathise and is associated with performing collaborative tasks (Pelphrey et al., 2005; Saxe, 2006). Riem et al. (2011) argue that orbitofrontal cortex and insula are also involved in empathy.

Buchheim et al. (2006) used line drawings representing people who are isolated, ill or abused, and found that participants with organised attachment patterns activated the right amygdala, left hippocampus, and right inferior frontal gyrus more when being exposed to them than participants with disorganised attachment patterns. The authors suggested that this might be caused by participants with organised attachment patterns experiencing greater distress in response to the images and argued for the involvement of these areas in empathy and social distress.

Another study has looked at human brain activation during support-giving, which may be a particularly important aspect of maternal responsiveness (Inagaki & Eisenberger, 2012). The authors reported that support-giving activated the ventral striatum of the basal ganglia and septal areas, and that activation of septal regions correlated positively with reduction in amygdala activation. They argued that activation of the striatum was associated with the reward that comes with socially supporting another person, whereas the activation of septal areas was related to fear-attenuation. Social isolation on the other hand, has been found to be associated with activation of the anterior cingulate (Eisenberger et al., 2003); similarly social rejection has been associated with cingulate activation, as well as activation of insula, striatum and frontal areas (Crowley et al., 2010; Masten et al., 2009).

Several studies have examined brain activation in response to emotionally laden sounds, of which infants' utterances may represent a subcategory, especially to mothers. Sander et al. (2003) presented emotionally laden adult vocalisations to participants and found that the stimuli activated bilateral amygdala, insula and temporal cortex, with a right hemisphere advantage for the amygdala. This was the case for stimuli of both positive and negative valence (i.e. laughing and crying), leading the authors to argue for the involvement of these regions in responding to emotional stimuli in general, with valence being represented by other parts of the brain.

Sander et al. (2005) found orbitofrontal cortex activation in response to angry utterances which correlated with participants' emotional sensitivity. Bodini et al. (2004) reported insula activation following emotion recognition, while Carr et al. (2003) found that right amygdala, right insula and bilateral inferior frontal and temporal cortex were involved in imitation of emotions. Dapretto et al. (2006) found that insula activation played a significant role in social and emotional interaction in people with autism. Interestingly, the anterior portions of the insula have also been associated with experiencing pleasant touch (Olausson et al., 2002).

1.5.2.2. Human brain responses to adult attachment figures

Studies of brain activation associated with romantic attachment are relevant to the present research because of the intensity of attachment experienced by new mothers with their infants (Swain e al., 2005). Fisher at al. (2005) exposed participants to pictures of romantic partners, producing activation of the right tegmental area and caudate nucleus of the basal ganglia; both dopamine-rich areas associated with mammalian reward and motivation. They also found that activation in the right anteromedial caudate correlated with intensity of romantic passion, and that activity in the left insula-putamen-globus pallidus correlated with trait affect intensity, whereas activity in limbic and cortical regions, including insula, cingulate, parietal, inferior temporal and middle temporal cortex, correlated with the length of time in love.

In two small studies, Bartels and Zeki reported regions activated in response to images of romantic partners included putamen, globus pallidus and caudate nucleus of the striatum (all part of the basal ganglia), middle insula, the dorsal part of the anterior cingulate cortex, dentate gyrus/hippocampus, and parts of the hypothalamus in both men (Zeki & Bartels, 2000) and women (Bartels & Zeki, 2004). Several of these areas have been associated with the reward system and contain a high density of oxytocin and vasopressin receptors. Compared to control images, images of romantic partners suppressed activity in middle prefrontal cortex and posterior cingulate cortex (both associated with social assessment), in temperoparietal regions (associated with self-other distinction, avoidance behaviour and touch; Tsakiris et al., 2008), and in amygdaloid regions (associated with negative emotions such as fear).

Acevedo et al. (2012) reported that long-term romantic love was associated with the reward-associated basal ganglia, including the ventral tegmental area, striatum and globus pallidus, substantia nigra, thalamus, insular cortex, and anterior and posterior cingulate. Activation of the ventral tegmental area and the caudate correlated with romantic love score and inclusion of the other in the self. Globus pallidus activation

correlated with friendship-based love; and caudate, septum, posterior cingulate, and posterior hippocampus correlated with obsession with the other person. Gobbini and Haxby (2007) found that the insula, as well as the amygdala, activated in response to close family and friends more than in response to familiar faces of people with whom participants had no personal connection such as celebrities. Based on these findings, Swain (2011) argued that romantic love may use subcortical motivation and reward systems to focus thoughts and behaviours on a specific individual, while limbic cortical regions process individual emotional factors.

Nijab et al. (2004) investigated brain activation associated with loss of a loved one. Sad thoughts related to loss of a romantic relationship were associated with deactivation of anterior cingulate, insula, and temporal cortex; in addition activity of the insula, anterior cingulate and amygdala inversely correlated with participants' experience of grief. Finally, using near-infrared spectroscopy, Nakato et al. (2011) found that seven to eight month old infants activated the left and right temporal cortex when viewing faces of their mothers and of strangers, but only left temporal cortex in response to their mothers.

1.5.2.3. Brain responses to children in non-mothers

1.5.2.3.1. Nulliparous women and men

Purhonen et al. (2001a) reported that nulliparous women showed greater response in anterior cingulate and temporal cortex in response to baby cries compared to neutral adult vocalisations. Other researchers have reported that nulliparous women (Glocker et al., 2009; Kringelbach et al., 2008) and nulliparous men (Kringelbach et al., 2008) activated the amygdala and cingulate cortex in response to baby face stimuli versus control stimuli. Caria et al. (2012) compared brain responses to infant versus matched adult faces in nulliparous women and men; both groups activated the thalamus, cingulate cortex, anterior insula and motor cortex in response to human infant faces, and this activation was specific to *human* infant faces.

However, nulliparous women showed less of a N100 response to both the infant cry and the adult vocalisation than mothers (Purhonen et al., 2001b), which may represent mothers' greater alertness to human sounds. Nishitani et al (2011) used near-infrared spectroscopy and found that compared to mothers, nulliparous women activated the right prefrontal cortex less in response to emotional faces of unknown infants. They suggested that these areas are involved in maternal distinction of infant emotions.

Differences in brain responses to children between nulliparous women and men have also been reported. Seifritz et al. (2003) reported that, unlike nulliparous men, nulliparous women showed decreased activation in anterior cingulate in response to audio stimuli of infants. In addition, nulliparous women activated the right amygdala in response to infant laughter, but not in response to infant cries. In contrast, Sander et al. (2007) reported that in response to children's laughing and crying versus a neutral control sound, the posterior cingulate and auditory cortex activated in both sexes. Women displayed stronger activation of the amygdala and the anterior cingulate in response to infant stimuli, whereas men activated these areas more in response to the control stimuli. Swain et al. (2007) have argued that the decrease of anterior cingulate activation found by Seifritz et al. (2003) may have been due to the short blocks used in the study design and noted that this is absent if longer blocks of stimuli are used.

1.5.2.3.2. Fathers

Fathers' brain responses might provide important clues, since like mothers, they are exposed to their children, with similar (although not equal) emotional and behavioural effects to those of mothers. Two studies have examined paternal brain responses to infant cries, and one study has looked at paternal responses to infant photographs. Seifritz et al. (2003) found that fathers activated middle cingulate, insula and ventral prefrontal cortex in response to generic infant cries. In contrast to non-parents, fathers activated the right amygdala in response to baby cries, but not

laughter. Swain et al. (2004) presented the audio stimuli for longer and found that fathers activated anterior cingulate, striatum of the basal ganglia, insula, and orbitofrontal cortex in response to unknown cries more than to a control sound. When they compared responses to own baby cries to those of unknown baby cries, they found greater activation in anterior cingulate and hippocampus. In addition, compared to control pictures, fathers activated cingulate and orbitofrontal cortex more in response to photographs of infants (Swain et al., 2004).

1.6. Relevant brain areas in focus

The following provides a closer look at the brain areas which the animal literature and imaging studies with non-mothers imply might be involved in maternal responsiveness in humans.

- *Midbrain.* Midbrain structures, especially the periaqueductal grey, have in previous studies been linked to nurturing and defensive behaviour (Sukikara et al., 2010), and suppression of anxiety (Miller et al., 2010). In addition, they are rich in receptors for the 'bonding hormone' oxytocin (Jenkins et al., 1984), and it is therefore conceivable that they could be associated with nurturing, protective and approach behaviour towards children.

- *Thalamic and hypothalamic regions (including MPOA/VBNST of the basal forebrain).* The hypothalamus is responsible for the synthesis and secretion of several neurohormones, including oxytocin, which is synthesised in the magnocellular neurosecretory cells of the supraoptic and paraventricular nuclei. From here oxytocin is innervated into the nucleus accumbens of the basal ganglia (Ross et al., 2009). Moreover, the hypothalamus, as well as septal regions including the MPOA, are considered part of the 'reward system' (Novakova et al., 1993).

  The thalamus acts as a relay between subcortical and cortical regions for sensory systems including the somatosensory system,

may be related to increased emotional experiences and has been linked to reward and obsessive behaviour, which is seen in mothers (Baxter, 2003).

- *Limbic structures including cingulate and amygdala.* Cingulate cortex has in previous research been shown to be involved in emotion formation and processing, as well as executive functioning in more general (Allman et al., 2001). Anterior cingulate has been linked to mood regulation, including anxiety (Drevets et al. 2008), decision-making, and reward-based learning (Bush et al., 2002). Posterior cingulate has been associated with memory retrieval (Nielsen et al., 2005).

  The amygdala has been associated with emotional salience (Sander et al., 2003; Britton et al., 2006). The animal literature implies that different sub-regions and types of neural populations of the amygdala are involved in facilitation and inhibition of maternal behaviour. The amygdala has also been found to play a role in general face recognition, which is thought to occur at least to some extent by identifying an individual's unique emotional expression (Gobbini & Haxby, 2007). Overall, limbic structures could be involved in maternal responsiveness by being linked to emotional, as well as executive functions.

- *Basal ganglia.* The basal ganglia are high in oxytocin and vasopressin receptors and are part of the 'reward network'. Particularly ventral tegmental dopaminergic neurons that innervate portions of the striatum have been implicated in feelings of reward (Peters & Buchel, 2010). The basal ganglia are also involved in emotion regulation and drives (Gutman et al., 2009). Imaging studies have shown that such structures are activated in response to emotional stimuli, as well as unexpected or intense stimuli. It has been suggested that the determining factor for its activation is salience. The basal ganglia have also been linked to obsessive

behaviour (Baxter, 2003), and Swain et al. (2004) argued that the basal ganglia may also be related to maternal preoccupations, as well as maternal reward.

- *Insula.* There is some evidence for a role of the insula in face recognition, which again is likely to be due to the recognition of specific emotional expressions in individuals (Gobbini & Haxby, 2007). There is also consistent evidence coming from imaging studies for the involvement of the insula in the experience of emotions, including anger, fear, disgust, happiness and sadness. It has been proposed that it may play a role in mapping visceral states that are associated with emotional experience, giving rise to conscious feelings (Adolphs et al., 2003). It has also been linked to empathy (Singer, 2006), selective attention (Eckert et al., 2009), the processing of norm violations (Sanfey et al., 2003), assessing emotional salience (Britton et al., 2006), and the integration of emotional and cognitive information, all of which are skills relevant to maternal responsiveness (Carr et al., 2003; Critchley, 2009; Perlman and Pelphrey, 2010).

- *Frontal cortex.* This part of the brain is responsible for higher cognitive functions, especially control of behaviour. The medial frontal cortex has been implied in mood regulation (Gutman et al., 2009). The orbitofrontal cortex is thought to be involved in the planning of behaviour sensitive to reward and punishment (Bechara et al., 1994), including the inhibition of socially inappropriate behaviour (Snowden et al., 2001), and the integration of emotional and cognitive information (Carr et al., 2003; Critchley, 2009; Perlman and Pelphrey, 2010), functions which may be important for effective parenting. Imaging studies in fathers implied the orbitofrontal cortex to be involved in paternal responsiveness. In addition, the orbitofrontal cortex, the dorsomedial frontal cortex and the frontal pole are known as motivation and reward regions (Bechara et al., 1994).

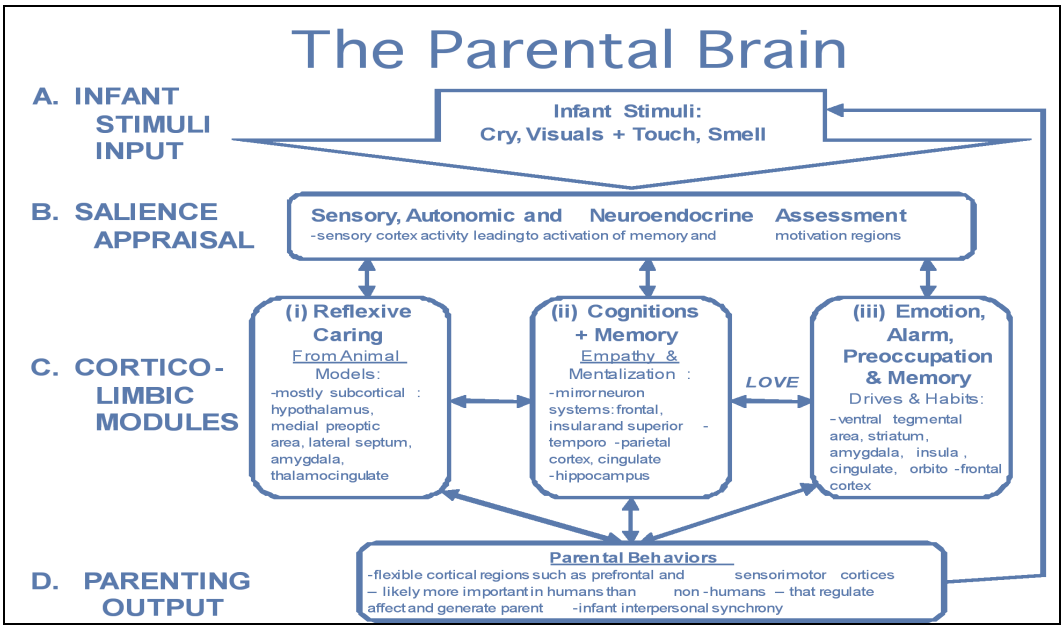
- *Temporal/parietal cortex.* The temporal cortex is involved in the recognition of objects, and the parietal cortex is involved in localisation of objects and motion (Morel & Bullier, 1990). Both have been reported to play a role in the integration of emotional and cognitive information (Carr et al., 2003; Critchley, 2009; Perlman and Pelphrey, 2010), and have been related to social cognition (Schulz, 2005). As discussed above, such skills are important parenting skills. The fusiform gyrus of the temporal lobe is specifically involved in the recognition of faces (Sergent et al., 1992; Axelrod, 2010). The temperoparietal gyrus has been associated with self-other distinction (Tsakiris et al., 2008), which is of interest considering mothers often report a relative lack of distinction between themselves and their child (Swain et al., 2005). The parietal lobe is the site of somatosensory cortex and hence plays a role in touch (Bolognini et al., 2011).

- *Cerebellum.* Apart from its role in the calibration of movement (Burke & Fahn, 1985), the cerebellum has been implicated in the control of attention, the regulation of fear and pleasure responses, and learning (Wolf et al., 2009).

1.7. Swain's model for the brain basis of parental responsiveness

Based on previous animal and human research, James Swain (2008) suggested that there may be a specific neural network associated with human maternal responsiveness and proposed a model for the brain basis of parental responsiveness in humans (see Figure 1).

Figure 1: Swain's model for the brain basis of parental responsiveness



Source: Swain (2008); used with the permission of the author

In his model, Swain suggests than when infant/child stimuli are perceived by mothers a salience appraisal occurs, involving sensory, autonomic and neuroendocrine assessment, and that this activates sensory cortex.

This activates three responses: 1) 'Reflexive caring', located in the subcortical brain, including hypothalamus, medial preoptic area, lateral septum, amygdala and thalamocingulate regions. 2) 'Empathic and related cognitive emotional responses associated with mentalization', including mirrorneuron systems in the frontal, insular and superior temperoparietal cortex, cingulate and regions associated with memory such as the hippocampus. 3) 'Drives and habits related to emotions, alarm and preoccupations', including the ventral tegmental area, striatum, amygdala, insula, cingulate and orbitofrontal cortex. According to Swain, empathy, mentalization and emotions combine to create the experience of maternal love.

The activation of these 'cortico-limbic modules' is, he claims, responsible for the activation of flexible cortical regions such as the prefrontal cortex and sensorimotor cortices, which in turn are responsible for parental

behaviours by regulating affect and generating sensitive responses to children.

Several studies have used fMRI to research the brain basis of human maternal responsiveness, but none has formally assessed Swain's model.

1.8. Study outline

A systematic review will qualitatively summarise brain activation reported in previous research. Included studies will be those using fMRI to assess maternal responsiveness to either generic children or mothers' own children. Both types of stimuli could assist in establishing biomarkers which may be used to develop and assess parenting interventions, either with non-mothers, preterm or new mothers.

Following this, studies will be meta-analysed using the software GingerALE (Eickhoff et al., 2009), which has previously been used to meta-analyse structural and functional imaging studies. Studies with generic infants or own infants as the experimental stimulus will be synthesised in separate meta-analyses. Similarly, studies with stimuli relating to different senses (i.e. auditory and visual) will be included in separate meta-analysis as they may activate different areas within the maternal brain.

Providing the research question is comparable between studies, it is possible to conduct meta-analyses using GingerALE even if the number of studies is small. However, the larger the number of included studies, and the larger the number of participants and foci, the more likely the results will be reliable, especially if there is heterogeneity in the sample.

1.9. Hypotheses

It is hypothesised that:

1) In accordance with Swain's (2008) model, maternal responsiveness in healthy new mothers is associated with an extensive neural network.

2) As predicted by Swain's (2008) model, this will include midbrain, thalamus, hypothalamus, frontal areas, temporal cortex, insula, limbic structures including cingulate and amygdala, and basal ganglia.

3) As suggested by research in nulliparous people and fathers, these brain areas will be activated for both the contrast child versus control stimuli, and for the contrast own versus control child.

4) Neural regions associated with reward (resulting from the experience of love) will be activated more in response to own versus other children. This includes basal ganglia, thalamus, hypothalamus, septal regions, and orbitofrontal cortex.

2. Systematic review

2.1. Methods

2.1.1 Inclusion criteria for studies

In order to summarise (and meta-analyse) past studies on the neural basis of maternal responsiveness, a systematic review of the literature was carried out. For inclusion, studies were required to be original fMRI studies in which healthy mothers were exposed to infant and/or child stimuli (own or other) as well as control stimuli, and a comparison of maternal brain activation in response to these stimuli was undertaken. Studies were included in the review/synthesis even if activated/deactivated foci for such a contrast were not reported. There were two reasons for this: First, it was considered possible to obtain the foci from the authors upon request; second, it provided a more complete synthesis of the relevant literature. The experimental stimuli could relate either to the mother's own children, familiar children or unknown children. The search was carried out in early 2012 and included studies were required to be published before the end of 2011.

2.1.2. Identification of studies

Papers were identified by typing the word combination ['parent' or 'mother' or 'maternal'] and ['fMRI' or 'imaging'] into the search engines 'PubMed', 'Web of Knowledge' and 'Google Scholar'. The words 'fMRI'/'imaging' and 'parent'/'mother'/'maternal' had to appear in the title or abstract in order for the papers to be identified. Words that incorporated one of these words, such as 'mother*ing*,' were also valid. Relevant studies, as well as relevant review papers, were searched for mention of additional studies. Researchers who were identified to be the leading researchers in the field were also contacted to enquire whether they had carried out additional research. This methodology was in line with the principles of systematic reviews as outlined by the Cochrane Handbook for Systematic Reviews of Interventions (2011).

2.1.3. Qualitative synthesis of identified studies

The details of identified papers were collated and summarised in a table (Table 2). All papers were searched for reported contrasts, and a qualitative synthesis of brain activation/deactivation was compiled.

2.2. Results

2.2.1. Identified studies

Twenty studies were identified which used fMRI to compare maternal brain responses to children (own and/or other) versus control stimuli. Of these:

- Seven used auditory stimuli (i.e. sounds)
- 13 used visual stimuli. Of these:
    - Nine used static images (i.e. photographs)
    - Four used moving images (i.e. videos)

Six studies using auditory stimuli were identified via web searches; an additional one (Swain et al., 2003) was identified by reading a review paper.

Seven relevant studies using static visual stimuli were identified via the web search; two additional ones (Swain et al., 2003; Strathearn et al., 2005) were identified by reading a review paper. Upon request, one of these studies (Strathearn et al., 2005) was reported to be an earlier version of the authors' later papers (Strathearn et al., 2008; Strathearn et al., 2009), and was hence excluded from reported summaries and further analyses.

Three papers using moving images (i.e. videos) as stimuli were identified through web searches; results for an additional unpublished study (Wan et al., in preparation) were obtained directly from the researchers.

Table 2 provides a chronological summary of all identified audio and visual studies (both static images and videos), the stimuli used, their research design, and the contrasts they provided.

Table 2: Identified studies concerning brain activation associated with maternal responsiveness

Study	Type of stimuli	Study design	Experimental stimuli	Control stimuli	Number of participants	Contrasts reported				
						Activation generic child versus neutral control	Deactivation generic child versus neutral control	Activation own child versus control child	Deactivation own child versus control child	Additional contrasts reported
Lorberbaum et al. (1999)	Audio	1.5T, 30s blocks	Pain/separation cry of unknown infant (1 month and 1 week old respectively)	White noise	4 mothers (child less than 4 years old)	**Yes**	No	No	No	None
Lorberbaum et al. (2002)	Audio	1.5T, 30s blocks	Cry of unknown infant (3 days old)	White noise	10 right-handed breastfeeding first-time mothers (4 to 8 weeks postpartum)	**Yes**	No	No	No	None
Swain et al. (2003)	Audio	3T, 30s blocks	Cry of own and unknown infants (2 weeks to 4 months old)	White noise	7-14 mothers; 7-8 fathers (2 to 4 weeks postpartum)	**Yes**	**Yes**	No	No	Responses own baby cry versus neutral control sound (white noise); fathers' responses
Seifritz et al. (2003)	Audio	1.5T, 6s blocks	Cry and laugh of unknown infant (age unknown)	Sound made up of average of cry and laugh frequency spectral components	10 mothers (child < 3 years); 10 fathers mothers (child < 3 years); 10 nulliparous women; 10 childless men	**Yes**	**Yes**	No	No	Fathers', nulliparous women's and nulliparous men's responses; comparison between responses to cries and laughs
Kim et al. (2010)	Audio	3T, 30s blocks	Cry of unknown infant (2 to 4 weeks old)	White noise	26 mothers (2 to 4 weeks postpartum)	**Yes**	No	No	No	Response of mothers with perceived high maternal care in childhood to cry of unknown infant vs control sound > response of mothers with perceived low maternal care in childhood to cry of unknown infant vs control sound

Kim et al. (2011)	Audio	3T, 30s blocks	Cry of own infant (<2 weeks old)	White noise	17 mothers (2 to 4 weeks postpartum)	No	No	No	No	Breastfeeding mothers (own infant cry > unknown infant cry) versus bottle-feeding mothers (own infant cry > unknown infant cry)
Laurent at al. (2011)	Audio	3T, 23s blocks	Cry of own infant (15 to 18 months old)	White noise	22 first time mothers (15 to 18 months postpartum)	No	No	No	No	Correlation between activation of brain areas (cry of own infant > control) and stress response
Mean values (and standard deviations (SDs)) for audio studies	*All used audio stimuli*	*2.36T (SD: 0.80T), 25.57s blocks (SD: 9.02s)*	*5 studies used cries of unknown infants, 3 used cries of own infants, one used laughs of unknown infants; average infant age: 13.83 weeks (SD: 25.72 weeks)*	*All used a form of white noise*	*14.21 mothers (SD: 7.76); 11.38 months postpartum (SD: 9.87 months)*	*Provided by 5 studies*	*Provided by 2 studies*	*Provi-ded by none of the studies*	*Provided by none of the studies*	*n/a*
Strathearn & McClure (2002)	Visual (static images)	3T, 6s events	Photographs of own infant (3 to 8 months old)	Photographs of unknown infants (3 to 8 months old)	8 mothers (3 to 8 months postpartum)	No	No	**Yes**	No	None
Bartels and Zeki (2004)	Visual (static images)	2T, 15s blocks	Photographs of own child (9 months to 6 years old)	Photographs of familiar children (9 months to 6 years old)	19 mothers (child < 7 years old)	No	No	**Yes**	**Yes**	Responses own child versus familiar children (similar, exaggerated, results to own child versus unknown child; details not reported)
Leibenluft et al. (2004)	Visual (static images)	1.5T, 15s events	Photographs of own child (5 to 12 years old)	Photographs of familiar children (5 to 12 years old)	7 right-handed mothers (child 5 to 12 years old)	No	No	**Yes**	**Yes**	Responses familiar children versus unknown children
Swain et al. (2003)	Visual (static images)	3T, 30s blocks	Photographs of own and unknown infant (2 weeks to 4 months old)	Images of houses, Photographs of unknown infants (2 weeks to 4 months old)	9-14 mothers; 4-9 fathers (2 weeks to 4 months postpartum)	**Yes**	No	**Yes**	**Yes**	Fathers' responses

Nitschke et al. (2004)	Visual (static images)	1.5T, 30s blocks	Photographs of own infant (2 to 4 months old)	Photographs of unknown infants (2 to 4 months old)	6 right-handed mothers (2 to 4 months postpartum)	No	No	**Yes**	**Yes**	Correlation between brain activation (in response to own versus unknown children) and mood
Strathearn et al. (2005)	Study excluded from further synthesis as it was an earlier version of Strathearn et al. (2008) and Strathearn et al. (2009).									
Lenzi et al. (2008)	Visual (static images)	3T, 2s mini blocks	Photographs of own child (6-12 months old; neutral, distressed, joyful and ambiguous expressions)	Photographs of unknown children (6-12 months old; neutral, distressed, joyful and ambiguous expressions)	16 right-handed mothers (6-12 months postpartum)	No	No	**Yes**	No	Emotional infant expressions > neutral emotional expressions
Strathearn et al. (2008)	Visual (static images)	3T, 2s events	Photographs of own infant (5 to 10 months old; happy, neutral and sad expressions)	Photographs of unknown infants (5 to 10 months old; happy, neutral and sad expressions)	28 right-handed first-time mothers (5 to 10 months postpartum)	No	No	**Yes**	No	Own children with happy expressions > Unknown children with happy expressions
Strathearn et al. (2009)	Visual (static images)	3T, 2s events	Photographs of own infant (7 months old)	Photographs of unknown infants (7 months old)	30 securely or insecurely attached right-handed first-time mothers (7 months postpartum)	No	No	No	No	Secure versus insecure mothers for photographs of own children > photographs of unknown children; secure versus insecure mothers for happy own infant faces, and for sad own infant faces
Mean values (and SDs) for studies using static images	*All used static images*	*2.5T (SD: 0.71T), 12.75s blocks (SD: 11.94s)*	*All 8 studies used images of own infants; one also used images of unknown infants; average infant age: 10.94 weeks (SD: 11.84 weeks)*	*6 studies used images of unknown infants as control; 2 used images of familiar infants; one also used images of houses; average infant age: 10.94 weeks (SD: 11.84 weeks)*	*15.69 mothers (SD: 9.36); 22.94 months postpartum (SD: 35.31 months)*	*Provided by one study*	*Provided by none of the studies*	*Provi-ded by 7 studies*	*Provided by 4 studies*	*n/a*

Ranote et al. (2004)	Visual (videos)	1.5T, 2--40s blocks	Videos of own and unknown infants (4 to 8 months old)	Traffic videos; videos of unknown infants (4 to 8 months old)	10 mothers (4 to 8 months postpartum)	**Yes**	No	**Yes**	**Yes**	None
Noriuchi et al. (2008)	Visual (videos)	1.5T, 32s blocks	Videos of own child (16 months old)	Videos of unknown children (16 months old)	13 right-handed mothers (16 months postpartum)	No	No	**Yes**	**Yes**	None
Atzil et al. (2011)	Visual (videos)	3T, 2min blocks	Videos showing own infants both by themselves and interacting with their mother (4 to 6 months old)	Videos of unknown infants (both alone and with their mothers; 4 to 6 months old)	23 mothers (4 to 6 months postpartum)	No	No	**Yes**	No	Synchronous mothers versus intrusive mothers (for own versus other infant)
Wan et al. (in preparation)	Visual (videos)	1.5T, 30s blocks	Videos of own and unknown infants (4 to 9 months old)	Traffic videos; videos of unknown infants (4 to 9 months old)	20 mothers (4 to 9 months postpartum)	**Yes**	**Yes**	**Yes**	**Yes**	None
Mean values (and SDs) for studies using videos	*All used videos*	*1.88T (SD: 0.75T), 26s blocks (SD: 16.57s)*	*All 4 studies used images of own infants; 2 also used images of unknown infants; average infant age: 8.38 weeks (SD: 5.12 weeks)*	*All 4 studies used images of unknown infants as control; 2 also used images of traffic; average infant age: 10.94 weeks (SD: 11.84 weeks)*	*16.5 mothers (SD: 6.03); 8.38 months postpartum (SD: 5.12 months)*	*Provided by 2 studies*	*Provided by one study*	*Provi-ded by 4 studies*	*Provided by 3 studies*	*n/a*

As can be seen in Table 2, all but two (Laurent at al., 2011; Kim et al., 2011) of the identified audio studies compared maternal responses to a generic infant sound (i.e. cry of unknown infant) versus a control sound such as white noise. Two of these studies also reported deactivation associated with the infant stimulus. None of the audio studies reported results for maternal activation in response to sounds of own versus control infants. Additional comparisons reported in individual studies were: i) Responses to own infant cry versus neutral control sounds (Swain et al., 2003); ii) Mothers' versus fathers' brain responses (Swain et al., 2003); iii) Mothers' versus fathers', nulliparous women's and nulliparous men's brain responses (Seifritz et al., 2003); iv) Brain responses to infant cries versus infant laughs (Seifritz et al., 2003); v) Brain responses to cries in mothers with perceived high maternal care in childhood versus mothers with perceived low maternal care in childhood (Kim et al., 2010); vi) Breastfeeding mothers' brain responses versus bottle-feeding mothers' (Kim et al., 2011); and finally vii) A correlation between maternal activation in response to infant cries and maternal stress response (Laurent et al., 2011).

Table 2 also shows that all of the twelve visual studies (using either static pictures or videos) reported maternal brain activation relating to own versus other children. Seven of these (four using static images; three using videos) also reported deactivation relating to mothers viewing own versus control infants (i.e. greater brain activation when viewing control infants). In addition, two studies using videos (Ranote et al., 2004; Wan et al., in preparation) also reported maternal brain responses to visual cues of children (including both known and unknown children) versus control images (i.e. traffic), with one of these also reporting the corresponding deactivation (Wan et al., in preparation). Additional contrasts reported by individual studies using visual stimuli were as follows: i) Brain responses to familiar versus unknown children (Leibenluft et al., 2004); ii) Mothers' versus fathers' responses (Swain et al., 2003); iii) Maternal brain activation in response to emotional infant expressions versus neutral emotional expressions (Lenzi et al., 2008); iv) Maternal brain responses to own

children with happy expressions versus unknown children with happy expressions (Strathearn et al., 2008); v) Brain responses of securely attached versus insecurely attached mothers (Strathearn et al., 2009); vi) Brain responses of synchronous versus intrusive mothers (i.e. mothers displaying coordination of maternal behaviour with infant signal versus the excessive expression of maternal behaviour; Atzil et al., 2001); and finally vii) A correlation between brain activation (in response to own versus unknown children) and mood (Nitschke et al., 2004).

2.2.2. Summary of studies' methodology, findings and limitations

2.2.2.1. Auditory studies (Infant sounds versus control sounds)

1) Lorberbaum et al. (1999): In a study with very small sample size (N=4 mothers), significantly increased activity in anterior cingulate and right medial prefrontal cortex in response to infant cry versus white noise was reported.

2) Lorberbaum et al. (2002): In a follow-up study with a bigger sample size (N=10) breastfeeding first-time mothers four to eight weeks postpartum displayed greater activity in response to infant cries as compared to white noise in areas known to be important for rodent maternal behaviour (Numan, 1994), including the midbrain, hypothalamus, striatal and septal regions, as well as the thalamus, cingulate, medial, and orbitofrontal cortex.

3) Swain et al. (2003): Reported that infant cries versus white noise activated mothers' septal regions, thalamus, anterior cingulate, striatum, globus pallidus, insula, cerebellum orbitofrontal and medial frontal cortex, temporal/parietal and occipital cortex. Also reported that if the cry came from own infant and was compared to a control sound, midbrain, hypothalamus and amygdala activated.

4) Seifritz et al. (2003): Reported increased activity in amygdala and insula in mothers up to three years postpartum when presented with baby laughs

or cries. Contrary to the findings of Lorberbaum et al. (1999), this research group reported decreased activity in the anterior cingulate to baby stimuli. Swain et al. (2007) argued that this may be due to them using an event-related rather than a block design, in which stimuli were presented for only six seconds. Accordingly such short stimuli may have a different meaning to new parents compared to longer blocks.

5) Kim et al. (2010): Reported activation in mothers' frontal, temporal and hippocampal regions in response to infant cries versus white noise. Also reported that perceived quality of maternal care in childhood affects mothers' brain responses to children. Thus mothers who reported higher maternal care in childhood exhibited higher activations in the middle frontal gyrus, superior temporal gyrus, and fusiform gyrus, whereas mothers reporting lower maternal care showed increased hippocampal activation.

6) Kim et al, (2011): Found that breast-feeding versus bottle-feeding mothers activated basal ganglia, amygdala, insula, orbitofrontal cortex, superior frontal gyrus, temporal, parietal and occipital cortex more in response to infant cries versus white noise. Brain activation for overall results (i.e. all mothers) for the contrast infant cries versus control stimuli were not reported.

7) Laurent et al. (2011): Reported that the activation of midbrain, thalamus, anterior cingulate, striatum, insula, cerebellum, orbitofrontal, temperoparietal and occipital cortex correlated positively with mothers' stress responses to infant cries: Activation of these areas indicated a longer, but less peaked, stress response. The authors only reported details for the correlation, and did not report details regarding overall brain activation for the contrast infant versus control sound.

Limitation of all audio studies

White noise, which was used as a control stimulus in all audio studies, does arguably not represent a neutral stimulus, and may have been considered aversive by participants.

2.2.2.2. Visual studies (Child versus control stimuli; static images)

1) Swain et al. (2003): Reported that mothers activated limbic regions, including amygdala, basal ganglia, orbitofrontal and medial frontal cortex, temperoparietal cortex, occipital cortex, and cerebellum in response to pictures of infants versus houses.

2) Leibenluft et al. (2004): Reported that mothers activated the fusiform gyrus, intraparietal sulcus, precuneus, and posterior superior temporal sulcus in response to unattached child versus adult faces.

3) Strathearn et al. (2008): Found that the ventral visual pathway, which comprises parts of the occipital and temporal cortices, and is associated with the processing of visual stimuli, including people (Goodale & Milner, 1992), activated more in mothers in response to photographs of own and unknown infants compared to a baseline. This activation included the fusiform face area, an area believed to be involved specifically in face processing (Sergent et al., 1992; Axelrod, 2010).

2.2.2.3. Visual studies (Child versus control stimuli; videos)

1) Ranote et al. (2004): Reported greater activation of mothers' occipital and temporal cortices in response to video clips of own and unknown infants versus that of a neutral control stimulus depicting moving traffic. However, traffic arguably does not represent a neutral stimulus, and may for example be considered aversive.

2) Wan et al. (in preparation): Reported mothers activated anterior cingulate, insula, cerebellum, orbitofrontal, medial frontal, temporal and occipital cortex in response to infant videos versus a control (traffic). Also reported *de*activation of anterior and posterior cingulate, medial frontal

cortex, temporal regions and cerebellum. However, again, traffic arguably does not represent a neutral stimulus, and may for example be considered aversive.

2.2.2.4. Visual studies (Own versus other child; static images)

1) Strathearn and McClure (2002): Reported that in a small sample (N=8 mothers) there was maternal activation of thalamus, hippocampus, striatum, globus pallidus, fusiform gyrus, occipital cortex and cerebellum.

2) Bartels and Zeki (2004): Found that, compared to pictures of familiar or unknown children, pictures of mothers' own children were more likely to activate the anterior cingulate, insula, striatum of the basal ganglia, and the periaqueductal grey of the midbrain, areas which according to the authors may mediate the emotionally rewarding aspects of maternal responsiveness. They also found decreased activation in the middle prefrontal cortex and the posterior cingulate cortex, areas which are associated with social assessment, in temperoparietal regions, associated with self-other distinction and avoidance behaviour, and in amygdaloid regions, associated with negative emotions such as fear. Findings were bilateral but particularly pronounced in the right hemisphere and when compared to unknown rather than familiar infants. Bartels and Zeki suggested a push-pull mechanism for maternal responsiveness in which infant stimuli activate reward- and shut down avoidance-circuits.

3) Leibenluft et al. (2004): Found that in a relatively small sample of seven mothers, pictures of own versus unknown children were more likely to activate the amygdala, insula, and anterior paracingulate regions, which are associated with the processing of emotion and ‘theory of mind’ abilities.

4) Swain et al. (2003): Found activation in mothers’ brains in the amygdala, basal ganglia, cingulate cortex, occipital cortex, and brainstem in response to pictures of own versus unknown infants at two to four months postpartum.

5) Nitschke et al. (2004): In a study with a relatively small sample size (N=6), the authors found that mothers displayed greater activation of areas in occipital cortex and bilateral orbitofrontal cortex in response to photographs of their own versus unknown infants. Activation in orbitofrontal cortex was associated with ratings of pleasant moods, and the authors concluded that orbitofrontal cortex may act as an important centre for rewarding affective aspects of a mother's attachment to her child. Analyses with regards to amygdala activation were also conducted, but results were inconclusive. The authors also reported that there was deactivation in bilateral anterior temporal cortex.

6) Lenzi et al. (2008): Reported that mothers' own infants activated amygdala, insula, orbitofrontal, ventral prefrontal and temperoparietal cortex more than unknown infants. With the exception of ventral prefrontal cortex, these regions were more active in response to emotional versus neutral infant expressions.

7) Strathearn et al. (2008): In a study with a large sample size (N=28 mothers) and infants displaying happy, sad or neutral emotional expressions, the authors found that there was activation in many of the dopamine-associated reward processing areas reported in previous studies. This included frontal regions, including 1) medial prefrontal cortex, anterior cingulate, and insular cortex, which are associated with emotion processing, 2) dorsolateral prefrontal cortex, which is involved in cognition, and 3) the primary motor area, associated with behavioural outputs; as well as the striatum and substantia nigra of the basal ganglia, and the ventral tegmental area of the midbrain.

8) Strathearn et al. (2009): In a follow-up study with a similarly large sample size (N=30), the authors found that mothers with an attachment to their child that was rated as secure were more likely to show activation in brain reward regions including the ventral striatum, hypothalamus and pituitary regions in response to their own infants versus unknown ones as compared to mothers rated as having an insecure attachment. Foci for

overall results (i.e. all mothers) for the contrast own versus other infants were not reported.

Limitations of all studies using static images

Although studies using photographs have provided a great deal of insight into the brain activity associated with maternal responsiveness to visual stimuli, their static nature reduces the ecological validity of the research.

2.2.2.5. Visual studies (Own versus other child; videos)

1) Ranote et al. (2004): Reported in a relatively small sample (N=9 mothers) greater activation to own versus unknown infants in the amygdala, as well as the temporal pole and occipital cortex. Also found *de*activation in left postcentral gyrus, left hippocampal formation, bilateral visual processing regions, right dorsolateral prefrontal cortex, right medial prefrontal cortex, left frontal pole, bilateral lateral orbitofrontal cortex, and cerebellum.

2) Noriuchi et al. (2008): Reported greater activation to mothers' own versus unknown infants in bilateral orbitofrontal cortex, periaqueductal grey of the midbrain, anterior insula, and dorsal and ventrolateral parts of the putamen of the striatum (which is part of the basal ganglia). Activation in anterior and posterior cingulate cortex, prefrontal cortex (including dorsomedial parts), thalamus, substantia nigra and caudate nucleus of the basal ganglia, dorsal regions of orbitofrontal cortex, and posterior superior temporal sulcus, which had been reported in previous studies, as well as the right inferior frontal gyrus, was found only when infants were expressing distress, but not when they were expressing happiness. They also found *de*activation in the right superior temporal gyrus and the fusiform face area of the temporal cortex, as well as the bilateral postcentral gyrus, bilateral putamen, right frontal pole, inferior parietal lobule, precuneus, and left parahippocampal gyrus.

3) Atzil et al. (2011): Videos of infants alone and interacting with their mothers versus control infants activated mothers' septal regions,

thalamus, amygdala, striatum, insula, medial frontal gyrus, temperoparietal cortex and cerebellum. Parts of the medial frontal gyrus were more active in synchronous mothers (i.e. mothers displaying coordination of maternal behaviour with infant signal), whereas other parts were more active in intrusive mothers (i.e. mothers displaying excessive expression of maternal behaviour). Intrusive mothers were more likely to activate the fusiform gyrus, occipital cortex and cerebellum in response to their own infants (versus control children) than synchronous mothers, but synchronous mothers activated septal regions, the insula, orbitofrontal cortex and some temporal regions more than intrusive mothers.

4) Wan et al. (in preparation): Found that for the contrast own versus unknown infant, the amygdala, cerebellum, and medial frontal, temporal and occipital cortex were activated in mothers. There was *de*activation of medial frontal cortex, temporal cortex and cerebellum.

2.2.3. Summary of identified brain activity

The identified studies reported activation of several brain areas when mothers were exposed to auditory or visual stimuli relating to generic infant cues versus control stimuli, and when they were exposed to own infant versus control infant stimuli. An overview of which brain areas were associated with maternal responsiveness for the various contrasts in audio studies, studies using static images and studies using videos, is given in Tables 3, 4 and 5, respectively. Activation patterns are given for maternal responses to infants versus neutral control stimuli, as well as maternal responses to own infants versus control infants. Any additional contrasts relating to maternal responsiveness which were given are also included. Paternal responses and responses of nulliparous women and men were not included in the tables (with the exception of Seifritz et al.'s (2003) study, which reports mothers' and fathers' combined responses). All reported findings satisfy the criteria of $p \leq 0.001$ for fixed effects, or $p \leq 0.05$ for random effects.

Table 3: Maternal brain responses to auditory stimuli of infants

Author (year)	Lorberbaum et al. (1999)	Lorberbaum et al. (2002)	Swain et al. (2003)		Seifritz et al. (2003)	Kim et al. (2010)		Kim et al. (2011)	Laurent et al. (2011)
Number and type of participants	N=4 mothers	N=10 mothers	N=7-14 mothers		N=20 mothers and fathers	N=26 mothers		N=17 mothers	N=22 mothers
Age of infants at time of scan	3 weeks – 3.5 years	1 – 2 months	Time 1: 2 – 4 weeks Time 2: 3 – 4 months		<3 years	< 1 month		2-4 weeks	15-18 months
Study design	1.5T, 30s blocks	1.5T, 30s blocks	3T, 30s blocks		1.5T, 6s events	3T, 30s blocks	3T, 30s blocks	3T, 30s blocks	3T, 23s blocks
Infant sounds and contrast used	Pain/separation Cry of unknown infant > white noise	Cry of unknown infant > control noise	Cry of own infant > control	Cry of unknown infant > control	Cry and laugh of unknown infant > control sound	Cry of unknown infant less than 2 weeks old > control	Response of mothers with perceived high maternal care in childhood cry vs control > response of mothers with perceived low maternal care in childhood cry vs control	Breastfeeding mothers (own infant cry > white noise) > bottle-feeding mothers (own infant cry > white noise)	Correlation between activation of brain areas (cry of own infant > control) and stress response
Septal regions (MPOA/ VBNST/caudate head)		ACT	ACT	ACT					
Midbrain		ACT	ACT						COR
Hypothalamus		ACT	ACT						
Thalamus		ACT		ACT					COR
Limbic structures:									
Amygdala		ACT (cry – rest)	ACT		ACT (cries only)			ACT	
Anterior cingulate	ACT	ACT	ACT	ACT	DEACT (mothers only)				COR
Middle cingulate		ACT			ACT				
Posterior cingulate		ACT				ACT			
Hippocampus			ACT						
Basal ganglia:									
Striatum/putamen/nucleus accumbens		ACT	ACT	ACT				ACT	COR
Lentiform nucleus Globus pallidus		ACT	ACT	ACT				ACT	
Insula		ACT	ACT	ACT	ACT	ACT		ACT	COR
Frontal cortex:									
Orbitofrontal/Inferior frontal gyrus	ACT	ACT	ACT	ACT		ACT		ACT	COR
Medial/middle frontal gyrus	ACT	ACT	DEACT	ACT	DEACT	ACT	ACT		
Ventral prefrontal cortex	ACT				ACT				
Superior frontal gyrus						ACT		ACT	
Precentral gyrus						ACT	ACT		
Dorsolateral prefrontal cortex							ACT		
Temporal/parietal cortex:									
Temperoparietal cortex		ACT	ACT	ACT	ACT	ACT	ACT	ACT	COR
Fusiform gyrus		ACT	ACT	ACT			ACT	ACT	
Temporal/auditory cortex		ACT	ACT					ACT	
Parahippocampal/limbic lobe			ACT						
Occipital cortex	Not examined	Not examined	ACT	ACT		ACT		ACT	COR
Cerebellum	Not examined	Not examined	ACT	ACT					COR

ACT= activated; DEACT= deactivated; COR= correlated with activation; based on Swain et al. (2007)

Table 4: Maternal brain responses to visual stimuli of infants using static pictures

Author (year)	Strathearn & McClure (2002)	Bartels and Zeki (2004)	Leibenluft et al. (2004)		Swain et al. (2003)		Nitschke et al. (2004)		Lenzi et al. (2008)		Strathearn et al. (2008)		Strathearn et al. (2009)		
Number and type of participants	N=8 mothers	N=19 mothers	N=7 mothers		N=9-14		N=6		N=16		N=28		N=30		
Age of infants at time of scan	3 – 18 months	9 months – 3.5 years	5 – 12 years		Time 1: 2 – 4 weeks Time 2: 3 – 4 months		2 – 4 months		6 - 12 months		5 – 10 months		7 months		
Study design	3T, 6s events	2T, 15s blocks	1.5T, 1.5s events		3T, 30s blocks		1.5T, 30s blocks		3T, 2 s mini-blocks		3T, 2s events		3T, 2s events		
Infant visuals and contrast used	Photos of own infant > unknown infant	Photos of own children > photos of other known or unknown children	Photos of own child > photos of familiar child	Photos of familiar children > unfamiliar children	Photos of own infant > unknown infant	Photos of infants > neutral control (house)	Photos of own children > unknown children	Correlation with positive mood	Photos of own infant > unknown infant	Emotional infant expressions > neutral emotional expressions	Photos of own versus unknown children in happy, sad and neutral moods	Photos of own versus unknown happy infants	Mothers with secure versus insecure infant attachments viewing pictures of own vs unknown child in happy, sad and neutral moods	Securely versus insecurely attached mothers (happy own infant faces)	Securely versus insecurely attached mothers (sad own infant faces)
Septal regions (MPOA/ VBNST/caudate head)			.	DEACT	ACT										
Midbrain (including periaqueductal grey):		ACT			ACT	ACT					ACT	ACT			
Hypothalamus					ACT						ACT		ACT		
Thalamus	ACT	ACT	ACT/DEACT	DEACT	ACT	ACT					ACT	ACT			
Limbic structures:															
Amygdala		DEACT	ACT			ACT			ACT	ACT		ACT			
Anterior cingulate		ACT	ACT	ACT	ACT	ACT									DEACT
Middle cingulate					ACT	ACT					ACT				
Posterior cingulate		DEACT	ACT	ACT											
Anterior paracingulate			ACT												
Hippocampus	ACT														
Basal ganglia:															
Striatum/putamen/ nucleus accumbens	ACT	ACT	ACT			ACT					ACT	ACT		ACT	ACT
Lentiform nucleus Globus pallidus	ACT		ACT			ACT									
Insula		ACT	ACT	ACT/DEACT					ACT	ACT	ACT		ACT/DEACT		DEACT
Frontal cortex:															
Orbitofrontal/Inferior frontal gyrus		ACT	ACT	ACT/DEACT	ACT	ACT	ACT	COR	ACT		ACT		DEACT	ACT	ACT/DEACT
Medial frontal gyrus		DEACT	ACT		DEACT	ACT							ACT/DEACT	ACT	DEACT
Superior frontal gyrus			ACT	DEACT							ACT		ACT/DEACT	DEACT	ACT/DEACT
Ventral prefrontal cortex		ACT							ACT						
Precentral gyrus			ACT								ACT		DEACT	DEACT	DEACT
Gyrus rectus			ACT												
Temporal/parietal cortex:															
Temperoparietal cortex		DEACT	ACT	ACT/DEACT	ACT	ACT			ACT	ACT	ACT				
Fusiform gyrus	ACT	ACT			ACT	ACT					ACT				
Temporal/auditory cortex			DEACT	ACT/DEACT			ACT/DEACT		ACT	ACT					
Parahippocampal/limbic lobe						ACT					ACT				
Occipital cortex	ACT	ACT	ACT	DEACT	ACT	ACT	ACT				ACT				
Cerebellum	ACT		ACT	DEACT	ACT	ACT	ACT				ACT				

ACT= activated; DEACT= deactivated; COR= correlated; based on Swain et al. (2007)

Table 5: Maternal brain responses to visual stimuli of infants using video clips

Author (year)	Ranote et al. (2004)		Noriuchi et al. (2008)	Atzil et al (2011)		Wan et al. (in preparation)	
Number and type of participants	N=10		N=13	N=23		N=20	
Age of infants at time of scan	4 – 8 months		16 months	4 - 6 months			
Study design	1.5T, 20 – 40s blocks		1.5T, 32s blocks	3T, 2min blocks		1.5T, 30s blocks	
Infant visuals and contrast used	Silent video clips of infants > videos of traffic (control)	Silent video clips of own children > silent video clips of unknown children	Silent video clips of own children > silent video clips of unknown children	Silent video clips of own infants both playing individually and interacting with their mothers > Silent video clips of unknown infants both playing individually and interacting with their mothers	Synchronous mothers (own > other infant) > Intrusive mothers (own > other infant)	Silent video clips of infants > videos of traffic (control)	Silent video clips of own children > silent video clips of unknown children
Septal regions (MPOA/ VBNST/caudate head)				ACT	ACT		
Midbrain (including periaqueductal grey)			ACT				
Hypothalamus			ACT				
Thalamus			ACT	ACT			
Limbic structures:							
Amygdala		ACT		ACT			ACT
Anterior cingulate						ACT/DEACT	
Middle cingulate							
Posterior cingulate			ACT			DEACT	
Hippocampus		DEACT					
Basal ganglia:							
Striatum/putamen/ nucleus accumbens			ACT/DEACT	ACT			
Lentiform nucleus Globus pallidus							
Insula			ACT	ACT	ACT	ACT	
Frontal cortex:							
Orbitofrontal/Inferior frontal gyrus		DEACT	ACT		ACT	ACT	
Medial frontal gyrus			ACT	ACT	ACT/DEACT	ACT/DEACT	ACT/DEACT
Ventral prefrontal cortex							
Dorsomedial prefrontal cortex			ACT				
Precentral gyrus			ACT				
Temporal/parietal cortex:							
Temperoparietal cortex	ACT	DEACT	DEACT	ACT		ACT	ACT
Fusiform gyrus			DEACT		DEACT	ACT	
Temporal/auditory cortex		ACT/DEACT	ACT		ACT	ACT/DEACT	DEACT
Parahippocampal/limbic lobe			DEACT			ACT/DEACT	
Occipital cortex	ACT	ACT/DEACT			DEACT	ACT	ACT
Cerebellum	ACT	DEACT		ACT	DEACT	ACT/DEACT	ACT/DEACT

ACT= activated; DEACT= deactivated; based on Swain et al. (2007)

2.2.4. Summary of brain basis of maternal responsiveness as identified by the systematic review

There are six main findings from the systematic review of past functional imaging studies which use either auditory of visual infant/child stimuli. First, studies suggest that maternal responsiveness is associated with a distributed neural network which includes 1) septal regions, 2) the midbrain including the periaqueductal grey, 3) the hypothalamus, 4) the thalamus, 5) limbic strictures, 6) the basal ganglia, 7) the insula, 8) frontal cortex, especially orbitofrontal cortex, 9) temperoparietal cortex, and 10) the cerebellum.

Second, many of the studies also suggest that there is deactivation of certain brain areas associated with maternal responsiveness (or greater activation in response to control stimuli), including anterior cingulate and medial frontal gyrus. Such deactivation was found by audio studies comparing maternal brain responses to infant sounds versus control sounds, as well as studies comparing maternal brain responses to images of own versus control children. In addition, in visual studies comparing responses to own versus control children, some studies have reported deactivation (i.e. greater activation in response to control children) of the thalamus, posterior cingulate, amygdala, orbitofrontal cortex, superior frontal cortex, precentral gyrus, temporal and parietal areas, and the parahippocampal lobe.

Third, there is a great deal of overlap of brain responses associated with maternal responsiveness between studies utilising different stimuli and contrasts. This is true for studies in which maternal responsiveness was measured by comparing maternal responses i) to generic infant sounds versus control sounds; ii) to own infant sound versus a neutral control sound; iii) to generic infant images versus neutral images, and iv) to images of own versus control children.

Fourth, despite the observed overlap, there seem to be some differences in the patterns of activation and deactivation depending on the stimuli

used and the contrasts compared. Thus, several studies have reported that these brain areas become differentially activated when mothers are exposed to infant sounds versus control sounds, to images of children versus control images, or to images of own versus control children. However, due to the large number of studies and activated foci, any differences are difficult to entangle, and the meta-analyses to be carried out in the next step are anticipated to assist in this task.

Fifth, there is some ambiguity in the findings, with some studies reporting contradictory findings. Thus, for example, some visual studies have reported activation of the amygdala in relation to maternal responsiveness for the contrast own versus control child, whereas others have reported deactivation.

Finally, each of the individual studies has been small or of only a moderate size (N=4-30) and to date no formal quantitative analysis combining past studies has been carried out. Due to the complex patterns of brain activation, a qualitative analysis of findings is limited. In order to obtain a more accurate understanding of the meaning of previous studies, and hence the brain basis of maternal responsiveness, it is therefore useful to analyse the findings quantitatively using meta-analysis.

3. Meta-analyses

3.1. Method

Previous estimates of association were meta-analysed in order to obtain a more accurate understanding of the brain basis of maternal responsiveness. Given the heterogeneity of results presented in the systematic review, the aim was to describe distinct activation patterns specific to maternal responses to own children, as well as other children. Contrasts of interest were thus those that compared mothers' responses to child stimuli to their responses to control stimuli, as well as mothers' responses to their own children to their responses to other children. In undertaking this analysis, it was anticipated to determine a set of imaging patterns which may act as biomarkers for subsequent studies of the effects of novel parenting interventions for maternal responsiveness and sensitivity.

The systematic review of the literature revealed the use of auditory stimuli or visual stimuli (photographs or videos) in studies of maternal responsiveness. These different paradigms are likely to elicit differential activation. Separate meta-analyses for studies using visual and auditory stimulus modalities were therefore undertaken. Studies using photographs or videos of infants were combined in the analyses.

Confirmation was obtained from studies' authors that data did not overlap between studies in order to ensure that data points were not included in the meta-analysis more than once.

3.1.2. Studies included in the meta-analyses

3.1.2.1. Audio Studies

Out of the seven identified auditory studies, three reported foci concerning the difference between maternal responses to a generic infant cry versus a control sound (i.e. white noise; Lorberbaum et al., 1999; Lorberbaum et al., 2002; Kim et al., 2010). One study reported foci for brain areas that

correlated with mothers' cortisol response for their brain responses to own infant sound versus control sounds (Laurent at al., 2011). Another study reported foci for brain areas showing greater activation in breast-feeding mothers versus non-breastfeeding mothers in response to a generic infant cry versus a control sound (Kim et al., 2011). For the remaining two studies (Swain et al., 2003; Seifritz et al., 2003) it was not possible to obtain any foci of activation, as they were not reported in the papers and authors were unable to provide them upon request.

Therefore, there was only one comparison for which foci were reported in more than one study and only one meta-analysis could be carried out from the audio studies' data:

1) Maternal brain activation to generic infant cries versus control sounds (i.e. white noise; 'Meta-analysis 1')

The remaining four studies (Swain et al., 2003; Seifritz et al., 2003; Laurent et al., 2011; Kim et al. 2011) were excluded from the analysis. None of the included studies reported *de*activation foci for this contrast. For one of the included studies (Kim et al., 2010), foci were provided for mothers who, based on self-report, had been categorised into receiving high or low maternal care in childhood, as well as the foci of activation for their combined results. For the purpose of the analysis, the foci for the combined results were utilised (i.e. including all mothers). Table 6 shows a summary of included and excluded audio studies, how many participants took part in each study, and how many relevant foci were provided by each study.

Table 6: Included and excluded audio studies (Activation infant cry versus control sound)

Study	Included/Excluded	Reason for exclusion	Number of participants	Number of reported foci
Lorberbaum et al. (1999)	Included	n/a	4	3
Lorberbaum et al. (2002)	Included	n/a	10	37
Swain et al. (2003)	Excluded	Unable to obtain foci	7-14	Unable to obtain foci
Seifritz et al. (2003)	Excluded	Included both mothers and fathers. Unable to obtain foci.	20	Unable to obtain foci
Kim et al. (2010)	Included	n/a	26	15
Laurent at al. (2011)	Excluded	Reported correlations with cortisol response own infant sound versus control; relevant foci not possible to obtain	22	Unable to obtain foci
Kim et al. (2011)	Excluded	Reported difference between breast-feeding and non-breast-feeding mothers, not possible to obtain foci for responses of all mothers for infant sound versus control	17	Unable to obtain foci
Overall	**3 Studies included**	**4 Studies excluded**	**40 participants included**	**55 foci included**

3.1.2.2. Visual studies

Out of the twelve identified studies using visual stimuli, two (Ranote et al., 2004; Wan et al., in preparation) provided foci for the maternal brain activation in response to generic child/infant images versus control images (i.e. traffic). One study (Wan et al., in preparation) provided foci for *de*activation in response to generic infant images versus control stimuli (i.e. greater activation to control images versus infant images). Ten studies (Strathearn & McClure, 2002; Bartels & Zeki, 2004; Leibenluft et al., 2004; Nitschke et al., 2004; Ranote et al., 2004; Noriuchi et al., 2008; Lenzi et al., 2008; Strathearn et al., 2008; Atzil et al., 2011; Wan et al., in preparation) provided foci for maternal brain activation in response to images of own versus control children (familiar or unknown), and six

studies (Bartels & Zeki, 2004; Leibenluft et al., 2004; Nitschke et al., 2004; Ranote et al., 2004; Noriuchi et al., 2008; Wan et al., in preparation) provided foci for *de*activation to images of own versus control children (i.e. activation greater for control versus own children). Two studies (Swain et al., 2003; Strathearn et al., 2009) were excluded as it was not possible to obtain any relevant foci for them - they were not reported in the papers and the authors were unable to provide them upon request. For one of these studies (Strathearn et al., 2009), an additional reason for exclusion was that the authors reported that its data overlapped with one of their previous studies (Strathearn et al., 2008).

It was possible to carry out meta-analyses for the following three contrasts (as more than one study provided relevant foci):

1) Activation to children versus control images ('Meta-analysis 2')
2) Activation to own versus control children ('Meta-analysis 3')
3) *De*activation to own versus control children ('Meta-analysis 4')

One study (Atzil et al., 2011) reported foci for both intrusive and synchronous mothers; however, for the purpose of the analyses, foci for the combined results were used (i.e. including all mothers). Another study (Strathearn et al., 2008) reported foci for activation in response to happy, sad and neutral infant faces; however, again, for the purpose of the analysis, the combined results (i.e. responses to all faces) were used.

Several studies reduced the threshold for the detection of activation for specific regions of interest, which were determined based on a priori hypotheses, using small volume correction. Small volume corrections were made by the following studies for the specified regions of interest:

- Bartels and Zeki (2004): Insula, anterior and posterior cingulate, caudate nucleus, putamen/globus pallidus, periaqueductal grey, substantia nigra and frontal, temporal and parietal regions, and amygdala

- Ranote et al. (2004): Amygdala
- Lenzi et al. (2008): Ventral premotor cortex, inferior frontal gyrus, insula and limbic system
- Atzil et al. (2011): Nucleus accumbens and amygdala
- Wan et al. (in preparation): Amygdala.

The results obtained using the reduced thresholds for these regions were included in the meta-analyses.

Since only one study provided foci for the *de*activation of generic infant images versus neutral control images (i.e. traffic), it was not possible to conduct a meta-analysis relating to this contrast. Table 7 shows a summary of included and excluded visual studies, how many participants took part in each study, and how many relevant foci were provided by each study.

Table 7: Included and excluded visual studies

Study	Included/ Excluded	Reason for exclusion	Number of partici-pants	Number of reported foci			
				Activation child versus control image	Deactivation child versus control image	Activation own child versus control child	Deactivation own child versus control child
Strathearn & McClure (2002)	Included	n/a	8	n/a	n/a	9	n/a
Swain et al. (2003)	Excluded	Unable to obtain foci	9-14	n/a	n/a	n/a	n/a
Bartels and Zeki (2004)	Included	n/a	20	n/a	n/a	28	27
Leibenluft et al. (2004)	Included	n/a	7	n/a	n/a	33	3
Nitschke et al. (2004)	Included	n/a	6	n/a	n/a	6	3
Ranote et al. (2004)	Included	n/a	10	12	n/a	3	15
Noriuchi et al. (2008)	Included	n/a	13	n/a	n/a	14	12
Lenzi et al. (2008)	Included	n/a	16	n/a	n/a	7	n/a
Strathearn et al. (2008)	Included	n/a	28	n/a	n/a	50	n/a
Strathearn et al. (2009)	Excluded	Unable to obtain relevant foci and study not independent from Strathearn et al. (2008)	30	n/a	n/a	n/a	n/a
Atzil et al. (2011)	Included	n/a	23	n/a	n/a	21	n/a
Wan et al. (in preparation)	Included	n/a	20	38	21	20	7
Overall	**10 Studies included**	**2 Studies excluded**	**151 partici-pants included**	**50 foci inclu-ded (from 2 studies)**	**21 foci obtained from a single study - no meta-analysis possible**	**191 foci inclu-ded (from 10 studies)**	**67 foci included (from 6 studies)**

3.1.2. Conduct of analyses

The meta-analyses were carried out using 'GingerALE' software (version 2.1.1.; Eickhoff et al., 2009). Foci for each of the four meta-analyses (one from audio data and three from visual data), as well as the number of participants for each study, were typed into four separate Excel files.

For meta-analysis 1 (activation in response to generic auditory stimuli of infants versus control sounds) 55 foci were provided overall by three studies.

For meta-analysis 2 (activation in response to images of generic infants versus control images) 50 foci were provided overall by two studies.

For meta-analysis 3 (activation in response to images of own versus control children) 191 foci were provided overall by ten studies.

For meta-analysis 4 (deactivation in response to own versus other children) 67 foci were provided overall by six studies.

All studies provided coordinates in Talairach space, apart from one visual study (Noriuchi et al., 2008), which reported activation/deactivation coordinates in MNI space. These were converted into Talairach space using GingerALE.

For each of the meta-analyses the foci were imported from Excel into GingerALE. Probability maps were generated and thresholded controlling the False Discovery Rate (FDR). The pN calculation of the FDR was used as this is a conservative method that does not assume independence of foci. The rationale for this was that the possibility could not be excluded that activation of calculated foci were influenced by activation of other surrounding foci. The analyses were carried out using a significance level of both 0.05 and 0.01.

Once the analysis had been run in GingerALE, 'Mango' software was used to produce images of activated and deactivated brain areas.

3.2. Results

3.2.1. Meta-analysis 1: Audio Studies - Maternal brain activation to infant cries versus control sounds

For the audio studies comparing maternal brain activation to infant cries versus control sounds, GingerALE revealed that three out of the 55 foci were outside of the mask (i.e. outside of the surface of the average brain; coordinates: 54, 39,-9; 63,9,-12; 51,27,-18). These were excluded from the analysis. This is a standard quality control step in GingerALE and stops activations appearing 'outside' of the brain. Meta-analysis 1 included the remaining 52 foci. Table 8 shows the results for the meta-analysis of the three studies at the 0.05 and 0.01 levels of significance.

Table 8: Meta-analysis of maternal brain activation to infant cries versus control sounds[a]

Coordinates			Hemisphere[+]	Label[++]	Volume (mm3)	Maximum ALE value
x	y	z				
8	56	24	R	Superior frontal gyrus (BA 9)	240	0.0094*
0	-74	-4	L & R	Lingual Gyrus/Occipital lobe (BA 18), declive	96	0.0083
-30	16	12	L	Insula	96	0.0083
0	2	60	L & R	Medial Frontal Gyrus (BA 6)	96	0.0083
52	-20	8	R	Superior temporal gyrus (BA 41)	80	0.0086
12	-78	8	R	Cuneus/Occipital lobe	80	0.0086
46	-38	10	R	Superior temporal gyrus (BA 41)	80	0.0086
-52	12	10	L	Inferior frontal gyrus (BA 44)	80	0.0086
-40	12	26	L	Middle frontal gyrus (BA 9)	80	0.0086
42	8	32	R	Precentral gyrus (BA 9)	80	0.0086
-4	26	48	L	Superior frontal gyrus (BA 8)	80	0.0086
0	-8	2	L & R	Thalamus, mammillary body	64	0.0076
0	-6	-6	L & R	Hypothalamus	Not given	0.0074
2	-38	24	L & R	Posterior cingulate, cingulate gyrus (BA 31)	64	0.0081
43	-6	46	R	Precentral gyrus (BA 6)	64	0.0081
-54	-18	8	L	Superior temporal gyrus (BA 41)	56	0.0089
20	44	44	R	Superior frontal gyrus (BA 8)	56	0.0075
6	16	52	R	Superior frontal gyrus (BA 8)	56	0.0089
-42	-12	54	L	Precentral gyrus (BA 4)	56	0.0089

[a] Significant clusters with a false discovery rate set at p<0.05 (except *p<0.01) and no cluster extent threshold. [+] L=Left; R=Right; [++] BA=Brodmann Area. All coordinates in Talairach space.

As can be seen in table 8, there was an extended brain network associated with maternal responses to infant sounds as compared to control sounds. The following areas showed significant activation:

1) Midbrain
    - Mammillary body
2) Left insula
3) Thalamus
5) Hypothalamus
6) Cerebellum
    - Declive
7) Limbic structures:
    - Left and right posterior cingulate
    - Left and right cingulate gyrus (BA 31)
8) Frontal regions:
    - Left (BA 8) and right (BA 9) superior frontal gyrus
    - Left and right medial frontal gyrus (BA 6)
    - Right prefrontal gyrus (BA 6)
    - Left inferior frontal gyrus (BA 44)
    - Left middle frontal gyrus (BA 9)
    - Left (BA 4) and right (BA 9) precentral gyrus
9) Temporal regions:
    - Left and right superior temporal gyrus (BA 41)
10) Occipital lobe:
    15) Lingual gyrus (BA 18)
    16) Right cuneus

Figure 2 shows the activation of these areas.

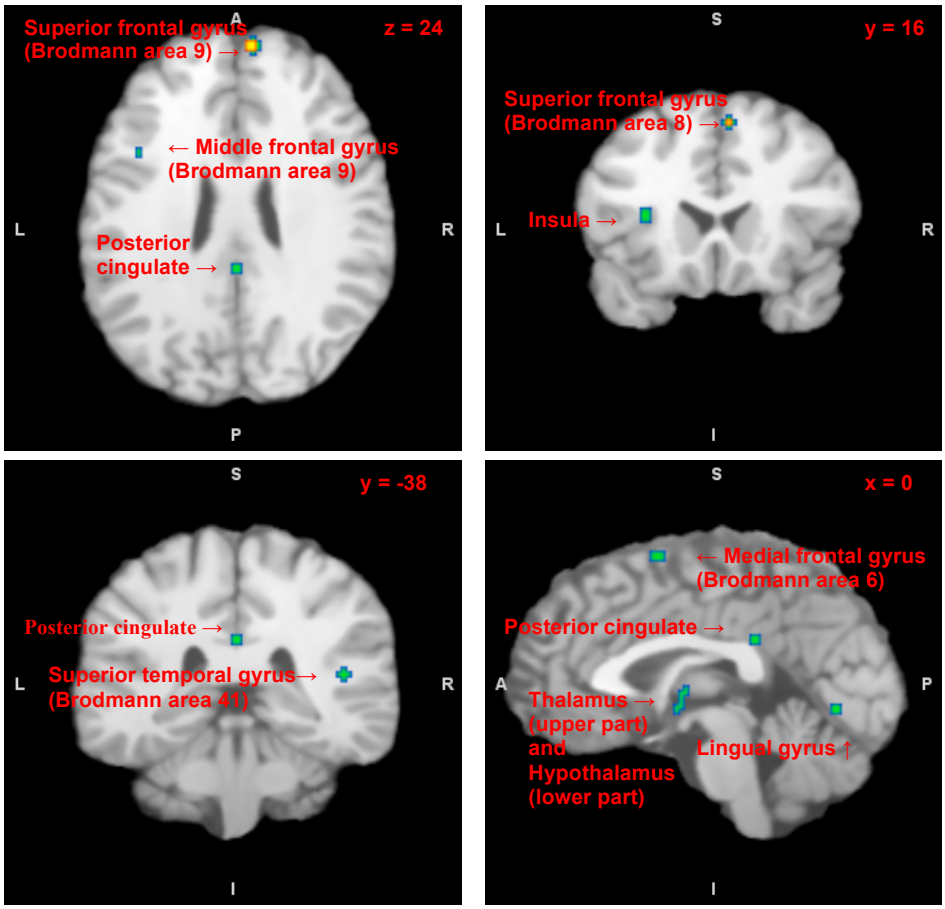


Figure 2: Greater activation of areas within frontal regions, superior temporal gyrus, insula, posterior cingulate, thalamus, and lingual gyrus in response to infant cries versus control sounds. Blue/green colour = level of significance of ≤0.05; red/yellow colour = level of significance of ≤0.01.

3.2.2. Meta-analysis 2: Visual Studies - Maternal brain activation to generic infant images versus control images

Two studies provided foci for meta-analysis of maternal activation patterns in response to generic infant images versus neutral control images (i.e. traffic). Out of the 50 foci that were provided in total by the two studies, three were outside of the mask (-45,-72,-96; 54,-69,-6; 45,15,-39) and were excluded from the analysis. The GingerALE analysis thus included 47 foci. Table 9 shows the results for the meta-analysis of the two studies at both the 0.05 and 0.01 levels of significance.

Table 9: Meta-analysis of maternal brain activation to images of children (own and other) versus neutral stimuli (traffic)[a]

Coordinates x	y	z	Hemisphere[+]	Label[++]	Volume (mm3)	Maximum ALE value
40	-48	-18	R	Fusiform gyrus (BA 37), culmen	280	0.0093*
48	-54	-18	R	Declive (cerebellum)	Not given	0.0088*
0	56	22	L & R	Superior frontal gyrus (BA 9)	264	0.0099*
8	16	60	R	Superior frontal gyrus (BA 6)	200	0.0091*
8	18	56	R	Superior frontal gyrus (BA 6)	Not given	0.0091*
-41	-52	-18	L	Culmen (cerebellum), fusiform gyrus	192	0.0087*
-41	-58	-18	L	Declive (cerebellum)	Not given	0.0086*
2	-62	-20	R	Declive (cerebellum)	168	0.0090*
0	-56	-24	L & R	Nodule (cerebellum)	Not given	0.0090*
42	10	50	R	Middle frontal gyrus (BA 6)	64	0.0076
-40	12	-4	L	Insula (BA 13)	48	0.0084
-40	18	2	L	Insula (BA 13)	48	0.0084
-24	8	-22	L	Superior temporal gyrus (Brodmann area 38)	32	0.0079
8	-76	-20	R	Declive (cerebellum)	32	0.0079
-40	20	-14	L	Inferior frontal gyrus (BA 47)	32	0.0085
18	-6	-14	R	Amygdala	32	0.0079
41	32	13	R	Middle frontal gyrus (BA 46)	32	0.0079
10	-94	16	R	Middle occipital gyrus (BA 18)	32	0.0079
60	-30	42	R	Postcentral gyrus (BA 2)	32	0.0079
-44	10	-30	L	Superior temporal gyrus (BA 38)	24	0.0085
34	-78	-26	R	Uvula (Cerebellum)	24	0.0083
54	18	32	R	Middle frontal gyrus (BA 9)	24	0.0085
48	12	36	R	Middle frontal gyrus (BA 9)	24	0.0085
26	-84	-26	R	Uvula (Cerebellum)	16	0.0083
26	8	-24	R	Superior temporal gyrus (BA 38)	16	0.0082
-40	-78	-6	L	Inferior occipital gyrus (BA 19)	16	0.0082
54	-60	6	R	Middle temporal gyrus (BA 37)	16	0.0082
-8	-96	8	L	Cuneus (Cerebellum)	16	0.0081
-16	30	13	n/a	No grey matter found	16	0.0081
-40	10	18	L	Insula (BA 13)	16	0.0081
2	-12	23	R	Cingulate gyrus (BA 23)	16	0.0081
60	-32	24	R	Inferior parietal lobule (BA 40)	16	0.0081
8	30	54	R	Superior frontal gyrus (BA 6)	16	0.0082
34	16	-28	R	Superior temporal gyrus (BA 38)	8	0.0085
28	28	-18	R	Inferior frontal gyrus (BA 47)	8	0.0084
-16	-66	-14	L	Declive (cerebellum)	8	0.0084
0	-52	32	L	Precuneus (cerebellum, BA 31)	8	0.0084

[a] Significant clusters with a false discovery rate set at p≤0.05 (except *p≤0.01) and no cluster extent threshold. [+] L=Left; R=Right; [++] BA=Brodmann Area. All coordinates in Talairach space.

As can be seen in table 9, there was an extended network associated with maternal brain responses to images of generic infant stimuli versus control images. The following areas showed significant activation:

1) Left insula (BA 13)

2) Limbic system:

- Right amygdala
- Right cingulate gyrus (BA 23)

3) Cerebellum:

- Declive
- Culmen
- Module
- Cuneus
- Uvula

4) Frontal regions:
- Right superior frontal gyrus (BA 6)
- Left superior frontal gyrus (BA 9)
- Right middle frontal gyrus (BAs 6, 9 and 46)
- Left and right inferior frontal gyrus (BA 47)

5) Somatosensory cortex:
- Right postcentral gyrus (BA 2)
- Right inferior parietal lobule (BA 40)

6) Temporal regions:
- Right fusiform gyrus (BA 37)
- Left and right superior temporal gyrus (BA 38)
- Right middle temporal gyrus (BA37)

7) Occipital regions:
- Right middle occipital gyrus (BA 18)
- Left inferior occipital gyrus (BA 19)

Images of the activation of these areas can be seen figure 3. Due to the low number of studies included in the analyses (N=2), these results may only be moderately reliable.

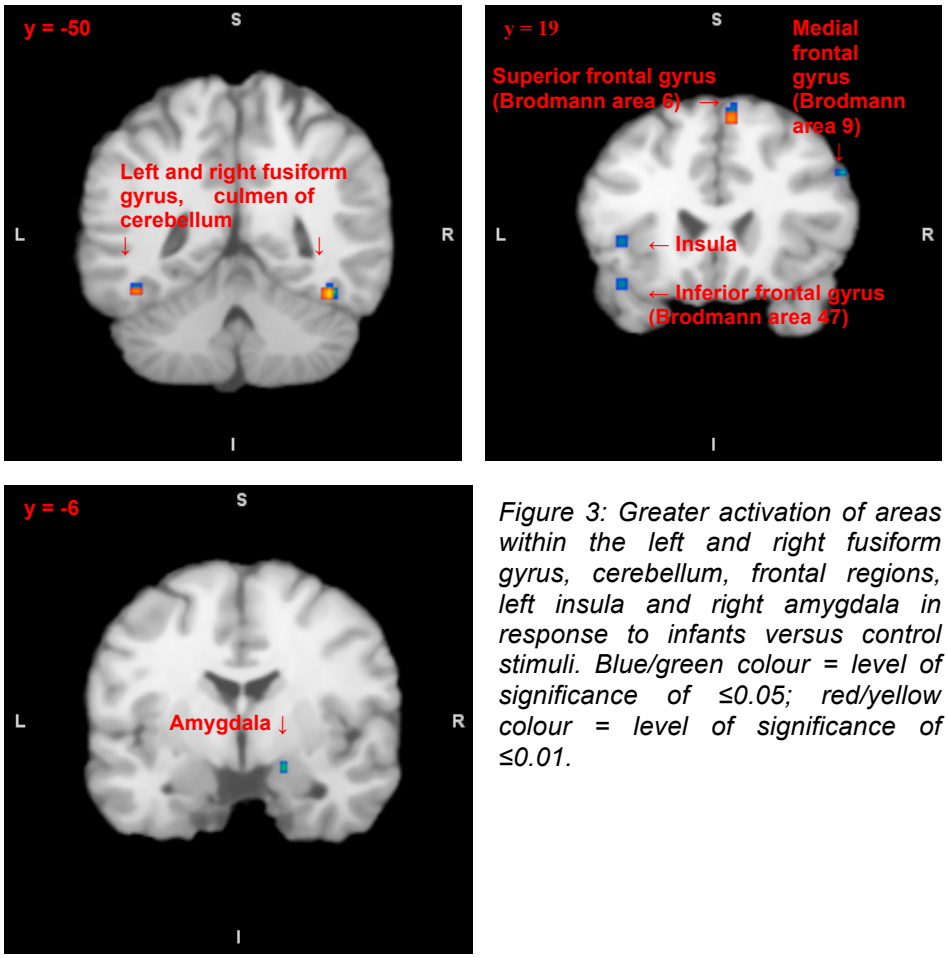


Figure 3: Greater activation of areas within the left and right fusiform gyrus, cerebellum, frontal regions, left insula and right amygdala in response to infants versus control stimuli. Blue/green colour = level of significance of ≤0.05; red/yellow colour = level of significance of ≤0.01.

3.2.3. Meta-analysis 3: Visual studies - Maternal brain activation to images of own versus control children

Ten studies provided foci for maternal brain activation in response to images of own versus control children. GingerALE revealed that six out of the 191 reported foci were outside of the mask (coordinates: 54,38,-2.0; -28,46,-14; 26,54,-14; 45,81,15; 47,3,49; -1,-53,69) and were hence not included in the analysis; the analysis included the remaining 185 foci. Table 10 shows the results for the meta-analysis of the ten studies at both the 0.05 and 0.01 levels of significance.

Table 10: Meta-analysis of maternal brain activation to images of own versus control children[a]

Coordinates x	y	z	Hemisphere[+]	Label[++]	Volume (mm3)	Maximum ALE value
-12	-16	6	L	Thalamus (including pulvinar), Mammillary body, Hypothalamus	2848	0.0216*
-12	2	16	L	Caudate Body	Not given	0.0153*
50	2	32	R	Precentral gyrus (BA 6), Inferior frontal gyrus (BAs 6 and 9)	1592	0.0175*
52	2	44	R	Precentral gyrus (BA 6)	Not given	0.0111
-2	-22	-8	L & R	Red Nucleus (midbrain), Substantia nigra (midbrain)	960	0.0181*
4	-8	2	L & R	Thalamus, Hypothalamus, Mammillary body	848	0.0151*
-6	-8	-8	L	Mammillary body (midbrain), Hypothalamus, Medial globus pallidus	Not given	0.0115
-28	-12	2	L	Putamen (Lentiform nucleus)	768	0.0171*
22	4	2	R	Putamen (Lentiform nucleus)	704	0.0187*
-22	2	4	L	Putamen (Lentiform nucleus)	696	0.0154*
-40	2	30	L	Precentral gyrus, Inferior frontal gyrus (BAs 6)	520	0.0140*
-40	-58	-22	L	Declive (cerebellum)	288	0.0141*
-22	2	-20	L	Uncus (Brodmann area 34), Amygdala	264	0.0134*
-6	40	26	L	Medial frontal gyrus (BA 9), Anterior cingulate (BA 32)	232	0.0125
30	20	10	R	Insula (BA 13)	176	0.0136*
10	4	10	R	Caudate Body	128	0.0119
4	10	58	L & R	Superior frontal gyrus (BA 6)	128	0.0120
40	-50	-4	R	Parahippocampal gyrus (BA 19), Fusiform gyrus (BA 37)	104	0.0114
46	24	24	R	Middle frontal gyrus (BA 46)	80	0.0108
-42	24	2	L	Inferior frontal gyrus (BA 47)	48	0.0109
18	-20	-12	R	Parahippocampal gyrus (BA 35)	40	0.0101
-40	0	48	L	Middle frontal gyrus (BA 6)	40	0.0101
28	-48	-22	R	Culmen (cerebellum)	32	0.0100
-44	-16	38	L	Precentral gyrus (BA 4)	16	0.0102
14	-2	-8	R	Medial globus pallidus (Lentiform nucleus)	8	0.0099
14	-10	8	R	Ventral lateral nucleus (Thalamus)	8	0.0098
40	-42	12	R	Superior temporal gyrus (BA 41)	8	0.0098
-4	-52	18	L	Posterior Cingulate (BA 30)	8	0.0098
-52	-50	28	L	Supramarginal gyrus (BA 40)	8	0.0098

[a] Significant clusters with a false discovery rate set at p≤0.05 (except *p≤0.01) and no cluster extent threshold. [+] L=Left; R=Right; [++] BA=Brodmann Area. All coordinates in Talairach space.

As can be seen in table 10, there was an extended network of brain activation associated with maternal responses to images of own versus control children. The following areas showed significant activation:

1) Midbrain:

- Red nucleus
- Substantia nigra
- Mammillary body

2) Basal ganglia:
    - Left and right medial globus pallidus
    - Left and right putamen
3) Limbic system:
    - Brodmann area 30 in the left posterior cingulate
    - Left anterior cingulate
    - Left uncus and amygdala
4) Right insula (BA 13)
5) Cerebellum:
    - Declive
    - Culmen
6) Thalamus
7) Hypothalamus
8) Caudate body (Septal region)
9) Frontal regions:
    - Left (BAs 4 and 6) and right (BA 6) precentral gyrus
    - Left (BA 6 and 47) and right (BAs 6 and 9) inferior frontal gyrus
    - Left medial frontal gyrus (BA 9)
    - Superior frontal gyrus (BA 6)
    - Right middle frontal gyrus (BA 46)
10) Right parahippocampal gyrus (BA 19)
11) Temporal regions:
    - Right fusiform gyrus (BA 37)
    - Right superior temporal gyrus (BA 41)
12) Supramarginal gyrus (BA 40)

Images of the activation of these areas can be seen figure 4.

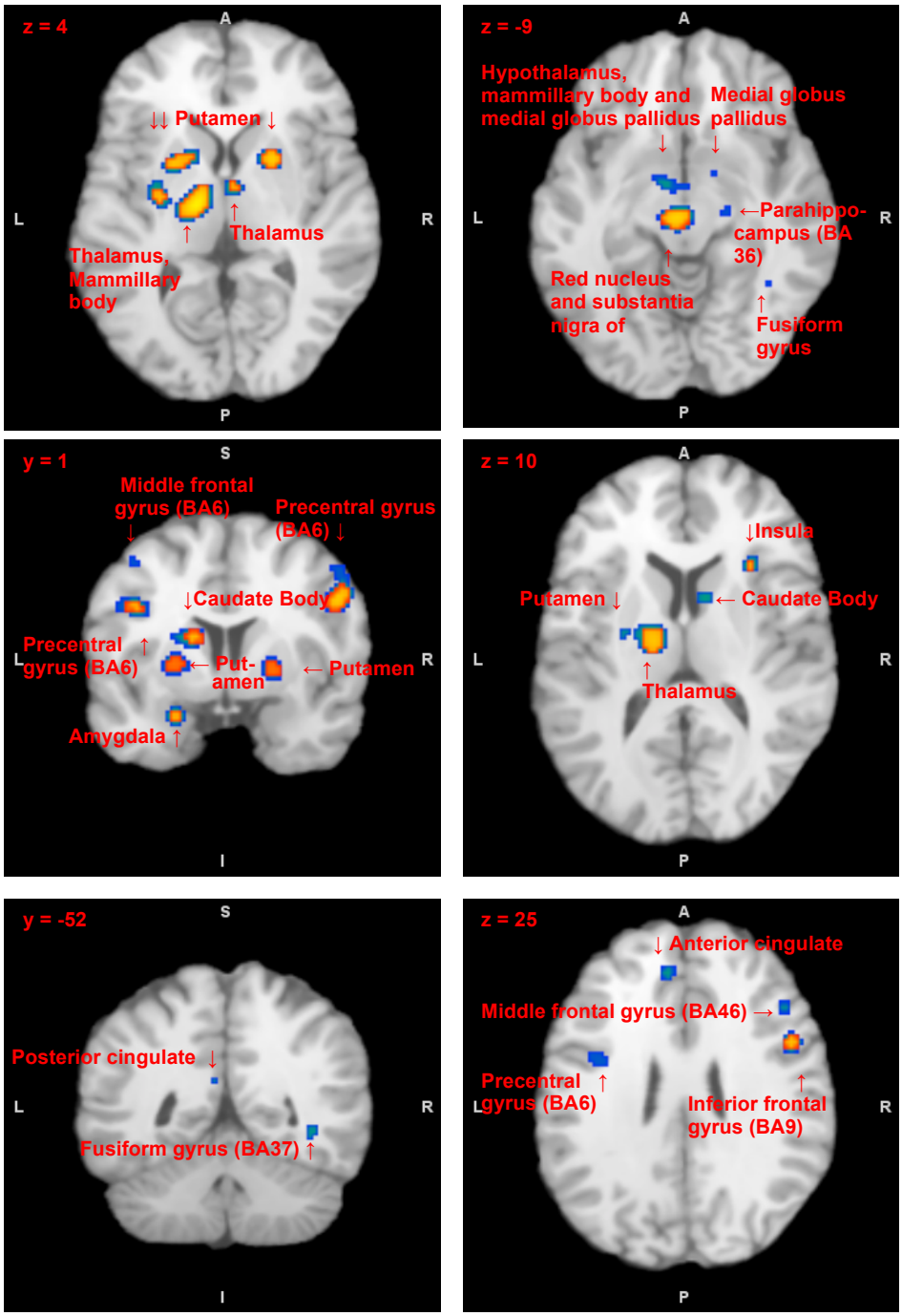


Figure 4: Greater activation of areas within the thalamus, hypothalamus, caudate body, mammillary body, basal ganglia, left amygdala, anterior and posterior cingulate, right insula, frontal regions, midbrain, parahippocampal lobe and fusiform gyrus in response to images of own versus control children. Blue/green colour = level of significance of ≤0.05; red/yellow colour = level of significance of ≤0.01.

3.2.4. Meta-analysis 4: Visual studies - Maternal brain deactivation to images of own versus control children (i.e. activation control versus own children)

Six studies provided foci for maternal brain *de*activation in response to images of own versus control children. GingerALE revealed that ten out of the 67 reported foci reported were outside of the mask (coordinates: -30,40,42.0; 34,44,42; -40,16,-42; 42,14,-46; -33,60,12; -33,60,-9; 39,39,42; 15,48,48; 51,48,-3; -9,-57,69) and were hence not included in the analysis; the analysis included the remaining 57 foci. Table 11 shows the results for the meta-analysis of the six studies at both the 0.05 and 0.01 levels of significance.

Table 11: Meta-analysis of brain deactivation to images of own versus control children (i.e. activation control versus own children)[a]

Coordinates			Hemisphere[+]	Label[++]	Volume (mm3)	Maximum ALE value
x	y	z				
62	-26	-8	R	Middle temporal gyrus (BA 21)	1888	0.0135*
60	-6	8	R	Superior temporal gyrus (BA 22), Transverse temporal gyrus (BA 42), Precentral gyrus (BA 43)	592	0.0140*
34	42	40	R	Middle frontal gyrus (BA 8)	416	0.0102*
30	42	32	R	Middle frontal gyrus, superior frontal gyrus (BA 9)	Not given	0.0098*
56	-24	-22	R	Inferior temporal gyrus (BA 20)	56	0.0085
-28	-14	-20	L	Hippocampus	56	0.0084
-50	-26	-6	L	Middle temporal gyrus (BA 21)	56	0.0085
-58	-40	10	L	Superior temporal gyrus (BA 22)	56	0.0085*
22	-60	26	R	Precuneus (Parietal lobe; BA 7)	56	0.0086*
-38	-24	-26	L	Fusiform gyrus (BA 20)	40	0.0084
10	36	-12	R	Medial frontal gyrus (BA 10)	32	0.0079
-4	38	-12	L	Medial frontal gyrus (BA 11)	32	0.0079
30	28	50	R	Superior frontal gyrus (BA 8)	32	0.0084
-62	-18	2	L	Superior temporal gyrus (BA 22)	24	0.0084
46	-67	-34	R	Pyramis (Posterior lobe)	16	0.0081
-12	24	-12	L	Subcallosal gyrus (BA 11)	16	0.0081
-6	-46	6	L	Posterior cingulate (BA 29)	16	0.0084
10	-44	8	R	Posterior cingulate (BA 29)	16	0.0084
22	-6	-34	R	Uncus (BA 36)	8	0.0084
42	-54	6	R	Middle temporal gyrus (BA 39)	8	0.0084
26	64	12	R	Superior frontal gyrus (BA 10)	8	0.0084
-22	-60	16	L	Posterior cingulate (BA 31)	8	0.0084
44	-20	16	R	Insula (BA 13)	8	0.0084
-50	-22	18	L	Insula (BA 40)	8	0.0084
-40	-52	26	L	Superior temporal gyrus (BA 39)	8	0.0084
46	-46	30	R	Supramarginal gyrus (BA 40)	8	0.0084
46	-74	36	R	Precuneus (BA 39)	8	0.0084
0	-74	46	L	Precuneus (BA 7)	8	0.0084
-4	44	46	L	Superior frontal gyrus (BA 8)	8	0.0084

[a] Significant clusters with a false discovery rate set at p<0.05 (except *p<0.01) and no cluster extent threshold. [+] L=Left; R=Right; [++] BA=Brodmann Area. All coordinates in Talairach space.

As can be seen in table 11, there was an extended network of brain deactivation associated with maternal responses to images of own children versus control children. The following areas showed significant deactivation (i.e. greater activation in response to control versus own children):

1) Left (BA 40) and right (BA 13) insula
2) Limbic system:
    - Left and right posterior cingulate (BA 29)
    - Left posterior cingulate (BA 31)
    - Right uncus
    - Left hippocampus
3) Frontal regions:
    - Right precentral gyrus (BA 43)
    - Right middle frontal gyrus (BAs 8 and 9)
    - Left (BA 8) and right (BA 8, 9 and 10) superior frontal gyrus
    - Left (BA 11) and right medial frontal gyrus (BA 10)
    - Left subcallosal gyrus (BA 11)
4) Temporal regions:
    - Left fusiform gyrus (BA 20)
    - Left (BA 21) and right (BA 21 and 39) middle temporal gyrus (BA 21)
    - Left (BA 22 and 39) and right (BA 22) superior temporal gyrus
    - Right transverse temporal gyrus (BA 42)
    - Right inferior temporal gyrus (BA 20)
5) Parietal lobe:
    - Left and right precuneus
6) Right pyramis

Images of the deactivation of these areas in response to own versus control children (or activation to control versus own children) can be seen figure 5.

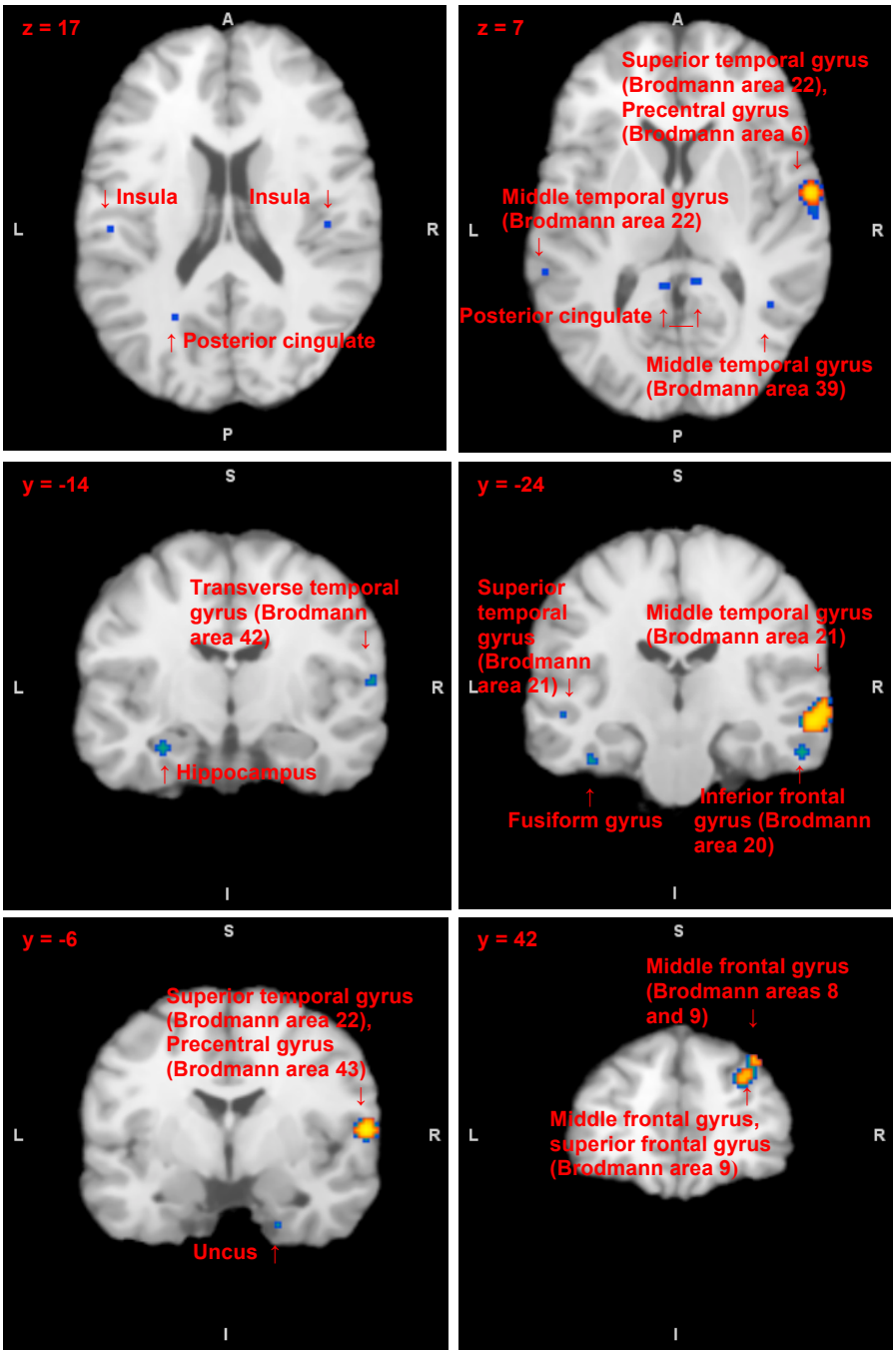


Figure 5: Images showing the greater activation of areas within the insula, posterior cingulate, temporal and frontal regions, including fusiform gyrus, hippocampus, and uncus in response to images of control versus own children. Blue/green colour = level of significance of ≤0.05; red/yellow colour = level of significance of ≤0.01.

3.2.5. Summary of brain basis of maternal responsiveness as identified by the meta-analyses

Table 12: Summary of brain activity as identified by meta-analyses

	Audio studies - Generic infant sound versus control sound (activated)		Visual studies - Generic infant stimuli versus neutral control stimuli (traffic; activated and deactivated*)		Visual studies - Own infants versus control infants (activated and deactivated)	
	Left	**Right**	**Left**	**Right**	**Left**	**Right**
Septal regions (MPOA/ VBNST/caudate head)					ACT	ACT
Midbrain					ACT	ACT
Hypothalamus	ACT	ACT			ACT	ACT
Thalamus	ACT	ACT			ACT	ACT
Limbic structures:						
Amygdala				ACT	ACT	
Anterior cingulate				DEACT	ACT	
Middle cingulate				ACT		
Posterior cingulate	ACT	ACT		DEACT	ACT/DEACT	DEACT
Hippocampus					DEACT	
Basal ganglia:						
Striatum/putamen/nucleus accumbens					ACT	ACT
Lentiform nucleus Globus pallidus					ACT	ACT
Insula	ACT		ACT		DEACT	ACT/DEACT
Frontal cortex:						
Orbitofrontal/Inferior frontal gyrus	ACT		ACT	ACT	ACT	ACT/DEACT
Medial/middle frontal gyrus	ACT	ACT	DEACT	ACT/DEACT	ACT/DEACT	DEACT
Ventral prefrontal cortex						
Superior frontal gyrus	ACT	ACT	ACT	ACT	ACT/DEACT	ACT/DEACT
Precentral gyrus	ACT	ACT			ACT	ACT/DEACT
Dorsolateral prefrontal cortex						
Temporal/parietal cortex:						
Temperoparietal cortex				ACT	DEACT	DEACT
Fusiform gyrus			ACT	ACT	DEACT	
Temporal/auditory cortex	ACT	ACT	ACT/DEACT	ACT/DEACT	DEACT	ACT/DEACT
Parahippocampal/limbic lobe			DEACT			ACT
Occipital cortex	ACT	ACT	ACT	ACT		
Cerebellum	ACT	ACT	ACT	ACT/DEACT	ACT	ACT

ACT= activated; DEACT= deactivated

**Deactivation for visual studies comparing a generic infant stimulus versus a control stimulus are based on a single study (Wan et al., in preparation).*

Based on the meta-analyses, there were four main findings. First, from results of three studies, maternal exposure to auditory stimuli of infants versus control sounds was associated with the activation of the thalamus and hypothalamus, left and right posterior cingulate, left insula, left orbitofrontal cortex, bilateral medial, ventral prefrontal and superior frontal cortex, bilateral precentral gyrus and temporal/auditory cortex, and the cerebellum.

Second, based on the combined results of two studies, maternal exposure to generic visual stimuli of children (own and unknown) versus control visual stimuli was associated with activation of the right amygdala, right middle cingulate, left insula, bilateral orbitofrontal and superior frontal cortex, right medial frontal gyrus, right temperoparietal cortex, bilateral fusiform gyrus and temporal cortex, bilateral occipital cortex and the cerebellum.

In addition, the one study that looked at deactivation to stimuli of infants compared to a neutral control stimulus (i.e. traffic; Wan et al., in preparation) found deactivation of right anterior and posterior cingulate, bilateral medial frontal and temporal cortex, left parahippocampal lobe and right cerebellum. Thus, some parts of right medial frontal cortex, bilateral temporal cortex, and right cerebellum were found to be activated, whereas other parts of them were found to be deactivated, in response to the child stimuli.

Third, based on the combined results of ten studies, maternal exposure to visual stimuli of own versus control children was associated with activation of septal regions, midbrain, thalamus, hypothalamus, left amygdala, left anterior and posterior cingulate, bilateral striatum, putamen and globus pallidus, right insula, bilateral orbitofrontal and superior frontal cortex, bilateral precentral gyrus, left medial frontal gyrus, right temporal cortex, right parahippocampal lobe and the cerebellum.

Finally, the meta-analysis of the six studies that looked at the *de*activation of the maternal brain in response to visuals of own versus control children revealed that there was deactivation associated with bilateral posterior cingulate, left hippocampus, bilateral insula, right orbitofrontal cortex and precentral gyrus, bilateral medial frontal and ventral prefrontal cortex, bilateral temperoparietal and temporal cortex, and left fusiform gyrus. Thus, parts of the left posterior cingulate, right insula, right orbitofrontal cortex, left medial frontal gyrus, bilateral superior frontal gyrus, right precentral gyrus and right temporal cortex were found to be activated in

response to own versus control children, whereas other parts were found to be *de*activated, in response to own versus control children.

4. Discussion

4.1. Summary and interpretation of findings

4.1.1. Summary and interpretation of systematic review

Several imaging studies have examined the brain basis of maternal responsiveness. Many, especially earlier ones, used auditory stimuli such as infant cries, and compared mothers' brain responses to these to their brain responses to a control sound such as white noise. Several of the studies suggested that activation of septal regions, midbrain, thalamus, hypothalamus, limbic structures, basal ganglia, frontal regions, temporal and parietal cortex, parahippocampal lobe, occipital cortex, and cerebellum was associated with exposure to infant sounds. However, there was heterogeneity in the findings and while some studies found these regions to be activated, others did not. In addition, two studies (Swain et al., 2003; Seifritz et al., 2003) suggested deactivation, not activation, of the medial frontal gyrus in response to infant sounds versus a control, and one study (Seifritz et al., 2003), using relatively short blocks of presentation, found deactivation, rather than activation, of the anterior cingulate.

Later studies examining the brain basis of maternal responsiveness tended to use visual stimuli - either photographs or (more ecologically valid) videos. Some studies compared generic infant stimuli to control stimuli and reported that mainly the visual pathway was activated in response to infants. In addition, Swain et al. (2003) found that, similar to the audio studies, there was activation of the midbrain, thalamus, limbic structures, basal ganglia, and frontal regions. Wan et al. (in preparation) reported activation in limbic structures, insula, cerebellum, and frontal, temperoparietal and occipital cortex, but also *de*activation in anterior and posterior cingulate, medial frontal gyrus, temporal cortex, parahippocampal lobe and cerebellum. In these studies, infant stimuli included both mothers' own children as well as unknown infants.

Most studies using visual stimuli compared maternal responses to own versus control children (familiar or unknown), and this is arguably the contrast most relevant to the brain basis of maternal responsiveness and sensitivity, as well as related public health concerns. Several of these studies suggested activation of septal regions, midbrain, thalamus, hypothalamus, limbic structures, basal ganglia, frontal, temporal, parietal and occipital cortex, parahippocampal lobe, and cerebellum, but again there was heterogeneity between studies. In addition, some studies suggested *de*activation of thalamus, anterior cingulate, posterior cingulate, amygdala, orbitofrontal cortex, medial frontal gyrus, superior frontal cortex, precentral gyrus, temporal and parietal areas, and parahippocampal lobe in response to own versus control children (i.e. greater activation in response to control children). What is more, some studies reported that these areas were both activated and deactivated at the same time, which may reflect differing functions of different parts of these areas.

Each of the individual studies had a small to moderate sample size (N=4-30), and due to the complex patterns of brain activation a qualitative analysis of findings is limited. In order to obtain a more accurate understanding of the meaning of previous studies, and hence the brain basis of maternal sensitivity, data were analysed quantitatively using meta-analysis.

4.1.2. Summary and interpretation of meta-analyses

Four meta-analyses were carried out: One for maternal activation in response to infant sounds versus control sounds; one for maternal activation in response to generic images of children versus control images; one for maternal activation in response to images of own versus other children; and one for maternal *de*activation in response to images of own versus other children.

4.1.2.1. Meta-analysis 1: Audio studies (Activation; infant versus control sounds)

For the audio studies comparing responses to infant versus control sounds the occipital cortex, Brodmann area 41 of the superior temporal gyrus,

several frontal areas, posterior cingulate of the limbic system, cerebellum, the left insula, thalamus, and hypothalamus were activated.

- The activation of occipital (visual) regions may suggest that infant cries caused greater visualisation (of infants) compared to control sounds (white noise).

- Brodmann area 41 is the prime site of the auditory cortex and its activation may be explained by the infant sounds requiring more auditory interpretation compared to white noise.

- Frontal regions are associated with executive functions, and their activation may relate to the cognitive responses required for the interpretation and management of responses to infant sounds reported in qualitative research (Leckman et al., 1999).

- Limbic regions such as posterior cingulate are associated with emotion processing (Allman et al., 2001), and its activation may reflect the emotive nature of the infant sounds. In fact, most studies used cries - stimuli which are of a very emotional nature.

- The cerebellum is thought to be involved in attention, as well as regulation of emotional responses and learning (Wolf et al., 2009), and its activation may imply mothers' greater attention, as well as management of greater emotional responses, to infant sounds versus controls, and this has been implied in previous qualitative research (Swain et al., 2005).

- The insula has been linked to the experience of emotion and empathy (Riem et al., 2011), and its activation may reflect mothers' greater emotional response and empathy to the highly emotive infant sounds versus the neutral control sounds which has been implied in previous qualitative research (Swain et al., 2005). In addition it has been linked to the appraisal of salience and may

reflect mother's greater attention towards infants (Britton et al., 2006, LeDoux, 2003). Only the left insula was activated, which is in line with previous studies: Sander et al. (2005) reported left hemisphere dominance of the insula in emotion processing.

- Similarly, the thalamus is associated with increased emotional experience (Baxter, 2003), and the reported activation may therefore relate to mothers' increased emotions in response to infant sounds versus the more neutral control sounds.

- The hypothalamus is the site of synthesis for the 'social' and 'bonding' hormone oxytocin, and its activation may reflect the increase in the production of oxytocin in response to infants that has been reported in previous research (Feldman et al., 2010). This may be an important factor in enabling a bond and empathy between a mother and a newly encountered infant.

Limitations

- Only three studies were included in the meta-analysis, and data for 26 out of the 40 participants that were included came from a single study (Kim et al., 2010). Further research is thus necessary to carry out a more reliable meta-analysis.

- The white noise the included studies used as a control stimulus may not represent a neutral control, but may have been considered aversive. It is therefore possible that brain responses associated with aversion such as the amygdala were activated in response to infant cries, but that these were cancelled out by the aversive nature of the control stimuli.

4.1.2.2. Meta-analysis 2: Visual studies (Activation; infant versus control images)

For the visual studies comparing responses to infants versus control stimuli the main areas of activation were occipital cortex, frontal regions,

fusiform gyrus, somatosensory cortex, right limbic regions, including right middle cingulate and right amygdala, left insula, and cerebellum. In addition, one study (Wan et al., in preparation) suggests that bilateral medial frontal gyrus, temporal cortex, cerebellum, anterior and posterior cingulate, and left parahippocampal lobe are *de*activated for this contrast.

- The activation of the occipital (visual) cortex may relate to the greater visual complexity of infants (or people in general) versus control stimuli.

- Like for the audio studies, frontal region activation may be associated with carrying out executive functions such as management of behavioural responses in response to children, which has been reported by mothers in previous research (Leckman et al., 1999). Orbitofrontal regions have been associated with reward (Bechara et al., 1994), and its activation may relate to mothers experiencing rewarding feelings when seeing children. Since the child stimuli included own as well as other children, this activation may be due to being exposed to own children, which previous research involving interviews with mothers found triggers feelings of reward (Swain et al., 2005).

  Medial frontal cortex was *de*activated in response to infants versus control stimuli, and this may suggest participants' cognitive assessment of the control stimuli, which represented complex traffic. Different frontal regions may therefore be involved in the assessment of different complex stimuli.

- The greater activation of the fusiform gyrus in response to infants versus control stimuli is unsurprising considering its association with the processing of faces (Sergent et al., 1992; Axelrod et al., 2010).

- The activation of the somatosensory cortex in response to infants may signify mothers' desire physically to interact with the infants

and a desire to touch them, which has been reported by mothers in relation to their own infants in previous research (Leckman et al., 1999).

- Like for the audio studies, the activation of the middle cingulate of the limbic system may show mothers' greater need for emotional processing of the infant stimuli, as these are of a more emotive nature than control stimuli such as traffic, which was designed to be emotionally neutral.

- The right amygdala was also activated. Whereas the left amygdala is generally associated with both positive and negative emotions and is part of the reward system, the right amygdala has been associated only with negative emotions such as fear (although there is come contention in the literature concerning hemispheric variation of the amygdala; Best, 2004). The activation of the right rather than left amygdala may therefore reflect mothers' experience of anxiety in response to the unknown infants.

- As for the audio studies, and in line with mothers' self-reports (Swain et al., 2005), activation of the left insula may signify mothers' greater emotional response, salience appraisal and empathy to the highly emotive infant sounds versus the neutral control sounds.

- The activation of the cerebellum may again signify greater allocation of attention towards infants versus control stimuli, as well as emotion regulation and learning.

  Part of the right cerebellum also showed *de*activation in response to infants versus traffic. This suggests that different parts of the cerebellum may be involved in different types of attention or learning, and the demanding nature of the control stimuli (traffic) may have caused parts of the cerebellum to be active.

- The deactivation of right anterior cingulate (part of the limbic system) in response to infants versus control stimuli may also be explained by the nature of the control stimuli. Anterior cingulate is involved in cognitive functions such as decision-making (Bush et al., 2002) and since the control stimuli represented traffic, its greater activation in response to these may be explained in terms of the need for the assessment of response to potentially dangerous stimuli.

- The deactivation of posterior cingulate and the parahippocampal lobe in response to infants versus control stimuli may also be explained by the control stimuli used. Both the posterior cingulate and the parahippocampal lobe have been linked to memory retrieval (Nielsen et al., 2005). The stimuli in the included studies represented traffic, which was filmed in the same city (Manchester) in which the research took place, and participants may have attempted to retrieve memories in order to place the exact location.

- The activation in temporal/auditory cortex in response to infants may be explained by the loud noise expected to be heard in response to images of traffic.

Limitations

- The meta-analysis for the visual studies of infants versus control stimuli included only two studies, so even fewer than the audio studies, and data for 20 of the 30 participants that were included came from a single study (Wan et al., in preparation). More research is thus necessary to obtain more reliable results.

- Both included studies applied small volume corrections to the amygdala, and this may have introduced some bias to the results.

- Again it may be argued that the control stimuli, which represented traffic, were not neutral, but aversive in nature. This may have

reduced chances to pick up on any activation associated with aversive brain responses to infants (although it should be noted that amygdala activation, which has been associated with aversive emotions (Best, 2004), was observed).

4.1.2.3. Meta-analyses 3 and 4: Visual studies (Activation and deactivation; own versus other child images)

For the visual studies comparing responses to own versus control children there was activation of left anterior and posterior cingulate, left amygdala, right insula, thalamus, hypothalamus, frontal regions, right temporal lobe, including right fusiform gyrus and auditory cortex (Brodmann area 41), right parahippocampal lobe, cerebellum, basal ganglia, septal regions, and midbrain.

In addition, there was *de*activation of bilateral insula, frontal regions, temporal regions, including left fusiform gyrus, bilateral posterior cingulate, and left hippocampus.

The activation of several of these areas is similar to the findings reported for the other contrasts described above, suggesting these regions activate in response to children in general, but perhaps even more so in response to own children.

- The greater activation in response to own versus other children of left anterior and posterior cingulate of the limbic system may be related to mothers' greater investment in the processing of their own infants' emotional states. This may play an important role in responding appropriately to their own children, which in previous research has been reported to be a maternal concern (Leckman et al., 1999).

- The activation of the right insula may relate to an amplified emotional response, salience appraisal and empathy towards own versus other children, which is in line with mothers' self-reports from

previous qualitative research (Swain et al., 2005). It has also been linked to addiction (Naqvi et al., 2007) and may represent mothers' craving to be close to their infants, which has also been reported by previous research (Swain et al., 2005).

However, parts of the insula also *de*activated in response to own infants. It is therefore possible that different parts of the insula relate to the amplification of different emotions, for example love versus fear. The deactivation of left insula, which has been linked to emotion processing (Sander et al., 2005), may relate to the greater effort required in interpreting the emotional expressions of unknown infants.

- Greater activation of the thalamus may relate to an increase of emotional experience when exposed to own infants, which has been reported by mothers in previous research (Swain et al, 2005).

- The activation of the hypothalamus may relate to the synthesis and release of oxytocin in response to a mother's own child, associated with and promoting a feeling of a strong bond, as well as social abilities such as empathy. The synthesis of oxytocin in response to one's own child has been reported in previous research (Feldman at al., 2010).

- The greater activation of frontal regions associated with executive functioning may be associated to mothers' investment in the management and planning of their responses to their child's needs; a skill necessary in order for adequate mothering.

  However, other parts of the frontal cortex *de*activated in response to own versus other children, and this may be due to the importance of different executive functions when viewing own or other children. Both own and other children warrant complex assessment of emotional and behavioural responses, although for

own children this may relate more to parenting behaviours, whereas for other children it may relate more to initial assessment.

This may explain greater activation of (left) orbitofrontal cortex in response to own children, as this has been associated with reward (Bechara et al., 1994). Such rewarding feelings in response to own children has been reported by mothers in previous research (Swain et al., 2005).

- The right fusiform gyrus was activated more in response to own infants, whereas the left fusiform gyrus (as well as other temporal regions) was deactivated (i.e. greater activated in response to control infants). Since the right hemisphere has been found to be more dominant in the interpretation of emotions (Carr et al., 2003), it may be that the reported activation of right fusiform gyrus reflects mothers' greater attention to and interpretation of the emotional aspects of their own infants' faces, which is necessary for maternal care, and that the greater activation of left fusiform gyrus (and other temporal regions) in response to control infants related to the recognition and encoding necessary when encountering unknown infant faces.

- The greater activation of right auditory cortex in response to own infants may reflect mothers' desire to interpret their own infants' (emotional) utterances, which is an important part of maternal behaviour and is in line with mothers' reports that they want to please their own children (Leckman et al. 1999).

- Increased cerebellar activation may be related to mothers' greater allocation of attention towards their own versus other children - an important factor in being able to prepare maternal care behaviour and responding to the child's needs appropriately - as well as emotion regulation and learning.

- The activation of the basal ganglia, including striatum, putamen and globus pallidus, was unique to the contrast own versus other infants. This region is associated with the reward pathway and obsessions (Peters & Buchel, 2010), and therefore likely represents the rewarding and obsessional response mothers experience when exposed to their own children. This has been reported in qualitative research (e.g. Leckman et al., 1999; Swain et al., 2005). The activation of the basal ganglia in response to own infants mirrors findings which relate to people's responses to romantic partners (Bartels & Zeki, 2004) and may be associated with the feeling of reward that comes from feeling love and attachment towards another person.

- Similarly, activation of the septal regions, midbrain and the right parahippocampal lobe were unique to the own versus other child contrast.

  Septal regions are also part of the rewards system, are involved in fear attenuation (Novakova et al., 1993), and their activation may therefore also suggest greater reward (and less aversion) experienced by mothers in response to their own children.

  The midbrain has in previous research been linked to nurturing behaviours (Sukikara et al., 2010) and the suppression of anxiety (Miller et al., 2010), and is rich in oxytocin receptors (Jenkins et al., 1984). Its activation may therefore imply greater bonding with, and nurturing feelings towards, own infants, which is in line with mothers' self-reports (Swain et al., 2005).

  The parahippocampal lobe plays an important role in memory encoding and retrieval (Ferreira et al., 2003). However, only the right parahippocampal lobe was activated, and research has suggested that the right, but not the left, parahippocampal lobe plays a crucial role in identifying social context and the

paralinguistic elements of communication (Rankin et al., 2009). It therefore seems likely that the right parahippocampal lobe was activated because mothers were more likely to assess their own child's social context and expressions versus a control child.

- As in the visual studies with the contrast of generic infants versus control stimuli, for the contrast of own versus other child there was deactivation of the posterior cingulate, which has been associated with memory retrieval (Nielsen at al. 2005). Since some of the studies included familiar infants as control infants, there is the potential that the activation was due to participants' greater need to retrieve memories in order to 'place' the control infants compared to their own.

- This would also explain the greater activation of the hippocampus, an area associated with memory formation and retrieval (Clark et al, 2005), in response to control infants. Alternatively, greater activation of the hippocampus may follow a greater need to form memories for the newly encountered faces.

Limitations

- All included studies compared responses to own versus other children. None of the studies compared responses to other attachment figures or other reward stimuli. It is therefore not possible to establish whether the activation of the identified brain areas, including the reward network, is unique to mothers being exposed to own infants.

- Several of the included studies applied small volume corrections to specific regions of interest, including the amygdala, limbic system and insula, and this may have introduced some bias to the results.

4.1.3. Summary of main findings and interpretations

- All child stimuli activated brain areas associated with:
    - Visual processing (occipital and temporal cortex)
    - Executive functioning (frontal and cingulate cortex)
    - Attention and salience appraisal (insula, cerebellum)
    - Social/emotional skills/processing (insula and limbic system).
    - Reward (thalamus, orbitofrontal cortex)
- Regions associated with attention, social skills, emotion processing and reward were activated more in response to own versus other children.
- Cortical regions associated with executive functioning showed stronger activation in response to own children in some parts, but stronger activation to unknown children in others.
- Several regions in the reward network (basal ganglia, septal regions), some of which are also associated with obsession (basal ganglia), as well as regions associated with the suppression of negative emotions (midbrain), activated in response to own, but not other children.
- Reward regions activated in response to generic infant versus control stimuli may have been exaggerated by negative or aversive emotions experienced in response to the control stimuli (white noise; traffic).
- For the audio studies only:
    - Auditory cortex activated more in response to infant stimuli versus control stimuli.
- For the visual studies only:
    - Regions associated with memory retrieval activated more in response to control stimuli versus generic infants, but this may have been due to the type of control stimuli used (i.e. traffic filmed in participants' home town).
    - Regions associated specifically with face processing and memory retrieval activated more in response to unknown or familiar versus own children.

4.2. How do these findings fit the hypotheses?

- In line with hypothesis 1, and as suggested by Swain's (2008) model, there was a distributed neural network associated with maternal responsiveness. How specific this activation was to maternal responsiveness is unclear, and will be discussed further below.

- In line with hypothesis 2, and as predicted by Swain's (2008) model, the activation included midbrain, thalamus, hypothalamus, frontal areas, temporal cortex, insula, limbic structures including cingulate and amygdala, and basal ganglia. The cerebellum was also activated.

- In line with hypothesis 3, most of these regions were activated in response to both own and control children.

- In line with hypothesis 4, several regions associated with reward/love (basal ganglia and septal regions) were activated only in response to own children. Other parts of the reward network (thalamus, hypothalamus, orbitofrontal cortex) were activated by both own and control children, but more so by own children.

4.3. To what extent do our findings support Swain's (2008) model of parental responsiveness?

- Overall, the findings support Swain's model of parental responsiveness, although there is a lack of evidence as to how specific the network is to maternal responsiveness. The majority of the brain areas predicted by the model were activated in response to own or unknown children. Some of the areas predicted by the model to be involved in the experience of love (i.e. basal ganglia) were activated only in response to own children.

- Contrary to the models' predictions, the hippocampus was not activated in response to children versus control stimuli, or own

versus control children. In fact, activation was greater in response to control versus own children. Memory formation and retrieval may therefore play a greater role in being exposed to or meeting unknown or less-well known children.

- Although the Swain model did emphasise the importance of salience appraisal in maternal responsiveness, it did not predict that cerebellar activation (which is associated with salience appraisal and learning) would be associated with maternal responsiveness.

- The Swain model is also unclear about the exact role of activated regions.

Conclusion

Whilst James Swain's (2008) model provided much heuristic value and allowed greater insight into the involvement of several brain areas in maternal responsiveness, this study suggests that an updated model is required which incorporates the most up to date imaging findings and data from other related literature. Within such a model, clarification is needed concerning the exact nature of brain activations and deactivations, as well as greater detail regarding the potential roles of activated and deactivated brain regions involved in different aspects of maternal responding to own infant and to generic infant stimuli. This is important if we are to understand the cause of insensitive parents and parental neglect/abuse of children. An updated model also requires clarification and delineation of the role of the cerebellum, and the role of the hippocampus should be reconsidered.

4.4. Is the identified neural network specific to maternal responsiveness?

Although the present study suggests that there is neural activation associated with maternal responsiveness, is it unclear whether this is specific to mothers' responses to children. The stimuli activated networks associated with vision, executive functioning, attention, social/emotional

processing and reward. These networks have been reported to be activated in response to an array of other non-infant stimuli.

4.4.1. May the responses be specific to children?

Studies identified by this systematic review and meta-analysis are not able to reveal whether the activated network is specific to infant stimuli, as responses were generally not compared to maternal responses to other rewarding control stimuli such as adult attachments figures. Had any of the studies used other emotionally rewarding attachment stimuli, such as other close family members, sexual partners, or inanimate rewarding stimuli as control stimuli, these may have activated the reward system and networks associated with vision, attention and emotional processing in a similar fashion. One of the identified studies (Bartels & Zeki, 2004) qualitatively compared their findings of maternal responsiveness to previous reports of participants' neural responses to romantic partners. Both types of stimuli activated overlapping areas in the reward system which are high in oxytocin and vasopressin receptors. The involvement of the reward system also somewhat resembles the activation seen in response to romantic partners as reported by Fisher et al. (2005). Orbitofrontal cortex and the periaqueductal grey of the midbrain were active only in response to children (Bartels & Zeki, 2004).

4.4.2. May the responses be specific to mothers?

4.4.2.1. Mothers versus fathers

Two studies (none of which were included in the meta-analyses as coordinates for foci could not be obtained) have compared mothers' and fathers' neural responses to children. Seifritz et al. (2003) found similar activation in mothers and fathers to cries and laughter of unknown infants. In both groups, the middle cingulate, insula and ventral prefrontal cortex were activated. In addition, as opposed to non-parents, both mothers and fathers activated the right amygdala in response to baby cries. One significant difference the researchers found between mothers and fathers

was that mothers exhibited deactivation of the anterior cingulate in response to infant laughter and cries, whereas fathers did not.

Swain et al. (2003) carried out similar research and found different results. They argued that this may have been due to the use of longer stimuli. They found that in response to unknown infant cries mothers and fathers both activated the anterior cingulate, as well as the striatum of the basal ganglia, insula, and orbitofrontal cortex more than in response to control stimuli. When they compared responses to own baby cries to those of unknown baby cries, on the other hand, they found significant differences between mothers and fathers. Both showed greater activation in anterior cingulate and hippocampus in response to own infants; however, mothers also displayed greater activation in the amygdala, striatum and globus pallidus of the basal ganglia, insula, and orbitofrontal cortex in response to own infants, whereas fathers did not. Fathers also did not show the deactivation of the medial frontal gyrus present in mothers. Overall there was less difference between responses to cries of own and unknown infants in fathers than there was in mothers.

Swain et al. (2003) also compared maternal and paternal responsiveness using photographs. Again, some similarities were observed. Thus both mothers and fathers activated the cingulate and orbitofrontal cortex in response to own infants. Again, there was greater difference in responses to own versus unknown infants in mothers than there was in fathers. For example, in response to own infants mothers displayed decreased activation in the medial frontal cortex whereas fathers did not. In addition, mothers displayed increased activation of the basal ganglia to unknown infants versus control pictures, whereas fathers did not. These findings are in line with behavioural research, which reported both similarities and differences in relation to maternal and paternal behaviour (Gordon et al., 2010; Swain et al., 2004).

4.4.2.2. Mothers versus nulliparous women

Sander et al. (2007) reported that amygdala and anterior cingulate activation in response to infant sounds is common to all women, but not men, and argued for a predisposition in women to respond to children. In line with this argument, Seifritz et al. (2003) found similarities between mothers and nulliparous women which were absent in fathers as well as non-fathers. However, contrary to Sander's (2007) findings, nulliparous women and mothers showed *decreased* activation in anterior cingulate. As mentioned above, Swain et al. (2007) have noted that the decrease of anterior cingulate activation was not observed in studies which used longer blocks of stimuli.

Seifritz et al. (2003) also found differences in responses between mothers and nulliparous women. Whereas mothers activated the right amygdala in response to infant cries, nulliparous women did not. In contrast, nulliparous women activated the right amygdala in response to infant laughter, whereas mothers did not. These findings are in line with a study which reported differences in sympathy displayed by mothers and nulliparous women in response to children (Giardino, 2008), and suggest that while there is overlap between mothers' and nulliparous women's responses to children, there are also some differences.

4.5. Is the observed activity caused by the transition to maternity?

As reported in Chapter 1, neuronal changes associated with maternal responsiveness include the development of new connections through dendritic growth and arborisation that create a mechanism for plasticity and new learning in somatosensory cortex (Xerri et al., 1994) and the amygdala (Rasia-Filho et al., 2004), and changes in grey matter volume of the prefrontal cortex, parietal lobes, and midbrain areas (Kim et al., 2010). Through pregnancy, parturition and lactation, significant changes occur in the oxytocin system, which includes the supraoptic and paraventricular nuclei of the hypothalamus, the basal ganglia and parts of the amygdala.

These areas were activated in mothers in response to child stimuli, especially in response to own children. It is therefore possible that the maternal responses observed in these areas were only able to develop because of the neuronal plasticity associated with the transition to maternity. The evolutionary importance of maternal care behaviour for infants and for survival of mammalian species in general (see Curley, 2011) suggests that maternal brain plasticity and responsiveness may be pronounced in response to emotional infant expressions, perhaps particularly in relation to extreme emotions.

4.6. The impact of infant emotion

Lenzi et al. (2009) found that mothers have increased activity in the amygdala, insula, and mirror neuron system, which includes ventral premotor cortex, inferior frontal gyrus, and posterior parietal cortex (Iacoboni et al., 1999) in response to (and mimicking of) photographs of infants with distressed, joyous or ambiguous versus neutral expressions. This activity correlates with levels of empathy, and is particularly pronounced if the infant is the mother's own child. The researchers also found that, compared to distressed or ambiguous expressions, joyous expressions were more likely to activate limbic and paralimbic areas, including the amygdala, insula, temporal cortex, hippocampus and basal ganglia. Strathearn et al. (2008) reported that activation of the reward network was present when mothers were exposed to infants with neutral or happy expressions, but not in response to sad expressions.

Previous research has confirmed that compared to mothers, nulliparous women and fathers have different brain responses to baby vocalisations of different valences. As mentioned above, Seifritz et al. (2003) reported that, compared to nulliparous women, mothers showed stronger activation in the amygdala and interconnected limbic areas to infant cries versus infant laughs, whereas nulliparous women showed stronger activation in these regions to infant laughs. In addition, compared to fathers, mothers showed decreased activation in anterior cingulate cortex in response to both infant cries and laughter.

4.7. The effect of maternal sensitivity and maternal mental health

Natural variation in affiliative and attachment behaviour to infants is well described (e.g. Feldman et al., 2010). Few studies have assessed brain activation to infant stimuli in mothers who have been formally assessed as showing low or high sensitivity to infants. This is, however, important as brain activation associated with high maternal sensitivity may be used as a benchmark for adequate parenting in future research.

Kim et al. (2010) found that activity in amygdala (as well as frontal cortex) in response to baby cries versus control sounds correlated with maternal sensitivity, and Swain et al. (2008) suggested that activity in amygdala (as well as insula) also positively correlated with risk of psychopathology (Swain et al., 2008). Reduced maternal care has also been associated with reduced amygdala activity to happy own infant faces (Barrett et al., 2012). This is consistent with a report from Lenzi et al. (2009) that the more empathic a mother is rated, the greater amygdala and insula activity occurs during emotion imitation when viewing her own versus an unknown infant.

Strathearn et al. (2009) examined securely attached mothers viewing own versus control infants and reported that parts of the hypothalamus, insula, and medial and superior frontal gyrus were more active, whereas other areas within the insula, medial and frontal gyrus, as well as orbitofrontal cortex and precentral gyrus, were found to be more activated in insecurely attached mothers. Another study (Atzil et al., 2011) suggested that, when comparing responses to own versus control infants, parts of the medial frontal gyrus were more active in synchronous mothers (i.e. mothers displaying coordination of maternal behaviour with infant signal), whereas other parts were more active in intrusive mothers (i.e. mothers displaying excessive expression of maternal behaviour). In addition, they reported that intrusive mothers were more likely to activate the fusiform gyrus, occipital cortex and cerebellum in response to their own infants (versus control children) than synchronous mothers, but that synchronous mothers

activated septal regions, insula, orbitofrontal cortex and some temporal regions more than intrusive mothers.

Results reported in the present study have included data only from healthy individuals. Further research is needed to examine how brain activation is affected by a mother's mental health, especially serious mental illnesses, such as schizophrenia, which is associated with poor parenting outcomes and high rates of loss of children to social care (Abel et al., 2005), but also antenatal and postnatal depression, which affects around 10% to 15% of women, and is associated with poor maternal sensitivity (Mallikarjun & Oyebode, 2005). Laurent and Ablow (2012) reported that, in response to infant cries versus control sounds, depressed mothers had less striatal, medial thalamic and fusiform gyrus activation than healthy mothers. In addition, mothers rated lower on depressive symptoms activated left orbitofrontal, dorsal anterior cingulate and medial superior frontal regions more than mothers who had been rated higher on depressive symptoms. It therefore may be that the activation reported here is unique to healthy mothers and, considering the difficulties depressed mothers experience with parenting, necessary for adequate parenting.

4.8. Study limitations

- The included studies were unable to confirm whether the identified neural network is specific to maternal responsiveness to child stimuli.
- Two of the conducted meta-analyses (audio studies for generic infant versus control sounds; visual studies for generic infant versus control images) included a small number of studies (N=3 and N=2, respectively), with data for 26 out of 40 participants (Kim et al., 2010), and 20 out of 30 participants (Wan et al., in preparation), respectively, coming from a single study. Further research is needed to obtain more reliable and accurate results for these contrasts.
- It was not possible to conduct a meta-analysis of deactivation of the audio studies (no foci were provided by the identified studies) or of

the visual studies comparing responses to generic versus control images (only one study provided foci).

- Neither was it possible to conduct a meta-analysis for the contrast own versus other child for the audio studies (no foci were provided by the identified studies).
- The included studies were not able clearly to disentangle the role of the different activated/deactivated brain areas.
- Control stimuli for both audio and visual studies (comparing generic infant stimuli to control stimuli) may not have been perceived as neutral:
    - The white noise used as control stimuli in the audio studies may arguably be experienced as negative. The control stimuli may have thus neutralised activation of brain areas associated with negative emotions which may be activated in response to infant cries, for example the amygdala.
    - The control stimuli in the visual studies represented traffic. This may have evoked complex brain processes, for example those involved in attention, the assessment of danger and the planning of responses. In addition, the stimuli may have evoked negative responses such as anxiety and reduced any responses associated with negative emotions in response to unknown infants.
- FMRI has a relatively poor temporal resolution and it was not possible to determine the temporal aspects of the neural basis of maternal responsiveness.
- The ecological validity of the studies was compromised:
    - FMRI research provides limited response possibilities.
    - All stimuli were only representations of children, which is likely to affect maternal neurological responses. The audio stimuli were presented without visual, olfactory or tactile cues. The visual stimuli were presented without auditory, olfactory or tactile cues (although videos provided higher ecological validity than static images).

- Several of the included visual studies applied small volume corrections to specific regions of interest, including the amygdala, limbic system and insula, and this may have introduced some bias to the results.
- It is possible that the results for the meta-analysis comparing responses to images of own versus other children were driven by larger studies which included stimuli of different valences, including happy expressions (e.g. Strathearn et al., 2008). The audio studies included in the meta-analysis, in contrast, used infant cries (which express negative emotions), and it is possible that the absence of the activation of the reward network in this case was due to this difference in valence (rather than the infant stimuli referring to unknown rather than own infants). This would be in line with findings reported by Strathearn et al. (2008).
- Heterogeneity between the samples, stimuli and designs used by included studies may have reduced identified brain activation. Examples of heterogeneity include:
    - Child's age: In the studies using auditory stimuli the infant age ranged from three days to four weeks, and in studies using visual stimuli the age of children ranged from three months to twelve years. However, it should be noted that only three studies (Bartels & Zeki, 2004; Leibenluft et al., 2004, Noriuchi et al., 2008) featured children above the age of one year.
    - Design: Most studies used a block design but Strathearn and colleagues used an event design (Strathearn & McClure, 2002, Strathearn et al., 2008).
    - Control stimuli: For the own versus other child contrast, there was heterogeneity between the control stimuli. Most used unknown children as control stimuli, but two studies (Bartels & Zeki, 2004; Leibenluft et al., 2004) used familiar children.
    - Participants: Some of the studies included first-time and/or right-handed mothers only, while others did not control for these factors.

4.9. Future research

Future research is necessary for a better understanding of the brain basis of maternal responsiveness and the following questions should be addressed:

- How unique is the activation of Swain's neural network to child stimuli? For example, how do they compare to other rewarding stimuli such as adult attachment figures, or other stimuli associated with attention, executive functioning or emotion regulation?
- Is the activation of Swain's network unique to mothers? For example, more comparisons should be made with matched fathers of the same infant.
- Do the changes occur as a result of a transition to maternity? For example, there should be longitudinal research with women who become pregnant.
- What is the role of the child in the activation of these areas, for example what is the role of different child emotions and the child making eye contact? In order to explore the latter eye tracking could be used alongside fMRI.
- What is the exact role of the different identified brain areas?
- What are the temporal aspects of the brain basis of maternal responsiveness? For this, research may use electroencephalography (EEG) or functional near-infrared spectroscopy (fNIR), which have a good temporal resolution (Hamalainen et al., 1993; Cui et al., 2011).
- What is the effect of previous maternal experience, for example whether a mother has had previous children, or her own experiences of parenting in childhood (for the latter there is only one study: Kim et al., 2010)?
- What is the relationship between the activation of identified brain areas and neurotransmitters such as oxytocin and cortisol?
- What is the impact of variation in maternal sensitivity and maternal mental health problems, especially postpartum depression, on the activation of the identified brain areas?

- What is the impact of maternal attachment style on the activation of the identified brain areas?
- How would findings differ if olfactory and tactile stimuli were used? Mothers can recognise their own infants within ten minutes by smell (Porter & Cernoch, 1983) and within one hour by tactile cues. In addition, touch has been reported to elicit caring behaviour (Kaitz et al., 1992). The addition of such cues could therefore add ecological validity to the research design.

4.10. Conclusion

The present study suggests that neural activation of an extended network is associated with healthy mothers' exposure to child stimuli, and that this is stronger in response to their own children. The response includes a broad range of brain areas associated with visual processing, attention, executive functioning, emotion processing, obsession and reward. The activation of many of the brain regions associated with reward and obsession, as well as the deactivation of areas associated with negative emotions, appears to be specific to exposure to mothers' own children.

These findings are consistent to a great extent with the model of parental responsiveness as proposed by Swain (2008). However, should this model become the basis for identifying biomarkers for future research into healthy maternal responsiveness and deviations therefrom, significant alterations to the model are required. This thesis suggests that at the very least clarification and delineation of the role of the cerebellum, reconsideration of the role of the hippocampus, and greater detail regarding the potential roles of activated and deactivated brain regions involved in different aspects of maternal responding to infants, are necessary.

In spite of a lack of evidence of specificity of identified neural activation to maternal responsiveness, regional brain activations, especially to own versus other children, may serve as a benchmark of healthy maternal responsiveness for future research. New research is beginning to detail

ways in which brain responses to children may be modulated in new parents. Such approaches are likely to be of increasing interest in the development of novel parenting interventions, for example those involving the administration of intranasal oxytocin alone or in combination with behavioural approaches.

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