The Association of Postpartum Mood and Neural Responses to Infant-Related and Generally Rewarding Stimuli: An fMRI Study

Submitted by Katie Williams, to the University of Exeter as a thesis for the degree of Doctor of Clinical Psychology, May 2014

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Functional Magnetic Resonance Imaging (fMRI) Investigations of Reward in Depression

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Abstract

Background: Neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have been used to explore the neurobiological basis of reward processing in humans. People with major depressive disorder (MDD) report feeling less motivated to seek out pleasurable or rewarding experiences, or that their ability to experience reward is diminished. The aim of the current review was to summarise and discuss fMRI research investigating the neural activity associated with reward processing in adult depression.

Methods: Web of Knowledge and psychINFO databases were searched for fMRI studies investigating reward processing in adult participants with subclinical, current, or remitted depression. Studies published between 1994 and 2014 were sought.

Results: 220 articles were screened and 16 were included in the review. Unmedicated MDD participants demonstrated reduced activation in reward-related regions when anticipating and obtaining monetary reward, as well as in response to pleasurable stimuli. This was also shown in some medicated MDD samples but findings were generally more heterogeneous. Differences in reward-related neural activity were even detected in remitted and recovered MDD participants. Several correlations between severity of depressive and anhedonic symptoms and reduced activation in the neural reward circuitry were reported.

Conclusions: The findings of the current review highlight that in response to pleasant and rewarding stimuli, neural activation in reward-related brain areas (namely the striatum, PFC including the OFC, and ACC) differentiates between participants with and without MDD. A direction for future research would be to aim for greater consistency in terms of the methodological approaches. Researchers might attempt to agree on a limited set of robust tasks, contrasts, and analysis methods in order to better determine reproducibility of findings and reliability of effects.

Introduction

Although low mood is a traditional feature of depression, reduced interest or pleasure, commonly termed anhedonia, is equally integral to a diagnosis of Major Depressive Disorder (MDD) (APA, 2013). Experiencing reward produces feelings of pleasure, satisfaction, and generally positive affect within us. We are motivated towards engaging in behaviour that results in a rewarding outcome, and reward serves to reinforce and maintain behaviour. We are fundamentally motivated by primary rewards, such as food, as well as more abstract, cognitively represented secondary rewards such as money. People with MDD often report feeling less motivated to seek out pleasurable or rewarding experiences, or that their ability to experience reward is diminished. Eshel and Roiser (2011) provide a brief review of some of the evidence demonstrating that when compared to healthy controls, people with MDD respond differently to reward and punishment during task performance. They conclude that depressed individuals show blunted responses to reward and impaired ability to adapt behaviour according to prior reinforcement. In relatively recent years, research has begun to explore whether depression-related behavioural deficits such as reduced motivation correspond with abnormalities in reward-related brain systems. However, it is important to consider what is known about the neurobiological basis of reward processing in the healthy brain, and such research is ongoing.

More than a decade ago, Schultz (2000) described the regions that the literature was consistently showing to be sensitive to reward in humans and animals. Dopamine cells in the substantia nigra and ventral tegmental area (often mutually considered), the striatum (incorporating the caudate, putamen

and ventral striatum which includes the nucleus accumbens (NAcc)), subthalamic nucleus, frontal cortex (including dorsolateral and orbitofrontal cortex (OFC)), and the anterior cingulate cortex (ACC), amygdala, and lateral hypothalamus were posited to be involved in the detection and perception of reward. These regions constitute the mesolimbic and mesostriatofrontal dopamine pathways that are integral to motivation and reward. Expectation of future rewards was said to be processed in the striatum, OFC, and amygdala. Neurons in the striatum, supplementary motor area and dorsolateral premotor cortex were proposed to be involved in using information about predicted reward to engage in behaviour directed towards reward. The human reward circuit has since been more clearly defined by Haber and Knutson (2010), of which the NAcc and ventral tegmental area are believed to be key structures. This complex system consists of the ventral striatum, which receives inputs from the OFC, ACC, and midbrain and projects to the ventral pallidum and ventral tegmental area/substantia nigra and then back to the prefrontal cortex (PFC). Regulating it are the amygdala, hippocampus, and specific brainstem circuits.

A variety of neuroimaging techniques have been used to explore the brain structures involved in the processing of reward in humans. One method, magnetic resonance imaging (MRI), is a non-invasive brain imaging technique that provides structural and functional data. In functional magnetic resonance imaging (fMRI), it is assumed that increases in regional blood oxygenation in response to stimuli indirectly reflect increases in brain neural activity. The sensitivity of MRI measurements to oxygen changes is called the blood-oxygen-level-dependent (BOLD) response. As the oxygenation levels change there is a change in the MR signal of a few percent, thus indicating the areas of the brain

where the activity is occurring. Previous fMRI studies of reward processing mainly focus on two types of stimuli: positive stimuli, for example happy facial expressions or positive valence words, and monetary rewards. Neural responses to such stimuli are compared with neutral or negative stimuli to identify brain regions that might be specifically related to the experience of reward. Investigations with healthy participants have consistently demonstrated significant activation in response to reward in prefrontal structures including the mesial PFC (Knutson, Westdorp, Kaiser, & Hommer, 2000), the medial OFC (O'Doherty, Critchley, Deichmann, & Dolan, 2003), the ventral striatum incorporating the NAcc (Knutson, Adams, Fong, & Hommer, 2001a; Delgado, Locke, Stenger, & Fiez, 2003), the amygdala (Gottfried, O'Doherty, & Dolan, 2003), and the ventral tegmental area (D'Ardenne, McClure, Nystrom, & Cohen, 2008).

The fMRI literature supports the idea that reward processing involves multiple components (liking, wanting, anticipating, obtaining) with partly distinct underlying neural circuitry, although results have been heterogeneous and even conflicting. The anticipation of reward has been shown to significantly activate striatal regions in response to anticipating monetary reward vs. non-reward (Knutson, Fong, Adams, Varner, & Hommer, 2001b), happy facial expressions vs. anticipation of non-reward and consumption (Rademacher et al., 2010) and pleasant tastes vs. unpleasant tastes and consumption of a pleasant taste (O'Doherty, Deichmann, Critchley, & Dolan, 2002). The consumption of reward and been shown to significantly activate the thalamus in response to obtaining monetary reward vs. no monetary reward and social reward (Rademacher et al., 2010), the ventromedial prefrontal cortex (VMPFC) in response to winning money vs. non-reward (Knutson et al., 2001b), and the amygdala in response to

monetary reward vs. no reward (Ernst et al., 2005) and when viewing happy faces vs. no social reward (graphically dysmorphed faces) and monetary reward (Rademachers et al., 2010). Some studies have demonstrated the absence of NAcc activation during the reward outcome phase in response to consuming a pleasant taste vs. a neutral taste (O'Doherty et al., 2002) and monetary gain vs. no win (Knutson, Fong, Bennett, Adams, & Hommer, 2003) whilst others have shown this region to be involved in response to monetary reward vs. loss (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000) and no win (Ernst, et al., 2005).

It follows that a growing number of fMRI studies have been conducted in an attempt to elucidate brain reward processes involved in MDD. These studies are paramount to the understanding of neural mechanisms that mediate reward-related processing in MDD and will inform the development of detection and intervention techniques. The aim of the current review is to identify whether brain areas activated in healthy adult populations during reward processing are also activated in depressed adult samples, whether the neural activity in these areas has been found to be different in studies comparing healthy and depressed participants, or whether other brain regions are activated in depressed individuals during reward processing. To address these questions, research from the past two decades investigating the neural activity associated with reward processing in adult depression using fMRI will be summarised and discussed. The subsequent empirical paper aims to explore the impact of postpartum mood on reward processing in mothers, but a review of this literature was not possible since it remains an emerging area within fMRI research. Studies of reward processing in general depression will be key to understanding and interpreting reward-related neural activation in mothers with depressive symptoms.

Methods

Information Sources

The University of Exeter's electronic library was used to access the Web of Knowledge and psychINFO databases. These databases were last searched on the 11th of March 2014.

Search Strategy

The search strategy for the psychINFO database consisted of specifying the terms 'depression', AND 'fMRI', AND 'reward' within the abstracts of articles published between 1994 and 2014. The psychINFO database gave the option of specifying the search mode as 'Boolean/Phrase' or 'find any of my search terms'. Both were selected in order to widen the number of articles detected. The search strategy for the Web of knowledge database consisted of specifying the terms 'depression', AND 'fMRI', AND 'reward' in the topic of articles published between 1994 and 2014.

Study Selection

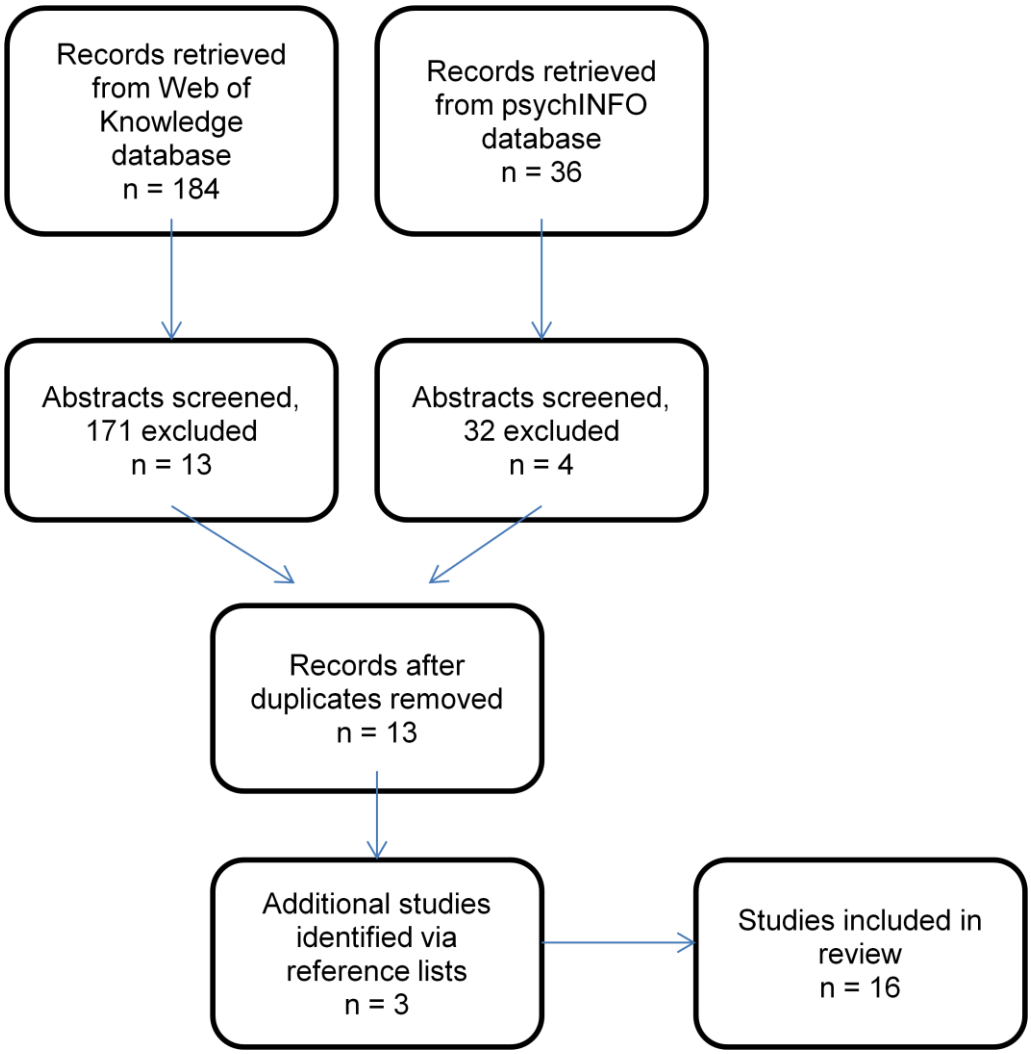
Eligible studies were published primary studies of adult participants (medicated and un-medicated) with subclinical, current, or remitted depression. All tasks designed to investigate reward processing during an fMRI neuroimaging procedure were included. Both whole-brain and regions of interest approaches to data analysis were included. Studies with a comparison group of healthy, non-depressed participants as well as those with no comparison group were included. Exclusion criteria were studies of children and adolescents, studies in which the comparison group were participants with other

mental health disorders and diagnoses, studies investigating the effect of medication on reward processing, and articles not written in English. Studies published between 1994 and 2014 were specified since fMRI was used with human subjects for the first time in the early 1990s and in psychological research relatively recently.

Results

In total, 220 articles were screened for inclusion in the current review (PsychINFO: 36; Web of knowledge: 184) and 13 met criteria. The reference lists of the 13 articles were read to identify additional studies that may be appropriate and subsequently a further three studies were included. A flowchart indicating the search outcome at each stage is provided below (see Figure 1).

Figure 1. Flow diagram of literature search



Review

The studies included in this review are summarised in alphabetical order in Table 1. In the following section, they are reviewed and organised according to participant characteristics to enable more direct comparison of their findings. They will subsequently be collectively discussed.

Table 1. Summary of fMRI Studies of Reward in Depression

fMRI study	Participants	Method	Findings
Dichter et al. (2012)	19 rMDD,19 age & verbal IQ-matched controls.	Monetary incentive delay task. Whole-brain analysis.	During anticipation of potential wins vs non-potential wins rMDD showed increased activation in the left caudate, bilateral anterior cingulate gyrus, & right OFC & midfrontal gyrus. Analysis of unmasked group differences during reward outcome vs no-win showed reduced activation in bilateral OFC, thalamus, right frontal pole, & left insular cortex in the rMDD group. The number of lifetime episodes of MDD positively correlated with frontal pole activation during reward anticipation (not corrected for multiple comparisons).
Epstein et al. (2006)	10 unmedicated MDD, 12 education-matched controls.	Positive, negative, & neutral words presented in block design. Ham-D. Whole-brain & ROI analyses.	MDD showed less activation in bilateral ventral striatal regions, with the left contrast maximum in the NAcc, to positive stimuli. Decrease in activation to positive words in MDD & an increase in activation to positive words in controls. Decreased activity in bilateral ventral striatal regions found in MDD responses to positive vs neutral words. Increased severity on Ham-D item relating to interest, pleasure in, & performance of activities correlated with less activation in bilateral ventral striatal regions & left DLPFC.
Felder et al. (2012)	12 females, subclinical depressive symptoms.	Monetary incentive delay task. BDI. Whole-brain analysis.	The left ACC & right OFC were activated during reward selection. Bilateral NAcc & right putamen & thalamus were activated during reward anticipation. The OFC, left putamen & ACC, and the right thalamus & amygdala were activated during reward outcome. BDI scores negatively correlated with activation in the right caudate & posterior cingulate gyrus, middle & superior frontal gyrus, & left paracingulate gyrus during non-win outcomes.
Hall et al. (2013)	29 medicated MDD (inc. first treatment episode & multiple episode), 25 age & sex-matched controls	Monetary incentive delay task presented in event-related design. Whole-brain & ROI.	In response to reward, controls showed increased activation in bilateral NAcc, ACC, & right hippocampus. Controls showed greater activation in these areas compared to multiple episode MDD. Multiple episode MDD showed greater activation in the VMPFC compared to controls & first episode MDD. First episode MDD showed more VMPFC activation than controls. Response to differences in the magnitude of reward showed increased activation in bilateral NAcc, inferior frontal cortices, & ACC in controls compared to MDD. Controls showed greater activation in these areas compared to multiple episode & first episode MDD. First episode showed greater activation in these regions compared to multiple episode MDD.

Keedwell et al. (2005a)	12 MDD (11 medicated).	Sad & happy emotional personal stimuli presented in block design. BDI, FCPS. Whole-brain analysis.	In response to positive vs neutral stimuli, anhedonia scores correlated positively with activation in the bilateral OFC, right VMPFC & ventral anterior cingulate gyrus & left middle temporal gyrus. Anhedonia correlated negatively with activation in the left insula, anterior caudate, bilateral putamen, & right amygdala. Depression severity correlated positively with dorsal PFC activation & correlated negatively with activation in the putamen, caudate, NAcc, & amygdala. Happy mood ratings correlated positively with activation in the putamen & insula, & negatively with activation in the VMPFC.
Keedwell et al. (2005b)	12 medicated MDD, 12 age & sex-matched controls.	Sad & happy emotional personal stimuli presented in block design. BDI, FCPS. Whole-brain analysis.	In response to happy vs neutral stimuli, MDD showed increased activation in the bilateral VMPFC extending to left VLPFC, middle cingulate gyrus, & other dorsal prefrontal regions; controls showed increased activation in the bilateral precentral gyrus, & left cerebellum & inferior parietal lobe. MDD showed sig. increased neural responses to happy stimuli in the right VMPFC, extending bilaterally, ventrally & dorsally. There were relative increases and decreases in response to happy & sad stimuli, respectively, in the VMPFC.
Knutson et al. (2008)	14 unmedicated MDD, 12 age & verbal ability-matched controls.	Monetary incentive delay task. Whole-brain and VOI analyses.	Direct comparisons of group analyses showed greater activation in the medial PFC, including the dorsal ACC, in the MDD group during gain versus non-gain anticipation. Controls showed greater activation in the medial PFC, putamen, & insula in response to gain vs non-gain outcomes. Analysis of peak activation revealed MDD showed linear increase in ACC activation during anticipation of gains, whilst controls showed increase during anticipation of losses. Analysis of peak activations did not yield sig. group difference in medial PFC activation in response to gain outcomes.
Kumar et al. (2008)	15 medicated MDD, 18 age, sex & verbal IQ-matched controls.	Reward-learning paradigm, event-related design. Ham-D & BDI. Whole-brain & ROI.	MDD showed reduced reward-learning signals in the ventral striatum & dorsal ACC, & increased signals in the ventral tegmental area. MDD had stronger reward-learning signals in the ventral tegmental area & depression severity positively correlated with stronger signals.
McCabe et al. (2009)	13 recovered MDD, 11 age, gender, chocolate-liking & BMI-matched controls.	Pleasant & aversive images & tastes presented in event-related design. Whole-brain analysis.	Recovered MDD showed less activation in the ventral striatum & pregenual & subgenual cingulate cortex in response to the pleasant taste of chocolate, & less activation in the ventral striatum, caudate, superior temporal gyrus, & anterior, pregenual, & posterior cingulate gyrus in response to the sight & taste of chocolate combined. Group comparison of the increased activation resulting from combinations of pictures & tastes vs the sum of pictures & tastes presented alone (supralinearity) indicated that controls activated the VMPFC & medial OFC sig. more than recovered MDD.

Mitterschiffthaler et al. (2003)	7 medicated MDD, 7 controls.	Positive & neutral IAPS images presented in block design. Whole-brain analysis.	When viewing positive vs neutral images, MDD showed increased activation in the right inferior frontal gyrus, left superior & middle temporal gyrus, putamen, thalamus, & anterior & posterior cingulate gyrus, & insula. Decreased activation was found in the right precentral gyrus & left medial frontal gyrus.
Osuch et al. (2009)	16 MDD (1 medicated), 15 age & sex-matched controls.	Favourite & neutral music presented. BDI & SHPS. Whole-brain and ROI analyses.	Listening to favourite vs neutral music activated the left medial OFC in controls & not the depressed group & activated the bilateral ventral striatum/NAcc sig. more in controls. In the depressed group, increased capacity to experience pleasure correlated with increased activation in the left medial/superior frontal gyrus & reduced activation in the right middle temporal gyrus & globus pallidus. Depression severity correlated with increased activation in the left parahippocampul gyrus.
Pizzagalli et al. (2009)	30 unmedicated MDD, 31 controls.	Monetary incentive delay task. BDI. Whole-brain and ROI analyses.	MDD showed reduced activation in the left putamen during reward anticipation vs no-incentive cue. During reward gain vs no change feedback, MDD showed less activation in the dorsal caudate bilaterally, including sub-regions in the right & left caudate. MDD caudate activation was not modulated by win, loss, or no-change feedback. In response to gains, MDD also showed less activation in the NAcc; left accumbens activation was not modulated by win, loss, or no-change feedback. Controls showed greater activation in the caudate in response to gains. No correlations between brain activation & anhedonic symptoms.
Smoski et al. (2009)	14 unmedicated MDD, 15 age & verbal IQ-matched controls.	Monetary incentive delay task. Ham-D. Whole-brain analysis.	During reward selection controls showed greater activation in the paracingulate gyrus, middle frontal gyrus, & right caudate. MDD showed greater activation in left OFC & hippocampus, & superior frontal gyrus & fusiform gyrus. During reward anticipation controls showed greater activation in the right caudate, ACC, & hippocampus, & bilateral thalamus. MDD showed greater activation in parietal operculum. During win outcomes MDD showed greater activation in the left inferior frontal gyrus & bilateral thalamus. Increased severity on Ham-D correlated with bilateral midfrontal activation to reward selection.

Smoski et al. (2011)	9 medicated (4 medicated) MDD, 13 controls.	Monetary incentive delay task. Pleasant & neutral images presented in block design. Whole-brain analysis.	During anticipation of monetary reward MDD showed greater activation in a medial region of the frontal pole & controls showed greater activation in the ACC, right OFC, & left hippocamupus. On receipt of monetary reward vs no-win, controls showed greater activation in right temporal pole. When anticipating pleasant images, controls showed greater activation in the ACC, paracingulate gyrus, right middle frontal gyrus, pallidum, & bilateral precentral gyrus. When viewing pleasant images, controls showed greater activation in the frontal pole, ACC, & right caudate, putamen, & precentral gyrus. Comparing anticipatory neural responses to monetary reward & pleasant images, MDD showed greater activation to monetary reward in right putamen & controls showed greater activation in the right hippocampus & thalamus. During outcome, MDD showed greater activation to winning money in the right precentral gyrus & insula.
Steele et al. (2004)	15 medicated MDD, 14 age & verbal IQ-matched controls.	Card guessing paradigm presented in event-related design. Ham-D. ROI analyses.	MDD showed increased predictive error signal in the rostral anterior cingulate & parahippocampal gyrus. Severity of depression positively correlated with activation in these regions.
Steele et al. (2007)	15 medicated MDD, 14 age & verbal IQ-matched controls.	Card guessing paradigm presented in event-related design. Ham-D. ROI analysis.	In response to win feedback, MDD showed less activation in the bilateral ventral striatum. In response to loss feedback, MDD showed less activation in the medial frontal cortex.

ACC: anterior cingulate cortex
BDI: Beck Depression Inventory
DLPFC: dorsolateral prefrontal cortex
FCPS: Fawcett-Clark Pleasure Scale
Ham-D: Hamilton Depression Rating
IAPS: International Affective Picture System
MDD: Major Depressive Disorder
NAcc: Nucleus accumbens
OFC: Orbitofrontal cortex
PFC: Prefrontal cortex
rMDD: Remitted Major Depressive Disorder
ROI: Region of Interest
RRS: Rumination Response Scale
SHPS: Snaith-Hamilton Pleasure Scale
VLPFC: Ventrolateral prefrontal cortex
VMPFC: Ventromedial prefrontal cortex
VOI: Voxel of Interest

Unmedicated MDD

In all but one of these studies, participants with MDD were not taking psychiatric medication although information about past use is available in some studies. Of 16 MDD participants in Osuch et al's (2009) study, only one was on a stable dose of a selective serotonin reuptake inhibitor (SSRI) thus the study was included with those of unmedicated MDD participants.

The studies using monetary incentive tasks involve participants completing simple reaction time tasks or card guessing tasks in order to win money and trials involve win, loss, or no change outcomes. Studies using such tasks showed that when participants anticipated monetary gains, those with MDD showed increased activation in the ACC (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008), the same pattern being observed in controls when they anticipated losses. MDD groups showed less activation compared to controls in ventral striatal regions including the putamen (Pizzagalli et al., 2009) and caudate as well as the hippocampus (Smoski et al., 2009). In response to reward outcomes participants with MDD again showed less activation in the ventral striatum including the putamen, bilateral subregions of the dorsal caudate and the NAcc (Knutson et al., 2008; Pizzagalli et al., 2009). Positive valence words were shown to elicit less activation in bilateral ventral striatal regions in a depressed group (Epstein et al., 2006) and listening to favourite music elicited less activation in MDD participants' NAcc and ventrial striatum (Osuch et al., 2009). Ventral striatal areas were also less activated in MDD groups when they obtained monetary reward (Knutson et al., 2008; Pizzagalli et al., 2009). In two studies, increased severity of depressive and anhedonic symptoms negatively correlated with bilateral midfrontal gyrus activation during reward selection (Smoski et al., 2009) and activation in the bilateral ventral

striatal regions when viewing positive words (Epstein et al., 2006). Pizzagalli et al. (2009) however, found no correlations between brain activation in response to monetary reward and anhedonic symptoms.

No Control Group

Keedwell, Andrew, Williams, Brammer, and Phillips (2005a) explored neural responses to happy, neutral, and negatively-rated personal memories in a group of participants with MDD, of whom all but one were medicated with antidepressants. The pleasure ratings for positive life events did not differ from a group of non-depressed participants recruited in a previous study by the authors. In response to positive stimuli, increased severity of depression and anhedonia correlated with reduced activation in the caudate, putamen, NAcc, and amygdala, as well as the insula (anhedonia only). Participants who reported feeling happier in response to the happy memories showed more neural activity in the putamen and insula. More activation in the dorsolateral prefrontal cortex (DLPFC) and VMPFC was associated with increasing scores on the Beck Depression inventory (BDI) and increased anhedonia, respectively. Participants who reported feeling happier in response to the happy memories showed less activity in the VMPFC. To summarise, in response to happy memories, participants who reported feeling happy showed increased striatal activity and reduced VMPFC activity, whereas anhedonic and depressed participants showed the opposite; less striatal activity and increased activity in the VMPFC.

Remitted and Recovered MDD

Even when comparing people who no longer meet criteria for MDD and are currently well with healthy controls, fMRI investigations detect differences in

reward-related neural activity, suggesting that this may be a trait associated with vulnerability to MDD. The recovered MDD participants in McCabe, Cowen, and Harmer's (2009) study had had at least one previous episode of MDD and only differed from the control group in terms of their BDI scores, although they were not currently depressed. Ratings of chocolate stimuli for pleasantness, wanting, and intensity were comparable across groups yet the recovered depressed participants showed less activation in the ventral striatum including the caudate and several regions of the cingulate cortex in response to the sight and taste of chocolate. The increase in neural activity responses when pleasant visual and taste stimuli were experienced simultaneously was also smaller in this group compared to controls. Dichter, Kozink, McClernon, and Smoski (2012) used a monetary incentive paradigm, in which participants with remitted MDD (rMDD) did not differ from controls in terms of BDI scores, although they reported significantly more rumination. When participants anticipated reward those with rMDD showed increased activation in the caudate and anterior cingulate gyrus (similar regions found to be less active in response to viewing and tasting chocolates (McCabe et al., 2009)). Activity in the OFC was also found to be increased, which then decreased in comparison to controls, during the receipt of monetary reward. The inconsistencies in similar areas showing increased and decreased activation in response to rewarding stimuli highlight the importance of investigating the different components of reward processing, as well as using different rewarding stimuli.

Subclinical Symptoms of MDD

The sample of women in Felder et al's (2012) study had BDI scores in the moderate range and did not meet criteria for MDD. Using a monetary

incentive delay task they described neural activation of the ACC and OFC elicited during reward selection, ventral striatal activation (including the NAcc and putamen) during reward anticipation, and OFC, putamen, ACC, thalamus, and amygdala activation during receipt of monetary reward. Higher depressive symptoms however, only correlated with reduced activation in regions including the right caudate and posterior cingulate gyrus, the middle and superior frontal gyrus, and the left paracingulate gyrus in response to non-win outcomes.

Medicated MDD

The MDD participants in these studies were taking a variety of psychotropic medications and most authors provided details.

During the card-guessing paradigm employed by Steele, Meyer, and Ebmeirer (2004) and Steele, Kumar, and Ebmeirer (2007) participants were required to select one card from a pair that was deemed correct according to a pre-programmed rule. They received feedback on whether their choice was correct and the rule changed intermittently, requiring participants to work out a new rule. In comparison to the monetary incentive delay tasks, Steele et al's (2004; 2007) paradigm placed more cognitive demand on participants and arguably the reward came from correctly working out the rule. In these studies, participants were encouraged to aim to win the maximum 'points' but were not playing for monetary reward. In the first study, the authors were investigating the brain's prediction error signals which occur when an outcome differs from the predicted or expected outcome, for example, when an expected reward is not obtained. The MDD participants were found to have increased prediction error signals within the ACC when experiencing unexpected reward or the omission of an expected reward. A single type of predictive error signal was calculated here;

the authors did not account for distinct responses when expected rewards were omitted or obtained. However, a subsequent study in which win and loss outcomes were investigated independently showed that in fact, response to loss feedback elicited ‘reduced’ activation in the medial frontal region in MDD. This is consistent with a follow-up study by Kumar et al. (2008) which demonstrated that MDD participants had reduced reward-learning signals or a blunted response to loss feedback within the ACC when attempting to learn which images resulted in them receiving a drink of water when thirsty. The remaining studies using a monetary reward paradigm showed that the ACC, as well as the hippocampus, were less active in MDD during both the anticipation (Smoksi, Rittenberg, & Dichter, 2011) and receipt (Hall, Milne, & MacQueen, 2013) of monetary reward. Reduced reward-learning signals or blunted response to win feedback were also found in the ventral striatum in Steele et al’s (2007) MDD participants. Across the two studies that used positive and negative valence images, contradictory findings emerged in that pleasant pictures increased ACC activity in both control (Smoski et al., 2011) and MDD groups (Mitterschiffthaler et al., 2003). A more consistent finding is that healthy controls in Smoski et al’s (2011) study activated their precentral gyrus whilst anticipating and viewing pleasant images, and in Mitterschiffthaler et al’s (2003) study, MDD participants showed significantly decreased activation in this area when viewing pleasant images. Moreover, the precentral gyrus was activated in control participants when presented with happy autobiographical memories (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005b).

Discussion

The selection of studies reviewed here illustrate the variety of methods used to investigate the neural basis of reward processing. Generally, two very different experimental paradigms are employed. During affective processing tasks, participants' neural responses to positive, pleasant stimuli are compared to responses to neutral or negative stimuli. Among the studies using positive valence stimuli to elicit activation in reward-related areas, words (Epstein et al., 2006), personal memories (Keedwell et al., 2005a; 2005b), food (McCabe et al., 2009), music (Osuch et al., 2009), and pictures (Mitterschiffthaler et al., 2003; Smoski et al., 2011) were used. Food is innately rewarding to us i.e. it is a primary reinforcer, whilst the other types of stimuli used are secondary reinforcers; less likely to reinforce behaviour and potentially less rewarding. Although, subjective pleasantness judgments are directly related to brain regions described as part of the reward circuitry (Kuhn & Gallinat, 2012). Ventral striatal regions, specifically the NAcc, putamen, and caudate, and the VMPFC and medial OFC were generally found to be less active in response to positive stimuli in medicated, unmedicated, and recovered MDD participants. Although in Keedwell et al's (2005a; 2005b) studies, MDD participants showed increased activity in the VMPFC in response to happy compared to sad autobiographical memories. They proposed that this extended more dorsally and was due to the nature of their task which prompted participants to voluntarily generate positive affect whilst remembering happy personal experiences. In all but one of these studies there were no group differences in participants' ratings of stimuli for pleasantness or arousal, which rules out the possibility that group differences in brain activation were caused by the MDD

groups experiencing the stimuli as less positive or pleasant that controls. Mitterschiffthaler et al. (2003) was the only study to identify significant group difference in valence ratings for positive images, although ratings did not correlate with depression or anhedonia severity.

Amongst the studies that used monetary reward paradigms there is variation in the tasks. Arguably, an advantage of using one task over another is how often it has been used in the literature, which enables greater comparison with other studies. The Monetary Incentive Delay task (Knutson et al., 2000) was used in three studies. For a comprehensive review of this task see Lutz and Widmer (2014). During this task, participants anticipated monetary reward, loss, or no consequences whilst completing a simple reaction time task on which the monetary outcome depended. They received feedback as to whether they had won or lost money, or whether their balance remained unchanged, and were also shown their sum total at that point. In these three studies, medial frontal regions were more activated in unmedicated, medicated, and rMDD participants as they anticipated winning money vs. non-win anticipation. The ACC was more activated in the unmedicated and rMDD groups (Knutson et al., 2008; Dichter et al., 2012), yet it was the control group in Smoski et al's (2011) study who showed greater ACC activation during reward anticipation. It is possible that the ACC activation in Dichter et al's (2012) rMDD group replicates Smoski et al's (2011) finding since the rMDD participants had similar BDI scores to controls in this study. In response to win vs. non-win outcomes, no areas were significantly more activated in the depressed groups but reduced activation in the OFC (Dichter et al., 2012) and MPFC (Knutson et al., 2008) was observed. However, the MPFC finding was less robust and the authors advised further exploration. The limited number of comparable findings in three

studies that used the same monetary incentive task might be due to variability in participant characteristics regarding medication and illness severity, or it may be as a result of the individual variability in how reward is processed in those with MDD. Two studies employed the wheel of fortune (WOF) task (Ernst et al., 2004) in which participants chose between two options displayed within a circle or wheel, which each had an assigned probability of winning. It is composed of selection, anticipation, and outcome phases. During anticipation, participants indicated how sure they were of winning and during the outcome phase they either won or did not win money. In a control condition participants were asked to select the colour of the wheel (which was of a single colour), therefore it lacked probabilistic reasoning and the anticipation of, and response to monetary gain. Although participants differed between these studies in that one MDD group were unmedicated (Smoksi et al., 2009) and the other assessed a group of women with subclinical symptoms (Felder et al., 2012) increased activation in regions within the OFC during reward selection vs. control condition was found in the unmedicated MDD and subclinical groups. During the anticipation phase vs. control condition, Felder et al. (2012) reported increased activation in reward areas including the NAcc and putamen, whilst Smoski et al. (2009) reported reduced caudate activation in their MDD group. However, Felder et al. (2012) found that BDI severity was associated with reduced activation in the caudate in response to non-win outcomes. Therefore findings from the studies using the WOF task suggest increased activation during choice, with potentially reduced activation during the anticipation and outcome processing phases. Comparing the MID and WOF paradigms, the MID task evokes the anticipation of reward and punishment and monetary outcome is contingent on participants' reaction times, whereas the WOF task incorporates the weighing up of the value of

different probabilistic monetary outcomes and choice selection. These two tasks probably tap into different kinds of decision-making and approach for rewards. Since the MID paradigm requires no computation or decision-making, it could be argued that this is a purer measure of reward anticipation and receipt than the WOF task.

Variability in the methodological approaches used means that comparing and contrasting studies and drawing conclusions about the brain reward processes involved in MDD is challenging. The affective processing tasks incorporate a range of pleasant, stimuli designed to tap into the hedonic, pleasure (liking) component of reward processing. Other studies explore the motivation (wanting) component of reward processing; using different tasks to do so. There is further variability in experimental design, anatomical labeling, in the contrasts examined, in the determining of thresholds, analyses approaches, and in what measures of brain activity are analysed. Nevertheless, this review identified that compared to healthy controls, depressed participants show reduced activation in striatal regions when processing pleasant stimuli (Epstein et al., 2006; McCabe et al., 2009; Osuch et al., 2009; Smoski et al., 2011). Striatal regions were also implicated in some MDD groups in response to the anticipation (Pizzagalli et al., 2009; Smoski et al., 2009) and receipt (Hall et al., 2013, Knutson et al., 2008, Pizzagalli et al., 2009) of a monetary reward outcome. Since these regions are thought to be involved in the experience of pleasure (Der-Avakian & Markou, 2012) it may be that the hedonic aspect of anehdonia (Treadway & Zald, 2011) is a core feature of MDD, which consequently impacts on the motivation to engage in goal-directed actions to obtain stimuli. However, as already noted, in the affect processing tasks group differences in valence ratings were not evident, yet altered neural activation in

reward areas differentiated between depressed and non-depressed samples. Reduced neural activation in reward-related areas might correspond with depression-related behavioral deficits in other reward-related processes; for example the motivational aspect of anhedonia. Striatal regions are also integral to motivation and the monetary reward paradigms demonstrate that obtaining money is rewarding. Unlike positive, pleasant stimuli and primary rewards such as food, money is not in itself rewarding. But primary rewards can be obtained through secondary rewards, therefore monetary gain is rewarding. The evidence suggests that those with MDD show neural reward deficits when processing both primary and secondary reinforcers.

The Hamilton Depression scales (Ham-D) and the BDI were used to measure depressive and anhedonic symptoms in several of the studies. Relationships between participants' scores on the clinical measures and brain activation were reported for various regions during receipt of monetary reward or pleasant stimuli outcome. Decreased neural activity within ventral striatal regions in response to pleasant words (Epstein et al., 2006) and happy autobiographical memories (Keedwell et al., 2005a) were found to be correlated with either increasing severity of depression or anhedonia. With regard to monetary reward, reduced activation in these areas during non-win outcomes was correlated with depressive symptoms (Felder et al., 2012). Interestingly this finding was observed in medicated and unmedicated participants with MDD, but also a sample of women with a low mean BDI score of 11 who did not meet criteria for MDD, although their scores ranged between 0 to 26, 26 being a moderate score on this measure. This might suggest that altered neural responses to no-win outcomes may be a more sensitive marker of subclinical

depressive symptoms than neural responses during other phases of reward processing.

An important fact to consider when attempting to synthesise the studies of medicated MDD participants is the potential impact that treatment might have on neural activity and more generally on test performance. In one study (Mitterschiffthaler et al., 2003), four of the medicated participants had been previously treated with electroconvulsive therapy (ECT), an invasive treatment during which electrical currents are induced across the brain. Of the studies that included details regarding medication, MDD participants were taking 20 different medications at widely varying daily doses. Some authors did not explain the nature of a stable dose, but participants who had taken the same medication for as little as two weeks prior to testing were deemed to be on a stable dose (Steele et al., 2004), others indicated one month (Kumar et al., 2008). Two studies attempted to explore medication effects and Steele et al. (2004) found no relationship between amount of medication and depression severity (which they reported to correlate with the magnitude of abnormal predictive error signals in their MDD group). Conversely, Keedwell et al. (2005) found that although those taking high and low medication doses did not differ in terms of depression severity, high doses were found to be related to greater neural activity in the VMPFC in response to happy and sad stimuli. In this study, anhedonia was associated with reduced activation in the VMPFC, so greater activation in the high does group could be regarded as a normalization of response. Since the mechanisms by which medication impacts on brain structure and function are not yet fully understood, the potential role of medication effects on study findings must be considered a limitation of the studies with medicated MDD participants. With this in mind, it might be argued

that studies of unmedicated people with MDD may offer a more valid illustration of the neurobiological basis of the disorder.

Conclusions and Future Directions

The findings of the current review highlight that in response to pleasant and rewarding stimuli, neural activation in reward-related brain areas (namely the striatum, PFC including the OFC, and ACC) differentiates between participants with and without MDD. Broadly, those who are not medicated demonstrated reduced neural activity when anticipating and obtaining monetary reward, as well as in response to pleasurable stimuli. In medicated MDD samples, this was also found during a card-guessing paradigm, but findings were generally more heterogeneous which may be due to the effects of medication. Differences in reward-related neural activity were even detected in remitted and recovered MDD participants, potentially indicating a trait vulnerability for the disorder. Finally, several correlations between severity of depressive and anhedonic symptoms and reduced activation in the reward circuitry were reported.

A direction for future research would be to aim for greater consistency in terms of the methodological approaches. Researchers might attempt to agree on a limited set of robust tasks, contrasts, and analysis methods in order to better determine reproducibility of findings and reliability of effects. Studies incorporating functional connectivity analyses will also advance our speculations about how remote brain regions interact during reward processing by producing functional connectivity maps. This could help to combine the changes in activation in the diverse brain regions reported in the literature, and

clarify the pattern of reward-related abnormalities associated with MDD. Discovering whether depression is associated with abnormal functional integration between areas might also be feasible. Furthermore, MRI scanners with greater magnetic fields that offer images of increased clarity and anatomical detail are becoming increasingly available. Use of such scanners in this research will facilitate the delineation of the specific reward-processing circuitry.

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The Association of Postpartum Mood and Neural Responses to Infant-Related and Generally Rewarding Stimuli: An fMRI Study

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Abstract

Background: The neurobiological basis of human maternal behaviour has primarily been explored functional magnetic resonance imaging (fMRI). Structures including the nucleus accumbens (NAcc) orbitofrontal cortex/ventromedial prefrontal cortex (OFC/VMPFC) and amygdala are consistently and specifically activated in the maternal brain by infant-related stimuli and thought to be important for the experiences of pleasure and reward and the evaluation of emotional salience in response to a range of rewarding stimuli. Less is known about how these brain areas respond in mothers experiencing low mood or Postpartum Depression (PPD).

Methods: During fMRI, mothers 3-9 months postpartum with a range of subclinical depressive symptoms completed a task involving the anticipation and receipt of monetary reward and a second task eliciting maternal reward using unknown infant faces. Participants completed general and postpartum-specific questionnaire measures of mood. Correlations were used to explore associations between neural responses to different rewarding stimuli in pre-determined regions of interest (ROIs).

Results: When anticipating monetary reward compared to baseline, mothers higher in anhedonia and lower in trait positive affect showed relative deactivation in the right NAcc and amygdala. Exploratory analyses suggested that quicker reaction times (RTs) to distressed baby faces was associated with higher state positive affect and less activation in the right NAcc and bilateral amygdala in response to distressed baby compared to adult faces. Deactivation of the left NAcc was associated with higher postnatal depressive symptoms.

Conclusions: Altered neural correlates of monetary reward anticipation may be a more sensitive marker of anhedonic depressive symptoms than reward outcome and thus should be assessed separately. Monetary reward paradigms might be less sensitive to mothering-specific depressive symptoms. Postnatal depressive symptoms may be linked to reward system recruitment but specifically in response to infant relative to adult distress.

Introduction

When a woman embarks on motherhood, she is required to engage in a variety of caregiving thoughts and behaviours in relation to her completely dependent newborn infant. Recognising and responding to infant signals are likely to involve complex neural processes involved in generating and organising emotional responses, attention, and reward and motivation. Evidence from the animal literature proposes a motivational system in which neural networks work to stimulate approach and attraction tendencies whilst suppressing avoidance tendencies towards infant cues, and initiate voluntary proactive maternal behaviours (Numan & Woodside, 2010). The neurobiological basis of human maternal behaviour, specifically, how the parental brain responds to infant cues, has been explored with neuroimaging techniques, primarily functional magnetic resonance imaging (fMRI) (Swain, Lorberbaum, Kose, & Strathearn, 2007). Neural responses to emotionally charged infant-related stimuli such as baby-cry and photographs and videos of infants are compared with neutral stimuli or with neural activation in non-mothers to identify brain regions that might be related to the parental experience. Findings are strengthened when the difference is correlated with psychological and behavioural measures relating to maternal thoughts and behaviours.

Research to date suggests that reward-related brain regions mediate the 'liking' and pleasure response that infants evoke in their mothers, the motivational 'wanting' to approach, care for, soothe, and play with their infant, and the learning from prior experiences that interacting with ones infant is rewarding (Berridge & Kringelbach, 2008). Structures including the nucleus accumbens (NAcc) (within the ventral striatum, which is part of the basal

ganglia) and orbitofrontal cortex (OFC) (within the ventral medial prefrontal cortex (VMPFC)) and amygdala, are consistently and specifically activated in the parental brain by own infant-related stimuli and thought to be important for the experiences of pleasure and reward and the evaluation of emotional salience in response to a range of rewarding stimuli (Swain et al., 2014).

Parental Responses to Auditory Infant Stimuli

Mothers are attuned to non-verbal auditory signals of infant distress in order to meet their infant's need for food and the relieving of pain or distress. Studies investigating neural activation in response to auditory infant stimuli have shown increased activation in the thalamus, medial prefrontal cortex (MPFC), OFC, midbrain, hypothalamus, and striatum (including the NAcc) in response to baby distress compared to white noise (Swain, Kim, & Ho, 2011). Increased amygdala activation was observed when cries were compared to rest period activity. First-time (primiparous) mothers in this study were 1-2 month postpartum (Lorberbaum et al., 2002). In parents with children under 3 years of age, Seifritz et al. (2003) reported increased activation in the right amygdala in response to other infant cries relative to intensity-matched infant laughter, whereas greater activation in the amygdala was elicited from laughter in non-parents. The amygdala has been shown to play a role in emotional salience and arousal, irrespective of whether stimuli are of positive or negative valence (Garavan, Pendergrass, Ross, Stein, & Risinger, 2001). When mothers listened to their own infant cry at 2-4 weeks postpartum, it elicited greater activation in the midbrain, basal ganglia, cingulate, amygdala, and insula than when exposed to other infant cries (Swain, 2011). Undergoing the same experiment when their infants were between 3-4 months, increased neural activity was

observed in medial prefrontal regions and not the amygdala or insula (Swain, 2011). It was hypothesised that earlier in the postpartum period there may be increased activity within emotional alarm and anxiety circuitry (amygdala, insula), particularly in response to baby cries, which is replaced by more activity in regulatory and hormonal control circuits as the mother adapts and habituates to her infant. Furthermore, breastfeeding mothers and those who gave birth vaginally have demonstrated increased activity in brain regions associated with the oxytocin hormone (insula, striatum, anterior cingulate cortex (ACC), amygdala, hypothalamus), which is important for social bonding and parenting, in response to own relative to other baby cry when compared to mothers who gave birth by caesarean section and those who were formula feeding (Swain et al., 2008; Kim et al., 2011). Interestingly, Kim et al. (2011) found that increased neural activation to own baby cry in the amygdala and frontal cortex 2-4 weeks postpartum was associated with greater independently-rated maternal sensitivity at 3-4 months postpartum.

Parental Responses to Visual Infant Stimuli

For mothers, the infant face is likely to elicit emotional responses involving motivation and reward (Parsons, Young, Kumari, Stein, & Kringelbach, 2011). Bartels and Zeki (2004) presented photographs of mothers' own children aged from 9 months-6 years and other age-matched children and found areas of activation unique to own infant included the ACC, striatum, thalamus, OFC and MPFC, but the amygdala was deactivated. The authors hypothesised that negative emotion systems (the amygdala) were suppressed to own-child stimuli whilst reward-related areas were selectively activated. However in Ranote et al. (2004), the amygdala was shown to be selectively activated in mothers 4-8

months postpartum in response to video clips of their own infants, perhaps again highlighting the amygdala's role in emotional arousal independent of valence (Garavan et al., 2001). Activation in the OFC, MPFC, and dorsolateral prefrontal cortex was elicited by unfamiliar infants (Ranote et al., 2004). Viewing photographs of their own infants, familiar adults, and unfamiliar infants and adults, Nitschke, et al. (2004) found that primiparous mothers 3-5 months postpartum exhibited OFC activation in response to their own compared to unfamiliar infants. Moreover, OFC activation positively correlated with pleasant mood ratings whereas other brain areas that discriminated between own infant and other stimuli did not. This finding implicated the OFC in mothers' experience of positive affect relating to their own infants. Viewing images of their own infants displaying happy facial expressions but not neutral or sad expressions uniquely activated parts of the substantia nigra, putamen and amygdala in primiparous mothers of infants aged 5-10 months. Independent of emotional valence, the ventral tegmental area/substantia nigra regions, the striatum, amygdala, and frontal lobe areas including MPFC, and ACC were activated in response to own relative to unknown infants (Strathearn, Fonagy, & Montague, 2008). Atzil, Hendler and Feldman (2011) grouped mothers according to whether they displayed synchronous (coordinated social engagement) or intrusive (offering stimulation or presenting objects when infant averted eye gaze or required rest) maternal behaviour towards their 4-6 month old infants. In response to viewing video clips of their own infants relative to unknown babies, synchronous mothers showed significantly greater activations in the left NAcc, whilst intrusive mothers exhibited higher activations in the right amygdala. Furthermore, right amygdala activity differentiated the two groups.

The range of literature reviewed above provides strong evidence that reward regions, particularly striatal regions including the NAcc, as well as the amygdala, and the OFC mediate neural responses to happy (smiling faces, laughter) and negative (sad faces, distressed baby cry) infant stimuli in healthy mothers.

Reduced Reward Sensitivity in Postpartum Depression

Postpartum depression (PPD) is a common mood disorder affecting between 10-15% of mothers (RCP, 2014), although some suggest a higher prevalence (Almond, 2009). It is associated with a mother's inability to bond with her infant and one way it exerts its effect is via the expression and quality of parenting (Lovejoy, Graczyk, O'Hare, & Neuman, 2000). Inadequate or aversive parenting disrupts the development of a secure attachment relationship between mother and infant, the absence of which is a risk factor for infants' subsequent development and functioning (Landry, Smith, & Swank, 2006).

At present, there are limited studies investigating the neurobiological basis of PPD and research is yet to determine whether it is distinct from that of major depressive disorder (MDD), although it would seem that mothering and depression share much overlap in terms of affecting brain systems involved in motivation and reward. Research has very recently begun to address this issue. Moses-Kolko et al. (2011) found that during a monetary reward card guessing task, depressed mothers' neural response in the ventral striatum on receipt of reward was comparable to that of non-depressed mothers. However, this activation returned to baseline significantly quicker than the healthy mothers who demonstrated normal, sustained activity in this reward-related brain area.

The authors concluded that these findings showed reduced reward responses in PDD, as is the case in MDD (see Literature Review). It has also been suggested that impaired processing of reward might impact on emotional (especially happiness) processing since the same neural systems are involved (Swain, 2007). In a recent study by Barrett et al. (2012), amygdala activation elicited by images of mothers' own 3-month old infants with happy expressions relative to unknown happy infants was related to postpartum mood, with greater amygdala response associated with less depressed mood and state anxiety. Exploratory correlations also revealed that increased amygdala activation was associated with mothers having higher positive attachment-related feelings about their infant.

The Current Study

Most studies of reward processing in mothers have investigated neural responses to infant-related rewarding stimuli. Whilst these authors have related their findings to studies of generally rewarding stimuli such as money, no-one has examined both types of rewards in mothers. The aim of our study was to address this gap in the literature by incorporating fMRI tasks involving both types of stimuli in order to compare and contrast how mothers' brains respond to infant-related and more generally rewarding stimuli. Monetary incentives elicit approach motivation, but non-monetary stimuli elicit other aspects of reward processing such as the initial hedonic, liking response and therefore may produce different patterns of brain activity. We aimed to examine associations between reward responses to these different rewarding stimuli in pre-determined regions of interest (ROIs) using correlations. We aimed to recruit a group of healthy mothers with a range of subclinical depression symptoms

rather than a between-groups approach (due to time constraints). Since reward processing is allegedly impacted in MDD and recently PPD, we were also interested in whether mothers' mood would be associated with the processing of monetary and infant-related reward. Again, we used correlations to examine associations between mood and responses in reward-related ROIs.

Based on the literature reviewed here and the literature on the neural processes underlying reward processing in healthy and depressed populations, we hypothesised that low postpartum mood would correlate with decreased activation in reward-related areas, specifically, the NAcc, amygdala, and medial frontal cortex (MFC) (this overlaps with OFC regions previously shown to respond to rewards) when anticipating and obtaining monetary reward, and in response to infant faces. We also predicted that responses within our ROIs to different rewarding stimuli would be positively correlated. We were interested in whether general mood measures (anhedonia and depression) or postpartum specific ones would show stronger associations with reward-related responses. Literature to date did not allow us to generate a-priori predictions about this, but we tentatively predicted that postpartum measures would correlate more with responses to infant-related stimuli and general measures more with responses to general, monetary reward. Finally, whilst the focus of this study was on neural measures of reward sensitivity, we also examined latencies to respond to the faces stimuli as a behavioural measure of engagement with infant-related stimuli. Pearson, Cooper, Penton-Voak, Lightman, and Evans (2010) showed that healthy mothers are biased to engage and approach infant distress, a bias which is perturbed in perinatal depression, therefore we included distressed infant faces as well as happy faces, to explore how our sample of mothers responded to infant faces showing different emotions. We examined

associations between relative reaction time (RT) bias towards infant-related stimuli and mood.

Methods and Materials

Design

An experimental design investigated associations between differences in postpartum mood and neural activation in reward-related brain regions. BOLD response to anticipating and receiving monetary reward in response to infant and adult faces of happiness and distress, and behavioural data (RTs), were correlated with maternal postpartum mood assessed using questionnaire measures.

Participants

Neuroimaging the maternal brain is still an emerging area of research and there is much variability in the sample sizes across studies. Power was calculated using data from an exploratory correlation conducted by Moses-Kolko et al. (2011) between depression severity and activity in the ventral striatum in a depressed group of mothers (Spearman $\rho = -.80$, $p = .002$). Assuming a significance level of 0.05, it was calculated that 11 participants would be required to achieve a power of 0.8 should we conduct a similar correlation with participants with higher levels of depressive symptoms. A larger sample was assumed to be necessary for the current study since healthy mothers with subclinical symptoms were sought.

Mothers of infants aged between 3-9 months were invited to take part in the study. Participants were recruited from the local community in Exeter, in person at children's centres and mother and baby groups and the study was promoted on posters and leaflets. The final sample consisted of 16 primiparous and multiparous mothers (mean age: 33.56; S.D: 4.15; range: 26-42 years). Participants were required to be aged 18 years and above and to have a good level of English in order to complete the measures and tasks. Since we aimed to recruit a sample of healthy mothers in order to examine associations between subclinical depression in the postpartum period and BOLD responses, potential participants were excluded if they self-reported a history of or current psychiatric disorder when asked. Even if currently well, a past diagnosis might indicate a vulnerability to blunted response to reward irrespective of subclinical symptoms in the postpartum period. For safety reasons participants were excluded if they had any fMRI contraindications (e.g. metal implants) in accordance with the MRI scanning centre safety policy. Those with a history of neurological illness or injury were also excluded from taking part. Initially, participants were required to have had a vaginal delivery and to have breastfed their infant for a minimum of 6 weeks, however these criteria was subsequently removed to enable more mothers to take part within the time available. Thirteen participants met the original inclusion criteria, one participant gave birth by caesarean section and had not breastfed for 6 weeks, one participant had a caesarean section but had breastfed for a minimum of 6 weeks, and one participant had a vaginal delivery but did not breastfeed for 6 weeks.

Measures

Questionnaire measures. Self-report measures of general and mothering-specific depressive symptoms and experience of state and trait positive and negative affect were administered to quantify participants' postpartum mood.

The Edinburgh Postnatal Depression Scale (EPDS). The EPDS (Cox, Holden, & Sagovsky, 1987) is a 10-item (α: .86) self-report questionnaire to screen for postpartum depression (see Appendix 1). The authors' validation showed that the EPDS had an overall sensitivity of 86% and specificity of 78% for all forms of depression. On this scale, scores of 10 or more suggest possible depression whilst mothers scoring above 13 are likely to be experiencing depressive illness of varying severity.

The Positive and Negative Affect Schedule (PANAS). The PANAS (Watson, Clark, & Tellegen, 1988b) is a 20-item measure of positive and negative affect (see Appendix 2). The PANAS scales have been shown to have a significant, moderate level of temporal validity and significant predictive validity (Watson & Walker, 1996). Positive affect represents the extent to which an individual experiences positive, pleasurable engagement. Negative affect is a dimension of subjective distress and unpleasurable engagement. We administered the state version to assess participants' mood at the time of the scan and the trait version to assess more general experiences of positive and negative affect. Cronbach's alphas for the 20 trait and 20 state PANAS items were .62 and .79, respectively.

The Mood and Anxiety Symptom Questionnaire (MASQ-62). The MASQ (Watson & Clark, 1991) is a 62-item self-rating scale to identity symptoms of anxiety and depression, including anhedonia (see Appendix 3).

The scales of depressive symptoms (11 items, α: .90) and anhedonic depression (22 items, α: .93) were of interest here. The subscales have been found to have both reasonable convergent and discriminate validity (Watson et al., 1995).

The Postpartum Bonding Questionnaire (PBQ). To obtain information about the quality of the maternal experience and mothers' relationships with their infants, the PBQ (Brockington, Fraser, & Wilson, 2006) was administered (see Appendix 4). It is a 25-item self-rating questionnaire designed to detect disorders of the mother-infant relationship. The PBQ has been shown to demonstrate good internal reliability and adequate validity (Wittkowski, Wieck, & Mann, 2007). The measure yields four scales, one of which is a general scale based on responses to 12 items. The other scales assess anger, anxiety, and abuse in the context of the mother-infant relationship. This general, 12-item (α: .75) scale was used in the current study. High scores are suggestive of a mild bonding disorder; the suggested cut-off score for problematic bonding is 12.

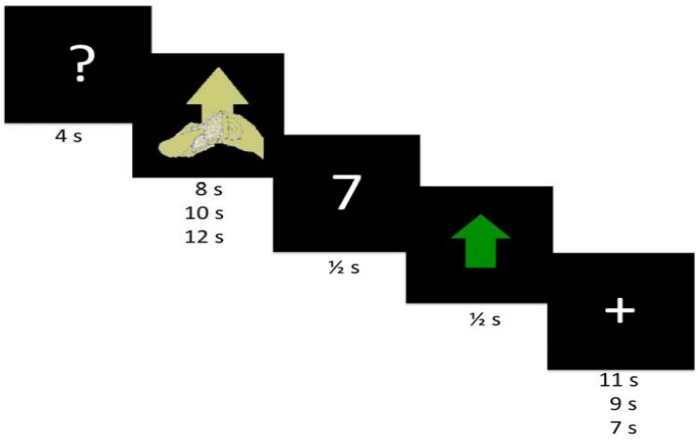
fMRI tasks. To investigate mothers' neural responses to reward, participants completed a gambling task with the potential to win money and a second task eliciting maternal reward using infant stimuli. E-Prime software (Psychology Software Tools, Inc.; www.psnet.com/eprime) was used to deliver and record responses. Stimuli were presented during scanning using an Epson EMP-74 digital projector system projected onto a screen at the foot of the scanner, and viewed via an angled mirror which was attached to the head coil. Responses were made by participants using their right or left index and middle fingers via two fibre-optic response button-boxes.

A card-guessing task (Forbes et al., 2009; Caseras, Lawrence, Murphy, Wise, & Phillips, 2013) that has been shown to reliably elicit striatal activation and to be associated with real-world positive affect was used to probe BOLD responses to anticipation and outcome of reward. It consisted of a slow event-related paradigm in which participants were required to guess whether a card with a possible value of 1 to 9 (excluding 5) would be lower or higher than 5. Each trial included an anticipation phase, during which participants waited for the outcome of their guess, followed by the actual outcome. Depending on the trial type and their guess, participants could win £1, lose 50p, or their balance would not change. During each trial, participants had 4 seconds to guess, after which the trial type was revealed (start of anticipation period): potential reward or potential loss. This anticipation period lasted 8, 10 or 12 seconds and was immediately followed by the actual numeric value of the card (500 ms) and the outcome: win, loss, or neutral feedback (500 ms). Finally, a blank screen with central fixation cross was presented for 7, 9, or 11 seconds to separate each trial from the next (see Figure 1). Note that the total presentation times for the anticipation (8, 10, or 12 sec) and outcome + fixation cross (500 ms + 500 ms + 7, 9, or 11 sec) were the same.

Trials were presented in a pseudorandom order with predetermined outcomes i.e. the task was responsive to participants' guesses. The nine minute task included a total of 24 trials: 12 anticipation of potential reward (leading to six actual reward and six non-reward trials) and 12 anticipation of potential loss trials (leading to six actual loss and six non-loss trials). So, if a participant guessed higher than 5 and they were on a loss-loss trial, the outcome would be lower than 5 to ensure the outcome was fixed. The number of trials and trial structure were identical to that used in Caseras et al. (2013). Participants were

told that they would be paid the final amount of money they had won. The task produced a final balance of £3 across participants, although they were never aware of the fixed outcome probabilities.

Figure 1. Example of trial during monetary reward card guessing task (Taken from Caseras et al, (2013). Used with permission)

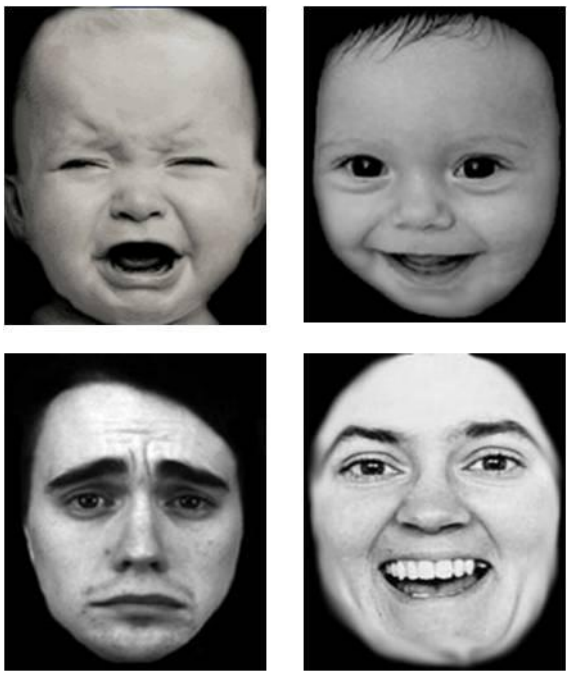


Participants made a guess and responded whilst the question mark was presented for 4 seconds, the anticipation phase followed, then they saw outcome. Participants were instructed to press any button to acknowledge the outcome.

The facial emotion processing task adopted an event-related fMRI design (as opposed to presenting stimuli in blocks) and used an implicit emotion processing task to probe brain responses activated by emotionally salient stimuli (adult or infant faces with emotional or neutral expressions). In two separate tasks, participants were presented with eight different facial identities of happy (one task) or sad/distressed (second task) adult and infant faces (eight of each), along with neutral adult and infant faces (eight of each). For adult faces, four male and four female identities were used for each emotional (and neutral) expression; gender was not obvious for the infant faces. Adult face stimuli were taken from two validated sets of face stimuli (Young et al., 2002)

and the Karolinska emotional faces (Lundqvist et al., 1998). Infant faces were provided by Rebecca Pearson and had been validated in her studies (Pearson et al., 2010) (see Figure 2 for examples of faces stimuli). Consistent with previous studies on facial emotion processing in MDD, separate scanning runs were performed for happy and distressed faces to avoid emotion carry-over effects. In one of the runs, participants viewed 20 happy adult faces (8 identities, each presented 2-3 times) and 20 neutral adult faces (8 identities). They viewed the same number of happy and neutral baby faces (again with 8 identities for each). In the other run, participants viewed similar numbers of sad/distressed adult and infant faces along with the same neutral adult and infant faces as in the happy task. Facial stimuli were presented for 2 seconds each and there were two pseudo-random presentation orders which were counterbalanced across participants. During the interstimulus interval (average of 4 seconds duration) participants viewed a crosshair. Since performance on implicit emotion recognition tasks requiring participants to decide the gender of faces is associated with responses in subcortical and extrastriate cortical regions (Morris et al 1996; Phillips et al 1997), participants were asked to decide the age rather than the emotional expression of each face by responding ‘young’ or ‘old’ using their index or middle finger. Asking participants to respond with a button press encourages them to attend to the task and engage with the stimuli being presented, without explicitly processing the emotional expression. They were instructed to respond as quickly and as accurately as possible because RT data were also of interest here.

Figure 2. Examples of Infant and Adult Faces Stimuli.



Procedure

The study was approved by the University of Exeter, School of Psychology Ethics Committee (see Appendix 5).

Interested individuals were given or emailed an information sheet (see Appendix 6) as well as an initial MRI screening form (see Appendix 7). Potential participants were also screened for current or history of psychiatric disorder (by asking whether they had ever seen a Psychiatrist) or substance abuse (by asking whether they had a history of alcohol misuse or drug abuse). If eligible, an appointment at the Peninsula Magnetic Resonance Imaging Research Centre was then arranged.

On the day of scanning, after providing written informed consent (see Appendix 8) participants were given verbal and written instructions of the experimental tasks that they would be doing in the MRI scanner, before being

placed in the scanner. The monetary reward task was completed first after a short practice, followed by the two emotion processing tasks (presented in a counterbalanced order across participants). After the scanning tasks were complete, participants returned to the waiting area and completed the PANAS ('right now' (state) and 'last week' (trait) time-frames), the MASQ-62, the PPBQ, and the EPDS. They were then de-briefed, given the opportunity to ask any questions about the study and their involvement, and given their winnings from the monetary incentive task (£3) and reimbursed £20 for their time and travel costs.

MR Image Acquisition, Preprocessing, and Analysis

Activation during the fMRI tasks was measured using a 1.5-T Philips Gyroscan MRI scanner fitted with a quadrature head coil. During each task, brain volumes of 26 slices (3.5 mm thick and ACPC orientated) were acquired interleaved using a gradient echoplanar imaging sequence (TR = 2s; TE = 45msec; voxel size = 3.5mm isotropic; FOV=270mm; flip angle = 90 degrees). For the basic emotion processing tasks, 240 volumes were acquired (lasting 8 minutes) and for the card guessing task, 270 volumes were acquired (9 minutes). For each participant, functional data were overlaid on a high-resolution T1-weighted anatomical image for registration into standard space and functional localisation (3D T1 FFE, TR = 252 ms, TE = 4.2 ms, Voxel size = $0.9mm^3$, Number of Slices = 160, FOV = 230 mm, Flip angle = 30 degrees).

fMRI data preparation. fMRI data pre-processing and statistical analysis were carried out using FEAT (fMRI Expert Analysis Tool) Version 5.98, part of

FSL (FMRIB's Software Library). For each participant, standard pre-processing steps were performed. These were: motion correction (Jenkinson, Bannister, Brady, & Smith, 2002), non-brain removal (Smith, 2002), spatial smoothing, (using a Gaussian kernel of FWHM 5mm), normalisation based on grand-mean intensity, and highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, sigma=50.0s). Registration of participants' functional data to high resolution T1 structural images was achieved using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001).

Analysis of monetary reward guessing task. The task was analysed as outlined in Caseras et al. (2013). The task was modeled within the general linear modeling framework with crosshair periods as baseline stimuli. Because of potential habituation effects, the analyses refer to the first 2 seconds of the anticipation period. Rewarding (win) outcomes (one second) were of primary interest, thus the contrasts examined included anticipation of reward relative to crosshair baseline and win outcomes relative to crosshair baseline. These contrasts were also those reported in Forbes et al. (2009) who showed associations between BOLD responses and mood, and on which the current study is based. The full model also included events for anticipation of punishment and negative outcomes and for missed trials (nuisance variable). However, these are outside the immediate focus of this study and will not be discussed in this report.

Analysis of emotion processing task. This task was also modeled within the general linear modeling framework described above. Here, events were defined as the onset time of each face stimulus (duration 2 seconds).

Individual brain activation maps were produced for each participant within each emotion experiment for each category of facial expression (emotional-adult, neutral-adult, emotional-infant, neutral-infant) compared with the intertrial crosshair baseline, and for each emotional expression compared with neutral expressions.

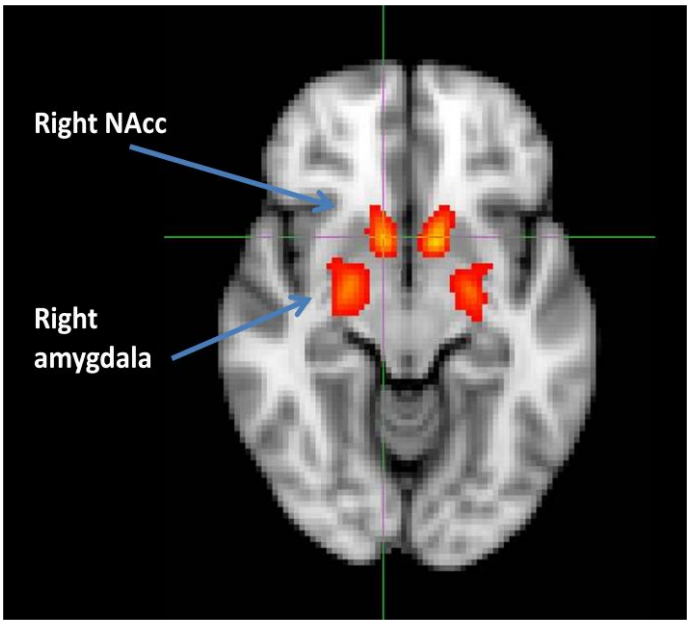
The resulting functional images (contrast maps) for all tasks were converted to the standard space of the Montreal Neurological Institute (MNI) using FMRIB's linear registration tool (FLIRT). Higher-level (group map) analysis was carried out using FMRIB's local analysis of mixed effects (FLAME) (Beckman, Jenkinson, & Smith, 2003).

Region of interest analyses. Due to the a priori hypotheses regarding activation in specific brain regions reviewed above, the anatomical region-of-interest (ROI) analyses focused on extracting the mean % BOLD signal change in three specific anatomical regions-of-interest: the NAcc (also referred to as the ventral striatum in the literature), amygdala, and medial frontal cortex (MFC) (this overlaps with OFC regions previously shown to respond to rewards) (see Figure 3 for NAcc and amygdala ROIs). This ROI analysis was implemented in FSL's Featquery tool using the Harvard–Oxford regional atlas in FSL. Note, in this atlas the NAcc and amygdala are separated into left and right hemisphere regions so results are reported for these separately. For the monetary reward guessing task, the mean % BOLD signal change was extracted from each participant for the contrasts reward anticipation vs. baseline and reward outcome vs. baseline, as explained above. For the emotion processing task, the mean % BOLD signal change was extracted from each participant in each ROI for the contrasts happy baby vs. baseline and distressed baby vs. baseline. The

contrasts for reward/emotions vs. crosshair baseline were focused on in this report to enable comparison with previous studies (e.g. Forbes et al., 2009) and across tasks (i.e. by comparing emotional conditions to a similar crosshair baseline in the different tasks).

Exploratory whole-brain analyses. Supplementary whole-brain regression analyses provided additional information about regions of activation outside our a-priori ROIs that were associated with questionnaire measures of mood. Individual statistical contrast maps for each contrast of interest (see above) were entered into a whole-brain group-level mixed-effects model. The mean-normalised questionnaire scores for each participant were entered as additional regressors (one for each questionnaire of interest) at this second (group) level. Contrasts were defined to examine positive and negative associations between activity across the whole brain and questionnaire scores. Data from all participants were then combined into a higher-level group analysis, using FLAME (FMRIB's Local Analysis of Mixed Effects; Beckman et al., 2003; Woolrich et al., 2004) and Z (gaussianized transformed) statistical maps were thresholded using clusters determined by $Z > 2.3$ and a whole-brain corrected cluster significance threshold of $P < 0.05$ (Worsley, 1992). These maps indicated regions showing significant correlations (corrected for whole-brain analyses) between questionnaire scores and brain activity for our contrasts of interest.

Figure 3. NAcc and Amygdala ROIs



ROIs from the Harvard-Oxford subcortical atlas shown on the MNI brain template. Note the figure is in radiological format so the left of the figure displays the right hemisphere of the brain.

Behavioural data preparation and analysis. Analysis of data was conducted using SPSS for Windows, version 21. Potential relationships between mood measures and NAcc, amygdala, and MFC activation (mean % BOLD signal change) in response to different rewards were examined using correlation analyses. Due to the large number of correlations, we adopted a more conservative alpha value of p = .01, focused on the size of the correlation coefficient and inspected scatter plots to check for outliers. RT data in response to the faces were compared using ANOVA followed by pairwise comparisons. RT data for the monetary reward guessing task was not analysed due to the low number of trials and the non-specific nature of this response (how rapidly participants made a guess).

Results

Sample Characteristics and Questionnaire Measures

All participants completed all experimental tasks and questionnaire measures. Scores on each of the measures tended to be in the subclinical, less severe range and appeared to be normally distributed within the sample. Descriptive statistics for questionnaire data including mean (SD) scores and the range are displayed in Table 1. Scores on the EPDS revealed that one mother met criteria for possible postnatal depression and two were likely to be experiencing postnatal depressive symptoms. Three participants (including one who was likely to be experiencing postnatal depressive symptoms) obtained a score of 12 or more on the PPBQ which might indicate problems in postpartum bonding. Using a cut-off score of 76 (Buckby, Yung, Cosgrave, & Killackey, 2007) a different participant met criteria for anhedonic depression.

To better understand the associations between the various questionnaire measures, we examined correlations between them. We were particularly interested in the overlap between general and postpartum-specific measures of mood. There were significant positive correlations between trait and state positive affect but not trait and state negative affect. The MASQ scales measuring depressive and anhedonic symptoms were significantly correlated and they were each negatively correlated with trait positive affect and positively correlated with trait negative affect. The measure of impaired postpartum bonding (PPBQ) was significantly positively correlated with general depressive symptoms, but not with postnatal depressive symptoms as measured by the EPDS. Postnatal depressive symptoms were positively correlated with general depressive symptoms (MASQ) and trait negative affect (see Table 2).

Table 1. Scores on Clinical Measures

Measure	Mean score *n=16*	*SD*	Min score	Max score
MASQ-62 depressive symptoms	23.56	7.50	13 (lowest possible score 11)	34/55
MASQ-62 anhedonic depression	60	13.64	32 (lowest possible score 22)	76/110
EPDS	6.50	4.76	0	17/30
PPBQ (general scale)	7.44	4.91	0	19/60
PANAS trait positive affect	30.06	7.01	18 (lowest possible score 10)	46/50
PANAS state positive affect	27.69	7.60	13 (lowest possible score 10)	45/50
PANAS trait negative affect	18.44	5.15	10 (lowest possible score 10)	29/50
PANAS state negative affect	12.13	2.47	10 (lowest possible score 10)	20/50

EPDS: Edinburgh Postnatal Depression Scale
MASQ: Mood and Anxiety Symptom Questionnaire
PANAS: Positive and Negative Affect Schedule
PBQ: Postpartum Bonding Questionnaire
SD: Standard Deviation

Table 2. Correlations between Questionnaire Measures

	statePOS	traitPOS	stateNEG	traitNEG	MASQ:dep	MASQ:anhed	PPBQ	EPDS
statePOS	____							
traitPOS	.55*	____						
stateNEG	.17	-.05	____					
traitNEG	-.26	-.46	.27	____				
MASQ: dep	-.29	-.59*	.35	.73**	____			
MASQ: anhed	-.48	-.92**	.07	.51*	.61*	____		
PPBQ	-.35	-.12	.02	.41	.52*	.27	____	
EPDS	.00	-.33	.06	.78**	.65**	.49	.30	____

** $p < 0.01$ level.
* $p < 0.05$ level.

EPDS: Edinburgh Postnatal Depression Scale
MASQ:dep: Mood and Anxiety Symptom Questionnaire depression scale
MASQ:anhed: Mood and Anxiety Symptom Questionnaire anhedonia scale
PBQ: Postpartum Bonding Questionnaire
StateNEG: Positive and Negative Affect Schedule (PANAS) state negative scale
StatePOS: Positive and Negative Affect Schedule (PANAS) state positive scale
TraitNEG: Positive and Negative Affect Schedule (PANAS) trait negative scale
TraitPOS: Positive and Negative Affect Schedule (PANAS) trait positive scale

Monetary Reward Guessing Task

Behavioural data for one participant were lost due to a technical fault during scanning, which prevented analysis of the neural data for this participant in this task.

fMRI data.

Anticipation of reward. Whilst anticipating potential monetary reward compared to baseline, neural responses in the right NAcc and bilateral amygdala were negatively correlated with anhedonia (NAcc: $r = -.61$, $p = .01$; right amygdala: $r = -.68$, $p = .006$; left amygdala: $r = -.65$, $p = .009$). There were

also complementary positive correlations between activity in these same regions and trait positive affect (NAcc: r = .69, p = .004; right amygdala: r = .63, p = .01; left amygdala: r = .71, p = .003). Responses in the left amygdala were also positively correlated with state positive affect (r = .63, p = .01). Figures 4 and 5 show plots illustrating some of these correlations. As can be seen, contrary to our predictions of positive activation in our ROIs to reward anticipation vs. baseline, most participants were showing negative changes in BOLD response, and these were greater in participants with higher levels of anhedonia. Whilst the relationship is in the anticipated direction, interpretation of this correlation is not straightforward. The correlation appears to be driven primarily by relative deactivation in those higher in anhedonia

Figure 4. Right Amygdala Activation and Anhedonia

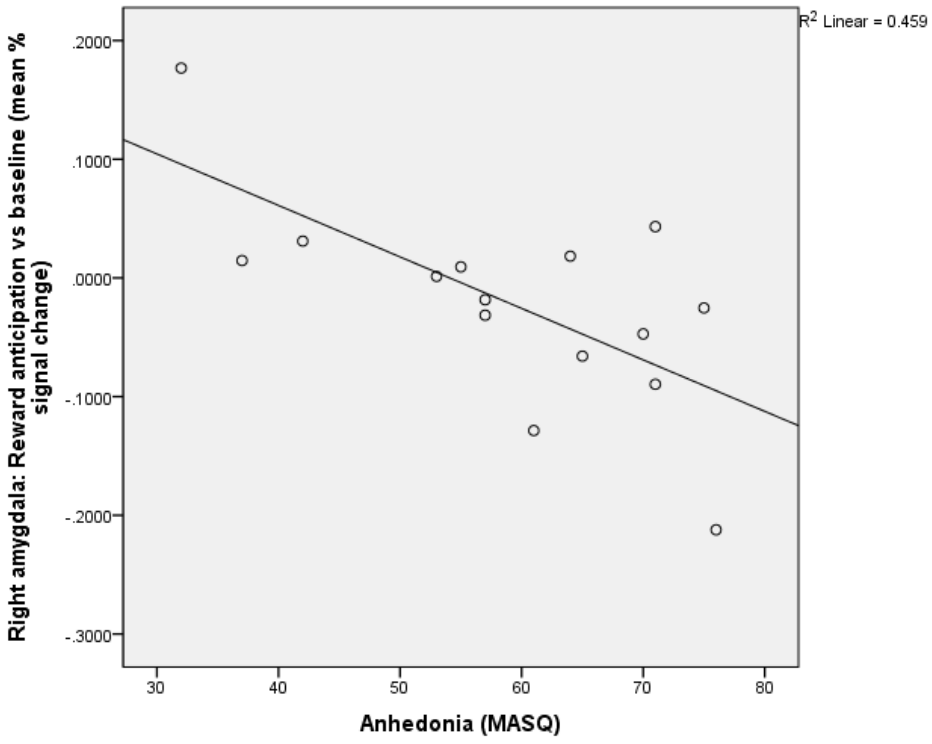
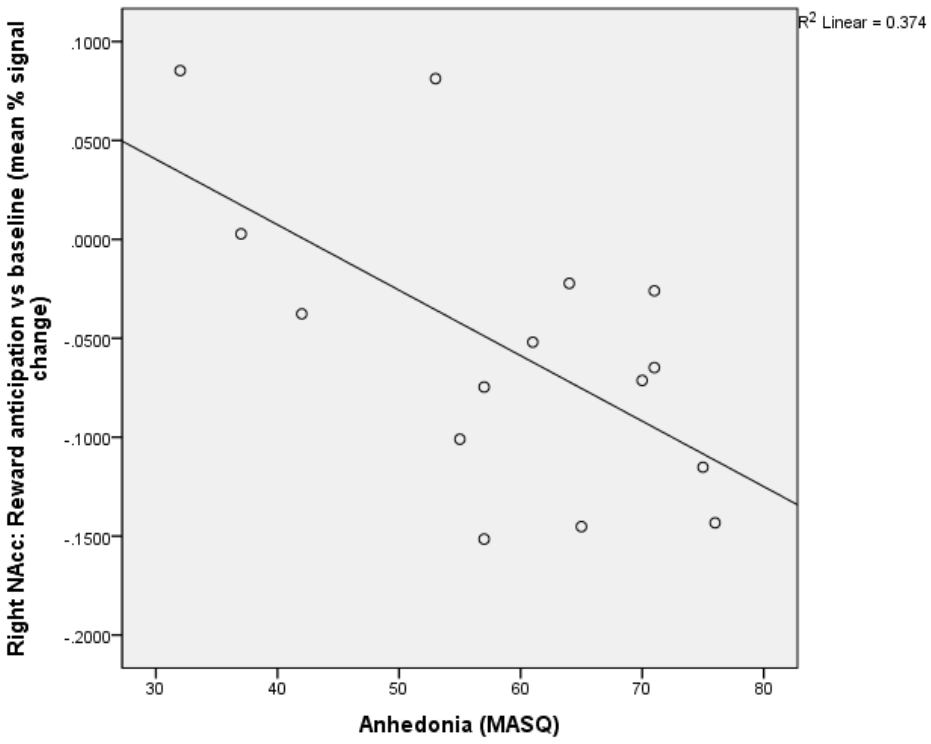


Figure 5. NAcc Activation and Anhedonia



Reward outcome. There were no significant correlations between activity in the ROIs for reward outcome vs. crosshair baseline and questionnaire measures.

Exploratory whole-brain analyses. To explore whether any brain areas outside of the ROIs were associated with mood, activation for the contrasts above was correlated with questionnaire measures of mood including the EPDS and the MASQ scales. At the whole-brain second (group map) level there were no significant areas of correlated activation for any contrast.

Emotion Processing Task

For one participant, a technical fault during the happy faces run of this task resulted in their data being lost therefore this could not be included in the analysis.

Participants correctly categorized the ages of faces in the happy task with a mean accuracy of 99% (S.D: .01; range: 94-100%). They showed similar high levels of accuracy in the distressed faces task (mean 99%, S.D: 0.016; range: 95-100%). Data from all participants was therefore included in subsequent fMRI and behavioural analyses.

fMRI data.

Happy baby versus baseline. There were no significant correlations between activity in the ROIs for this contrast and questionnaire measures.

Distressed baby versus baseline. There were no significant correlations between activity in the ROIs for this contrast and questionnaire measures.

Exploratory whole-brain analyses. In response to distressed baby faces vs. baseline, neural activity in the left superior parietal cortex (x = -56, y = -56, z = 36; Brodmann Area 39/40) was negatively correlated with anhedonia. There were no other correlations surviving correction for whole-brain analyses.

Comparing Neural Reward Sensitivity across Tasks

The above results indicated correlations between responses in the right NAcc and bilateral amygdala during reward anticipation and anhedonia / low

positive affect, in line with our first prediction. We were interested in whether this activation was correlated with BOLD responses to the other rewarding stimuli. There were no significant correlations for activity in the right amygdala across tasks but there were significant associations for activity in the NAcc and left amygdala. Surprisingly, there was a significant negative correlation between responses to the anticipation and receipt of monetary reward in the right NAcc (r = -.64, p = .01) and left amygdala (r = -.72, p = .002). This suggests that individuals who showed greater activation during the anticipation of reward, showed less response upon receipt of rewards. There were no relationships between neural activity in response to monetary and infant-related stimuli. These data do not support our second prediction of positive associations between reward-related responses in our ROIs.

Reaction time data. Due to technical issues with the response device in the scanner, RT data were incomplete for three participants in the happy faces task, and for one participant in the distressed faces task. Therefore, they were not included in the analysis of RT data.

Happy faces. Participants were quicker to respond to baby faces than adult faces in the happy task, with the fastest responses to happy baby faces (Figure 6). A repeated-measures ANOVA revealed a significant main effect of age on RT to faces, F (1, 12) = 12.95, p = .004. There was no effect of emotion or interaction between age and emotion on RT. Follow-up t tests confirmed that participants responded significantly faster to happy baby faces than happy and neutral adult faces (t (12) = -3.84, p = .002; t (12) = -2.94, p = .01, respectively),

and significantly faster to neutral baby faces than happy and neutral adult faces (t (12) = -2.21, p = .05; t (12) = -2.29, p = .04), respectively.

Distressed faces. Participants were slower to respond to distressed adult faces relative to baby faces and neutral adult faces (Figure 7). Response latencies were slower to distressed relative to happy baby faces (Figures 6 and 7). A repeated-measures ANOVA revealed a significant main effect of emotion on RT to distressed faces, F (1, 14) = 15.52, p= .001. There was no effect of age on RT, however there was a significant interaction between age and emotion, F (1, 14) = 7.02, p = .02. Follow-up t tests indicated that participants took significantly longer to respond to distressed adult faces compared to neutral adult faces (t (14) = 3.97, p = .001), distressed baby faces (t (14) = 2.50, p = .02), and neutral baby faces (t (14) = 2.66, p = .02)

Reaction time bias. The RT data reported above suggested that participants were responding faster to baby than adult faces, with a gradient of RTs following an assumed gradient of 'reward value' of the stimuli (i.e. fastest RTs to respond to happy babies, followed by neutral babies and adults, distressed babies and finally distressed adults). In order to examine these interesting RT differences in more detail, a measure of RT bias towards baby faces was computed by calculating the difference in RT to respond to baby and corresponding adult faces: The mean RT to baby faces was subtracted from the mean RT to adult faces so that positive RT differences indicated relative speeding to the baby vs. adult faces, and negative RT differences indicated relative slowing to the baby vs. adult faces. These RT biases were computed

separately for happy and distressed faces. Exploratory correlations then examined whether this RT bias was related to questionnaire measures of mood.

Figure 6. RTs to Happy and Neutral Faces.

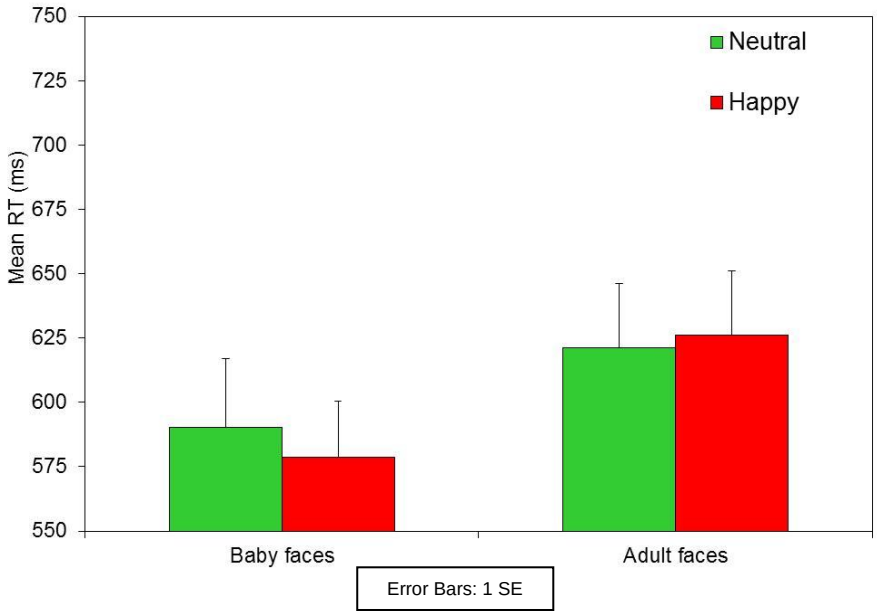
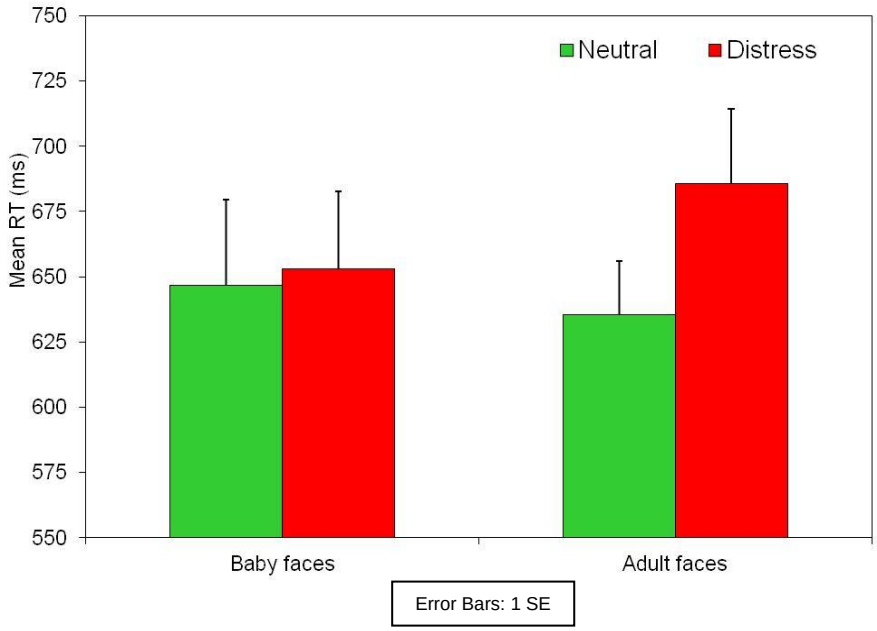
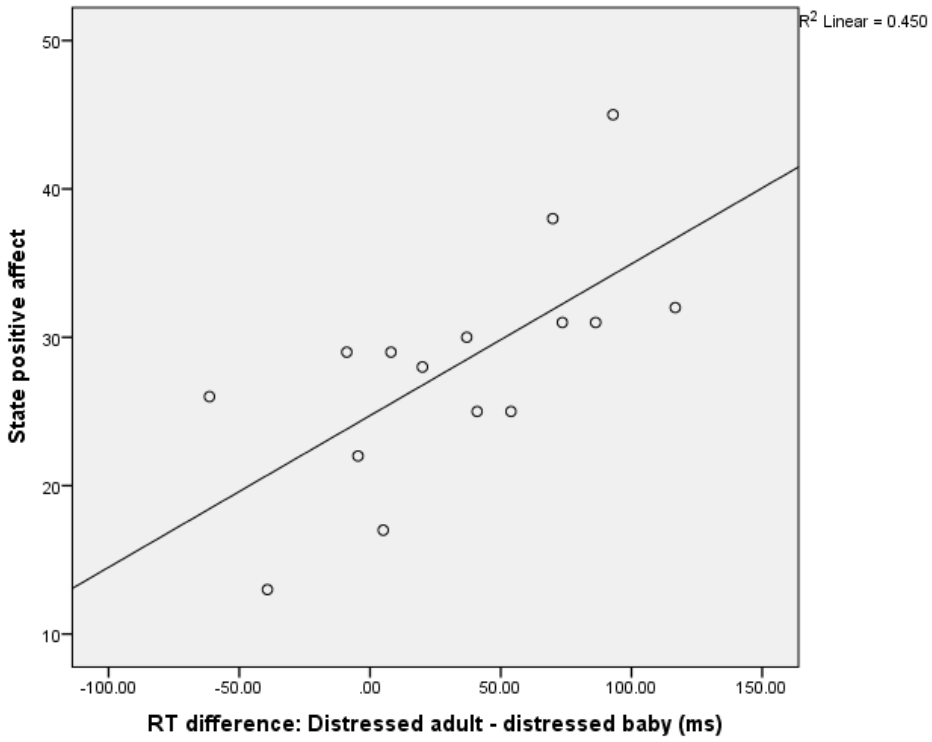


Figure 7. RTs to Distressed and Neutral Faces.



The RT bias towards distressed baby vs. distressed adult faces was positively correlated with state positive affect (r = .67, *p* = .006); i.e. relatively shorter RT to distressed baby faces were related to high state positive affect (see Figure 8). There were no significant (p < .01) correlations between happy baby RT bias and mood.

Figure 8. State Positive Affect and Difference in RT to Distressed Baby vs. Adult Faces

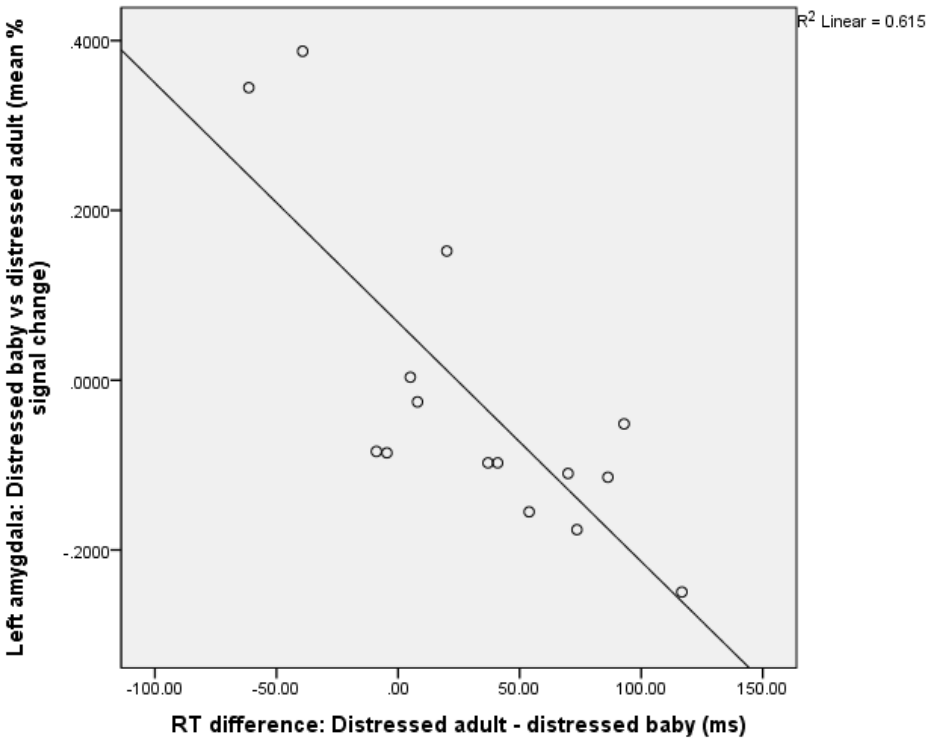


These findings indicated that RT bias to distressed baby vs. adult faces may be sensitive to mood, which supports previous investigations into attentional bias to distressed babies in the perinatal period (Pearson et al., 2010). Therefore, we decided to also check this contrast (distressed babies vs. adults) in our fMRI data for associations with mood and RT bias. Whilst these

further analyses were data-driven rather than planned, we felt that they could provide exploratory results for future studies.

The RT bias towards distressed baby faces was strongly associated with brain responses to distressed baby vs. adult faces in our ROIs. Participants who were relatively faster to respond to distressed baby faces (positive score) showed less activation, or more deactivation, in the right NAcc (r = -.75, *p* = .001) and in the bilateral amygdala (right amygdala: r = -.73, *p* = .002; left amygdala: r = -.78, *p* = .001). For an example of this correlation, see Figure 9.

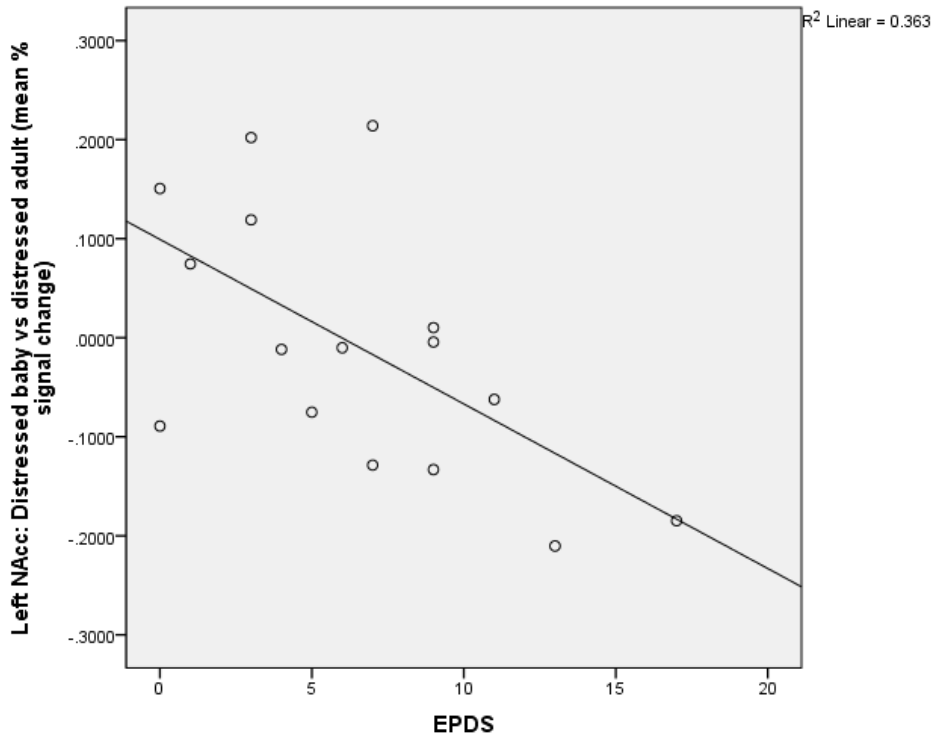
Figure 9. *Amygdala Activation and Difference in RT towards Distressed Baby vs. Adult Faces*



Activity for this fMRI contrast (distressed baby vs. distressed adult faces) in the left NAcc showed a negative correlation with postnatal depressive

symptoms (EPDS) (r = -.60, p = .01) (see Figure 10). Participants with higher scores on the EPDS showed greater deactivation to distressed baby faces relative to adult faces, whereas those with lower postnatal depressive symptoms showed relatively more activation to baby vs. adult faces.

Figure 10. NAcc Activation and the EPDS



Discussion

The aim of the present study was to explore neural activity in brain areas known to be involved in the processing of reward, in response to different types of reward, in mothers of babies. As well as employing a monetary reward task well-known to elicit activation within reward circuitry, a task to explore neural responses to pleasant and distressed infant-related stimuli was incorporated.

Mothers completed clinical measures of depression, anhedonia, and positive and negative affect, as well as a measure assessing postpartum bonding, in order to identify any relationships with neural reward responses.

Our main findings were as follows: When anticipating monetary reward, mothers higher in anhedonia and lower in trait positive affect showed relative deactivation in the right NAcc and amygdala. This partly supported our hypothesis that low postpartum mood would correlate with decreased activation in the reward-related ROIs. We found no evidence for associations between responses to happy baby faces in our ROIs and mood. Contrary to our predictions, responses within the ROIs to different rewarding stimuli were not positively correlated, in fact, there was a strong inverse correlation between BOLD response to the anticipation and outcome phases of processing monetary reward. Finally, when we examined RTs as a measure of engagement with infant-related stimuli, exploratory analyses suggested that quicker RTs to distressed baby faces relative to distressed adult faces was associated with higher state positive affect and less activation in the right NAcc and bilateral amygdala. Furthermore, in response to distressed baby faces compared to distressed adult faces, deactivation of the left NAcc was associated with higher postnatal depressive symptoms.

The negative correlations between anhedonia and neural responses in the right NAcc and amygdala during the anticipatory phase of reward processing, suggested that mothers with increased symptoms of anhedonic depression were showing less BOLD response in the NAcc and amygdala when anticipating monetary reward. This is in line with previous studies that reported reduced neural activation in bilateral ventral striatal regions and the amygdala with increasing severity of anhedonia (Epstein et al, 2006; Keedwell, Andrew,

Williams, Brammer, & Phillips, 2005). Results indicated complementary positive correlations between activity during reward anticipation in these regions and trait positive affect, suggesting that those with more experiences of positive, pleasurable engagement, as measured by the PANAS, were increasingly activating the right NAcc and amygdala. Although this finding was in the direction we expected, visual inspection of the relationships revealed that the majority of our sample were either not activating or were deactivating these brain regions during reward anticipation relative to baseline. This could have been due to insufficient power to detect BOLD responses using this paradigm with a low number of trials. Analyses of neural responses during reward outcome yielded no significant findings. Our pattern of results suggests that altered neural correlates of reward anticipation may be a more sensitive marker of anhedonic depressive symptoms than reward outcome.

This contrasts with Forbes et al. (2009) who found reduced striatal responses in depressed adolescents during both the anticipation and receipt of monetary reward, and with Pizzagalli et al. (2009) who found larger group differences between MDD and controls during the receipt of monetary gain. The authors argued that MDD was more closely associated with deficits in reward processing during outcome. It also contrasts with Knutson, Bhanji, Cooney, Atlas, and Gotlib (2008) who, contrary to their hypothesis, did not observe altered NAcc activation in response to reward anticipation in their MDD group. However, the idea that anticipation and receipt of reward are processed differently is supported by Caseras et al. (2013) who also showed that striatal activity during anticipation, but not outcome, differentiated bipolar participants from controls Responses during reward anticipation could have been more sensitive in this and the Caseras et al. (2013) study because of the larger

number of trials for reward anticipation vs. outcome (12 vs. 6). Our unexpected finding of a strong inverse correlation between BOLD responses to anticipation and outcome of reward also suggests that these phases of reward processing differ. In our sample, greater activation in the right NAcc and left amygdala whilst anticipating reward was associated with reduced activation upon receipt. We are not aware of any other studies demonstrating this, therefore it requires replication. Nevertheless, these findings suggest that anticipation and outcome phases of reward processing differ and should be assessed separately in studies examining the neural basis of anhedonia.

Based on previous research, we assumed that images of baby faces, particularly babies with positive facial expressions, would be rewarding stimuli for mothers of infants and consequently activate reward-related circuitry (Kringelbach et al., 2008; Glocker et al., 2009). We predicted that these neural responses would correlate with postpartum mood. However, we found no evidence for associations between responses to happy baby faces in our ROIs and mood. Instead, behavioural data (RT bias towards baby faces) and neural responses to distressed baby vs. adult faces appeared to be more sensitive to postpartum mood.

Across both emotion processing tasks, our sample of mothers demonstrated generally quicker responding towards emotional infant faces than emotional adult faces faster, suggesting that they processed and engaged with these stimuli more rapidly, perhaps because they were more attentionally- and motivationally-salient to the mothers. Using an emotional go/no-go task, faster reaction times to and greater commission errors for happy faces compared to sad faces suggested a bias or preference for happy faces (Schultz, Fan, Magidina, Marks, Hahn, & Halperin, 2007). In a recent study also using a go/no-

go task, Meule, Lutz, Krawietz, Stützer, Vögele, and Kübler (2014) showed that participants were faster to respond to images of food and omitted fewer food targets, compared to neutral stimuli. The authors suggested that faster reaction times to food-related stimuli evidenced an approach tendency to positive stimuli. The RT bias towards distressed baby compared to adult faces correlated with state positive affect, so mothers in a more positive mood were relatively faster to engage with distressed baby faces. This is potentially consistent with findings from attentional bias tasks that suggest that healthy mothers show a greater attentional engagement (bias towards) distressed babies than depressed mothers in the perinatal period (Pearson et al., 2010). It is possible that mothers with low mood are less responsive to distressed baby stimuli because they find them less rewarding or more aversive.

Exploring this bias towards infant vs. adult distress at the neural level suggested a negative association between RT bias and neural responses: those who were faster to respond to distressed babies vs. adults showed less corresponding activation in the right NAcc and bilateral amygdala ROIs. Viewed another way, this correlation indicates that relatively slower responses to distressed adult vs. baby faces were associated with increased BOLD responses to distressed adult faces. There is extensive evidence that the amygdala plays a key role in the processing of negative valence stimuli, including fearful and sad facial expressions (Davis & Whalen, 2001) and that this response is related to arousal (Garavan et al., 2001). Furthermore, attentional bias towards threat (difficulty disengaging from threat) is associated with increased amygdala responses in anxiety disorders (El Khoury-Malhame et al., 2011; Monk et al., 2008). Our findings are potentially consistent with this; they suggest that mothers who were showing greater distraction (slowing) in

response to distressed adult vs. baby faces showed correspondingly greater amygdala responses to distressed adults. Put another way, mothers who were relatively quick to engage with distressed babies (relative to adults) were not showing amygdala responses to distressed babies. This difference in attentional engagement vs. disengagement and amygdala activation in response to distressed babies vs. adults is a potentially interesting measure for future studies of PPD.

Exploration of associations between postpartum mood and BOLD responses to distressed baby versus adult faces suggested that increased activation in the left NAcc in response to distressed baby faces correlated with lower postnatal depressive symptoms. Therefore, our prediction that higher depressive symptoms would be associated with reduced neural activation in reward-related brain areas in response to infant-related stimuli was supported in this exploratory analysis. This finding suggests that postnatal depressive symptoms may be linked to reward system recruitment but specifically in response to infant relative to adult distress. Since this was the only fMRI measure to correlate with the postpartum-specific mood measure, future research comparing mothers with PPD with healthy mothers should examine neural responses to distressing infant vs. adult faces. This may advance our understanding of the neural basis of the abnormal attentional bias to infant distress that is associated with depression during the perinatal period (Pearson et al., 2010).

Finally, we did not identify any correlations between neural activity within the NAcc or amygdala during the anticipation or receipt of monetary reward and response to happy or distressed baby faces. This did not support our assumption that generally rewarding stimuli such as money and infant-related

rewarding stimuli would elicit similar neural activation in reward-related brain areas. Future neuroimaging studies comparing mothers with and without PPD may therefore benefit from including both generally-rewarding (money) and infant-related stimuli, to disentangle the effects of general depression symptoms / traits from those more specific to postpartum depression.

Limitations and Implications for Future Research

A notable limitation of the present study is the small sample size, therefore all our findings must be interpreted with caution and require replication in larger samples to allow for the comparison of healthy mothers to those with mood disorders and impaired postpartum bonding. We did not have sufficient power to look conclusively at mothers who met criteria for depression and the healthy mothers in this sample had a restricted range of subclinical depressive symptoms. Mothers in the present study were screened for psychiatric disorder and substance misuse but so as not to exclude those who might be experiencing depressive symptoms we did not enquire about the use of antidepressant medication. In addition, some exclusion criteria, namely caesarean section delivery and breast-feeding for six weeks or less, were removed to increase the sample size, although only three mothers in the final sample would have initially been excluded. Future studies should aim to limit the variation of such factors within their samples.

Overall, changes in positive and negative BOLD activation in our ROIs in response to monetary and infant stimuli vs. crosshair baseline were small and highly variable between participants. The lack of positive BOLD responses elicited by happy baby faces may be due, in part, to the fact that mothers did not view images of their own infants, and own compared to unknown infant

stimuli has been shown to produce more activation in reward-reward-related areas compared to unknown and familiar infant stimuli (Bartels & Zeki, 2004). Adapting the task used in the current study to include images of participants' own infants might have been more effective in eliciting activation in our specified ROIs, but this was not attempted due to time constraints on data collection. Own-infant rewarding stimuli might also be a more comparable to 'real-world' monetary reward.

Although the card guessing task we employed has been shown to engage striatal reward areas (Caseras et al., 2013) it consisted of only 12 anticipation of reward trials and six win outcome trials. Arguably, so few trials from which to measure participants' neural activation will be less sensitive than similar monetary reward tasks used elsewhere (Knutson, Wesdorp, Kaiser, & Hommer, 2000). Despite this, activation in our ROIs in response to reward anticipation was associated with mood measures as predicted, indicating some sensitivity to detect individual differences in mood.

Conclusion

To our knowledge, this is the first study to compare neural responses to generally rewarding and infant-related stimuli in mothers of infants, and as such, was exploratory in nature. In support of our hypothesis that low mood would be associated with reduced activity in reward-related areas, we found that the more anhedonic mothers and those with lower trait positive affect were deactivating their right NAcc and amygdala whilst anticipating monetary reward. Contrasting neural responses to infant relative to adult faces revealed that when viewing distressed infant faces, mothers experiencing higher postnatal depressive

symptoms showed less positive activation and more deactivation in the left NAcc. This could indicate that depressive symptoms selectively impact reward circuitry in response to infant distress. This is an interesting finding, and contributes to the debate about the role of anxiety and how women with PPD respond to negative or distressing affect or signals from their infants, relative to infant happiness. Whereas healthy mothers may respond to infant distress in a positive way i.e. activation of the NAcc and subsequent approach and engagement with their infant's distress, mothers with PPD may show more of an anxiety-related avoidance response. More understanding about this might have clinical implications for treatment approaches, in that as well as interventions to target depressed mood and anhedonia, adapting elements from anxiety disorder interventions, might be beneficial for this client group.

Appendices

Appendix 1: The Edinburgh Postnatal Depression Scale (EPDS)

Edinburgh Postnatal Depression Scale[1] (EPDS)

Name: _____ Address: _____

Your Date of Birth: _____ _____

Baby's Date of Birth: _____ Phone: _____

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
- ☐ Yes, all the time
- ☒ Yes, most of the time — This would mean: "I have felt happy most of the time" during the past week.
- ☐ No, not very often — Please complete the other questions in the same way.
- ☐ No, not at all

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   - ☐ As much as I always could
   - ☐ Not quite so much now
   - ☐ Definitely not so much now
   - ☐ Not at all

2. I have looked forward with enjoyment to things
   - ☐ As much as I ever did
   - ☐ Rather less than I used to
   - ☐ Definitely less than I used to
   - ☐ Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
   - ☐ Yes, most of the time
   - ☐ Yes, some of the time
   - ☐ Not very often
   - ☐ No, never

4. I have been anxious or worried for no good reason
   - ☐ No, not at all
   - ☐ Hardly ever
   - ☐ Yes, sometimes
   - ☐ Yes, very often

*5 I have felt scared or panicky for no very good reason
   - ☐ Yes, quite a lot
   - ☐ Yes, sometimes
   - ☐ No, not much
   - ☐ No, not at all

*6. Things have been getting on top of me
   - ☐ Yes, most of the time I haven't been able to cope at all
   - ☐ Yes, sometimes I haven't been coping as well as usual
   - ☐ No, most of the time I have coped quite well
   - ☐ No, I have been coping as well as ever

*7 I have been so unhappy that I have had difficulty sleeping
   - ☐ Yes, most of the time
   - ☐ Yes, sometimes
   - ☐ Not very often
   - ☐ No, not at all

*8 I have felt sad or miserable
   - ☐ Yes, most of the time
   - ☐ Yes, quite often
   - ☐ Not very often
   - ☐ No, not at all

*9 I have been so unhappy that I have been crying
   - ☐ Yes, most of the time
   - ☐ Yes, quite often
   - ☐ Only occasionally
   - ☐ No, never

*10 The thought of harming myself has occurred to me
   - ☐ Yes, quite often
   - ☐ Sometimes
   - ☐ Hardly ever
   - ☐ Never

Administered/Reviewed by _____ Date _____

Appendix 2: The Positive and Negative Affect Schedules (PANAS)

Participant ID:

Date:

This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you feel this way right now, that is, at the present moment. Use the following scale to record your answers.

1	**2**	**3**	**4**	**5**
very slightly or not at all	a little		moderately	quite a bit extremely

_____ interested	_____ irritable
_____ distressed	_____ alert
_____ excited	_____ ashamed
_____ upset	_____ inspired
_____ strong	_____ nervous
_____ guilty	_____ determined
_____ scared	_____ attentive
_____ hostile	_____ jittery
_____ enthusiastic	_____ active
_____ proud	_____ afraid

Participant ID:

Date:

This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you feel this way <u>in the past week</u>. Use the following scale to record your answers.

1	**2**	**3**	**4**	**5**
very slightly or not at all	a little	extremely	moderately	quite a bit

_____	interested	_____	irritable
_____	distressed	_____	alert
_____	excited	_____	ashamed
_____	upset	_____	inspired
_____	strong	_____	nervous
_____	guilty	_____	determined
_____	scared	_____	attentive
_____	hostile	_____	jittery
_____	enthusiastic	_____	active
_____	proud	_____	afrad

Appendix 3: The Mood and Anxiety Symptoms Questionnaire (MASQ)

Below is a list of feelings, sensations, problems, and experiences that people sometimes have. Read each item and then mark the appropriate choice on the answer sheet. Use the choice that best describes **how much** you have felt or experienced things this way **this past week, including today**.

Use this scale when answering:

Not at all	A little bit	Moderately	Quite a bit	Extremely
1	2	3	4	5

1. Felt sad
2. Startled easily
3. Felt cheerful
4. Felt afraid
5. Felt discouraged
6. Hands were shaky
7. Felt optimistic
8. Had diarrhea
9. Felt worthless
10. Felt really happy
11. Felt nervous
12. Felt depressed
13. Was short of breath
14. Felt uneasy
15. Was proud of myself
16. Had a lump in my throat
17. Felt faint
18. Felt unattractive
19. Had hot or cold spells
20. Had an upset stomach
21. Felt like a failure
22. Felt like I was having a lot of fun
23. Blamed myself for a lot of things
24. Hands were cold and sweaty
25. Felt withdrawn from other people
26. Felt keyed up, "on edge"
27. Felt like I had a lot of energy
28. Was trembling or shaking
29. Felt inferior to others
30. Had trouble swallowing
31. Felt like crying
32. Was unable to relax
33. Felt really slowed down
34. Was disappointed in myself
35. Felt nauseous
36. Felt hopeless
37. Felt dizzy or lightheaded
38. Felt sluggish or tired
39. Felt really "up" or lively
40. Had pain in my chest
41. Felt really bored
42. Felt like I was choking
43. Looked forward to things with enjoyment
44. Muscles twitched or trembled
45. Felt pessimistic about the future
46. Had a very dry mouth
47. Felt like a had a lot of interesting things to do
48. Was afraid I was going to die
49. Felt like I had accomplished a lot
50. Felt like it took extra effort to get started
51. Felt like nothing was very enjoyable
52. Heart was racing or pounding
53. Felt like I had a lot to look forward to
54. Felt numbness or tingling in my body
55. Felt tense or "high-strung"
56. Felt hopeful about the future
57. Felt like there wasn't anything interesting or fun to do
58. Seemed to move quickly and easily
59. Muscles were tense or sore
60. Felt really good about myself
61. Thought about death or suicide
62. Had to urinate frequently

Appendix 4: The Postpartum Bonding Questionnaire (PBQ)

PBQ

Name _____ Baby's age _____ Date _____

Please indicate how often the following are true for you. There are no 'right' or 'wrong' answers. Choose the answer which seems right in your recent experience:

	Always	Very often	Quite often	Some-times	Rarely	Never
I feel close to my baby						
I wish the old days when I had no baby would come back						
I feel distant from my baby						
I love to cuddle my baby						
I regret having this baby						
The baby doesn't seem to be mine						
My baby winds me up						
I love my baby to bits						
I feel happy when my baby smiles or laughs						
My baby irritates me						
I enjoy playing with my baby						
My baby cries too much						
I feel trapped as a mother						
I feel angry with my baby						
I resent my baby						
My baby is the most beautiful baby in the world						
I wish my baby would somehow go away						
I have done harmful things to my baby						
My baby makes me feel anxious						
I am afraid of my baby						
My baby annoys me						
I feel confident when caring for my baby						
I feel the only solution is for someone else to look after my baby						
I feel like hurting my baby						
My baby is easily comforted						

Appendix 5: University of Exeter ethical approval

Your application for ethical approval (2013/330) has been conditionally accepted

.

Ethical Approval system

Your application (2013/330) entitled The effect of postpartum mood on neural responses to infant-related and generally rewarding stimuli: an fMRI study. has been conditionally accepted

Please visit http://www.exeter.ac.uk/staff/ethicalapproval/

Please click on the link above and select the relevant application from the list. The conditions are as follows:

This study is approved, subject to the following conditions:The nature of participant remuneration (monetary reward) is unclear: Is this a fixed amount or is it contingent on participant responses? If the latter, this may constitute deception and, if so, that should be addressed in the debrief information sheet.In addition, the debrief information sheet should include a short introductory paragraph, acknowledging that the study may have made participants aware of certain aspects of psychological distress, and providing some guidance, for example, how it would be appropriate to visit the GP if this distress had been long-lasting.

Please email your response to these points to the Chair (C.N.W.Burgess@ex.ac.uk) for Chair's Action prior to commencing data collection.

Appendix 6: Participant information sheet

Participant Information Sheet

Lead Investigators: Ms Katie Williams (kw298@exeter.ac.uk)
Dr Natalia Lawrence (natalia.lawrence@exeter.ac.uk)
Dr Lamprini Psychogiou (l.psychogiou@exeter.ac.uk)

Study title: ***Brain activity and the mother-infant relationship***

Introduction

My name is Katie Williams and I am a Trainee Clinical Psychologist. I am doing some research to better understand the behaviours, thoughts, and brain activity associated with being a mother of a baby. At the University of Exeter we are conducting an interesting new study investigating whether there is a relationship between mood and how a mother's brain responds to different emotional material. We would like to speak to mothers with a range of experiences, including those who have felt well and those who have felt low, during pregnancy and/or after giving birth.

You are being invited to participate in this study, because you are a mother of an infant aged between 3-9 months. Before you decide whether to participate or not, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is not clear or if you would like more information, please ask me in person or via email – contact details are given above.

Thank you for reading this information sheet.

What is the purpose of the study?

The aim of the study is to look at how the brain responds to positive and negative emotional material, such as images of faces and money, and investigate any associations between brain activity and mood, and thoughts and feelings related to the mother-infant relationship. Our findings will further our understanding of the brain in parenthood and may contribute to the development of new ways of identifying mothers at risk of experiencing low mood in the postnatal period, as well as new psychological treatments to improve mood in mothers of infants.

Why have I been asked to take part?

You are being invited to participate in this study, because you are a mother of an infant aged between 3-9 months. Potential participants are also required to have given birth vaginally (i.e. not by caesarean section) and to have breast-fed their baby for a minimum of 6 weeks.

Do I have to take part?

It is up to you to decide whether or not to take part in this study. If you do decide to participate, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time, without giving a reason.

What will I have to do?

The study will involve **one appointment** which will take place at the MR Research Centre, University of Exeter. It will last **approximately 1 hour 30 minutes** in total. We will arrange a convenient time to speak to you on the phone to schedule your visit to the university and to ask you some brief questions about your general health.

During your visit to the University we will ask you to complete some short questionnaires relating to mood and one about your relationship with your baby. You will also be recorded speaking about your infant for 5 minutes. During the second part of your visit we will ask you to carry out 3 basic computer tasks lasting under 10 minutes each whilst lying comfortably in an MRI scanner. The tasks are (a) a card guessing task in which you could win money (b) 2 tasks in which you will be asked to make simple judgments about some photographs of faces. You will be given detailed instructions for each task before you are asked to carry it out. You will be asked to lie in the scanner for approximately 45 minutes. More detailed information about the MRI scan will can be found further on in this information sheet.

At the end of the study you will be provided with additional information and feedback about the purpose of the study and any further questions you may have will be answered by the researchers.

What about childcare?

Unfortunately the university cannot provide childcare for your infant whilst you are completing the study therefore we suggest that you arrange childcare and attend alone, or bring along a friend or relative to look after your baby. It will also be possible for two mothers who know each other to attend the university together and take it in turns to complete the study and look after the infants.

What do I have to do before the scanning sessions?

There are no restrictions on lifestyle or diet before taking part in this study. As the scan can be quite long, you may wish to use the toilet before the scan.

What are the possible benefits of taking part?

There are no direct benefits to you, however the information that we get from this study may help us to learn more about the brain activity underlying the experience of mothering. This study involves the recording of typical brain function. The scans are not intended to provide a medical diagnosis and the person conducting your scans will not be able to comment on the results of your scans.
As a thank you for volunteering for this study, you will be financially reimbursed for your time and transport costs at a rate of £10 per hour. On completion of the entire study, participants will also be sent a summary of the results by post or via email.

What happens if you find something unusual on the scan?

The researchers involved do not have expertise in MRI diagnosis, as they are psychologists or allied scientists and are not medical doctors. You should not regard these research scans as a medical screening procedure. Occasionally when we image participants, the researchers may be concerned that a potential abnormality may exist on the scan. In this case, we ask for your consent to send a copy of your scan to your General Practitioner for further investigation. We therefore request that you provide your GP's contact details prior to being scanned as part of this research study. However, in most cases medical professionals will not look at the images.

It is important that you realise that these scans will not provide any information that may help in the diagnosis of any medical condition. If you do have any health concerns, you should contact a qualified medical practitioner in the normal way.

Are the procedure and results confidential?

All information which is collected about you during the course of this research will be kept strictly confidential. Any information about your identity obtained from this research will be made anonymous by allocating participant numbers. In any report we might publish, we will not include information that will make it possible for other people to know your name or identify you in any way.

What will happen to the results of the research study?

The data obtained through your participation will be part of a scientific study to be published in scientific journals. Where appropriate, the results of this study will also be presented at medical and scientific conferences. You will not be identified in any report, presentation, or publication. The data collected for the study will be held for 5 years at the University of Exeter under the management of Dr. Natalia Lawrence (Lead Supervisor).

What will happen if I do not want to carry on with the study?

Nothing will happen. If you no longer wish to participate you can withdraw from the study whenever you wish, without giving a reason and without any negative consequences.

Who is organising and funding the research?

The study is funded and managed by the University of Exeter.

Who has reviewed the study?

The study has been reviewed and approved by the University of Exeter Psychology Department's Research Ethics Committee. If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee (Chris Burgess), Department of Psychology, University of Exeter, Perry Road, Exeter, EX4 4QG.

Appendix 7: MRI Screening Form

MAGNETIC RESONANCE IMAGING SCREENING FORM 1

NAME OF PARTICIPANT..... Sex: M / F
Date of birth…… Weight in kg…..……. Height in cm or m……..……

Please read the questions on the screening form CAREFULLY. Your safety in the magnetic environment is our primary concern. THIS IS VERY IMPORTANT. For a very small number of individuals, being scanned can be uncomfortable, or endanger health or even life. The purpose of these questions is to make sure that you are not such a person. The information you provide will be treated as strictly confidential and will be held in secure conditions. If you are unsure of the answer to any of the questions, please ASK the person who gave you this form or the person who will be performing the scan. Definitions of some of the more technical terms are given overleaf.

Please answer all questions	*Circle answer*
1. Have you been fitted with a pacemaker, artificial heart valve, cochlear implant or any other implanted device?	YES/NO
2. Have you any surgical clips, aneurysm clips, shunts or stents in your body?	YES/NO
4. Have you ever had any metal fragments in your eyes?	YES/NO
3. Have you been exposed in your life to metal debris as a result of welding, grinding, filing, sawing or drilling of metal either occupationally or recreationally?	YES/NO
5. Do you wear a hearing aid?	YES/NO
6. Have you ever had any metal fragments, e.g. shrapnel in any other part of your body?	YES/NO
7. Have you any surgically implanted metal in any part of your body (e.g. joint replacement or bone reconstruction).	YES/NO
8. Have you ever had any surgery that might have involved metal implants of which you are not aware?	YES/NO
9. Is there any possibility that you might be pregnant?	YES/NO
10. Do you have a contraceptive coil (IUD) installed?	YES/NO
11. Have you been sterilised using clips?	YES/NO
12. Do you have **any** dental work (including dentures, crowns, bridgework, braces) in your mouth, other than simple fillings?	YES/NO
13. Have you ever suffered from any of: epilepsy, diabetes or thermoregulatory problems?	YES/NO
14. Have you ever suffered from any heart disease?	YES/NO
15. Do you have any Tattoos? Do you have any permanent eye makeup?	YES/NO
16. Are you wearing any skin patches? (eg. Nicotine)	YES/NO

I have read and understood the questions above and have answered them correctly.

SIGNED…… DATE……

In the presence of …….. (Name) …….. (Signature)

Definition of Technical Terms

PACEMAKER: An electronic device that is surgically placed in the patient's body and connected to the heart to regulate the heartbeat. ***The safe operation of a pacemaker can be temporarily or permanently disrupted if a person with a pacemaker goes near an MRI scanner***.

COCHLEAR IMPLANT: An electronic medical device that bypasses damaged structures in the inner ear and directly stimulates the auditory nerve, allowing some deaf individuals to learn to hear and interpret sounds and speech.

ANEURYSM CLIP: A surgically implanted metal clip used to cut off blood flow through the neck of an aneurysm. An aneurysm is a deformity of a blood vessel in the body, which can swell and burst causing a haemorrhage.

SHUNT: A surgically implanted connector, which allows passage of fluid between two parts of the body. A common use of a shunt is to allow fluid to drain away from the brain, thus reducing pressure in the brain. May also describe a tube which allows blood to be moved from one part of the body to another.

STENT: A surgical implanted device that is inserted into a blood vessel to provide support, keep the vessel open and promote unblocked and enhanced blood flow. Sometimes used in other fluid carrying vessels in the body such as bile ducts etc.

THERMOREGULATORY PROBLEMS: Thermoregulation is the body's in-built ability to keep all parts of your body at their correct temperature. Some illnesses prevent the person from properly controlling the temperature of their body. If you think you may have such an illness, please answer "YES" and discuss it with the person who gave you the form, or the person who is in charge of the scan.

Appendix 8: Consent Form

Participant Identification Number:

CONSENT FORM

Title of Project: *Brain Activity and the Mother-Infant Relationship*

Name of Researcher: Katie Williams

	Please initial box
I confirm that I have read and understand the participant information sheet for the above study. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason.	☐
I agree to my GP being informed of my participation in the study if this is deemed necessary.	☐
I agree to take part in the above study.	☐

_____	_____	_____
Name of Participant	*Date*	*Signature*
_____	_____	_____
Name of Person taking consent	*Date*	*Signature*

Appendix 9: Dissemination Statement

On completion of the study, participants will be sent a summary of the results by post or via email. If possible, the findings will be disseminated to the research community by submitting a research paper for publication in Biological Psychiatry. The study will be particularly relevant to researchers and health professionals with an interest in motherhood and parenting, neuroimaging, and mood disorders. Opportunities to collaborate with other researchers, by using data from the current study in other research studies for example, will be sought.

Appendix 10: Biological Psychiatry Journal Guide for Authors

PREPARATION & SUBMISSION REQUIREMENTS All manuscripts must be submitted in electronic form through the *Biological Psychiatry* online submission and review web site (http://ees.elsevier.com/bps/). Submission is a representation that all authors have personally reviewed and given final approval of the version submitted, and neither the manuscript nor its data have been previously published (except in abstract) or are currently under consideration for publication elsewhere. Authors must identify figures, tables, and/or data that have been published elsewhere, and permission from the copyright holder must be obtained to reproduce or modify the materials.

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Acknowledgments This section should precede the References, and should include acknowledgments for personal and technical assistance, in addition to detailed information regarding all sources of funding, including grant and other material or financial support. The role of study sponsor(s), if any, should also be detailed. If a research group is listed as an author, then the individual members of the research team must be named here. Written permission should be obtained from all individuals named in this section. Data that was published previously, such as in an abstract or poster, should also be identified here.

Financial Disclosures This section **must** include the required conflict of interest statements for each author (see section on disclosure, below).

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2. American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Press.

3. Martin JH (1985): Properties of cortical neurons, the EEG, and the mechanisms of epilepsy. In: Kandel ER, Schwartz JH, editors. *Principles of Neural Science, 2nd ed.* New York: Elsevier, pp 461-471.

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