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Source Estimation of the Reward Positivity and Related Resting State Network Activity in Major Depressive Disorder

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Abstract

Anhedonia is a complex symptom of Major Depressive Disorder (MDD) that presents itself through multiple behavioral phenotypes of diminished reward processing. In order to better understand this deficit, we aim to look at a marker of reward that is sensitive to information content and valence, the Reward Positivity (RewP). The source of this signal is, however, up for debate. This study used concurrent EEG and MEG to establish the source of the RewP as a distributed network involving ventromedial prefrontal cortex (vmPFC), anterior midcingulate cortex (aMCC), and insulae. Additionally, only vmPFC showed a deficit in MDD. fMRI resting state functional connectivity analysis of these regions showed that these areas are all highly correlated with each other and with the nucleus accumbens (NAcc), a known, subcortical center of reward processing. Group comparisons of functional connectivity showed no differences between the MEG-derived regions and NAcc. Functional connectivity between vmPFC and aMCC was found to anticorrelate with MASQ – General Depression scores within the MDD+ group, but not MASQ – Anhedonia scores. These findings suggest that while vmPFC activation in response to reward may be diminished in MDD, the resting state network involved remains largely intact, perhaps with the exception of those with extreme symptom severity.

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Anhedonia, the "markedly diminished interest or pleasure in all, or almost all, activities" (APA, 2013), is often considered a deficit of an individual's ability to process rewards (Meehl, 1975; Berwian, 2020). While much is known about altered reward processing in depression, there are still many questions to be answered regarding the neurological sources of various aspects of reward processing and how these sources are affected by depression. While a common network of reward is apparent (Roy et al., 2012), subprocesses of reward, such as reward liking, wanting, and learning, show some variability in their activation. A meta-analysis of functional magnetic resonance imaging (fMRI) studies examining anhedonia found striatal hypoactivation was common across these processes (Borsini et al., 2020); however, some related regions appear to differ between processes in terms of both involvement and directionality of effects. This study aims to expand upon this literature by establishing a source for a specific reward response, the Reward Positivity (RewP) and examining how this source is affected by anhedonia and depression. In order inform this study, we first need an understanding of anhedonia and its behavioral phenotypes.

Anhedonia

Anhedonia, despite being one of two cardinal symptoms of depression, has wildly varying definitions across literature. Early descriptions of anhedonia referred to it as simply the absence of or inability to feel pleasure (Ribot, 1905). While this captures the broad idea of the symptom, it does not help to illuminate the causes of anhedonia and it is very hard to operationalize. Descriptions of anhedonic symptomology also vary across disorders. Cooper et al. (2018) describes the differences in depressed and schizophrenic anhedonia. Anhedonia in schizophrenia, as defined by the DSM-5 (APA, 2013), refers only to the lack of

reward responsivity or lessened recalled pleasure from past experiences. In the context of depression, however, anhedonia is considered a broader deficit in reward processing: encapsulating deficits in pleasure, motivation, and learning (Thomsen et al., 2015). These deficits, however, may not be consistent across all MDD+ individuals, making it important to understand the specific anhedonic phenotypes.

Reward Liking

In his 1975 paper, Meehl describes anhedonia as a lack of hedonic capacity that varies on an individual level, rather than a pathology which one either does or does not have. This idea acknowledges that anhedonia varies within depressed individuals as well as individuals that would not meet criteria for a diagnosis of MDD. This description is much more in line with the research domain criteria (RDoC; Insel et al., 2010) line of thinking with which we approach symptomology today. Meehl also conjectured that depressed individuals, or those with low hedonic capacity, do not receive the same level of reinforcement from positive reinforcers that individuals with a higher hedonic capacity do. This greatly ties into the reward liking aspect of anhedonia.

The idea that positive reinforcement is not received by anhedonic individuals is expounded upon by Pizzagalli et al. (2005) who describe anhedonia as a "lack of reactivity to pleasurable stimuli" or diminished reward responsivity. They go on to show that depressed individuals do not form a response bias towards more rewarding stimuli. These findings imply that depressed individuals either do not recognize rewarding stimuli as being rewarding or simply do not care.

Reward Wanting

Anhedonia has also been defined as a lack of reward-seeking motivation,. Treadway et al. (2009) examined this idea through a task in which participants had to decide the amount of effort they were willing to expend to receive a reward. They found that individuals with higher trait and state levels of anhedonia were less willing to expend more effort despite the chance at a larger reward, suggesting that anhedonia may in fact be an expression of altered motivation for rewards. This study primarily had individuals with a rather low range of anhedonia scores; however, Treadway et al. (2012) used the same task to look at group differences between MDD+ individuals and healthy controls. Depressed individuals were not only less willing to expend effort for a reward, they also seemed to be less effective in implementing information about the magnitude and probability of the reward when choosing whether to pursue it. They did not, however, examine whether anhedonia scores in MDD were correlated with effort expenditure meaning that there could be some other aspect of MDD driving this lack of reward motivation.

Reward Learning

Considering Pizzagalli's finding that depressed participants may not recognize rewarding stimuli, one might expect that depressed individuals would not perform well on reinforcement learning tasks. Pizzagalli et al. (2008) illustrated this through the use of a probabilistic selection task. This study showed that depressed subjects did respond to rewarding stimuli on a single trial, but were not able to form long term response biases towards rewarding stimuli, showing a lack of reward-based learning. This is consistent with the argument that depressed individuals are not receiving the same level of reinforcement from rewarding stimuli and either not responding to rewards or not learning from rewards.

Reward prediction error (RPE) is commonly used as a representation of reward-based learning. RPE is the difference between an outcome and a prediction and is often used to computationally model learning rates based on reward. In the context of reinforcement learning, this difference is effectively the level of surprise from receiving a reward or punishment. If an individual is surprised to receive a reward from a given stimulus, that means they have learned that stimulus may be less rewarding and vice versa. RPE has been shown to directly correlate with altered dopaminergic firing when reacting to a stimulus that has been associated with a reward (Schultz et al., 1997), showing that RPE can be used as an effective behavioral representation of reward-based learning. However, whether reinforcement learning is affected by MDD is highly debated. While some prior studies have shown a deficit in learning from reward (Kumar et al., 2018; Pizzagalli et al., 2008) others have shown that learning remains largely unchanged (Dombrovski et al., 2013; Kumar et al., 2008; Rutledge et al., 2017; Chase et al., 2009).

Altered Neural Activity Related to Anhedonia

As reward processing recruits a wide number of brain regions, specific anhedonic phenotypes can affect neural activity in many ways. These neural alterations common to anhedonia share some similarities across phenotypes, namely hypoactivation of ventral striatum; however, the neural underpinnings of phenotype-specific deficits vary greatly. Magnetoencephalography (MEG) and fMRI have provided evidence for the separation of these reward processes and their related anhedonic phenotypes.

Reward Liking

MEG work has potentially shown reward activation of the basal ganglia in a gambling task (Sepe-Forrest et al., 2021), though it is unclear whether this activity can be separated from insular activity. However, this does suggest that basal ganglia, insula, or both are involved in the reward liking system. Depressed individuals have also shown hyperactivation of the medial prefrontal cortex (mPFC) following reward (Price and Drevets, 2012). Stimulation of the ventromedial prefrontal cortex (vmPFC) using inhibitory transcranial direct current stimulation has also been shown to boost reward responsivity (Junghofer et al., 2017). fMRI studies have shown that diminished reward responsivity is linked to hypoactivation in the ventral striatum (Foti et al., 2014; Satterwaithe et al., 2015; Steele et al., 2007), including the nucleus accumbens (NAcc; Redlich et al., 2015), as well as dorsal striatal structures including the caudate (Pizzagalli et al., 2009; Forbes et al., 2009; Connolly et al., 2015; Antonesei et al., 2018; Forbes et al., 2006; Zhang et al., 2013) and putamen (Connolly et al., 2015) when either comparing participants with MDD to healthy controls or when correlating with anhedonia. Additionally, hypoactivation of the insula has been shown in response to reward for MDD participants when compared to healthy controls (Dichter et al., 2012; Satterwaithe et al., 2015; Sankar et al., 2019). MDD individuals also exhibit hyperactivation of the vmPFC (Forbes et al., 2009; Keedwell et al., 2005; Kumar et al., 2015) and the dorsolateral prefrontal cortex (dlPFC; Forbes et al., 2009). These neural alterations likely reflect changes to the broader valence and default mode networks.

Reward Wanting

Anhedonic deficits in reward wanting have been linked with hypoactivation of both dorsal (Yang et al., 2016; Smoski et al., 2009; Zhang et al., 2013; Takamura et al., 2017;

Pizzagalli et al., 2009) and ventral striatum (Hagele et al., 2015; Takamura et al., 2017; Stringaris et al, 2015; Misaki et al., 2016; Olino et al., 2011). In addition to striatal hypoactivation, orbital frontal cortex (OFC) hyperactivation is present in MDD when selecting between different reward options (Smoski et al., 2009; Forbes et al., 2009). Hyperactivation of mPFC and dlPFC was also found in depressed individuals when anticipating a reward (Forbes et al., 2009) as well as anterior cingulate cortex (ACC) hyperactivation (Zhang et al., 2013; Gorka et al., 2014). While this likely shows some reflection of altered valence and default mode networks, similar to reward liking, incorporation of ACC and OFC suggests additional alteration of the salience network.

Reward Learning

MEG research has suggested that PE signaling occurs in the frontal cortex, with a PE responsive signal having been shown at frontocentral sensors (Talmi et al., 2012; Liuzzi et al., 2021), though the specific source is unclear. fMRI work has shown that the striatum, again, appears to be involved in reinforcement learning. PE signaling in the striatum has been shown to be blunted in correlation with anhedonia scores (Kumar et al., 2008; Gradin et al., 2011; Kumar et al., 2018; Rothkirch et al., 2017; Segarra et al., 2016; Robinson et al., 2012). Unlike reward wanting, MDD participants exhibit hypoactivation of medial OFC rather than hyperactivation (Segarra et al., 2016). Additionally, a study looking at reversal learning in MDD participants found reduced activation of the vmPFC (Hall et al., 2014), again showing separation of these processes. Similar to reward wanting, it seems there are alterations in the salience network related to reward learning deficits.

Reward Network

Across subtypes of anhedonia, striatal hypoactivation following reward appears to be a commonality (Foti et al., 2014; Redlich et al., 2015; Takamura et al., 2017; Kumar et al., 2008). vmPFC and OFC also seem to be involved across these different subprocesses; however, their relationship with anhedonia does not appear to be consistent across subtypes. While vmPFC activation appears to be positively correlated with reward liking and wanting (Forbes et al., 2009; Kumar et al., 2015), it is diminished in reward-based learning tasks (Hall et al., 2014). OFC does not appear to be altered in relation to reward liking, but does show amplified activation in reward wanting tasks (Forbes et al., 2009) and hypoactivation in learning tasks (Segarra et al., 2016). The insula also shows selective hypoactivation for reward liking tasks (Dichter et al., 2012; Satterwaithe et al., 2015; Sankar et al., 2019), but not for reward wanting or learning. These similar but different neurological underpinnings of anhedonia point towards an overall deficiency in the reward network with varying deficiencies across anhedonic subtypes.

These deficiencies heavily overlap with the canonical network for reward and valuation (Roy et al., 2012). This network, consisting of vmPFC, mOFC, posterior cingulate cortex, and striatal structures such as NAcc, provides affective meaning to stimuli. This network's involvement in reward processing is further evidenced by the findings of Carlson et al. (2011) showing that ventral striatal activation and mPFC activation are both correlated with reward response. It has also been shown that vmPFC and NAcc are anatomically connected (Alexander & Crutcher, 1990; Öngür & Price, 2000). Further evidence is provided by Gordon et al. (2021), who found functional connectivity at rest between vmPFC and NAcc with high precision, individual mapping that aligns with primate research. Striatal

functional connectivity across hemispheres has been positively correlated with reward activation and reward-approach tendencies (Dong et al., 2018), implying that dysfunction of this reward network could affect an individual's approach to reward.

Reward Positivity

When discussing neurological representations of reward, one of the best candidates, in humans, is the Reward Positivity. The Reward Positivity is an electrophysiological signal observable in EEG. It is described as a positive-going component (Proudfit, 2015) in the ERP following rewarding feedback. This component typically occurs approximately 250-350 ms following a reward. This is also in line with Schultz et al.'s (1993) work showing that dopamine firing in monkey brains occurs 200-300 ms following an unlearned reward. Additionally, Schultz et al. found that the number of neurons firing during this window for an established reward was greatly reduced. While dopamine firing varies with a variety of stimuli, this provides solid evidence that the reward positivity is a neural correlate of reward processing, sensitive to learning.

Further evidence for the reward positivity's specificity to reward comes from its modulation by RPE. RPE can take the form of positive RPE (receiving an unexpected reward) or negative RPE (not receiving an expected reward). Positive RPE has been shown to modulate the reward positivity by boosting this positive component (Holroyd et al., 2011; Cavanagh, 2015). As stated before, prediction errors are a large part of what drives reinforcement learning and can be used to quantify learning through computational modeling. (Huys et al., 2013) This also allows us to examine anhedonic lack of motivation, as individuals with low hedonic capacity would hypothetically be less driven to learn in order to receive rewards.

The reward positivity can also be examined through spectral power, as it is thought to be caused by a burst of delta activity. Prior work has shown that midline delta power is increased around 250-350 ms after positive feedback (Bernat et al., 2015; Cavanagh, 2015; Foti et al., 2015). This allows us yet another way of representing the reward positivity and subsequently reward.

The reward positivity may also serve as a biomarker for depression (Proudfit, 2015; Cavanagh et al., 2021) and has been shown to be diminished in depressed individuals (Foti and Hajcak, 2009; Bress et al., 2012). While it is known to be enhanced by positive mood (Threadgill and Gable, 2017; Brown and Cavanagh, 2018), recent work by Jackson and Cavanagh (*under review*) has shown that the reward positivity is not reduced by induced sadness, contradicting previous work by Foti and Hajcak (2010). Jackson and Cavanagh used a more effective sad mood manipulation providing additional credence to the claim that state-level depression does not diminish the RewP, only trait-level depression. Given the reward positivity's modulation by trait-level depression, it seems to be the best neurological correlate of reward to use when examining anhedonia.

The Current Study

While the reward positivity seems promising as a potential biomarker of depression, the source of this signal is still unclear. It is also unclear why anhedonic neurological deficits in reward processing vary across subprocesses of reward. This variation may be, in part, a result of altered communication within the reward network. A combination of multiple neuroimaging methods was used to examine this hypothesis. Using MEG, we estimated the source of the well-established reward signal of the RewP as it is shown to be modulated by the three reward subprocesses discussed earlier and is diminished in MDD+. We

hypothesized this signal would localize to the vmPFC given its known involvement in reward and valuation. Activation of the source of the reward positivity was then examined in MDD and was hypothesized to be diminished in depression. We then examined group differences of resting state functional connectivity (rsFC) in MDD between this source and NAcc, given the cortical-striatal projection of the hypothesized source (vmPFC) to NAcc (Haber & Knutson, 2010). Additionally, we examined correlations with depressive symptomology within the MDD+ cohort.

Methods

Participants

Participants consisted of a community sample of 48 individuals (32 female) with MDD+ as diagnosed by the Structured Clinical Interview for DSM-5 (SCID) and 35 healthy controls (20 female). Six MDD+ participants had previously used antidepressants but had ceased medication at least six months prior to data collection. Power analysis using an expected effect size of $d=0.76$, the correlation between anhedonia and RewP amplitude found by Liu et al. (2014), suggested that a sample of 43 individuals with MDD+ and 21 healthy controls would yield a power of 0.8 making this sample size sufficiently powered. Due to data collection occurring around a scanner upgrade, fMRI data was collected using two scanners; however, the potential effect of scanner will be accounted for by including the scanner as a fixed effect. Due to scheduling difficulties, one participant had MEG recorded without an MRI session and five participants had MRI data collected without and MEG session. The MRI of another participant of the same sex and similar head size was used for source estimation for the participant missing MRI data. Additionally, two participants were excluded from the MEG analysis due to excessive noise and two participants were excluded

from MRI analysis due to errors in motion regression. EEG was only collected for a subset of the total sample due to a variety of causes (e.g., scheduling issues, bad cap replacement, large head, etc.). This brings the final sample size for each analysis to: EEG=24 (MDD+=19), MEG=76 (MDD+=42), MRI=80 (MDD+=45).

Table 1

Demographics

	Control	MDD+
N (female)	35 (20)	45 (32)
Age	28.7 (8.29)	28.2 (7.90)
Years of Education	14.7 (3.22)	15.3 (2.64)

Questionnaires

Participants were screened by phone to determine potential eligibility. Eligible participants then completed a battery of questionnaires including a basic demographics questionnaire as well as the Beck Depression Inventory (BDI-II; Beck et al., 1996)), the Mood and Anxiety Symptoms Questionnaire (MASQ; Lin et al., 2014), the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) and various other scales that informed analysis but were not analyzed in depth for this study (Rizvi et al., 2015; Ang et al., 2017; Carver and White, 1994; Snaith et al., 1995; Gard et al., 2006).

Task

During the MEG scan, participants completed a probabilistic selection task (PST) in which they were asked to learn, through trial and error, which of a pair of stimuli is most rewarding and earn as many rewards as possible. Stimuli consisted of six Hiragana

characters. Each stimulus was randomly assigned a probability of giving a reward at the start which remained consistent throughout. The task consisted of four training blocks consisting of 60 trials each in which each stimuli pair has opposite odds of giving a reward (80%/20%, 70%/30%, 60%/40%). Following this was a testing phase in which stimuli are pseudorandomized and participants do not receive feedback. Two participants did not have testing phase data so they were excluded from any testing phase analyses. Only the training blocks were used for EEG/MEG analysis.

MRI Acquisition and Processing

Acquisition

As previously mentioned, MRI images were collected using two scanners. The first subset of scans consists of T1-weighted structural MRI images obtained with a Siemens 3T Trio TIM scanner and a 32-channel coil using a multi-echo MPRAGE sequence [TR/TE/TI = 2530/1.64, 3.5, 5.36, 7.22, 9.08/1200 ms, flip angle = 7°, field of view (FOV) = 256 × 256 mm, matrix = 256 × 256, 1 mm thick slice, 192 slices]. Functional images were obtained while the participants were at rest for 5 minutes [TR/TE = 460/29 ms, flip angle = 44°, FOV = 248 × 248 mm, matrix = 82 × 82, 3 mm thick slice, 56 slices].

The second set of scans consisted of T1-weighted structural MRI images obtained with a Siemens 3T Magnetom PRISMA scanner and a 32-channel coil using a multi-echo MPRAGE sequence [TR/TE/TI = 2530/1.69, 3.55, 5.41, 7.27, 9.13/1200 ms, flip angle = 7°, field of view (FOV) = 256 × 256 mm, matrix = 256 × 256, 1 mm thick slice, 192 slices]. Functional images again were obtained while the participants were at rest for 5 minutes

[TR/TE = 480/29 ms, flip angle = 44°, FOV = 248 × 248 mm, matrix = 82 × 82, 3 mm thick slice, 56 slices].

Preprocessing

First, Heudiconv (Halchenko et al., 2020) was used to organize the data in BIDS format. Then data was processed with fMRIprep 1.5.0 software (Esteban et al., 2019). MPRAGE sequences were skull stripped, spatially normalized to MNI152NLin2009cAsym, tissue segmented, and then surface reconstruction was performed using Freesurfer 6.0.1 (Dale et al., 1999).

CONN functional connectivity toolbox v.18b (Whitfield-Gabrieli & Nieto-Castanon, 2012) was used for resting state functional connectivity analysis. Data were linearly detrended and motion outliers were removed using despiking. Twenty-four motion regressors, translation and rotation for x-, y-, and z-axis as well as derivatives, were regressed out of the data. Cortical ROIs were defined using the HCP-MMP1 atlas (Glasser et al., 2016) and subcortical ROIs were defined using the Freesurfer probabilistic asegmented subcortical atlas, both mapped to each individual's native source space.

Functional Connectivity Analysis

An MEG-derived seed was used to examine group differences of resting state functional connectivity with the *a priori* target of Nacc. In addition, functional connectivity of the MEG-derived seed with the whole brain was examined.

MEG and EEG Acquisition and Sensor-Level Processing

MEG data were obtained using a 306-sensor Elekta Neuromag System. Data were recorded continuously at a sample rate of 1000 Hz across a frequency range of .1 to 330 Hz. EEG data were collected concurrently using an EGI 128-electrode cap with a sample rate of 250 Hz.

EEG data were processed using EEGLab 2020 (Delorme &Makeig, 2004) in MATLAB R2022b. Data were re-referenced to a whole brain average, linearly detrended, then epoched around the presentation of a cue. Independent components analysis (ICA) was used to remove blink and heartbeat artifacts from the data. Data were baseline corrected with a baseline window of 500 to 200 ms before cue, then time shifted to be feedback-locked. Epochs were then lowpass filtered at 20 Hz then averaged at FCz to create the ERP. The time region of interest for MEG source estimation was determined based on the time of the RewP in this ERP.

MEG data were preprocessed using MNE-Python v.0.23.1 (Gramfort et al., 2013). Data were preprocessed using a maxfilter and temporal signal-space separation (tSSS) to remove external noise and adjust for motion correction. Sensor-level data were also aligned to the device origin during this step. Data were then high-pass filtered at 1 Hz to remove any slow drifts and notch filtered at 60 Hz to remove any powerline noise. Following this, data were down-sampled to 250 Hz. Signal-space projection (SSP) was then used to remove any artifacts from eye blinks and heart rate. Data were then epoched around the presentation of the cue.

Sensor-level MEG data were then baseline corrected to a period of 500 to 200 ms prior to cue then time shifted to be feedback-locked. Epochs were then lowpass filtered at 20 Hz and averaged to create sensor-level ERFs. The primary magnetometer for analysis,

MEG0511, was chosen due to two factors: (1) magnetometers tend to pick up deeper signals better than their hyper-focal gradiometer counterparts, (2) we found that lateral sensors tended to perform better than midline sensors at observing medial signals as the magnetic field is maximal at a point orthogonal to the source of the electrical dipole.

Source Estimation

Preprocessing and epoching for the MEG data were identical to sensor-level analyses, with the exception of aligning to device origin during tSSS. A volumetric source space for each individual was created from the T1 image using skull surfaces created by the watershed boundary element method (BEM) algorithm. This source space was used to create the forward solution. The epoched MEG data were then baseline corrected to a period of 500 to 200 ms prior to cue and low-pass filtered at 20 Hz. After creating a noise covariance matrix using the baseline period, MEG data were time-shifted to be feedback-locked. The inverse operator was then created using the forward solution, feedback-locked MEG data, and source space. This inverse operator was then be applied to each condition (reward/punishment) of the MEG data and projected onto a volumetric source space using dynamic statistical parametric mapping (dSPM).

Statistical Analysis

The source estimation contrast of Reward-Punishment was examined using a one-sample spatiotemporal permutation clustering test (permutations=1000, cluster threshold=0.05). This test was limited to the time ROI as determined by the EEG and MEG sensor analysis. These clusters of significant voxels were used as seed ROIs for functional connectivity analysis. rsFC between these clusters and NAcc was compared across groups

using a Welch's two-sample t-test and correlation with MASQ – Depression scores was done using a general linear model (GLM). The exploratory whole brain seed-ROI analysis was examined using two-sample t-tests for group differences and GLM for correlation with anhedonia scores. Given that the whole brain analysis is exploratory and intended to primarily inform future work, these results are reported without multiple comparisons correction.

Results

Questionnaires and Task Performance

Questionnaire data are summarized in Table 2. MDD+ participants had significantly higher scores for BDI ($t(81)=11.725$, $p<.001$) and all MASQ subscales (General Distress – Depression: $t(81)=4.15$, $p<.001$; General Distress – Anxiety: $t(81)=2.898$, $p=.005$; Anhedonic Depression: $t(81)=6.34$, $p<.001$; Anxious Arousal: $t(81)=2.63$, $p=.010$). There was no difference in AUDIT scores ($t(81)=-0.254$, $p=.800$).

Table 2

Questionnaires

	Control	MDD+
BDI	4.23 (3.97)	26.6 (10.8)
MASQ – General Distress – Depression	21.4 (8.56)	33.5 (14.8)
MASQ – General Distress – Anxiety	20.1 (7.63)	26.4 (11.0)
MASQ – Anhedonia	54.8 (12.3)	74.6 (13.6)
MASQ – Anxious Arousal	23.3 (13.6)	30.0 (12.7)
AUDIT	3.63 (4.21)	3.84 (3.40)

Of the 78 participants who performed the task, 18 (13 MDD+) had less than 55% accuracy. These 18 were excluded from further behavioral analysis as they did not learn the task. Overall, participants had a mean training accuracy of 73.7% (SD=11.9%). MDD+ participants had a significantly lower training accuracy (*M*=70.5%, *SD*=10.2%) than healthy controls (*M*=76.9%, *SD*=12.8%, *t*(58)=2.153, *p*=.035). Performance on the testing phase, however, did not differ (*M*=70.9%, *SD*=13.3%, *t*(56)=1.256, *p*=.214). Performance did not differ between sexes (*t*(76)=1.22, *p*=.227).

Table 3

PST Performance

	Control	MDD+
Training Accuracy	76.94 (12.84)	70.50 (10.2)
Test Accuracy	73.06 (11.61)	68.69 (14.76)

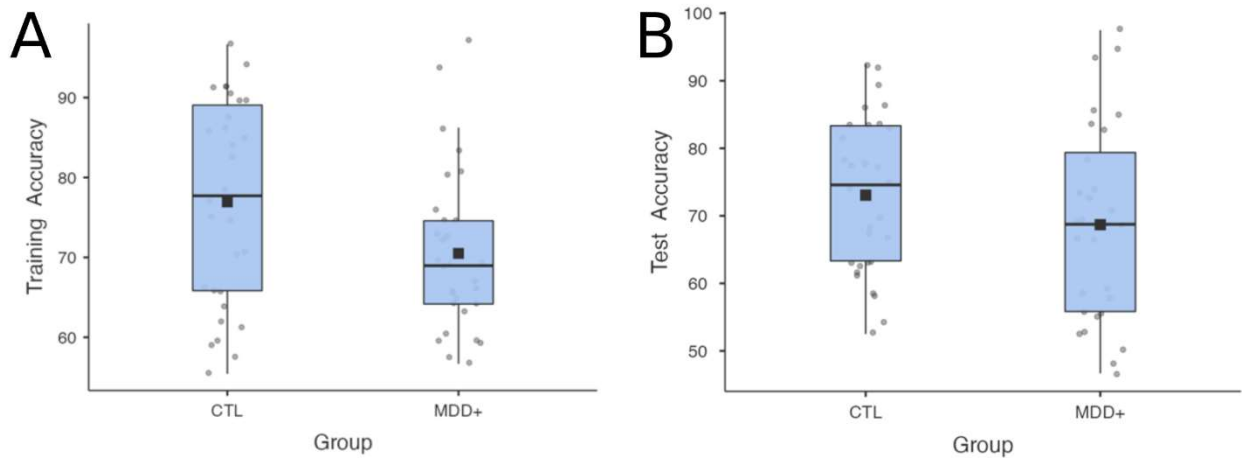

Figure 1 - (A) Overall accuracy on PST training blocks. (B) Overall accuracy on PST test phase with no feedback.

EEG and MEG Sensor Analysis

The ERP at a frontal midline sensor (FCz) showed the expected signal of the reward positivity following rewarding feedback while punishment showed a typical tri-phasic motif, exhibiting a clear P2, N2, P3 pattern. Reward showed greater activation than punishment from 270 ms onwards. Group comparisons of ERPs show no difference between healthy controls and MDD+ participants ($t(22)=-0.486$, $p=0.632$).

MEG sensor-level data showed a homologue to the reward positivity in an ERF taken at a frontolateral magnetometer (MEG0511). This signal was greater than punishment from 270-500 ms. Unlike the ERP, the ERF did differ across groups ($t(74)=2.48$, $p=.015$). Given that the ERP showed greater activation for win from 270 onwards, the ERF was used in conjunction to determine a time ROI of 270-500 ms.

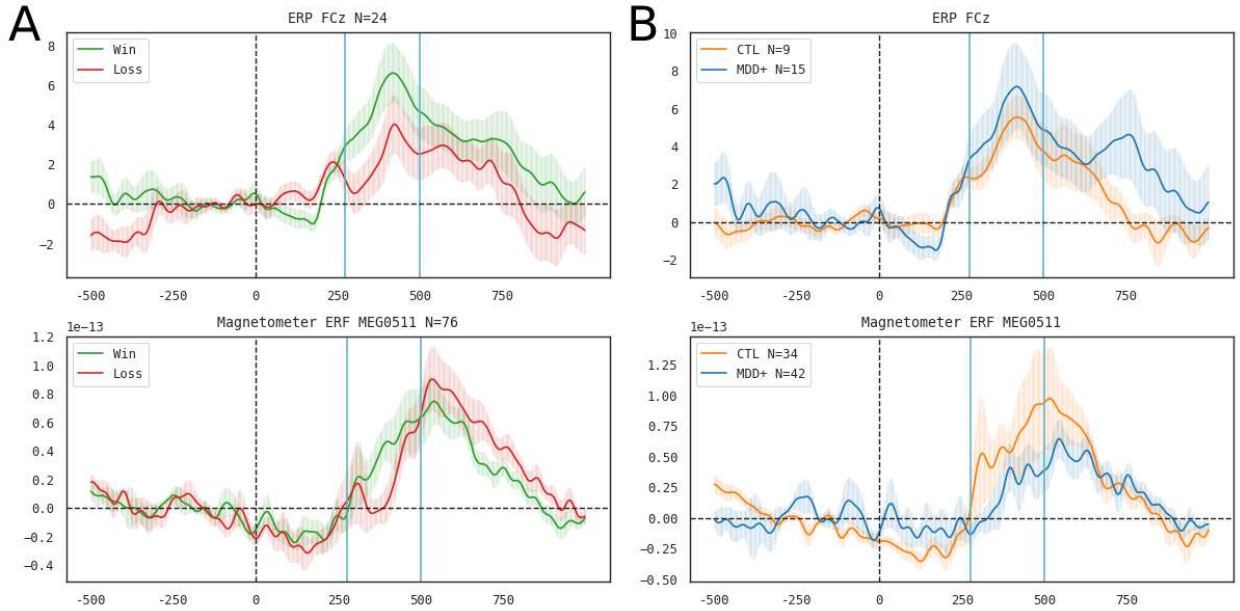

Figure 2 - (A) Win and Loss ERP at FCz for N=24 (top); Win and Loss ERF at magnetometer MEG0511 for N=76 (bottom). (B) Win ERP at FCz for controls (N=9) and MDD+ (N=15) (top); Win ERF at magnetometer MEG0511 for controls (N=34) and MDD+ (N=42) (bottom)

MEG Source Estimation

A spatiotemporal permutation clustering test of Reward-Punishment showed a significant cluster for 52 ms (voxel threshold=0.05, cluster threshold=0.05). This cluster was maximally active at 375 ms. This cluster encapsulated the entire frontomedial wall and insulae. Further thresholding to only include voxels that were spatiotemporally clustered for 20 ms or more showed a parcellation of this cluster into three more distinct bilateral clusters: vmPFC, anterior midcingulate cortex (aMCC), and insulae. Boundaries between these clusters were verified using the Harvard-Oxford cortical atlas. These ROIs were used as seeds for the rsFC analysis.

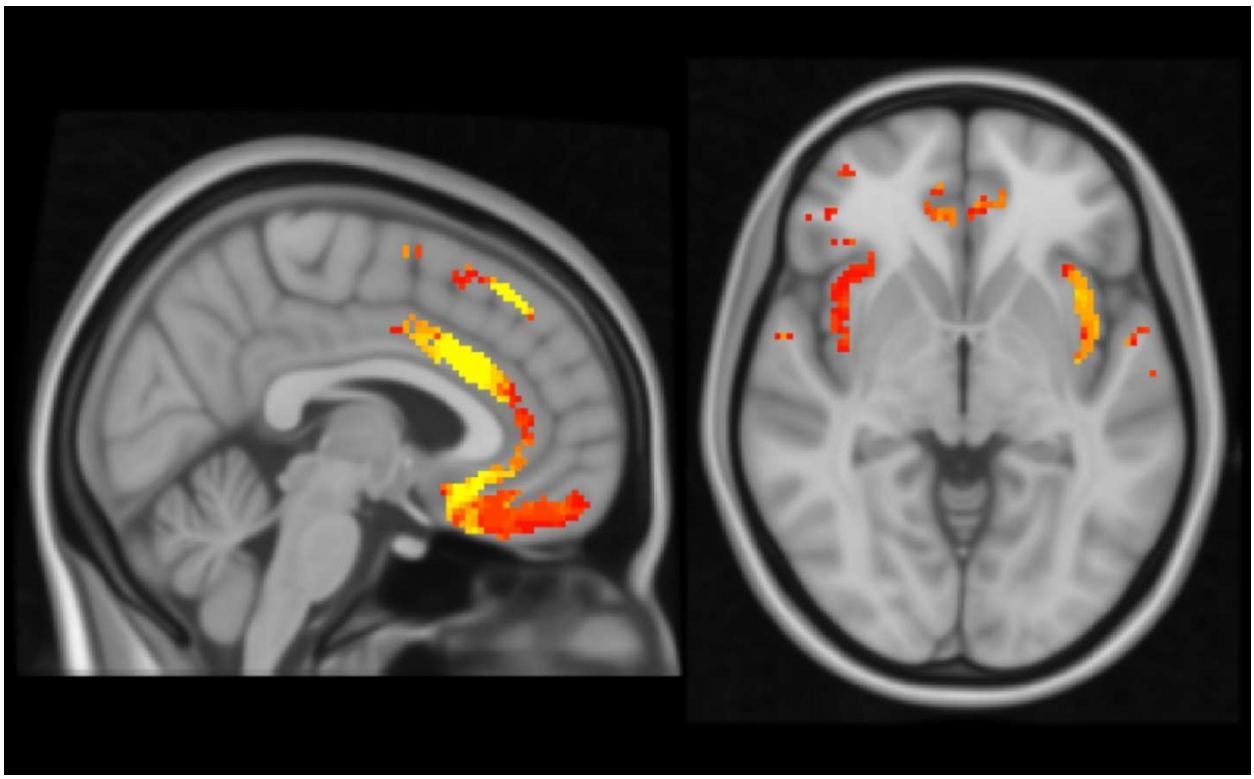

Figure 3 - Spatiotemporal permutation clustering test results for Win-Loss. Images thresholded at 20ms of temporal significance.

Spatiotemporal permutation clustering did not reveal any significantly different clusters across groups. However, group comparisons of activation in the ROIs determined by

the orthogonal Win-Loss contrast did reveal a significant difference in vmPFC activation from 275-375 (t(55.5)=2.284, p=.026), but not in aMCC (t(46.9)=1.346, p=.185) or insulae (t(55.2)=0.924, p=.360). Together, these findings suggest that while vmPFC, aMCC, and insulae are involved in generating the RewP, the only vmPFC is affected by MDD.

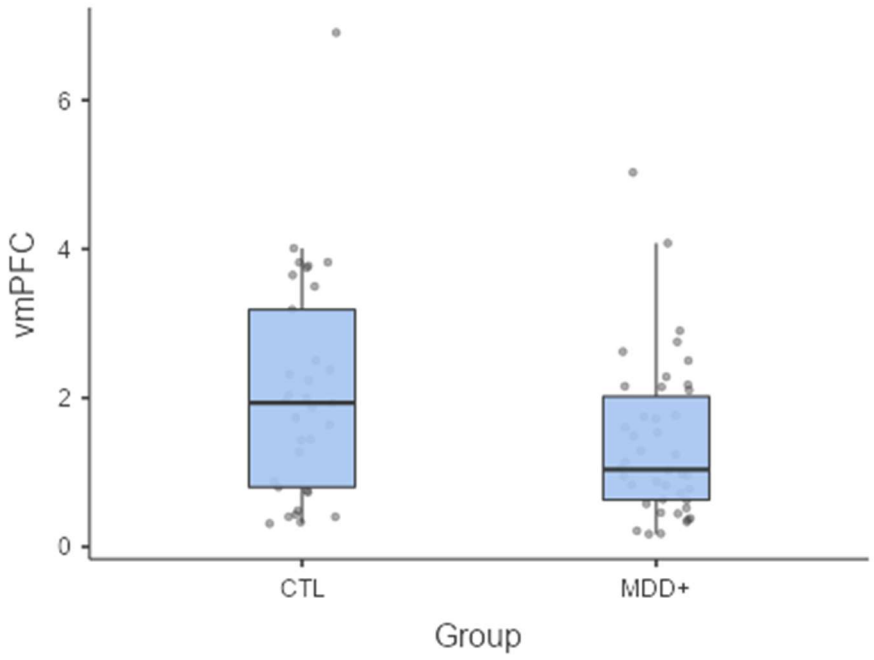

Figure 4 - Average activation of vmPFC from 275-325 ms following receipt of reward

Resting State Functional Connectivity Analysis

rsFC analysis showed no significant differences across hemispheres, so the average of left and right hemispheres is reported. Additionally, framewise displacement did not differ between groups (t(78)=-1.24, p=.217) nor did it correlate with MASQ Anhedonia or General Depression (MASQ Anhedonia: T(78)=-0.201, p=.842; MASQ General Depression: T(78)=-1.71, p=.094). Analyses revealed a significant correlation between the *a priori* MEG-derived vmPFC seed and NAcc (β=0.47, T(78)=13.07, p-FDR<.001). There was also a significant

correlation between the vmPFC seed and the MEG-derived aMCC (aMCC: β=0.34, $T(78)=10.51$, p-FDR<.001) and insula ROIs (β=0.25, $T(78)=6.62$, p-FDR<.001).

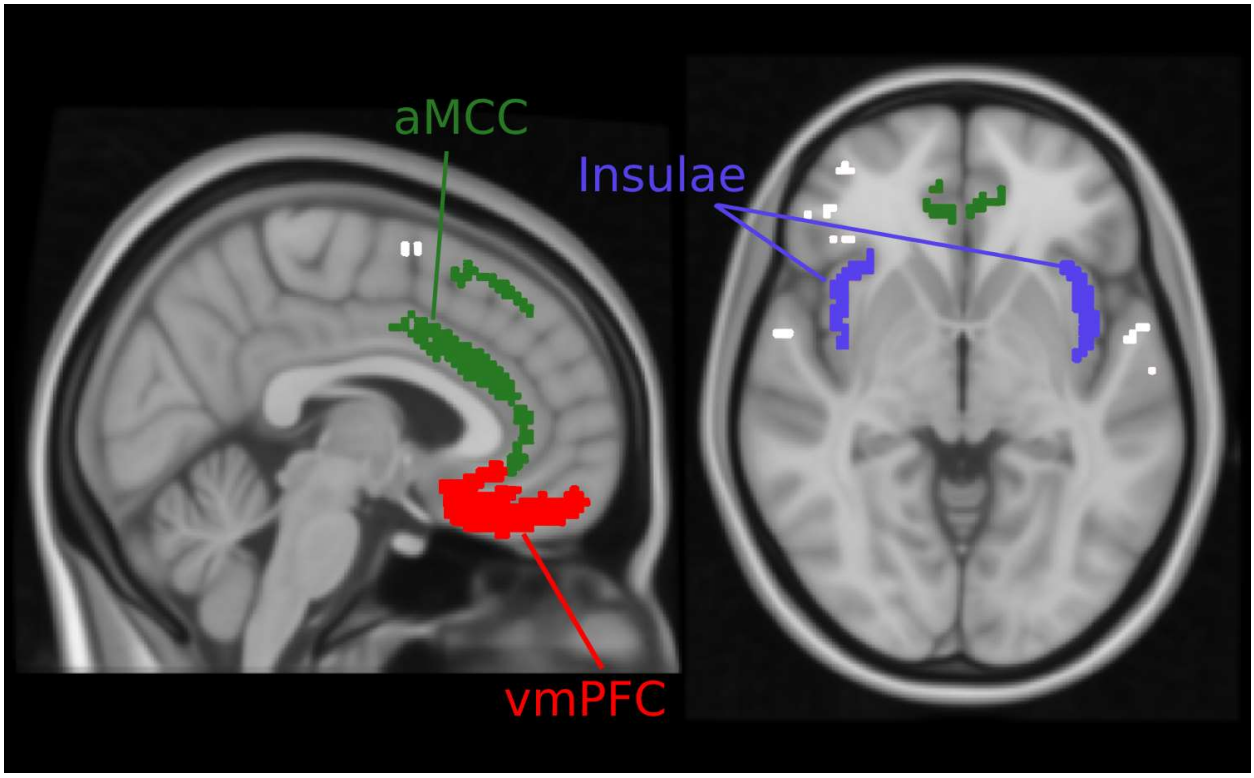

Figure 5 - MEG-derived seeds used for rsFC analysis

aMCC was also significantly correlated with NAcc (NAcc: β=0.44, $T(78)=11.77$, p-FDR<.001) and insulae (insula: β=0.93, $T(78)=21.31$, p-FDR<.001). Insulae were also significantly correlated with NAcc (NAcc: β=0.36, $T(78)=9.09$, p-FDR<.001). These findings held, even when accounting for multiple comparisons across all ROIs.

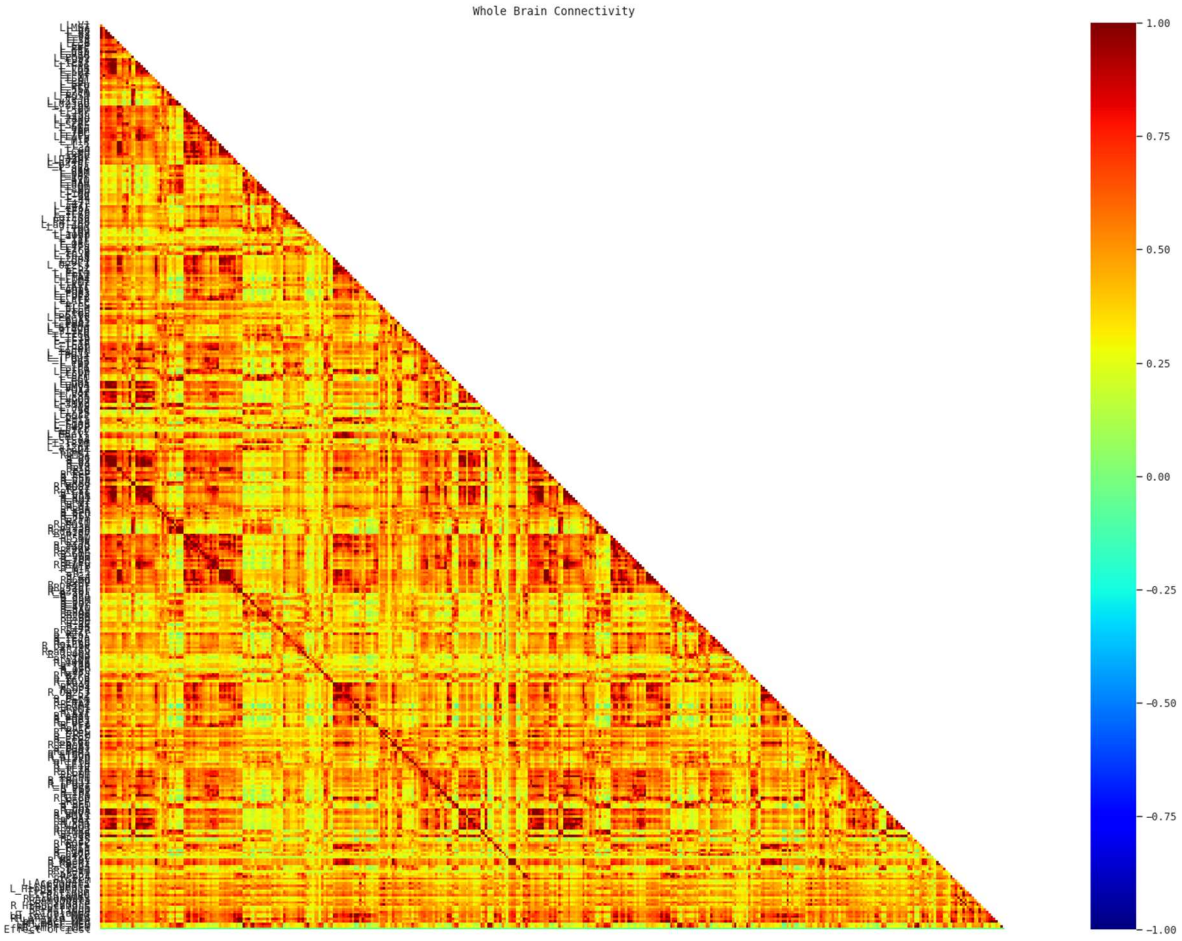

Figure 6 - Whole Brain Connectivity Analysis for All Subjects

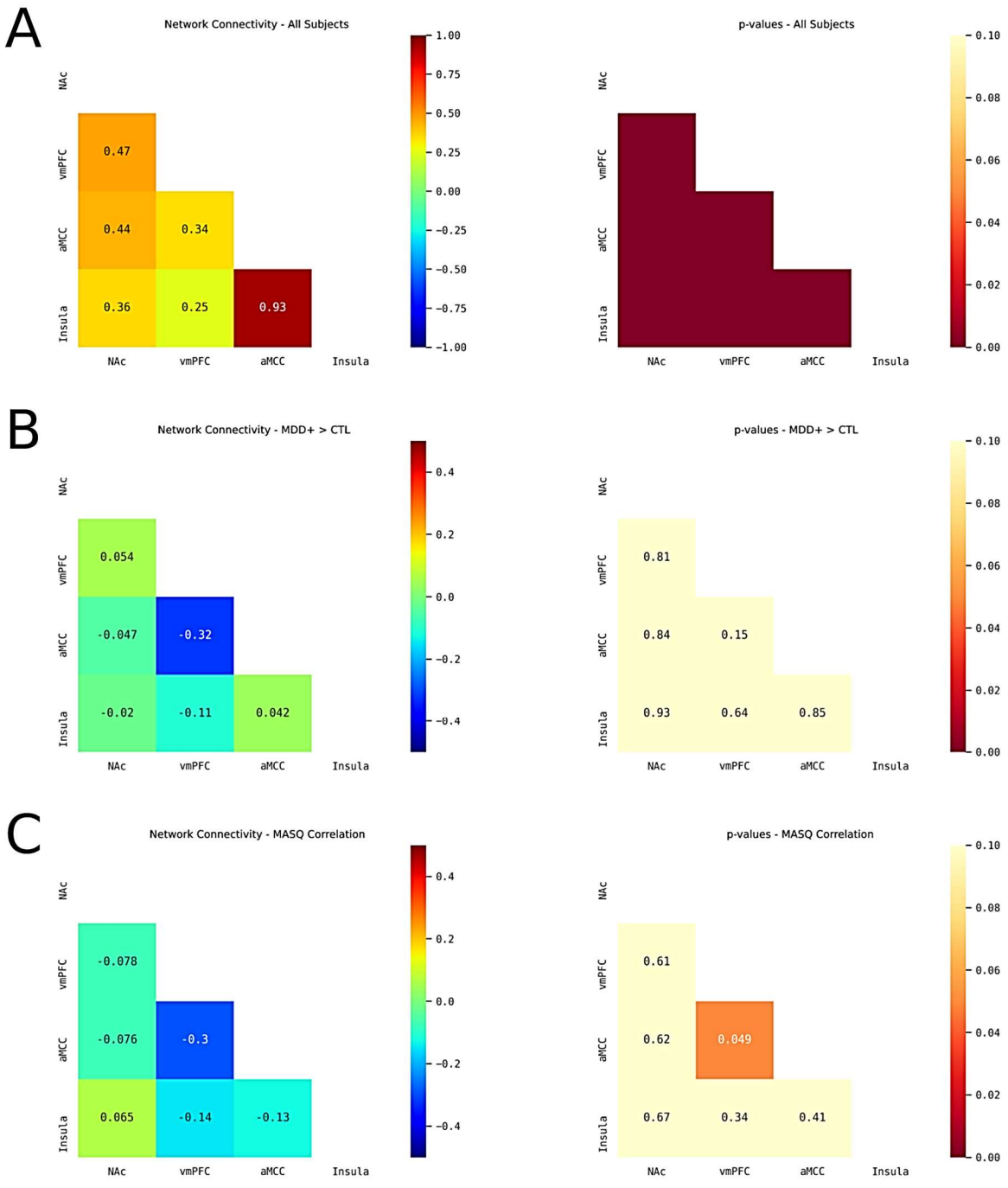

Figure 7 - (A) Unstandardized beta at rest for all subjects (B) Standardized beta differences at rest between groups (C) Standardized correlation between beta and MASQ - Depression within MDD+; Statistical significance of correlations is shown on the right

Group Differences

The MEG-derived vmPFC seed did not significantly differ across groups in correlation with any MEG-derived ROIs or NAcc. The largest difference in connectivity in MDD+ was vmPFC-aMCC connectivity, though not significant (β=-0.323, *T*(77)=-1.44, *p*-uncorrected=.153).

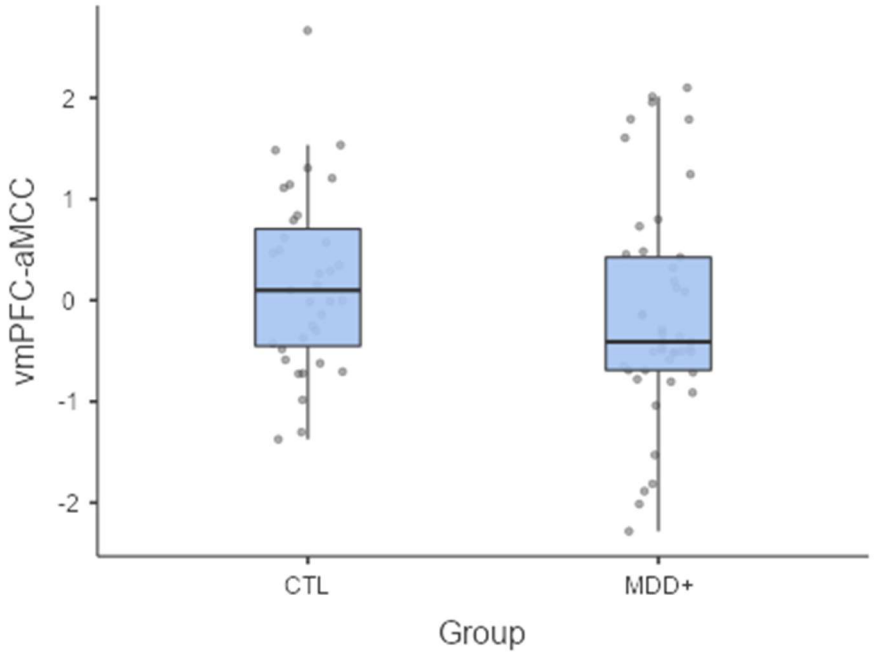

Figure 8 - Group difference in standardized resting state functional connectivity between vmPFC and aMCC

Anhedonia Correlation

MASQ-Anhedonia scores were not significantly correlated with functional connectivity between vmPFC and aMCC within the MDD+ group (β=-0.135, *T*(43)=-0.892, *p*-uncorrected=.377). However, functional connectivity between vmPFC and aMCC was anticorrelated with MASQ-General Depression scores within the MDD+ group (β=-0.296,

T(43)=-2.03, *p*-uncorrected=.049). There were no other significant correlations with MASQ scores.

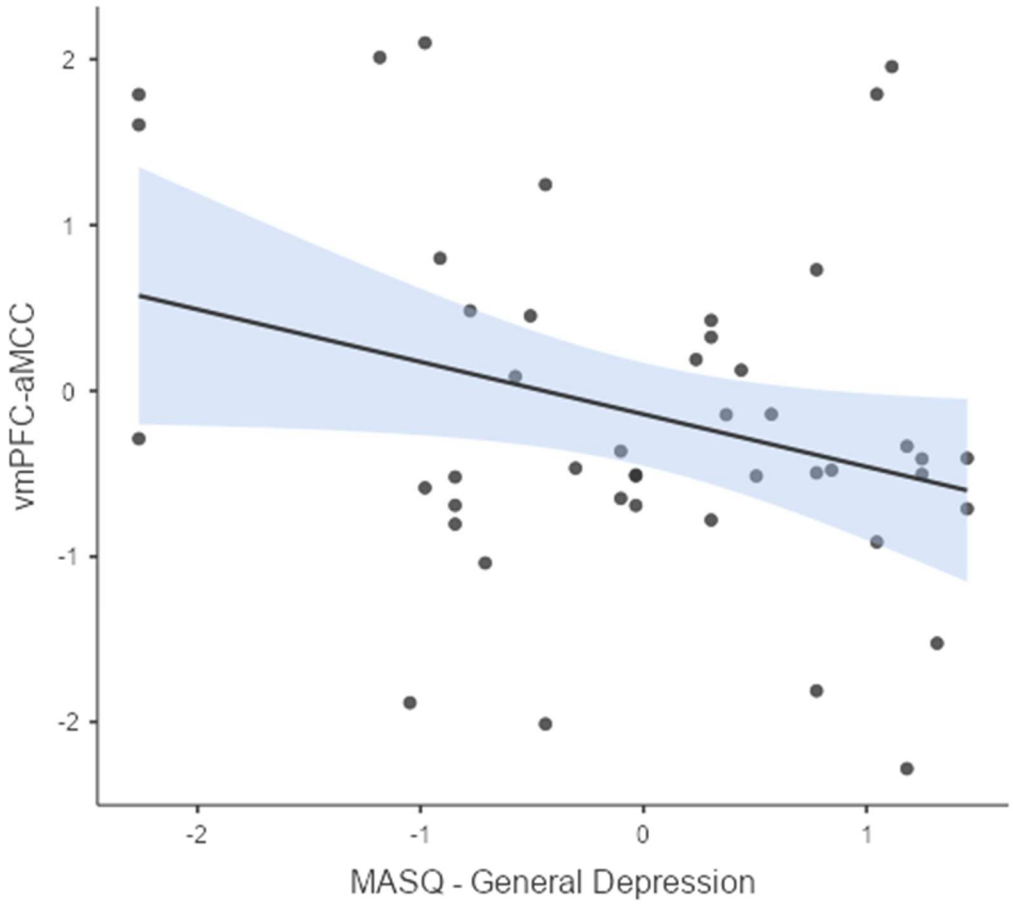

Figure 9 - Correlation of standardized vmPFC-aMCC rsFC and standardized MASQ - General Depression scores

Exploratory Analysis

Exploratory analysis including all sources in the Glasser (2016) atlas revealed no significant group differences in connectivity with vmPFC when accounting for multiple comparisons. When not accounting for multiple comparisons, significant group differences were found for the following regions in the salience network: right 33pr (β=0.17, *T*(77)=2.80, *p*-uncorrected=.006), left a32pr (β=0.13, *T*(77)=2.27, *p*-uncorrected=.03), left d32 (β=0.11,

T(77)=2.00, *p*-uncorrected=.05), MEG-derived left aMCC (β=0.12, *T*(77)=2.09, *p*-uncorrected=.04), right 10d (β=0.19, *T*(77)=2.66, *p*-uncorrected=.009), and left a10p (β=0.14, *T*(77)=2.35, *p*-uncorrected=.02). Additionally, the following regions were shown to be altered in the MDD+ group: right p47r (β=0.15, *T*(77)=2.41, *p*-uncorrected=.02), left DVT (β=0.15, *T*(77)=2.34, *p*-uncorrected=.02), right 6a (β=0.16, *T*(77)=2.28, *p*-uncorrected=.03), left H (β=0.12, *T*(77)=2.14, *p*-uncorrected=.04), right IP2 (β=0.13, *T*(77)=2.07, *p*-uncorrected=.04), left TE1p (β=0.11, *T*(77)=2.03, *p*-uncorrected=.05),. These significant differences in MDD+ suggest widespread alterations of functional activity which could best be examined by future analyses aimed at network level differences.

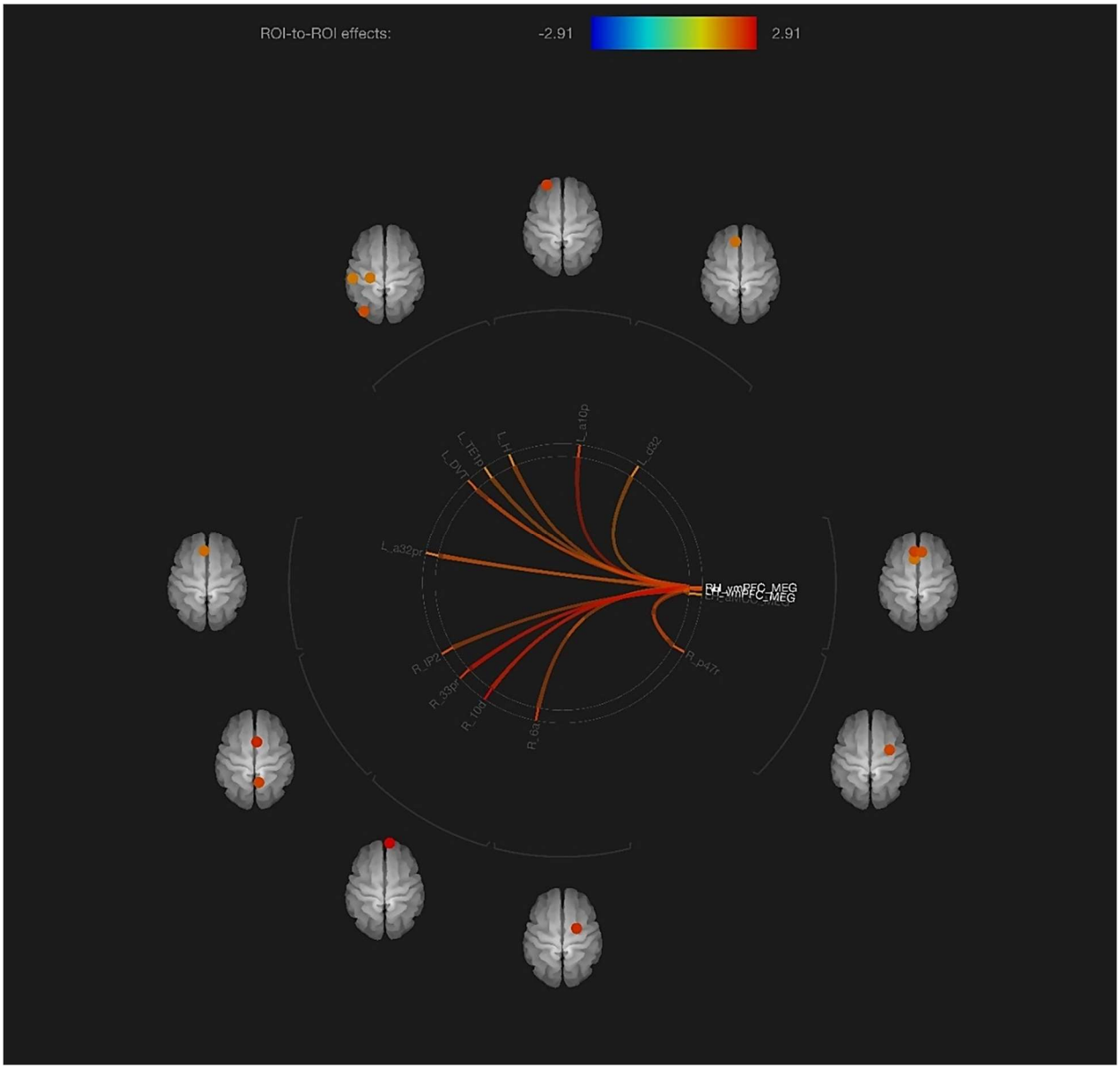

Figure 10 - Uncorrected connectome ring of group differences in rsFC with vmPFC

Discussion

Our MEG findings suggest that the Reward Positivity is generated by a distributed network consisting of vmPFC, aMCC, and the insulae. This network incorporates the valence and salience networks to create an informative response to reward. Resting state functional connectivity analysis suggests that these regions are highly correlated with each

other and NAcc. There were no significant differences across groups; however, functional connectivity between vmPFC and aMCC was anticorrelated with MASQ - Depression scores within the MDD+ group. Surprisingly, there was no significant correlation with MASQ – Anhedonia scores, suggesting this functional connectivity deficit may be related to other aspects of MDD.

The MDD+ group performed significantly worse on the training phase PST, both in overall accuracy and the number removed due to not learning the task at all. This might suggest that anhedonic depression does affect learning and performance. However, the MDD+ group showed no difference in the testing phase of the task, suggesting they did in fact learn the task but there may be something else altered in their behavior. Further computational modeling examining approach/avoid behavior may be useful in unpacking this finding.

While there was no group difference in the ERP of the reward positivity, there was a significant difference in the ERF. This supports the idea that there is a difference in reward responsivity in MDD. The difference in sensitivity to this deficit between the ERP and ERF may be a result of the choice of MEG sensor. The ERP was taken from FCz while the ERF was taken from a magnetometer 90 degrees contralateral to the expected source of the signal. Given the findings that insula and aMCC also contribute to the RewP and are not diminished in depression, it's likely that the ERF was more sensitive to the specific deficit in MDD whereas the ERP was less affected given the normal contribution of aMCC and insular activity.

The MEG source estimation revealed three bilateral clusters that contribute to the RewP: vmPFC, aMCC, and insulae. These regions span multiple known neural networks, though of interest to our study, aMCC is a common link between the valence network (including vmPFC) (Fouragnan et al., 2018), and the salience network (including insulae) (Seeley et al., 2007). Our finding that MDD+ participants had diminished activity in vmPFC but not aMCC or insulae suggests that the reward deficit is specifically related to the valence of the reward, not the salience or information content. This is further supported by the fact that the MDD+ group did effectively learn from rewards in order to perform similarly to the controls on the testing phase of the PST.

The resting state functional connectivity findings suggest that our MEG-derived ROIs were all significantly correlated with one another, as would have been expected given their significance in a spatiotemporal permutation clustering test. These ROIs were also correlated with our *a priori* target of NAcc. Amongst these ROIs, there were no significant differences across groups, the largest difference being that of vmPFC-aMCC connectivity, though it was not significant. There were also no significant correlations with MASQ – Anhedonia scores. However, there was a significant anticorrelation between MASQ – General Depression scores and vmPFC-aMCC connectivity within the MDD+ group. This further supports the earlier notion that the deficit in reward responsivity seen in MDD is related to a deficit of the valence network. Specifically, it suggests that severely depressed individuals have diminished functional connectivity between aMCC and vmPFC relative to depressed individuals with less severe symptomology, leading to a failure to incorporate both the valence and salience of reward. This may, however, not be driven by anhedonia, given that

anhedonic severity did not correlate with altered functional connectivity within the MDD+ cohort.

Exploratory analyses revealed many functional connections with vmPFC that may be altered in MDD+, though none survived multiple comparisons correction. For the sake of generating future hypotheses, some ROIs will be discussed here. Areas a32pr, d32, and 33pr are all located in the MCC (Baker et al., 2018) which provides some further evidence of the theorized deficit in valence/salience network communication. Additionally, a10p and 10d are part of the frontal pole which is known to activate relative to task complexity (Baker et al., 2018). This may provide divergent evidence for our theorized model of an unaffected salience network so it is worth investigating this further.

This study was greatly limited in its capacity to examine functional connectivity of the whole brain due to its sample size, as stable resting state networks often require hundreds or thousands of participants (Marek et al., 2022). Eighty participants is typically considered a small sample size in resting state analyses, though this is countered by the use of multiple neuroimaging techniques to provide convergent evidence within a sample and our theory-driven approach limiting our analyses to *a priori* comparisons. Future analysis could use the MEG-derived ROIs with a separate cohort to provide further validity to these findings. Our task was also a limiting factor, as it appeared to be too hard for many participants. Almost 25% of participants had to be excluded from behavioral analyses due to not learning the task at a low threshold of 55% accuracy, suggesting the task was either too challenging or participants did not try. While this is common with this task (Cavanagh et al., 2014), it does limit the scope of our analyses. Even amongst those that did learn the task, average accuracy for the training phase was only 73.7% and 70.9% for the testing phase. Assuming

participants did try, it may be beneficial to exclude the 60/40 condition of the task as it may be too challenging to differentiate.

Overall, these findings suggest that the RewP is contributed to by vmPFC, aMCC, and bilateral insulae. While aMCC and insular activity remain intact during reward receipt, vmPFC is hypoactive in MDD+. There were no differences between the MDD+ group and healthy controls; however, vmPFC functional connectivity with aMCC is anticorrelated with depressive symptomology. These findings, together, suggest that the reward responsivity deficit seen in severe MDD+ is due in part to a failure to balance relative contributions to the RewP by valence and salience networks.

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