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Increased Neural Response to Social Rejection in Major Depression

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* The work was carried out when Poornima Kumar was doing her PhD in the University of Aberdeen

ABSTRACT

Background: Being a part of community is critical for survival and individuals with major depressive disorder (MDD) have a greater sensitivity to interpersonal stress that makes them vulnerable to future episodes. Social rejection is a critical risk factor for depression and it is said to increase interpersonal stress and thereby impairing social functioning. It is therefore critical to understand the neural correlates of social rejection in MDD.

Methods: To this end, we scanned 15 medicated MDD and 17 healthy individuals during a modified cyberball passing game, where participants were exposed to increasing levels of social exclusion. Neural responses to increasing social exclusion were investigated and compared between groups.

Results: We showed that compared to controls, MDD individuals exhibited greater amygdala, insula and ventrolateral prefrontal cortex activation to increasing social exclusion and this correlated negatively with hedonic tone and self-esteem scores across all participants.

Conclusions: These preliminary results support the hypothesis that depression is associated with hyperactive response to social rejection. These findings highlight the importance of studying social interactions in depression, as they often lead to social withdrawal and isolation.

INTRODUCTION

Anhedonia is a core feature of major depressive disorder (MDD) characterized by diminished interest and pleasure in previously enjoyed activities. From a social perspective, anhedonic individuals often derive little enjoyment from interpersonal interaction, report social disinterest and reduced motivation to belong to a social group, and in addition, often report that such experiences are both stressful and anxiety-provoking (Kupferberg, Bicks, & Hasler, 2016). Social engagement is vital for survival of many species. When people are socially excluded or have a greater sensitivity to rejection, four fundamental needs are proposed to be affected: belonging, self-esteem, control and meaningful existence which are required for human survival and effective social functioning (Williams, Cheung, & Choi, 2000). The impairment of social functioning is proposed to be reliable indicator of depression (Cheng & Furnham, 2003; Hirschfeld et al., 2000) and these dysfunctions in social interactions were reported to persist even after three years of recovery from depressive symptoms (Rhebergen et al., 2010) and correlated with unemployment, disability and decreased work performance (Rizvi et al., 2015). Further, depressed individuals possess specific traits that increase the likelihood they will experience interpersonal stress and have subsequent depressive episodes (Hammen, 2005). In light of this work, it is critical to study social interactions in MDD, as these interpersonal difficulties could be due to altered neural responding during social interactions, specifically heightened perception of and reaction to social rejection (Zimmer-Gembeck, Nesdale, Webb, Khatibi, & Downey, 2016).

Social rejection is one of the strongest proximal risk factors for depression (Slavich, O'Donovan, Epel, & Kemeny, 2010) and there are indications that rejection prospectively predicts depression (Nolan, Flynn, & Garber, 2003) and internal life stressors, that further increases future depressive episodes (Liu, Kraines, Massing-Schaffer, & Alloy, 2014). A recent study reported that almost 50% of patients with MDD experience increased rejection sensitivity (Ehnvall et al., 2014). A recent study showed that compared to healthy individuals, MDD patients had elevated negative feelings for an extended period (Hsu et al., 2015) and increased distress (Jobst et al., 2017) after a rejection trial.

In the recent years, several fMRI studies have examined the neural correlates of social rejection in healthy participants. The most commonly utilized task is the cyberball passing game in adults that evaluates social exclusion and peer rejection task in adolescents. These studies have reported that social rejection network encompasses dorsal anterior cingulate cortex, medial

prefrontal cortex (including subgenual cortex), insula, amygdala, ventrolateral prefrontal cortex [VLPFC; (Cacioppo et al., 2013; Eisenberger, Lieberman, & Williams, 2003; Kawamoto, Ura, Nittono, & Osipowicz, 2015; Premkumar, 2012; Sebastian et al., 2011; Silk et al., 2014). Although no studies have investigated social rejection in MDD adults, studies in MDD and anxious adolescents have reported increased amygdala and insula activation in response to social rejection (Lau et al., 2012; Silk et al., 2014). Another region that has been critically implicated during social rejection mainly in adolescents is the subgenual cingulate. Increased sgACC neural activation has been reported to experiences of peer rejection and this was found to be correlated with at-the-moment self-reported distress (Masten et al., 2009), and depressive symptoms during the following year (Masten et al., 2011). To this end, we investigated neural responses to social rejection (by measuring social exclusion) in MDD using fMRI and a modified version of the 'cyberball' paradigm. Consistent with the adolescent literature (Lau et al., 2012; Silk et al., 2014), we hypothesized that MDD participants will have greater activation in the amygdala, insula and subgenual cingulate to social exclusion than healthy controls.

METHODS

Participants

The study was approved by the local ethics committee and all subjects provided written informed consent. Fifteen MDD and 17 healthy individuals (HC) matched for age, gender and verbal IQ (measured by National Adult Reading Test; Nelson and Willison, 1991) participated in this study.

The patients were all outpatients referred by consultant psychiatrists from the Royal Cornhill Hospital, Aberdeen, Scotland and diagnosed with a DSM IV diagnosis of (unipolar) MDD without comorbidity (except generalized anxiety disorder). A detailed clinical assessment consisting of a case note review, discussion with the patients' clinicians and a semi-structured psychiatric interview was carried out on all patients by one of the authors (J.D.S.), an experienced consultant psychiatrist. A Hamilton-21 depression rating (Hamilton, 1960) was obtained as a measure of MDD illness severity a few days before scanning by J.D.S. All patients had a duration of symptomatic illness >3 months despite continuous antidepressant treatment and medications were stable for 1 month before scanning. Patient medications as total dose per day were: escitalopram 15 mg, imipramine 200 mg, phenelzine 45-90 mg, trazodone 300 mg,

mirtazapine 30-60 mg, venlafaxine 150-225 mg, amitriptyline 200 mg, lithium carbonate 600-800 mg (as antidepressant augmentation), citalopram 20 mg, fluoxetine 40 mg and sertraline 25-150 mg. Healthy controls were recruited from the community.

Subject exclusion criteria were any current or history of DSM IV Axis I or II diagnosis (except depression and anxiety in MDD group) including personality disorder, a history of substance or alcohol misuse, structural brain abnormality, neurological disorder, use of non-antidepressant medication which might alter brain metabolism (in HC) and ECT within the last few months. Subjects with claustrophobia and fMRI contradictions were excluded. In addition, all participants completed the Beck Depression Inventory [BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)], Snaith-Hamilton pleasure scale (Snaith et al., 1995; a measure of hedonic tone), Spielberger trait anxiety (Spielberger, Gorsuch, & Lushene, 1970) and Rosenberg Self Esteem Scale (Rosenberg, 1965) on the morning of scanning. Demographics are listed in table 1.

Social interaction paradigm

Participants were scanned while they played a ball passing game [adapted from (Eisenberger et al., 2003) and successfully used in (Gradin et al., 2012)]. During the game, participants believed that they would be playing with two other people (represented by animated cartoons) present in adjacent rooms connected via the computer network. In reality, however, the ball passing was programmed such that each participant received the identical number of inclusion and exclusion trials. Subjects were instructed to press either of two buttons to pass the ball to one of the cartoon figures. In turn, each cartoon figure either passed the ball to the subject or passed it to the other cartoon figure. Throughout the task, the extent to which the subject was excluded in the game (ball not being passed to the participant) was systematically varied from 0% (ball equally shared between all three players) to 100% (ball only passed between the two cartoon figures) in steps of 25% after every block. Specifically, the task consisted of 17 blocks with 12 trials each with the following percentage of exclusion: 0, 25, 50, 75, 100, 75, 50, 25, 0, 25, 50, 75, 100, 75, 50, 25, and 0. To increase the impression that the cartoons represented real people making decisions, the time that the cartoon figures took to pass the ball was randomly varied between 800 and 3000 milliseconds. Participants had a short practice session before playing the task in the scanner. Participants were instructed to throw the ball to one of the other people once they received it and were not told in advance about the different levels of exclusion

that might occur throughout the game (Williams et al., 2000). The total task duration was ~10 minutes.

Social Ratings

Following previous work, a structured set of questions on a scale of 0 (not at all) to 10 (very much) were asked immediately after scanning to assess the subjects' emotional response to varying levels of inclusion during the game (Williams et al., 2000): (a) 'belongingness' was rated by "How much do you feel belonged to the group?", (b) 'inclusiveness' by "Did you feel you were ignored by the other participants?", (c) 'self-esteem' by ''To what extent do you think the other participants value you as a person?''. Two sample t-tests were used to test for hypothesized between-group differences.

Image Acquisition & Processing

A 1.5 Tesla GE scanner was used to acquire 244 gradient echo T2* weighted echo-planar images (TR = 2.5s; TE = 30ms; field of view = 240mm; voxel dimensions 3.75 x 3.75 x 5 acquired as 35 axial slices). In addition, a T1 structural scan was acquired (TR = 20ms, TE = 6ms, flip angle 35°, 124 contiguous 1.6mm axial slices of 256×256 voxels with an in-plane resolution of 0.938mm^2).

Functional MRI data was processed using FEAT (FMRI Expert Analysis Tool) version 6.0, part of FSL 5.0.6 (FMRIB's Software Library, http://fsl.fmrib.ox.ac.uk/fsl/). Pre-processing included: Motion Correction using FSL's Linear Image Registration Tool (Jenkinson, Bannister, Brady, & Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 5.0mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=60s) and pre-whitening to remove temporal autocorrelation (Woolrich, Ripley, Brady, & Smith, 2001). FSL's Linear Image Registration Tool [FLIRT; (Jenkinson et al., 2002)] was used to register functional images to 2mm Montreal Neurological Institute (MNI) standard space.

A block design with separate regressors for each percentage of social exclusion was constructed. Each event was modelled using a gamma function and constructed as a haemodynamic response function convolved with the block onset times. Temporal derivatives were included as covariates of no interest to increase statistical sensitivity. The six realignment

parameters were added as covariates of no interest to allow for residual movement artefacts not removed by the pre-processing. Linear contrasts were built to investigate the brain regions that activated as a degree of exclusion and beta weights from this contrast were taken to the group level to investigate within- and between-group differences. All analyses were performed at the group level using mixed-effects analyses. Z statistic images were thresholded using clusters determined by Z=2.0 and a family-wise corrected cluster significance of $p < 0.05$. Beta weights from linear exclusion contrast and individual exclusion blocks were extracted to conduct correlation analyses with anhedonia and self-esteem and explore the increasing effects of exclusion between groups using t-tests respectively.

RESULTS

Behavioral Results

As expected, patients (MDD) scored more highly than healthy volunteers (HC) on the BDI (HC: 3.35 ± 2.87; MDD: 22.93 ± 8.22, $p < 0.001$) and low on the Snailth-Hamilton anhedonia scale (HC: 51.00 ± 4.05; MDD: 35 ± 6.76, $p < 0.001$; indicating low hedonic tone in MDD group). The mean HAM-D score for patients was 23.2 ± 4.31. No differences in button presses (HC: 37.41 ± 4.08; MDD: 39.40 ± 7.10) or mean reaction times (HC: 2.77 ± 0.45; MDD: 2.72 ± 0.63) were observed between patient and control groups.

Social Ratings

No significant group differences were present for self-ratings of 'belongingness', 'inclusiveness' and 'self-esteem' all ($p > 0.1$, Table 2). This indicates that both groups were engaged in the task and perceived the social interaction paradigm in the same manner.

Imaging Results – Whole brain analyses

Within-group Analyses: Replicating previous work (Sebastian et al., 2011), healthy controls showed a significant increase in the medial frontal cortex with increasing social exclusion ($p<0.05$ FWE corrected, Fig 1 and voxel coordinates listed in Table 3). In contrast, MDD participants revealed no significant brain activations with increasing degree of social exclusion.

Between-group Analyses: Two sample t-tests showed that MDD patients exhibited increased neural responses in two clusters: Cluster 1 - encompassing right amygdala and insula; Cluster 2 - left VLPFC, to increasing social exclusion compared to controls ($p<0.05$ FWE corrected, Fig 2).

To explore if this group difference is driven by specific percentage of exclusion condition, we extracted parameter estimates from these functional ROIs. To separately evaluate the amygdala and insula, this cluster was separated into anatomically constrained functional ROIs by multiplying the right amygdala/insular clusters that showed the between-group differences with the anatomical ROIs defined by the Harvard-Oxford Atlas. Post-hoc analyses using SPSS revealed that this between-group difference was mainly driven by an increased neural response in the amygdala during 75% and 100% exclusion blocks and only during 100% block in the insula and VLPFC, Fig 2).

Exploratory post-hoc Correlations

Hedonic tone (as measured by Snaith Hamilton Inventory) correlated negatively with neural responses to increasing social exclusion in the amygdala ($r = -0.47$, $p = 0.007$), insula ($r = -0.41$, $p = 0.019$) and VLPFC ($r = -0.38$, $p = 0.032$) across all participants < 0.05; Fig 3).

Similarly, self-esteem as measured by Rosenberg self-esteem scale, correlated negatively with neural responses to increasing social exclusion in the amygdala ($r = -0.41$, $p = 0.02$), insula ($r = -0.47$, $p = 0.006$) and VLPFC ($r = -0.42$, $p = 0.019$) across all participants < 0.05; Fig 3).

DISCUSSION

The goal of the study was to investigate neural correlates of social exclusion in healthy and MDD individuals. Replicating previous work, healthy controls exhibited increased mPFC activation to increasing social exclusion (Sebastian et al., 2011). Between-group analyses revealed significant differences in neural activation to social exclusion. Specifically, MDD patients showed an increase, whereas healthy controls showed a decrease in neural activation in the amygdala, insula and VLPFC to increasing social exclusion. These results were significant even after controlling for trait anxiety. Interestingly, this neural response to exclusion in the insula, amygdala, and VLPFC correlated negatively with hedonic tone and self-esteem scores across all participants.

The insula is implicated in both affective and social functioning and acts as an integration to both external and internally focused states. As part of the salience network (Seeley et al., 2007), it is involved in processing both negative and positive emotions, and negative affective states such as disgust, aversive stimuli and social rejection. Supporting our findings, depressed

(Silk et al., 2014) and anxious youth (Lau et al., 2012) exhibited increased insular activity to social rejection during a slightly varied cyberball task. Our findings of increased insula activation with increasing social exclusion in MDD might suggest that these individuals experienced rejection trials as more salient and aversive than healthy controls. Supporting this, a recent study showed that during the cyberball game, individuals who showed greater activity in the insula reported greater feelings of social distress in response to social exclusion (Masten et al., 2009).

We found that amygdala activation increased in MDD individuals, but decreased in healthy controls, in response to increasing social exclusion. Previous studies have shown MDD patients to exhibit hyperactivation in the amygdala to negative emotional and threatening stimuli (Harmer & Cowen, 2013). Being socially ostracized leads to significant discomfort, and individuals fear exclusion and rejection. It is possible that healthy controls in the study were able to better regulate their fears than MDD individuals. Consistent with our findings, studies have reported hyperactivation in the amygdala to peer rejection in depressed and anxious youths (Lau et al., 2012; Silk et al., 2014). Amygdala response to social rejection in healthy (Hsu et al., 2013) and depressed individuals (Hsu et al., 2015) is thought to be regulated by endogeneous opioids and the μ-opioid receptor (MOR), which is involved in alleviating physical and emotional pain, including the effects of social rejection (Kupferberg et al., 2016). MOR activation in the amygdala to social rejection might act as a protective mechanism and reduce the impact of the stressors, as a greater magnitude of MOR activation in the amygdala has been reported in individuals with a higher predisposition to resiliency during social rejection (Hsu et al., 2013). In contrast, MOR deactivated the amygdala of MDD individuals during social rejection and this may contribute to BOLD hyperactivity in this region to social rejection as observed in this study (Hsu et al., 2015). Further supporting this, a polymorphism in the MOR gene has been recently found to influence neural and psychological responses to rejection, likely by affecting opioid receptor expression and signalling efficiency (Slavich et al., 2010). Our results remained significant after controlling for anxiety which suggests that increased amygdala activation to increasing social exclusion could be a potential biomarker for depression, consistent with other proposals for amygdala hyperactivity to negative stimuli being a potential biomarker for MDD (Harmer & Cowen, 2013).

Previous studies in healthy participants have reported effects of exclusion in the VLPFC and associated this with emotional regulation of distress (Eisenberger et al., 2003; Sebastian et

al., 2011). However, in our study, we observed an increase in the VLPFC activation with increasing social exclusion only in MDD, suggesting a compensatory mechanism in patients during social exclusion, as groups did not differ in subjective reports of distress caused by exclusion during the task.

Contrary to prior studies in peer rejection, we did not the find subgenual cingulate (sgACC) to be involved during increasing levels of social exclusion. Subgenual cingulate has been shown to be more active when socially rejected vs accepted in adolescents and this correlated with self-reported distress (Masten et al., 2009) and predicted depressive symptoms during the following year (Masten et al., 2011). This is consistent with patterns of increased baseline sgACC activity observed in adults with depression (Keedwell et al., 2009). Our negative finding could be due to the fact that our analyses were focused on probing regions that increased in activation with increasing levels of social exclusion and it is possible that the underlying baseline sgACC activity was overall higher in MDD irrespective of changing levels of exclusion. However, this interpretation should be regarded with caution and further investigation is needed. It is important to note that we did not find any significant brain region that increased with increasing degree of exclusion in MDD patients. It is possible that this might be due to patients experiencing both low and high levels of exclusion similarly. However, in the amygdala, insula and VLPFC, MDD participants do show a linear increase to exclusion.

Interestingly, neural response to increasing social exclusion across participants correlated with hedonic tone and self-esteem, suggesting that participants with higher anhedonia and lower self-esteem were associated with increased responses to increasing social exclusion. Several studies have reported that individual's trait self-esteem predicts their affective response to social exclusion (Kashdan et al., 2014; Onoda et al., 2010; Somerville, Jones, & Casey, 2010). According to sociometer theory, trait self-esteem is a reliable predictor on individuals' past experiences of being rejected and their perception of future interactions (Leary, Terdal, Tambor, & Downs, 1995; Onoda et al., 2010). Because people with low self-esteem perceive that others tend to reject and exclude them, experiences of social rejection should produce greater activation in regions including the amygdala and insula that are commonly associated with the distress of social rejection (Leary et al., 1995).

Anhedonia is suggested to be an endophenotype of depression and it is often associated with dysfunctional reward system in depression. However, in our study, anhedonia measure,

which includes measures on social anhedonia, predicted the neural response to social exclusion, suggesting that anhedonia might explain positive and negative, social and non-social symptoms of depression.

Our findings suggest that these abnormal neural responses to social exclusion could potentially explain the heightened rejection commonly reported in MDD patients (Ehnvall et al., 2014; Zimmer-Gembeck et al., 2016). One study recently reported that individuals with chronic depression react to social exclusion during the cyberball game with pronounced negative emotions and reduction in plasma oxytocin levels. One of the functions of oxytocin is to strengthen social bonding (Cochran, Fallon, Hill, & Frazier, 2013), suggesting that a reduction of oxytocin to social exclusion might be one of the contributing factors for the interpersonal dysfunction and difficulty in coping with aversive social cues (Jobst et al., 2017) often reported in depression. These findings suggest that therapeutic interventions using oxytocin targeting social impairments in depression might be a potential future area of investigation (Cochran et al., 2013).

Several limitations should be acknowledged. First, the sample size was small, hence results need to be interpreted with caution and it is important to replicate findings using larger samples. Second, patients were receiving antidepressant medication at the time of the study and results may be confounded by medication status. Third, when a correction for multiple correlations were applied using method described in (Sankoh et al., 1997), the correlations with anhedonia and self-esteem became weaker, but still within the trend level, again stressing the limitation of sample size. However, it is important to note that the correlation coefficients which represent the effect size were in the range of 0.36 – 0.48, implying a moderate effect size.

To our knowledge, this is the first study exploring neural correlates to increasing social exclusion in depressed individuals. Compared to healthy controls, MDD participants exhibited increased insula, amygdala and VLPFC activation to increasing social exclusion, suggesting a potential mechanism for rejection sensitivity in depression. This highlights the importance of studying social interactions in depression, as negative effects of social exclusion often lead to social withdrawal and isolation.

Figure Legend:

Figure 1: Whole brain Results: Medial prefrontal cortex (mPFC) that increased in activation to increasing social exclusion in healthy controls [cluster size = 764; peak voxel (12, 64, -18), z = 3.35]. Clusters are significant at Family-wise Error (FWE) $p < 0.05$.

Figure 2: Brain regions significantly different between MDD and healthy controls at whole brain Family-wise Error (FWE) $p < 0.05$ correction. **A.** Right Amygdala (24, -2, -14; Z = 3.02); **B.** Right Insula (38, 2, -18; Z = 3.33); **C.** Left VLPFC (-58, 14, 18; Z = 3.43). * indicates $p < 0.05$, ‡ indicates $p = < 0.01$. Error bars indicate standard error.

Figure 3: Correlation between neural response in the right amygdala (A & B), insula (C & D) and VLPFC (E & F) during increasing social exclusion and clinical severity symptoms (Hedonic Tone; Rosenberg Self-Esteem) across all subjects.

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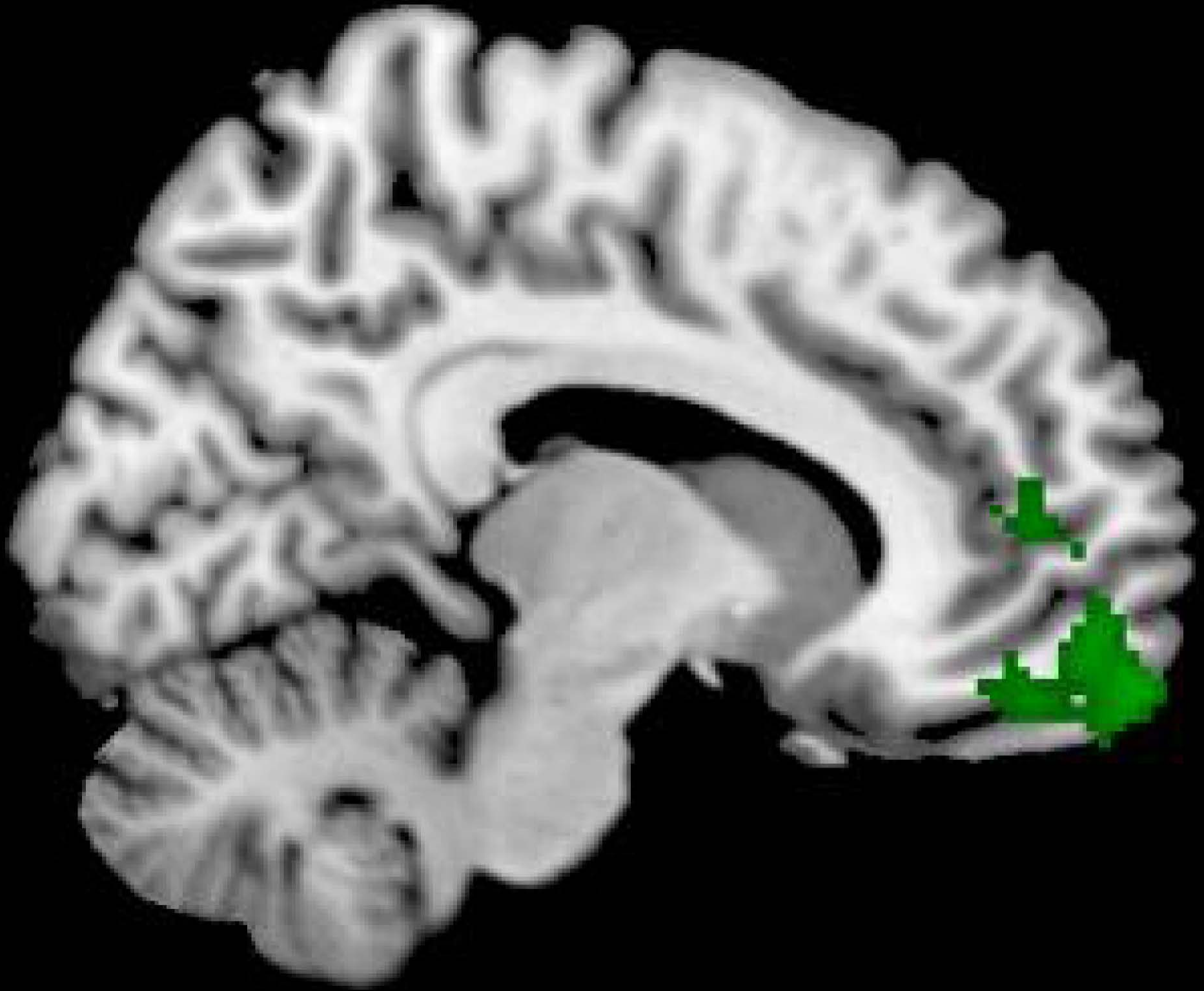

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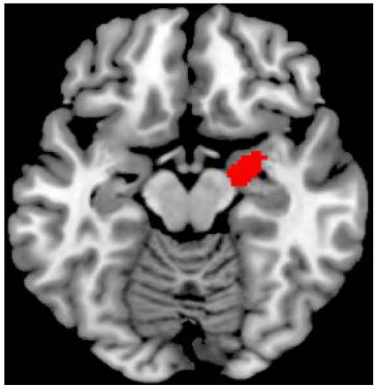

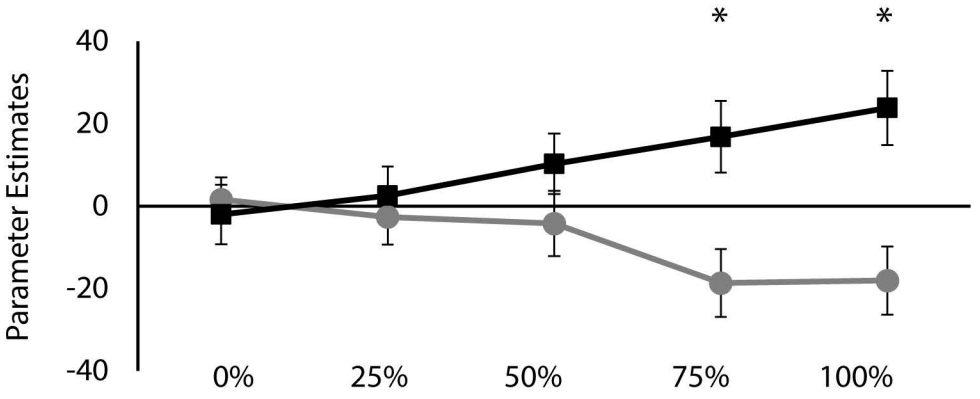

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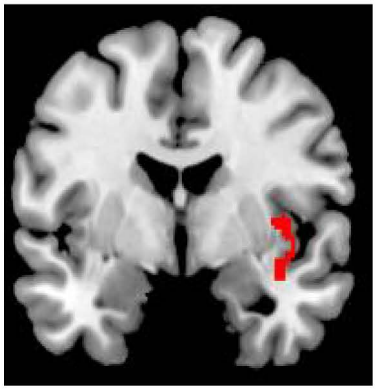

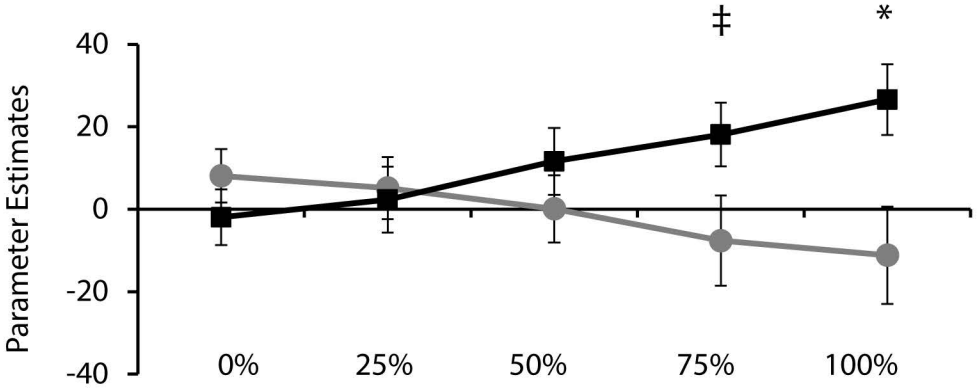

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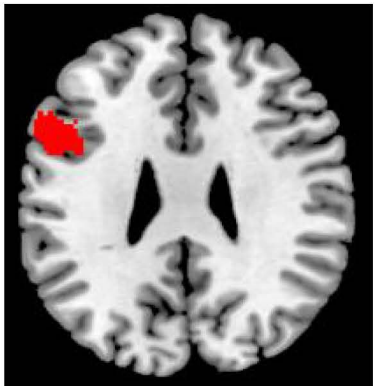

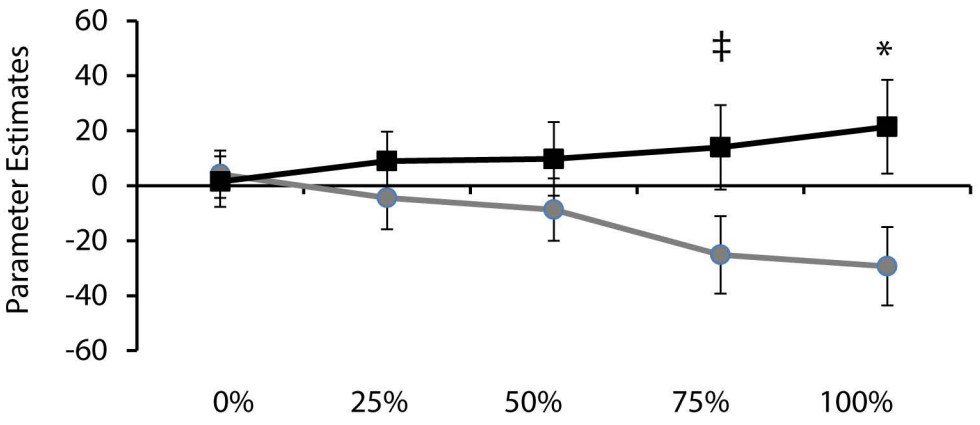

MDD Controls

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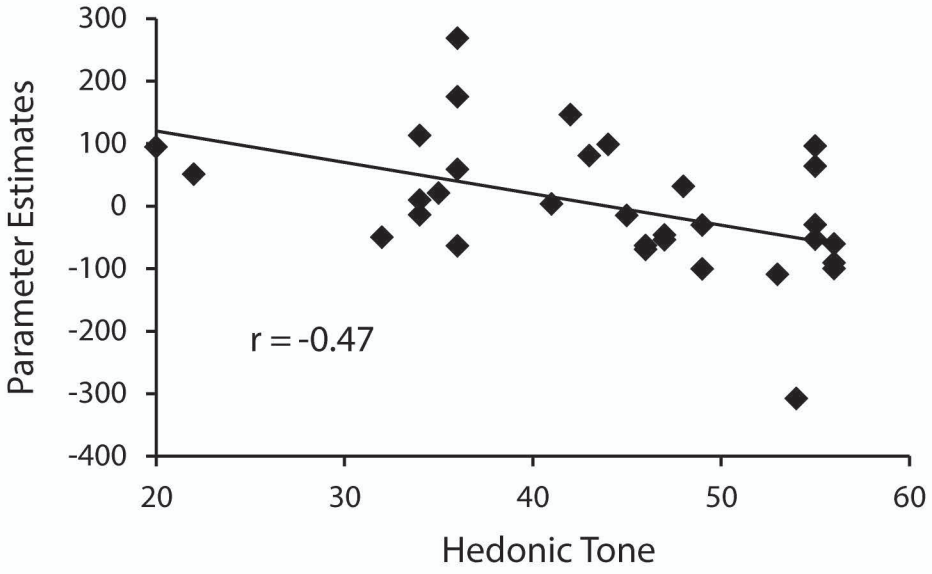

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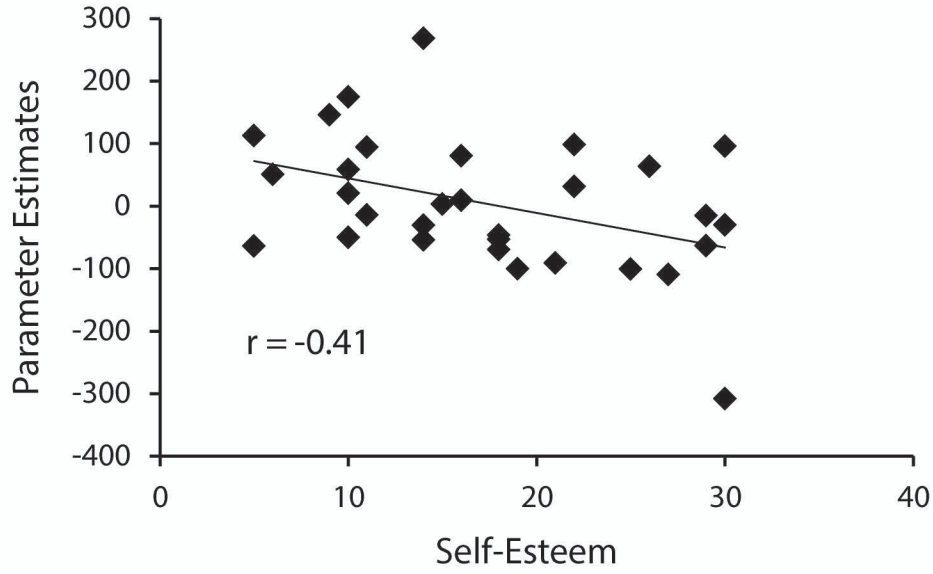
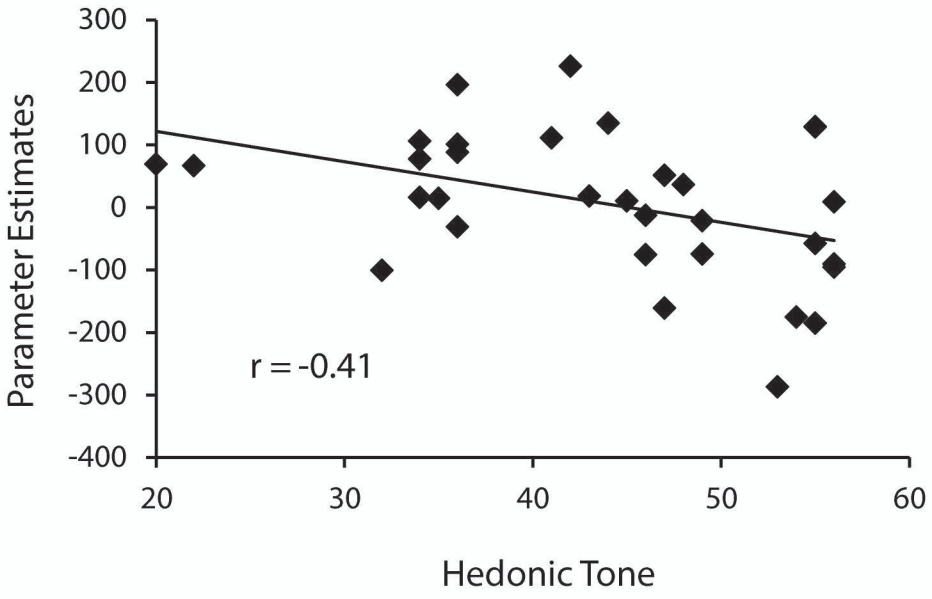
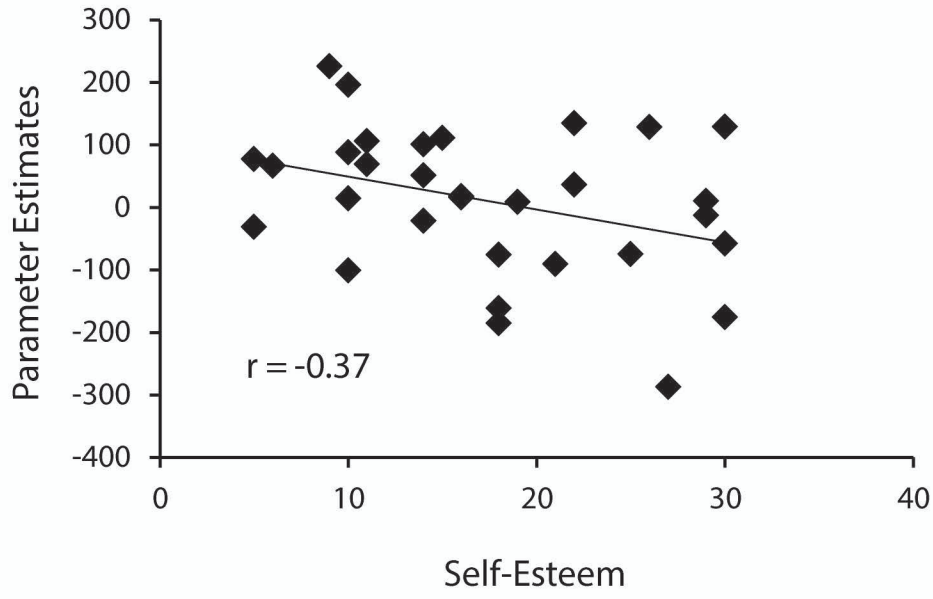


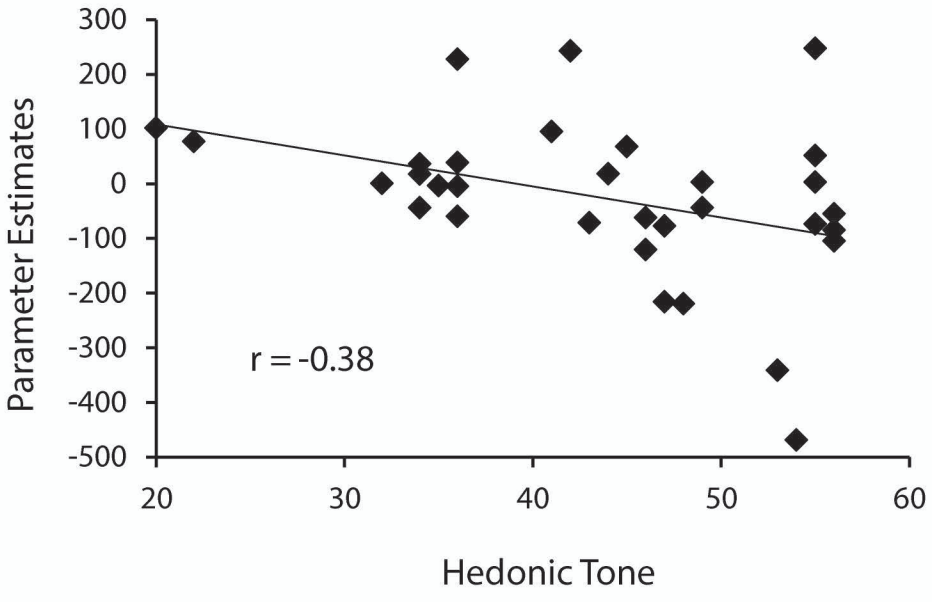
C. Insular Cortex



D. Insular Cortex



E. VLPFC



F. VLPFC