`Running Title: Meta-Analysis of Postpartum Depression and Self-Esteem

A Meta-Analysis: A Functional Neuroanatomical Comparison of Self-Esteem-related and Postpartum Depression-related Processing

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Table of Contents

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Abstract

Background: Postpartum depression (PPD) is a psychiatric mood disorder that effects 1 in 10 women in the United States. Symptoms can include irritability, inability to bond with child, sadness, lack/excessive sleep, etc. This diagnosis must be taken seriously for the reason that both children and mothers can be harmfully affected by the manifestations of this illness. Previous literature has shown an association between excessive gestational weight gain and postpartum depression. There have also been a separate handful of studies that show these same mothers, who have experienced increased gestational weight gain, are also more likely to experience low self-esteem. However, there are relatively few behavioral studies looking at the association between postpartum depression and self-esteem. There are even fewer studies (virtually none) looking at neuroimaging comparisons between postpartum depression and self-esteem. Neuroimaging studies could allow us to shed more light on the prognosis of postpartum depression and forge the path for more studies to be completed in this specific sector. The goal of this study was to look at the neuroanatomical overlap of activated brain regions involved in both self-esteem and postpartum depression processing. Based on previous literature it was observed that the right amygdala, PCC, inferior temporal gyrus, and insula were involved in PPD differential activation. We also found that ACC, PCC, right amygdala, and insula all appear to be involved in self-esteem processes. Therefore, we hypothesized that the right amygdala, PCC, and insula would be involved in both postpartum depression and self-esteem processing.

Methods: Six postpartum depression papers and twelve self-esteem papers were found using a specific inclusion/exclusion criteria (different for both samples). Individual activation maps were created for both samples using the MKDA program in MATLAB. These images were extent-based cluster-wise activation maps and were created using the Monte-Carlo Simulation at 5000

iterations. Both of these maps were then overlapped to find common regions of activation. We also created an individual cluster map of major depressive disorder to function as a positive control.

Results: The results supported part of our hypothesis. The insula, rostral anterior cingulate cortex, dorsal anterior cingulate cortex, and thalamus were involved in both self-esteem and postpartum depression processing. Therefore our prediction of the insula being involved in both processes was confirmed, however our prediction of PCC and right amygdala activation was not supported by our results.

Discussion: The insula, rostral and dorsal anterior cingulate cortex, and thalamus are all involved in emotional processing. Postpartum depression is a mood disorder that disrupts emotional stability and low self-esteem is often associated with sadness/anger or other negative feelings. Therefore, it is plausible to believe that these structures are involved in postpartum depression and self-esteem processing. Postpartum depression is vastly understudied for its prevalence in today's society, and more literature needs to be dedicated to investigating postpartum depressive neuroanatomical manifestations and pathology.

Introduction

Postpartum depression affects a strikingly large number of women who give birth every year. It is estimated that roughly 1 in 10 women in the USA are diagnosed with postpartum depression (Postpartum Progress, 2013). Postpartum depression has only begun to garner attention within the last 10 years. As a result, there are minimal neuroimaging studies available. There is a great deal of progress to be made in this field if science wishes to help new mothers. Neuroimaging studies have helped individuals diagnosed with depression receive a more focused/accurate treatment, and hopefully we can expect the same from PPD neuroimaging studies (Wise, Cleare, Herane, Young, & Arnone, 2014). The early stages in a child's development are shaped by their mother's care and support; postpartum depression can play a significant role in this (Brand & Brennan, 2009). Mothers suffering from postpartum depression can experience changes in physical and mental health, in addition to lowered body dissatisfaction (Clark et al., 2009). These health changes often play a significant role in a mother's care of her child, which can ultimately have

negative impacts on the child's development. Delayed cognitive development and language acquisition, emotional instability, and negative affect are common traits in children of mothers with postpartum depression (Tuovinen et al., 2018).

Previous literature has shown that excessive of gestational weight gain is associated with higher postpartum depression scores (Wright et al., 2013). This makes sense since, there is a plethora of research supporting the idea that depression is associated with weight gain (Sutin & Zonderman, 2012) . In addition to increased risk of postpartum depression, these women are also at higher risk of developing decreased self-esteem and increased body dissatisfaction (Skouteris, 2012. p. 667). Based on previous research, which suggests that women with increased gestational weight gain were more likely to develop postpartum depression and decreased self-esteem, we would guess there is a link between postpartum depression and decreased self-esteem. However, there are limited behavioral studies exploring the relationship between these domains. The few studies that do explore this topic suggest there may be similar regions/networks involved in both of these processes. Upon a preliminary literature review, it became clear that the anterior cingulate cortex, right amygdala, dorsolateral prefrontal cortex, and posterior cingulate cortex may be involved in both PPD and self-esteem processing. However, there are no studies exploring this anatomical overlap.. Before proceeding with a more thorough neuroanatomical comparison, we needed to ensure there was in fact a link between PPD and self-esteem. For this reason, a brief behavioral literature review exploring this association was conducted.

I. Behavioral Literature Review of Body Image Satisfaction/Self-Esteem in Relation to Postpartum Depression

Body image is one's evaluation and perception of their body. This image can be specifically contingent on weight fluctuations, which has also been known to impact self-esteem and mental well-being (Kékes Szabó, 2015) Pregnant mothers are especially susceptible to this, due to the nature of their rapid weight gain. Therefore, as the literature review will discuss, increased gestational weight gain is closely tied to body-image, and may leave the mothers more at-risk to a host of mental well-being issues.

Body dissatisfaction can be equated to self-esteem as determined by the literature below. The listed studies mention that body dissatisfaction is analogous to low self-esteem regarding physical appearances. Many of the mothers in the studies report having low self-esteem in the

qualitative data of the study (Weinberger, Kersting, Riedel-Heller, & Luck-Sikorski, 2017). Therefore, from this point on, low self-esteem will be considered equivalent to body image dissatisfaction

In their recent novel, "Body Image", which is directed at a general audience, Cash and Smolak (2012) bring together a large group of specialized experts to discuss the detrimental self-esteem effects overweight women experience. Each expert crafted a chapter of the book in their area of expertise and discussed body image's role in mental health. A study conducted by Foster and colleagues, found that a group of women who lost an average of 19 pounds in 24 weeks, reported significant improvement in body satisfaction levels. When these women regained 3 pounds in the following week, they reported slightly lower body satisfaction scores (Foster et al., 2015). Additionally, another study conducted by Annis and colleagues looked at currently obese/overweight, formerly overweight/obese, and never-overweight women. Their results show that currently overweight/obese women displayed higher body index dissatisfaction, overweight preoccupation, and dysfunctional appearance investment compared to never-overweight women. Furthermore, women who were previously overweight/obese do not show significant differences in body satisfaction scores compared to never-overweight women. The formerly overweight women were more likely to engage in overweight preoccupation and dysfunctional appearance investment than never-overweight women. This study highlighted the negative processes, and the negative behavioral tendencies these women (with weight gain) are likely to engage in (Annis et al., 2014).

However, a qualitative study conducted by Clark et al., (2009), found that pregnant women could avoid the negative perceptions of weight gain. In their study, women reported that certain protective characteristics of pregnancy shielded them from negative body image dissatisfaction. They also reported certain events unique to pregnancy that allowed them to cope with their body changes, including: a new sense of meaning of life- involving placing well-being of fetus above body aesthetic, feeling the fetus kick, and increased sense of social connectedness. However, due to the nature of these pregnancy-specific events, many of the women reported feelings of body dissatisfaction during postpartum period. This study exemplifies the likelihood of developing body image dissatisfaction during the postpartum period.

Unfortunately this is not always the case, and pregnant women still feel the pressure of weight gain. A study by Dipietro et al., (2003) studied pregnant women's weight-related attitudes

in relation to certain psychological characteristics, pre-pregnancy body evaluating habits, and gestational weight gain. Women with low-risk pregnancies, who were at least 36 weeks pregnant, were used as participants in the study. Psychological characteristics, such as, anxiety, depression, and social support, etc. were examined. Results showed women who were more self-conscious about their weight gain felt more hassled by their pregnancy, greater anger, and more support from their partners. Pregnancy BMI was unrelated to psychological symptoms, however, negative attitudes about weight gain persisted even amongst women who had gained appropriate weight during pregnancy. The study displayed the negative attitudes associated with gestational weight gain amongst all cohorts of pregnant women.

But perhaps the personal attitudes about a women's body pre-pregnancy can further impact their view on gestational weight gain. A study conducted by Duncombe et. al., (2008) assessed body image across pregnancy. One hundred and fifty-eight women were asked to report on psychological and physical changes from pre- to post-pregnancy. Women who described more concerns pre-pregnancy were more likely to maintain those concerns throughout, while those who reported the most dissatisfaction with their bodies were the most likely to report depressive symptoms post-partum. This analysis further exemplified the negative body perception associated with gestational weight gain in self-conscious women.

Clark et al., (2009) further develops the idea of negative affect in postpartum depression, by exploring the relationship between depression and body dissatisfaction across pregnancy and the first 12 months of postpartum. Results found that perceived attractiveness and strength/fitness remained stable over pregnancy, while feeling fat and salience of weight/shape decreased in late pregnancy. However, during the postpartum period, these feelings increased. Additionally, the study found that body dissatisfaction scores were correlated with depression across multiple time points.

As exemplified in the previous study, perhaps negative feelings of weight gain begin in last stage pregnancy. Sweeny and Fingerhut (2013) argue that body dissatisfaction in late stage pregnancy can be associated with postpartum depression as well. Healthcare providers recruited pregnant patients, with a gestational age of 28 weeks or later. They assessed postpartum depression scores using the Edinburg Postpartum Depression Scale, along with, body dissatisfaction and maladaptive perfectionism during the third semester of pregnancy. The study indicated that maladaptive perfectionism was not a predictor of postpartum depression, but body

dissatisfaction was. Therefore the study concluded that body dissatisfaction measured during the third trimester of pregnancy could serve as an indicator of postpartum depression.

These negative feelings of weight gain/body dissatisfaction can be harmful when it feeds into negative psychiatric tendencies. Downs, DiNallo, and Kirner (2008) examined the associations between depressive symptoms, body image satisfaction, and exercise behavior. Women completed self-reported measures for these variables midway through their first, second, third trimester, and 6-weeks postpartum. They found that depressive symptoms, body image satisfaction, and exercise behavior were associated across the pregnancy check points and postpartum. Additionally, their results indicate that depressive symptoms and body image satisfaction were highly predictive of later depression in pregnancy and postpartum depression. This study clearly displays the association between body image satisfaction and postpartum depression.

Rauff and Downs (2011) conducted another study that strengthened the relationship between body image satisfaction and postpartum depression. They found that body image satisfaction in second and third trimester, mediated the relationship between the first trimesters body image satisfaction and second trimester depressive symptoms, as well as, the relationship between body image satisfaction in the second trimester and depressive symptoms in the third trimester. Gestational weight gain was associated with body image satisfaction across all three trimesters. The study indicates the importance of maintaining pregnant women's body image as a means of combating postpartum depression.

. Previous literature has supported the association between low self-esteem and depressive symptoms during late stage pregnancy and the postpartum period (postpartum depression), in women who experience increased gestational weight gain. It could therefore be beneficial to explore the overlap in activated brain regions involved with self-esteem and postpartum depression processing. If more is known about postpartum depression pathology, doctors can better prescribe medications and treatments for women experiencing PPD.

II. Abnormal Brain Regions Regarding Postpartum Depression

This section of the literature review will discuss functional magnetic resonance imaging (fMRI). This form of neuroimaging measures the amount of oxygen specific brain sections

receive. An area that receives more oxygen compared to its surroundings and its rest state activity is considered to be “active”. An activated brain region is generally related to higher functional processing.

From a neural perspective there are differences in activated brain regions in women with PPD compared to healthy controls (P. Kim, Strathearn, & Swain, 2016). Specifically, there is evidence of decreased activity in the right amygdala, orbital frontal cortex, inferior temporal gyrus, insula, and dorsal prefrontal cortex in those with PPD .

The amygdala is especially discussed in postpartum depression literature. A study conducted by Silverman et al., (2011) attempted to compare the fMRI’s of women with PPD and major depressive disorder (MDD), while specifically looking at amygdala function. They compared the fMRI’s of women with PPD 6-8 weeks post-delivery, and they showed that those with PPD failed to activate the right amygdala, compared to those with MDD.. This study in addition to the previous study, indicate that that reduced right amygdala activity is likely associated with PPD symptomology.

Fiorelli et al., (2015) completed a meta-analysis which, also supports the idea of reduced right amygdala activity in PPD. This study simply looked at compilation of studies, with the purpose of gathering all existing fMRI data regarding PPD. Their results found that women experiencing PPD differ from women experiencing MDD, in terms of reduced right amygdala activity.

In addition to these studies, Silverman et al., (2007) conducted another whole-brain fMRI on women with PPD and found decreased right amygdala activity along with decreased inferior temporal gyrus, insula, and cingulate gyrus activity. Moses-Kolko et al., 2010 also found decreased right amygdala activity in PPD women. The listed studies have all identified the association between reduced right amygdala function and PPD. For this reason, it is plausible to assume the right amygdala plays a crucial role in mediating PPD.

Under the assumption that the right amygdala is a main player in PPD, Chase et al., (2014) focused on resting state-functional connectivity in the default mode network (DMN) regions involved with social cognition. Functional connectivity can be defined as temporally related neuronal activity across 2 different brain regions (Honey et al., 2009). Results show that posterior cingulate cortex-right amygdala connectivity was significantly disrupted in PPD mothers compared to health mothers for low frequency neural activity. This study suggests that,

the posterior cingulate cortex activity may also be dampened during PPD processing. This would make sense as well, PCC is also known to mediate emotional regulation (Uchida et al., 2015)

Duan, Cosgrove , & Deligiannidis, (2017) finding's also support the previous study. They completed a meta-analysis to further uncover brain structure, function, and metabolism in PPD women and looked at PPD imaging techniques. Their results state that PPD is associated with changes in default modal network, central executive network, salience network. The default modal network consists of the medial prefrontal cortex and posterior cingulate cortex, further suggesting that the posterior cingulate cortex may be involved with PPD regulation. The central executive network consists of the dorsolateral prefrontal cortex, which may also be involved with PPD processing.

The inferior temporal gyrus may be involved in PPD processing in addition to the posterior cingulate cortex, and the insula. A resting-state fMRI study, Wang et al., (2011) found decreased temporal regional activity in mothers with PPD. More specifically, they found decreased inferior, superior, and middle temporal gyrus activity in women experiencing PPD. This study in addition to the study by Silverman et al., (2007), indicated that the inferior temporal gyrus may be a region of interest as well.

Lastly, a study conducted by Laurent et al., (2013) found a large number of cerebral regions displaying decreased activation in mothers with PPD. Among those regions, dorsal anterior cingulate cortex, orbito-frontal cortex, and insula were observed to have the greatest difference compared to healthy controls. This study in addition to Silverman et al., (2007) suggest that decreased insula activity may be linked to PPD symptomology.

The few studies that do examine fMRI data of women with PPD show some similarities: reduced right amygdala, PCC, inferior temporal gyrus, and insula activity. These regions (most of which are involved in some aspect of emotional regulation) also happen to overlap with the some of the brain structures involved with self-esteem regulation.

III. Activated Brain Regions Regarding Self-Esteem Regulation

Neuroimaging regarding self-esteem has been thoroughly researched and documented. However, a majority of the research focuses on self-esteem in psychologically troubled populations (such as anorexic patient, bipolar patients, etc.) There are only a small handful of

studies that looked into brain regions activated in self-esteem in healthy individuals. The studies that have been published, cite the association between specific brain regions and self-esteem regulation. Some of the main regions of interest (described below) include: the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), right amygdala, dorsolateral prefrontal cortex (dlPFC), medial prefrontal cortex (mPFC) and insula. These regions are recognized as the main regulators of self-esteem and self-monitoring, although they carry out other psychological functions as well (see Discussion for more detailed functions).

A study conducted by Hoefler et al., (2015) found that the dorsal anterior cingulate cortex (dACC) correlated positively with self-esteem, specifically the way one interprets other's perception of themselves. Eisenberg et al., (2011) further supported the association of ACC with self-esteem in their study. Their results found greater activity in dACC was associated with lower state self-esteem. Also participants who showed decrease in self-esteem from pre-scan to post-scan had greater medial prefrontal cortical activity. This study introduced how the prefrontal cortex may play a role in mediating self-esteem, while further supporting the involvement of the ACC.

In addition to ACC, different regions of the prefrontal cortex and PCC also appears to play a role in self-esteem processing. Hoefler et al., (2015) conducted another study which looked at specific individual differences in valanced self-referential processing (SRP). SRP is a method requiring participants to associate themselves with positive or negative trait. The results displayed greater ventral medial prefrontal cortex (vmPFC), ACC, and medial prefrontal cortex (dmPFC) activity in women who experienced positive/negative affective during SRP. There was a difference in blood-oxygen-level dependent imaging (BOLD) responses in the PCC and right amygdala regions. This study suggests that different regions of the prefrontal cortex are associated with self-perception of positive/negative traits, along with the right amygdala and PCC. The prefrontal cortex was also found to be associated with self-esteem regulation in a study conducted by Pan et al., (2016) Their results found that strengths of functional connectivity between left cuneus/lingual gyrus and right dlPFC and ACC are positively related to trait self-esteem. They conclude that that trait self-esteem is related to core regions in the default mode network (PCC) and social cognition network.

An fMRI study conducted by Van Schie et al., (2018) bolstered the idea that the PCC was involved in self-esteem regulation. More specifically, they found that higher self-esteem related

to increased PCC and precuneus activity. On the other hand, lower self-esteem was related to decreased medial prefrontal cortex, insula, ACC, and PCC activity. This study highlighted the importance of the PCC, ACC, and insula in self-esteem regulation.

Additionally, another study by Doerig et al., (2014) found that when participants were presented with self-critical material it activated regions involved with emotional processing, such as the anterior insula, hippocampus, and amygdala. This study along with the previous study mentioned, introduce the idea of the insula mediating self-esteem processing. More importantly, it displays the ties between self-esteem processing and emotional regulation.

The listed studies all highlight certain structures that are associated with the regulation of self-esteem. The ACC, PCC, right amygdala, and insula all appear to mediate self-esteem. The prefrontal cortex is split into mPFC and dPFC. The mPFC has been shown to be associated with individuals who regard themselves negatively, indicating low self-esteem, while the dPFC appears to be associated with individuals with high self-esteem (Hoefler et al., 2015). However, the dlPFC has also been shown to be associated with overall self-esteem regulation (Pan et al., 2016). The synchronization and conjunction of these regions, along with others not listed, all work to regulate self-esteem and self-evaluation processes.

IV. The Current Study: Hypothesis

The current study will integrate previous behavioral and neuroimaging research to further the current literature on the potential relationships between depressed mood states, body image/self-esteem, and postpartum depression. Previous behavioral research has identified the association between body dissatisfaction/low self-esteem and PPD in postpartum and late stage pregnant women, particularly in those who have experienced greater gestational weight gain. Separate neuroimaging studies have investigated the relationships between brain activity and self-esteem, and brain activity and PPD, however, the brain-self-esteem-PPD link has not yet been investigated in a single study. Based on published literature, we hypothesize that the right amygdala, PCC, and insula (which have shown less activity compared to healthy controls) will also be involved in self-esteem processing in healthy individuals. This is plausible considering all 3 of these regions are involved in emotional regulation (see Discussion), which is also associated with PPD and self-esteem processing, as previously stated (Doerig et al., 2014). A

meta-analysis can help us statistically determine if the specified regions are involved in PPD and self-esteem processing. This will shed more light on the PPD diagnosis and can allow physicians better treat mothers by having a greater understanding of the implications of PPD.

Methods

Multilevel kernel density analysis (MKDA) technique

MKDA is a coordinate-based program, which creates a map of all significant clusters across the brain by determining the activation probability of each voxel. Each voxel is a 2x2x2 area, in which tens of thousands to millions of neurons reside (number of neurons depends on area and density, etc.) (Wagner, Lindquist, and Kaplan, 2007). This specific program was used for the meta-analysis due to the multiple benefits it possesses, such as, assessing the quality of the study (fixed vs. random, sample size) and weighting contrasts accordingly (Hayes and Northoff, 2011). This prevents a study with multiple activation points from biasing the results (each study, and its related activations, counts as one independent sample of data) (Hayes and Northoff, 2011). Additionally, this program is able to assess contrasts in which one statistical map is contrasted or compared directly to another for similarities or differences. In an fMRI, a specific brain region is said to be "active" when it receives a greater supply of oxygen compared to the surrounding regions. MKDA gathers all of these activated regions listed in the primary studies, and averages the voxels across contrasts to determine the proportions of contrasts that activate a given voxel (Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009). The program then determines what proportion of activated voxels are greater than what is expected by chance by comparing the activated voxel in the observed map to a number of studies that activate that same voxel by chance (Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009). A density map is produced which is compared to Monte Carlo simulations to determine if the activated voxel passes a statistical threshold ($p <= 0.05$) and displays activations that exceed frequency produced by chance (Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009). If the voxel passes the statistical threshold it is produced in the final output map (Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009). The program will generally output voxel clusters, which are a group of

activated voxels located adjacent to one another, referred to in the present paper as, 'activated cluster', or 'activation cluster'.

Postpartum Depression fMRI Scans

Literature Search

In order to gather a dataset of coordinates for activated brain regions in women experiencing postpartum depression, multiple PubMed searches were conducted. The search explicitly looked for papers discussing functional magnetic resonance imaging (fMRI) scans of women with postpartum depression that were published between 2005 and 2017. The search included keywords such as "fMRI", "functional magnetic resonance imaging", "fMRI scans", "fMRI imaging", "postpartum depression", "antenatal depression", "peripartum depression", and "neuroimaging". Additionally, we searched the reference list of identified articles and other meta-analyses and were able to identify other primary resources for PPD, major depressive disorder, and self-esteem studies .

Inclusion and exclusion criteria

There are about 16 studies on humans including 321 participants on PubMed discussing postpartum depression and neuroimaging. Of the 16 studies, 10 papers were primary sources and did not employ a meta-analytical approach, and only 7 papers (74 participants) met the inclusion/exclusion criteria. This essentially means, all studies used in the current meta-analysis were all primary sources. Therefore, in order to ensure a minimum threshold of studies were selected in the current meta-analysis, the inclusion/exclusion criteria were broadened to capture the greatest number of papers. This meant we were not as stringent when looking at medication usage, similarity in form of PPD measurement, or absence of co-morbid disorders. This inclusion criteria was set in place to include more studies in an already limited sample. The broadened inclusion/exclusion criteria allowed us to collect the maximum number of studies while still filtering for high quality work that assessed PPD.

All subjects were women, aged between 18-45 years old, and right-handed. Recruited mothers were all between 3-18 months postpartum. All of the participants were clinically diagnosed as having postpartum depression, either by the Edinburgh Postnatal Depression Scale (a score of 10 or greater was determined the threshold for indicating postpartum depression; 6

studies), Hamilton Rating Scale for Depression (a score of 15 or greater was determined the threshold for indicating postpartum depression; 1 studies), or the Chinese Classification of Mental Disorders (1 study). The current study includes women who qualified as having major depressive disorder during the designated postpartum period as well. Women who were taking anti-depressants during the study were included because the respective studies indicated that dropping their data made no significant difference to the overall results of the study (Laurent & Ablow, 2012). Other than the small number of women taking anti-depressants, all other participants were not taking any major medications (this excludes pain killers). Participants had no history of neurological or head injuries, or any other relevant medical or psychiatric disorders (besides major depression disorder) in the past. However, a couple of the studies included women who had reported major depressive disorder prior to the perinatal period. One of the studies included participants who had co-morbid illnesses with their postpartum depression but stated that postpartum depression had to be the dominant current complaint (Laurent & Ablow, 2013). Mothers in the current study were not pregnant (and did not have multiple gestational pregnancy), and had no history of drug/alcohol abuse.

The main contrasts were used for the PPD study compilation, healthy > PPD. A variety of stimuli were used inside of the scanner, including both visual and auditory. Essentially, the patient would sit in the fMRI scanner and be shown a sample of images/made to listen to something, or perform an activity, such as picking a happier face, etc. Both of these stimuli were used to generally test brain activations which are unique to PPD. Examples of the visual stimuli include, negative and positive word probes (these were displayed on a screen). Visual stimuli also included faces (either their own child/unfamiliar child) bearing a certain emotion, positive/negative word probes. Auditory stimuli included own children's cry/unfamiliar children's cry. We explicitly looked at emotional responding compared to neutral responding by taking all the studies that showed emotional pictures and excluded fMRI scans that used neutral stimuli. Therefore, we only tested emotional responses in women with PPD and the main contrast tested was healthy > PPD.

Explicitly whole-brain analyses were included. Additionally, studies were excluded if they did not include identification of a coordinate system, coordinates, or incomplete statistical information. Each study was individually filtered to ensure the coordinate system was either Montreal Neurological Institute or Talairach. We focused on brain activation and excluded all

studies looking at functional connectivity. This exclusion criteria applied to all self-esteem and major depressive disorder studies as well. As a result, 7 papers (74 participants) related to PPD were found on PubMed that met all inclusion/exclusion criteria.

Self-Esteem fMRI scans

Literature Search

Multiple PubMed searches were conducted explicitly looking for papers discussing functional magnetic resonance imaging (fMRI) scans of activated brain regions/circuits, in adult men and women during activities that modulate self-esteem. All studies used similar search criteria and were conducted between 2010-2016, in addition to one study published in 2006 The search included keywords such as "fMRI", "functional magnetic resonance imaging", "fMRI scans", "neuroimaging", "self-esteem", "self-referential processing", and "trait self-esteem".

Inclusion and Exclusion Criteria

Due to the intention of the study, and for the purpose of relating postpartum depression (mainly studied in humans) to self-esteem, all studies included in this search were restricted to human subjects. While there are an abundance of studies exploring self-esteem, all of these studies look at self-esteem in individuals with an additional illness. For example, there are a host of studies looking at self-esteem in women with anorexia nervosa. For the current study, the scans of individuals with a psychiatric illness were excluded and the healthy control scans were used. As a result, there were a limited number of studies that used human subjects and looked solely at activated brain regions involved with self-esteem. Additionally, all participants were aged between 18-52 years and included males and females. All subjects were right-handed and had no history of psychiatric disorders (including substance-related disorders), medical disorders, head injury with loss of consciousness. No participants were currently on any psychoactive medication. Only studies discussing self-referential processing and self-esteem explicitly were used for the analysis. Papers looking at how the mind perceives the self (awareness of the self) were excluded due to tangential nature and lack of cohesiveness with the topic of study (Silvia & Phillips, 2004).

All of the studies contrasted self > other, and had participants look at some sort of visual stimuli. All visual stimuli were filtered to test self-esteem and consisted of either a written

personality trait, a picture of themselves/other people, a face (of themselves or others), written trait adjectives, or written self-referential statements. The pictures tested happy/sad/angry/neutral images, and the same valanced qualities applied to the word/written stimuli as well. A portion of the included studies also had participants complete self-esteem related tasks (such as answering a survey evaluating their level of self-esteem) during the fMRI scanning procedure. All forms of emotional visual stimuli were included in the meta-analysis. Therefore, we did not differentiate/test emotional contrasts such as happy > sad, etc. The only contrast we tested in the current meta-analysis was self > other. We did not include coordinates relative to behavioral correlations. As a result, 12 papers (392 participants) were found on PubMed that met all inclusion/exclusion criteria.

Major Depressive Disorder fMRI scans

Literature Search

A PubMed search was conducted looking for papers discussing functional magnetic resonance imaging (fMRI) scans of activated brain regions/circuits, in adult men and women with major depressive disorder. All studies were conducted between 2005-2017. The search included key words such as “MDD”, “major depressive disorder”, “fMRI”, “neuroimaging’, “functional magnetic resonance imaging”, “emotional processing”, and “depression”.

Inclusion and Exclusion Criteria

Major depressive disorder studies were included in the analysis to produce an activation map and function as a positive control by ensuring reliability of the current study. For this purpose, we filtered for studies testing humans to match the conditions of the original hypothesis (which tests only humans). Because major depressive disorder is an extensively co-morbid disorder, we selected a few studies (enough to match the PPD studies found) that exclusively looked at fMRI imaging in depressed individuals. Additionally, all participants were aged between 18-65, and included males and females. Subjects were right-handed and had no other psychiatric disorder (other than MDD). All studies solely looked at MDD processing and no other co-morbid illnesses.

All of the studies contrasted MDD > Healthy Control. Only visual stimuli were used, and all were filtered to test mood processing. The visual stimulus generally consisted of

positive/happy images vs. negative/sad images. A couple of studies required the participant to complete a negative/positive tasks in the scanner and would measure mood processing as such. These tasks included activities such as, ensuring the participant lose money in a game, giving the participant money during a game, and an emotional Stroop task. All emotional stimuli were included in the study. We included scans that tested with both positive and negative images. Therefore, the current study only aimed to test one contrast, MDD > healthy. We did not include coordinates relative to behavioral correlations. As a result, 10 papers were found on PubMed that met all inclusion/exclusion criteria.

In total 6 PPD, 12 self-esteem, and 10 MDD studies were included in the meta-analysis. All papers reported blood oxygen level dependent imaging (fMRI BOLD) activation results for functional magnetic resonance images. Included studies are summarized in Table 1.

Table 1: All included MDD, PPD, and Self-Esteem Studies. All studies displayed BOLD activation results from fMRI imaging. Each study's number of subjects (n) and category (PPD, MDD, or self-esteem) were reported.

Study	**Subjects (n)**	**Category**
(Silverman et al., 2007)	8	PPD
(Silverman et al., 2011)	20	PPD
(Wang, Wang, Liu, Ming, & Zhang, 2011)	10	PPD
(Laurent & Ablow, 2013)	11	PPD
(Laurent & Ablow, 2012)	11	PPD
(Moses-kolko et al., 2012)	14	PPD
(Hoefler, Athenstaedt, Corcoran, Ebner, & Ischebeck, 2015)	46	Self-esteem
(Frewen, Lundberg, Brimson-Théberge, & Théberge, 2013)	20	Self-esteem
(Lemogne et al., 2011)	45	Self-esteem
(Heatherton et al., 2006)	30	Self-esteem
(Yang, Xu, Chen, Shi, & Han, 2016)	29	Self-esteem
(Yang, Dedovic, Guan, Chen, & Qi, 2014)	25	Self-esteem
(Araujo, Kaplan, Damasio, & Damasio, 2015)	19	Self-esteem

(Pankow et al., 2016)	62	Self-esteem
(K. Kim & Johnson, 2013)	24	Self-esteem
(Doerig et al., 2013)	20	Self-esteem
(Miyamoto & Kikuchi, 2012)	26	Self-esteem
(van Schie, Chiu, Rombouts, Heiser, & Elzinga, 2018)	46	Self-esteem
(Victor et al., 2012)	22	MDD
(Fournier, Keener, Almeida, Kronhaus, & Phillips, 2013)	30	MDD
(Cerullo et al., 2014)	25	MDD
(Van Tol et al., 2012)	51	MDD
(Lawson et al., 2017)	25	MDD
(Mitterschiffthaler et al., 2008)	17	MDD
(Siegle, Thompson, Carter, Steinhauer, & Thase, 2007)	27	MDD
(Anand et al., 2005)	15	MDD
(Townsend et al., 2010)	15	MDD
(Dichter, Felder, & Smoski, 2009)	14	MDD

Data-Analysis

Using the MKDA program in MATLAB, coordinate-based maps were formed for brain regions activated in self-esteem, PPD, and MDD processing individually. Voxel size in the present study was 2 mm x 2 mm x 2 mm (i.e., 1 voxel is $8mm^3$) and cluster sizes were all greater than or equal to 10 voxels (>= $80mm^3$). For the main hypothesis, the self-esteem and PPD activation maps were compared to find overlapping regions of interest using the Monte Carlo simulation. This determined the threshold of significance with 5000 iterations, and a map that displays the overlap in activated regions in PPD and self-esteem processing was produced. We then identified all overlapping activated regions. Further information about MKDA and MATLAB can be found at (Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009). Analyses were performed in Matlab 2009a (Mathworks, Natick, MA, USA) using MKDA software created by Tor Wager.

Results

Individual Maps

Individual activation maps were created for PPD, MDD, and self-esteem processing. The MDD map shows significant activations in the frontal cortex, temporal cortex, parietal cortex, hippocampus, caudate nucleus, posterior cingulate cortex, ACC, and right insula (Figure 1A). There are a small number of clusters in the ventral temporal cortex as well. The PPD map shows fewer activation clusters when compared to the MDD, this is likely due to the smaller PPD sample size (only 6 studies). These clusters are located at the thalamus, and dorsal anterior cingulate cortex (dACC), and rostral anterior cingulate cortex (rACC), and insula in both cerebral hemispheres (Hochman, Vaidya, & Fellows, 2014). Large clusters were also observed in occipital cortex (Figure 1B). The self-esteem processing map displayed a wider spread of clusters beginning at the frontal cortex, spreading to the parietal cortex, and ending at the ventral occipital cortex. Major areas of activation included large portions of the ACC, posterior cingulate cortex, medial prefrontal cortex, and hippocampus (Figure 1C). Sub-clusters were not included in Table 2, 3, or 4.

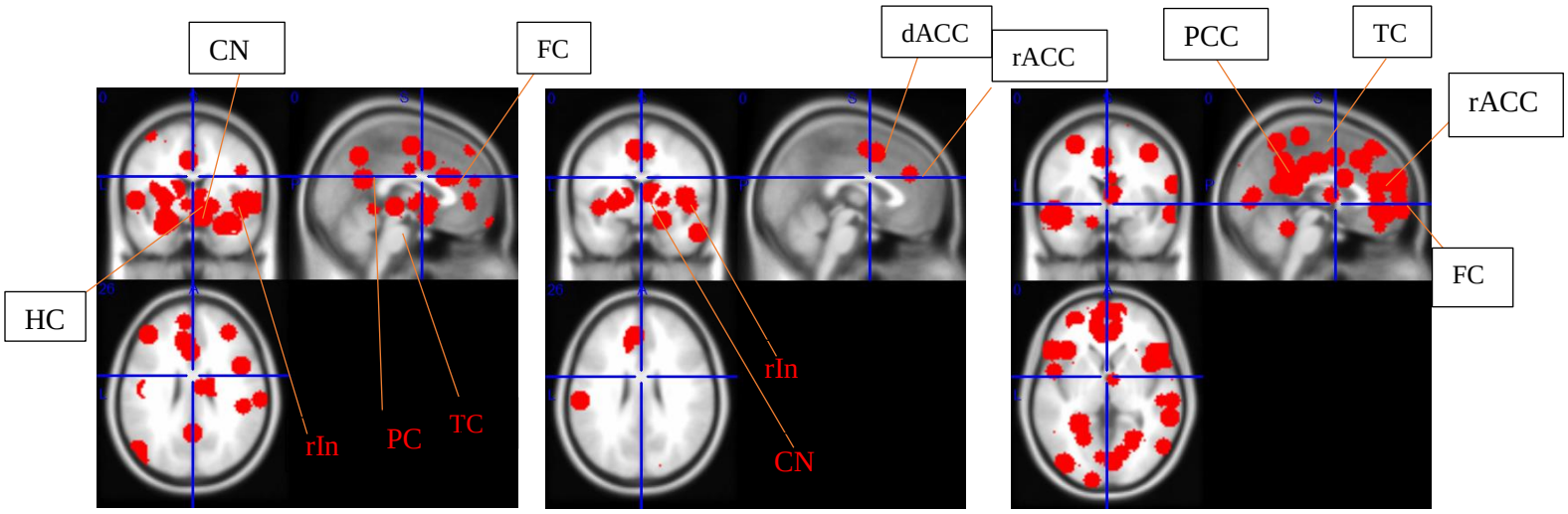

Figure 1A-C: Activation Maps for MDD, PPD, and Self-Esteem (left to right). Results of meta-analysis for human MDD, PPD, and self-esteem studies. Left most: Activation map for MDD studies with no contrasts. Middle: Activation map for PPD studies with no contrasts. Right

most: Activation map for self-esteem processing with no contrasts. Abbreviations: FC, frontal cortex; TC, temporal cortex, PC, parietal cortex; rIn, right insula; rACC, rostral anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; CN, caudate nucleus; HC, hippocampus. Red represents significant clusters. All results are family wise error rate whole brain corrected at $p<0.05$. Data is presented in Tables 2, 3, and 4.

Table 2: MDD network in humans – voxels clusters using Montreal Neurological Institute Coordinate System. Map available in Figure 1A

Cluster	**X**	**Y**	**Z**	**Number of voxels (within clusters >= 10 voxels)**
1	2	6	0	31650
2	38	-66	-10	511
3	-40	-60	-8	463
4	-54	-62	10	1638
5	64	-42	2	746
6	34	-90	2	498
7	44	-32	10	503
8	2	-58	34	1198
9	-46	-14	30	326
10	46	8	30	515
11	56	-28	32	863
12	34	40	32	509
13	4	44	50	758
14	-26	10	58	515
15	-38	-8	62	389

Table 3: PPD networks in humans- voxel clusters using Montreal Neurological Institute Coordinate System. Map available in Figure 1B.

Cluster	**X**	**Y**	**Z**	**Number of voxels (within clusters >= 10 voxels)**
1	54	-26	-28	390
2	54	4	-28	494
3	-18	38	-24	484
4	42	-62	-14	1024
5	16	4	-2	1401
6	12	-74	-8	515
7	-28	2	0	1514
8	44	2	2	892
9	54	-50	8	515
10	-58	12	8	469

11	18	-86	16	515
12	-58	-24	24	515
13	-8	36	26	678
14	-36	-48	42	479
15	-2	2	50	1226
16	-42	-18	62	478
17	-22	-28	64	514

Table 4: Self-esteem networks in humans – voxel clusters using Montreal Neurological Institute Coordinate System. Map available in Figure 1C.

Clusters	**X**	**Y**	**Z**	**Number of voxels (within clusters >= 10 voxels)**
1	-36	-68	-24	2072
2	26	-74	-30	824
3	6	-46	-24	515
4	-46	10	-12	5239
5	44	22	-8	3552
6	-16	-34	-20	515
7	-8	42	22	12125
8	-16	-10	-16	769
9	-60	-32	-12	841
10	60	-22	-8	1984
11	-26	-90	8	1647
12	-2	-46	28	9599
13	54	-68	6	476
14	4	2	16	996
15	-48	-62	26	2340
16	30	-78	32	1716
17	62	4	18	318
18	-24	-80	40	1249
19	50	-52	40	515
20	40	12	46	1004
21	44	-28	56	515
22	-30	-4	56	515
23	-36	-24	68	369
24	20	-10	72	369

Overlapping Activation Maps

PPD and Self-Esteem

Meta-analysis results indicate overlapping activated regions involved in PPD and self-esteem processing, while viewing emotional stimuli. Overlapping activated regions included, thalamus,

right and left insula, rostral anterior cingulate cortex, and dorsal anterior cingulate cortex (Hochman, Vaidya, & Fellows, 2014) (See Figure 2 for cluster-wise activation clusters).

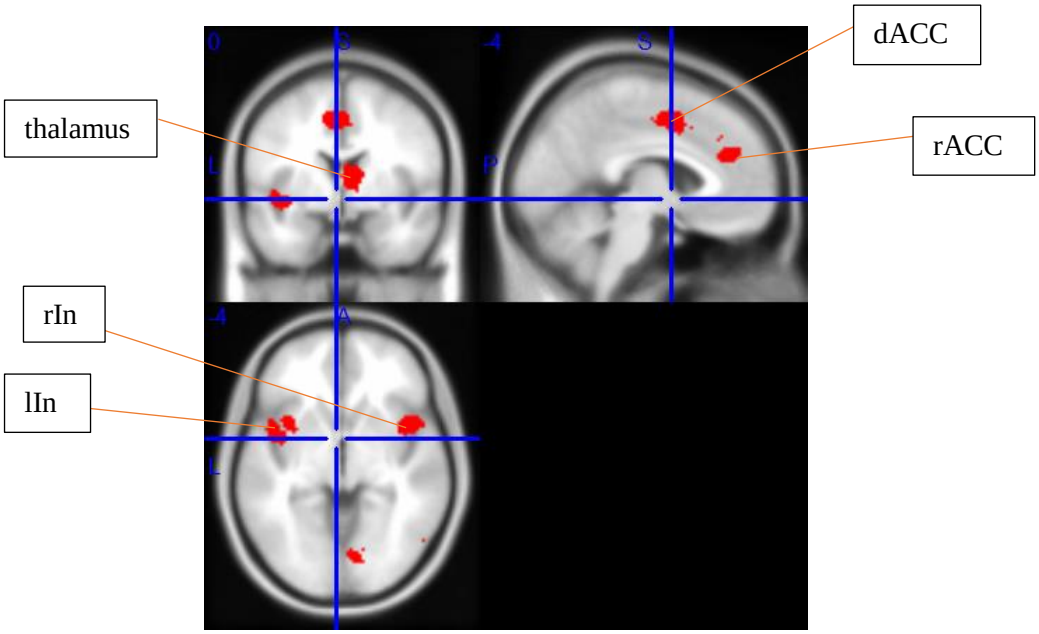

Figure 2: Overlap of Activated Regions Involved in PPD and Self-Esteem Processing. Results of meta-analysis for human PPD and self-esteem overlapping activation. Red represents significant clusters. All results are family wise error rate whole brain corrected at $p<0.05$. Abbreviations: rACC, rostral anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; rIn, right insula; lIN, left insula. Data coordinate points are presented in Table 5.

Table 5: Overlap of self-esteem and PPD activation network in humans – voxel clusters using Montreal Neurological Institute Coordinate System. Sub-clusters are reported. Map available in Figure 2.

Clusters	X	Y	Z	**Number of voxels (within clusters >= 10 voxels)**
1	52	10	-26	40
1a	50	12	-28	16
1b	54	10	-24	24
2	-14	40	-24	134
3	24	10	-14	21
4	-40	6	-6	321
4a	-42	6	-8	144

4b	-42	2	-4	92
4c	-36	8	-6	85
5	46	10	-2	289
5a	42	8	-4	123
5b	46	12	-4	87
5c	50	10	2	79
6	12	-76	-2	100
6a	8	-80	-4	30
6b	12	-74	-2	70
7	-22	-10	-8	14
8	58	-46	2	20
9	8	-2	10	286
9a	8	0	4	57
9b	6	-4	10	74
9c	12	-4	10	80
9d	6	2	14	75
10	-56	18	4	34
11	16	-80	10	26
12	26	-86	18	23
12a	26	-88	16	14
13	-4	38	26	180
13a	-4	40	24	93
13b	0	36	26	71
13c	-6	32	34	16
14	-44	-50	40	35
15	-4	0	46	344
15a	-4	4	46	199
15b	-4	-4	48	145
16	2	14	46	10
17	-38	-22	66	108
18	-28	-26	66	30

Discussion

The present study aimed to identify activated regions involved in both self-esteem and PPD processing (see Figure 2). An activation map of MDD patients was created to function as a positive control – in which the MKDA results of a few (n=10) MDD studies randomly sampled from the vast literature could be compared to more robust MDD meta-analysis (see Figure 1A). An overlapping activation map was created to find similar activated regions in both self-esteem and PPD processing, to test the current hypothesis (see Figure 2).

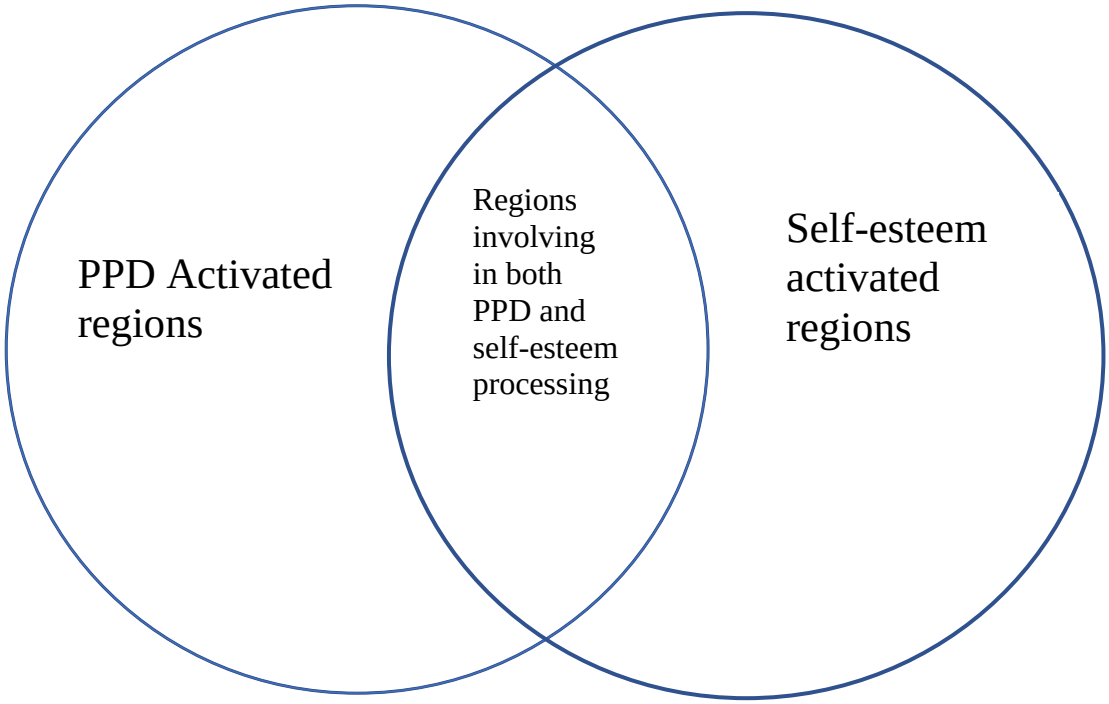

Figure 3: Overview of Methods Section. This study looks at the overlap of activated regions in self-esteem and PPD processing.

The original hypothesis identified the insula, PCC, and right amygdala as being involved in both self-esteem and PPD abnormal processing. Our results suggested that, from our indicated regions of interest stated in the hypothesis, only the insula appears to be involved in both self-esteem and PPD processing. However, we did find that the thalamus, dorsal anterior cingulate cortex, and rostral anterior cingulate cortex also appeared to be activated in the map that integrated both self-esteem and PPD processing (see Figure 2). The regions of interest (insula, rostral anterior cingulate cortex, and dorsal anterior cingulate cortex) will all be thoroughly discussed in terms of their anatomical structure, general function, and function in PPD and self-esteem processes. This study also had a couple of limitations regarding sample sizes and inclusions/exclusion criteria that will be addressed in more depth below.

Insula

The insula is a brain region consisting of various subgroups. It can be divided into anywhere between 2 to 13 distinct subdivisions (Uddin, Nomi, Hébert-Seropian, Ghaziri, & Boucher, 2017). This structure is deep within the lateral sulcus (see Figure 2) of the brain and can perform a large variety of functions, ranging from sensory and affective processing to higher level cognition (Uddin, Nomi, Hébert-Seropian, Ghaziri, & Boucher, 2017). The insula is one of the main areas of the brain that also allows us to determine whether we are inclined or repelled to a particular subject (Uddin, Nomi, Hébert-Seropian, Ghaziri, & Boucher, 2017). For example, the insula is also known to be involved with addictive tendencies and can partly create the extreme urges people with a dependency often feel(Uddin, Nomi, Hébert-Seropian, Ghaziri, & Boucher, 2017). In terms of affective processing, the insula is included in the limbic lobe and is known to have direct connections with the cingulate, amygdala, and orbitofrontal cortex (Suzuki, 2012). This makes sense because we also see the anterior cingulate cortex and the dorsal anterior cingulate cortex involved in both self-esteem and PPD processing, however, it is interesting that we do not see the amygdala involved in both processes as well (Figure 3). A study by Wonch et al., (2016) actually found decreased amygdala-right insular cortex connectivity in women with PPD. This indicates that there is less simultaneous activity in the amygdala and right insula which could indicate unusual abnormalities. Moreover, it has been shown that MDD presents decreased activation in the mesolimbic area ("Depression and Suicide", 2015). Because, PPD and MDD are known to have similar symptoms and similar activation deficits (Fiorelli et al., 2015), it is probable that the insula, which is also located within the mesolimbic area, is involved in PPD processing. Previous research has shown that the insula is known to contain the primary gustatory cortex (involved with taste perception), and therefore has been closely associated with the emotion of disgust (due to bad taste and smells) (Suzuki, 2012). These same feelings of disgust are what people with low body self-esteem report feeling towards either their body or social skills (Curtis, 2011). However, more recent research has focused on the insula and emotional processing as a whole (Suzuki, 2012). It has been shown that emotional processing is possible because the insula receives interoceptive inputs from the whole body and the connections to the prefrontal regions can provide contextual information for emotional processing as well (Suzuki, 2012). A couple of other studies have also shown that the anterior part of the insula may be involved with subjective feelings (Suzuki, 2012). Along with PPD,

emotions are associated with self-esteem as well (Doerig et al., 2014). A handful of studies have shown that people with low self-esteem tend to feel sadness, and anger more often than healthy controls (Sowislo & Orth, 2013). These feelings are not only a result of physical stimulus but also predictions and other cognitive factors (Sowislo & Orth, 2013). PPD is considered a mood disorder, which is intimately tied to emotions. If the insula is associated with emotional regulation it is probable that this structure is involved with PPD and self-esteem processing (Suzuki, 2012). Previous research has also shown that the insula may be involved with induced emotional processing as well, which means inducing certain emotions by placing a participant in a particular environment (Suzuki, 2012). For example, by showing a participant a crying/hungry baby, we are inducing emotions such as empathy and/or sadness. Previous research has made it clear the insula is partly responsible for emotional processing. This fits with the study's behavioral hypothesis, in seeing that, PPD is a mood disorder, and self-esteem is heavily associated with mood as well (Doerig et al., 2014). This structure was identified by Emmert et al., (2014)

Anterior Cingulate Cortex (rostral and ventral)

The results from the study support the involvement of the dorsal anterior cingulate cortex (dACC) and rostral anterior cingulate cortex (rACC) in PPD and self-esteem processing (see Figure 2 and 4). Many studies show the dACC as being part of the medial cingulate cortex as well (Vogt & Paxinos, 2012).

The ACC is a large structure and has a several functional subdivisions. It lies in the medial wall of each cerebral hemisphere, above, in front, below, and adjacent to the corpus callosum (Devinsky, Morrell, & Vogt, 1995). It also has direct connections to both the limbic system (emotional processing) and prefrontal cortex (Devinsky, Morrell, & Vogt, 1995).

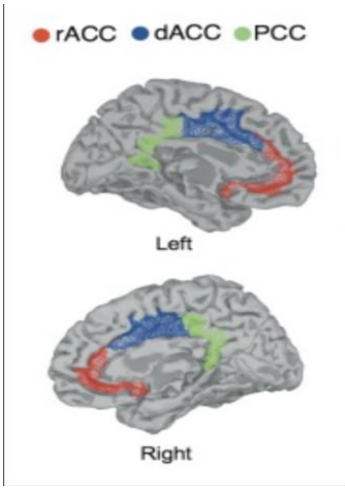

Figure 4: Structure and location of dACC, rACC, and PCC. Abbreviations: rACC, rostral anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; PCC, posterior cingulate cortex. (Hochman, Vaidya, & Fellows, 2014)

This region also has numerous projections to the motor systems, but because these projections originate from different parts of the ACC and contribute unevenly to brain functions, the ACC is divided into "affect" and "cognition" components (Devinsky, Morrell, & Vogt, 1995). The affect division contains areas 25. 33, an rostral area 24, with extensive connections to the amygdala and motor nuclei (Devinsky, Morrell, & Vogt, 1995). In terms of affect regulation, it is known to partially control uncomfortable emotions (Devinsky, Morrell, & Vogt, 1995). Previous research has also shown that ACC involvement with negative emotional stimulus activation (Etkin, Egner, & Kalisch, 2011). As mentioned above, this would coincide with the negative emotional aspect involved in low self-esteem and PPD regulation.

In addition to these emotional processes, the ACC is also involved in regulating autonomic and endocrine function, conditioned emotional learning, vocalizations of expressing internal states, assessing motivational content and deciding emotional state when viewing internal/external stimuli, and maternal-infant interactions. More importantly, previous studies have shown that a decrease in ACC activity is associated with behavioral disorders such as, akinetic mutism, diminished self-awareness, depression, reduced responses to pain, and unusual social behavior (Etkin, Egner, & Kalisch, 2011).

Based on previous literature showing that abnormal ACC activation is associated with depression, it is plausible that ACC response is involved in PPD (Laurent et al., 2013). However,

as mentioned in the introduction, many studies did not cite ACC, but rather the posterior cingulate cortex (PCC) as being involved with PPD processing (See Figure 4). PCC is involved in attention, and emotional regulation through direct connectivity with the amygdala (Uchida et al., 2015). We may have not seen PCC in our activation map due to the small number of PPD studies.

Because the ACC is also involved with emotional responses to positive/negative internal/external stimuli (Devinsky, Morrell, & Vogt, 1995), it is understandable that the emotional reaction to self-esteem tasks (as many of the studies in this meta-analysis used) induced activity in the ACC. In some of the studies involving self-esteem tasks, participants reported feeling angry or sad after being told they were "sloppy" or "boring" by a confederate. This is an example of how self-esteem is associated with emotional response to external stimuli. The ACC can be broken down into a couple of regions, two of these regions are, the dorsal anterior cingulate cortex (dACC), and the rostral anterior cingulate cortex (rACC). These were the specific ACC activated regions seen in the overlap map (see Figure 2)

Dorsal Anterior Cingulate Cortex

The dACC is a subdivision of the ACC located towards the end of the region (see Figure 2 and 4). Research available indicates that the dACC is involved with fear/anxiety management, monitoring/resolving conflict during information processing (Milad et al., 2007)(Wang et al., 2016). More recent research has also shown that the dACC may be involved higher order processing such as, managing cognitive dissonance (Wang et al., 2016). In general, a large portion of the research mentions the dACC is involved in conflict processing/resolution. This region was not predicted to be activated in both self-esteem processing or PPD processing, most likely because its main functions do not appear to be involved with PPD or self-esteem processing (Wang et al., 2016). However, it could be plausible this region was involved in both processes to manage negative feelings. In the case of PPD, the dACC may have been involved to manage conflicting emotions involved in PPD, or perhaps to manage any fear/anxiety. Similarly, the dACC could be involved in self-esteem processing to manage any conflicting emotions regarding one's image of themselves, or perhaps to even manage cognitive dissonance (Wang et al., 2016). More research needs to be done on dACC's function before we can fully understand why this region was shown to be involved in both processes.

Rostral Anterior Cingulate Cortex

The rostral anterior cingulate is the frontal area of the ACC (see Figure 2 and 4). It consists of Broadmann areas 24, 32, and 33 (Matsunaga et al., 2016). It is known for being involved with higher-level functions, such as attention division, reward processing, decision-making, impulse control, and emotion (Szekely, Silton, Heller, Miller, & Mohanty, 2016). In particular, a study by Matsunaga et al., (2016) found that rACC activation is associated with subjective happiness. It is plausible this region would be associated with PPD due to its influence on mood. Additionally, another study by Gyurak et al. (2012) found that activation in the rACC completely mediates the relationship between the interaction of self-esteem, attentional control, and emotional evaluation. The study also suggest that rACC is involved with emotional regulation. Based on previous literature it is acceptable that the rACC could be involved in both self-esteem and PPD processing as well. This result did not match our hypothesis, likely because the rACC is mostly known for attentional control (Gyurak, 2012), therefore most of the literature looks at rACC in relation to these cognitive domains. While it may have some hand in emotional regulation and self-esteem processing, it is probably not as heavily involved as the amygdala or other regions.

Thalamus

The thalamus is a critical structure in the brain and is located in the diencephalon (see Figure 2) (Martinez-Ferre & Martinez, 2012). The thalamus can be divided into the ventral thalamus, and dorsal thalamus (Herrero, Barcia, & Navarro, 2002). It is known as the relay center of the brain because all information processing is sent to the thalamus before being sent along to its final destination (Herrero, Barcia, & Navarro, 2002). It facilitates many cognitive domains such as, sensory and motor mechanisms, awareness, attention, memory, and language. It also serves a variety of functions. Some of its main functions include: relaying visual and auditory information, regulating information transmitted to cortical areas, cognition, and emotional processing (Herrero, Barcia, & Navarro, 2002). Specifically, the anterior thalamic nuclei has been implied to play a role in emotional processing with its connections to the orbitofrontal cortex and the ACC (Hirayama, 2015). A previous research study found that stimulation of the anterior thalamic nucleus increased reaction time due to threat-related emotional distractors (Sun et al., 2015). This implies that that thalamus plays a role in emotional

responses, and as mentioned above emotions are a key player in both self-esteem and PPD processing. The thalamus has also been known to mediate emotional expression and formation (Hirayama, 2015). This would concur with the fact that, there are multiple direct connections between the thalamus and the amygdala, ACC, and prefrontal orbitocortex (Hirayama, 2015). Recently, studies have come out that suggest that the pulvinar nucleus located in the posterior thalamus, mediates emotional visual processing through the through the colliculo-pulvino-amygdalar pathway (Hirayama, 2015). Lesions in the pulvinar nucleus have been associated with impaired reaction to visual threats (Hirayama, 2015). In general, disrupted activation of the thalamus is associated with a variety of mood disorder, including depression (Sun et al., 2015). Having said this, it is understandable that the thalamus is involved in PPD processing because PPD and MDD symptoms have similar activation differences compared to healthy controls (Fiorelli et al., 2015). Because it is activated in most emotional responses, the emotional responses caused by self-esteem modulating tasks could have activated the thalamus. Additionally, many of the tasks in the reported studies, involved participants to view pictures of crying children or other negative/sad pictures. This may have activated the pulvinar nuclei in the posterior thalamus, or it could have activated the thalamus because all visual stimuli processing passes through the thalamus as well (Herrero, Barcia, & Navarro, 2002). This structure was identified by Metzger, (2010).

MDD Map: Positive Control

A paper by (Sundermann, Olde lÃ¼tke Beverborg, & Pfleiderer, 2014) completed a meta-analysis of fMRI in depression. Their results found that there was hyperactivity/hyperconnectivity in cortical midline structures, such as, the posterior default modal network. This network includes precuneus, posterior cingulate cortices, subgenual anterior cingulate cortices, and medial frontal cortices. They also found activation in lateral prefrontal areas. Other areas of hyperactivity/hyperconnectivity included the left lateral parietal cortex, right hippocampus, and right cerebellum. The image produced in the current study replicated similar findings (see Figure 1A). The produced image found a number of clusters in the lateral parietal cortex as expected. We also observed activation in the medial frontal cortices and hippocampus, similar to the stated study. Our results also showed a small area of activation towards the top of the cerebellum. Additionally, we observe portions of the default modal

network activated in our results, further replicating the findings of the stated study (see Figure 1A). All sections of the posterior default modal network may not be found in our results because the current meta-analysis has a sample size of 10 studies. This small sample size drastically reduced the power of the study and may be the reason we do not see certain activations. This map served as a positive control and validates other results of this study.

Limitations/Future Research

The current meta-analysis posed a host of limitations, ranging from too few studies to indefinite self-esteem definitions scattered throughout the literature. Definitively, the number of studies is the most weighted limiting factor. After completing a thorough literature review, it was apparent that there is a severe gap looking at the neuroanatomical differences in postpartum depressed women. Taking the broad inclusion/exclusion criteria into consideration, there were still only 10-15 neuroimaging studies on postpartum women in total. This could be due to a number of reasons. New mothers are known to be sleep deprived and fatigued (Insana & Montgomery-Downs, 2012). This could contribute to their unwillingness to participate in a postpartum depression study. Additionally, hospitals tend to have regulations set in place to protect pregnant women/new mothers due to their vulnerable state. There is also the possibility that PPD is so understudied because male researchers do not choose to explore this topic (Lewis, Byers, Malard, & Dawson, 2010). There has also been research showing that PPD tends to be so heavily understudied because it is considered a transient depressive episode (similar to seasonal depression, but not as frequently (Lewis, Byers, Malard, & Dawson, 2010). Due to such few published PPD neuroimaging studies, the current study only found 6 studies (74 participants) that qualified for further analysis according to the inclusion/exclusion criteria (see Table 1). Subsequently, the results of this study should be taken with consideration. With such few studies, the produced activation map has less power (less statistical validity). This essentially means that the results of this meta-analysis should not be generalized to a larger population and may not be the most accurate representation of brain activity in postpartum depressed women. The individual PPD activation map had some large activation clusters that would likely not be present had there been more studies (see Table 3 and Figure 1B). We would expect to see more targeted and smaller activation clusters with higher statistical power. If the PPD map is not an accurate representation, then overlapping the self-esteem activation map on top of this inaccurate PPD

map would lead to inaccurate results. For example, a majority of the previous studies stated diminished amygdala activity in PPD processing (but still activity). However, the individual PPD map created from the 6 gathered studies did not report an activated amygdala. This could be from the insignificant number of studies analyzed for the results.

In addition to the limited PPD studies, finding self-esteem studies that coincided with the stringent inclusion/exclusion criteria proved to be difficult as well. Many of the studies looking at self-esteem, chose to sample a specific population. For example, there were a plethora of studies looking at self-esteem in depressed/anxious individuals. However, we chose not to include these studies as the psychiatric diagnosis could pose as a confounding variable. Therefore, attempting to find self-esteem processing in healthy individuals proved to be a difficult task. Additionally, self-esteem itself is hard to measure, as a result, there were a good number of studies that discussed self-referential processing, or the mind being aware of the self. Self-referential processing is the act of processing information about the self (Nejad, Fossati, & Lemogne, 2013). In order to narrow our scope we decided to exclude studies discussing mindful awareness of the self. However, the meta-analysis did include studies looking at self-referential processing. Specifically, we included studies with tasks that, assigned a positive/negative characteristic to participants and would likely affect their self-esteem. Most of the time this meant participants would read a characteristic that a stranger used to describe them. A drawback to this method could be that a measure of self-referential processing is not an accurate representation of self-esteem. This would decrease the validity of the study and not provide an accurate representation of activated brain regions involved in self-esteem processing. After filtering studies using the designated inclusion/exclusion criteria, we were left with 12 studies (392 participants) (see Table 1).

Lastly, because all forms of emotional stimuli were included in the sample collection. It was difficult determining whether the activated regions were activated due to the positive or negative stimuli. Essentially, because we did not test contrasts looking at type of emotional stimulus and included all positive/negative/neutral images as stimuli, we cannot determine if the structure was more activated as a result of viewing the positive or negative image. This leads to lack of specificity within the study. The results we have derived are more generalized and can be applied to overall emotional stimuli and not specific types of emotional stimuli. For example, we can say that the insula is activated in PPD when looking at emotional pictures (this can be a

smiling or crying baby), however, we cannot claim that the insula is activated only when viewing a crying baby. This limits the depth and detailed aspects of the study.

There is a great deal of work needed to be done in this field. More researchers need to be willing to look into PPD neuroimaging and its implications. Currently there is an imbalance in the number of behavioral studies vs. neuroanatomical studies. While behavioral studies are extremely useful and quite necessary for mood disorders which, mainly manifest as behaviors, neuroanatomical studies are equally as important and can provide valuable information as well. The implications of this research can be used to provide interventional treatment for PPD and perhaps lower PPD symptomology .

Additionally, it would be beneficial to test the association between PPD and gestational diabetes. Mothers with unchecked gestational diabetes tend to gain excessive gestational weight and struggle to lose it (Hedderson, Gunderson, and Ferrara, 2010). These mother are more at risk for developing lower self-esteem and possibly PPD as well (see Introduction). For this reason, it would be appropriate to test the association between these 2 variables. If we know a mother is likely to develop gestational diabetes due to her genetic history, we may be able to predict if she will also develop postpartum depression. Of course there are many other factors that go into postpartum depression, however an association between these 2 variables could help hundreds of providers take on a more preventative approach and know what to look for.

Conclusion

The current meta-analysis looked at the overlap of brain regions involved in both self-esteem and PPD processing. We hypothesized that the insula, PCC, and right amygdala would be involved in both processes, based on prior findings. Our results suggested that, in the present study, only the insula was involved in both processes (see Figure 2). However, the rACC, dACC, and thalamus were also found to be involved in both as well (see Figure 2). It was unexpected that the amygdala was not activated in both processes, however this could be due to the limited number of studies in the sample. More PPD neuroimaging studies need to be done in the future to gain a better depiction of what PPD accurately looks like in afflicted women. Understanding how much oxygen a specific brain region receives during a certain task can tell us a lot about how the brain functions and what may be causing the behavioral symptoms. When affected brain regions are determined, we can then properly analyze what medications to prescribe and possible

interventional methods to employ as well. Once we have more information on this diagnosis it will then be feasible to look for PPDs link to other diseases, such as gestational diabetes. PPD is an important diagnosis and can permanently impact a child's life, as well as their relationship with their mother. The time has come to start paying more attention to PPD neuroimaging.

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