Archival Report

Blunted Neural Responses to Reward in Remitted Major Depression: A High-Density Event-Related Potential Study

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ABSTRACT

BACKGROUND: Major depressive disorder (MDD) is a highly recurrent condition, and improving our understanding of the abnormalities that persist in remitted MDD (rMDD) may provide insight into mechanisms that contribute to relapse. Reward learning deficits linked to dysfunction in frontostriatal regions are characteristic of MDD. Although initial behavioral evidence of reward learning deficits in rMDD has emerged, it is unclear whether these deficits reflect impairments in neural reward processing that persist into remission.

METHODS: We examined behavioral reward learning and 128-channel event-related potentials (ERPs) during a well-validated probabilistic reward task in 26 individuals with rMDD and 34 control subjects with no history of depression. Temporospatial principal components analysis was used to separate overlapping ERP components, and group differences in neural activity in a priori regions were examined using low-resolution electromagnetic tomography.

RESULTS: Individuals with rMDD displayed reduced behavioral reward learning and blunted ERP amplitude to reward feedback. The reduction in ERP amplitude occurred at a principal components analysis factor that peaked during the time at which phasic reward feedback-related signaling—hypothesized to originate in the striatum and project to the anterior cingulate cortex—is thought to modulate scalp-recorded activity. Consistent with this finding, low-resolution electromagnetic tomography analyses revealed reduced activity in the anterior cingulate cortex in the rMDD group, and this blunting correlated with poorer reward learning.

CONCLUSIONS: These findings suggest that the reward learning impairment observed in acute MDD persists into full remission and that these impairments may be attributable to abnormalities in the neural processes that support reward feedback monitoring, particularly within the anterior cingulate cortex.

Keywords: Anhedonia, Anterior cingulate, ERP, Feedback-related negativity, Major depression, Reward learning

http://dx.doi.org/10.1016/j.bpsc.2015.09.007

One of the most debilitating features of major depressive disorder (MDD) is its recurrent nature, with patients experiencing, on average, five to nine major depressive episodes (MDEs) in their lifetime (1,2). Understanding the neural abnormalities that persist between depressive episodes may provide insight into the mechanisms underlying increased relapse risk in individuals with remitted MDD (rMDD).

Impaired reward learning has emerged as a key characteristic of MDD and may be a vulnerability marker in individuals with rMDD. Prior research has shown that individuals with acute MDD (3,4), particularly individuals reporting anhedonia (5), demonstrate diminished reward responsiveness on reward learning paradigms, and the degree of impairment has been linked to the severity of depressive symptoms (3). Although some studies report normalization of reward responsiveness following recovery (6), others have shown evidence of persistent impairments in remitted samples (7). Evidence of hyposensitivity to reward has also been found in nondepressed offspring of mothers with a history of depression (8,9) and in

adolescent girls who subsequently developed depression (10). Collectively, these emerging findings indicate that blunted reward learning may be an endophenotype of MDD that exists in symptomatic individuals and euthymic individuals who are at increased risk.

Event-related potentials (ERPs) possess millisecond temporal resolution, and examining modulations in ERP waveforms provides an ideal means of probing the integrity of reward learning systems in individuals with rMDD. Of particular interest are ERP components that reflect the activity of the performance-feedback monitoring system. This system causes a negative deflection—known as feedback-related negativity (FRN)—200–300 ms following receipt of feedback, which is larger for outcomes that are worse than expected (11). Smaller amplitudes are observed following rewards, and although this has been referred to in prior research also as FRN or feedback-related positivity, it has been argued more recently that the smaller amplitude results from a second reward positivity (RewP) that is superimposed on the FRN,

rather than variation in the FRN per se (12,13). In the present study, we refer to the variation in FRN amplitude following reward feedback as the RewP.

Studies using ERP in conjunction with functional magnetic resonance imaging (fMRI) (14,15) have linked variation in RewP amplitude to activation within the "brain reward pathway," particularly the ventral striatum, anterior cingulate cortex (ACC), and midfrontal cortex. A pharmacologic manipulation hypothesized to reduce phasic striatal dopaminergic responses has also been found to affect RewP and underlying ACC activation (16), suggesting that the RewP may provide an index of phasic reward signaling that originates in the striatum and projects to the ACC. Consistent with behavioral findings of blunted reward learning in MDD, reduced RewP amplitude has been observed in individuals with current MDD (17,18) and offspring with a family history of depression (9). Therefore, examining the RewP during reward learning may pinpoint mechanisms contributing to reward processing deficits in individuals with rMDD. However, few studies have examined the RewP in rMDD samples, and no study has done so in the context of reward learning. A critical question remains as to whether reward processing deficits persist into remission.

The aim of this study was to examine whether reward learning deficits persist in individuals with rMDD and whether any deficits are associated with abnormalities in discrete aspects of reward processing, as indexed by ERPs. Given that key reward processing components (e.g., FRN, RewP, P300) overlap in time, a temporospatial principal components analysis (PCA) was used to improve the separation of overlapping component processes (19). In line with prior evidence linking acute MDD with specific reductions in reward-related ERP amplitudes during the time frame of the RewP, we predicted that individuals with rMDD would also show specific blunting of the RewP during a probabilistic reward learning paradigm.

A second aim of this study was to identify neural sources of putative group differences in reward processing. Prior evidence has pointed strongly to the ACC as having a critical role in reward feedback monitoring, particularly when integration of reward probabilities is required (14,20). However, more recent meta-analyses indicate that, in addition to subcortical (e.g., striatal) regions and ACC, the posterior cingulate, insula, and pre–supplementary motor area (pre-SMA) also show increased activation during reward-based tasks (21,22). Therefore, we first capitalized on the millisecond temporal resolution of ERP to isolate time periods in feedback processing that differed between control subjects and rMDD subjects and then used a region-of-interest (ROI) approach with clusters defined on the basis of two meta-analyses of reward-related fMRI studies to identify potential group differences in activation within distinct regions of the reward circuit.

METHODS AND MATERIALS

Participants

For this study, 42 control subjects with no history of depression and 30 individuals with rMDD were recruited. Control subjects were eligible if they were free of lifetime DSM-IV diagnoses, had no first-degree relatives with psychiatric illnesses, had a Beck Depression Inventory-II (BDI-II) (23) score

<13, and had not used psychotropic medication in the past. The rMDD subjects were eligible if they had experienced at least one MDE in the past 5 years, had been in remission from depression for at least 8 weeks as indicated by a score of 1 on the Depressed Mood and Anhedonia items from the Structured Clinical Interview for DSM-IV (24) and no Structured Clinical Interview for DSM-IV score >2 for other MDD symptom items, were free of psychotropic medication (wash-out periods were applied), and had no lifetime DSM-IV diagnoses other than depression (substance abuse was allowed if in remission for at least 12 months, PTSD was allowed if in remission for at least 24 months, and other anxiety disorders were allowed if secondary to the MDD and in remission for at least 2 months). Exclusion criteria for all subjects were seizures, hypothyroidism, loss of consciousness >2 minutes, or a positive urine screen for illicit drugs (AmediCheck CLIA Waived 12-panel cup; Branan Medical Corporation, Irvine, California).

Procedure

The study consisted of two sessions. In the first session, subjects were administered the Structured Clinical Interview for DSM-IV by Masters-level or PhD-level clinical interviewers and completed the BDI-II. In the second session, participants performed a reward learning task while 128-channel ERPs were recorded. To ensure depressive symptom stability, the BDI-II was administered again at the second session.

Probabilistic Reward Task

To probe reward learning, participants completed a 15-minute computer-based probabilistic reward task (PRT) (3,25). Rooted within signal detection theory, the PRT assesses a person's propensity to modulate behavior based on reinforcement. The task consists of several trials in which cartoon faces are presented in the center of the monitor. Trials begin with a fixation cross (500 ms), followed by a face with no mouth. After a 500-ms delay, a short mouth (10 mm) or a long mouth (11 mm) is presented for 100 ms. Participants are instructed to indicate whether the short or long mouth was presented via key press. The PRT included two blocks of 100 trials, and 40 correct trials per block were followed by monetary reward feedback ("Correct! You won 20 cents"). Participants were told to try to win as much money as possible and that not all correct trials would be rewarded. Long and short mouths were presented at equal frequency; however, unbeknownst to participants, one of the mouth lengths (the "rich stimulus") was rewarded three times more frequently than the other (the "lean stimulus"). As this was part of a larger study, half of the participants in each group were administered a version of the PRT where the length of the nose varied instead of the mouth.

Behavioral and ERP Data Reduction

Behavioral Data. PRT data were subject to a quality control assessment that is outlined in detail elsewhere (25) and in Supplement 1. Briefly, trials where the reaction time (RT) was <150 ms or >1500 ms were excluded, as were remaining trials with RT falling ± 3 SD from the mean. Next, signal detection analysis (26) was used to calculate response bias (the tendency to bias responding to the rich stimulus) and

discriminability (the ability to distinguish between the mouth sizes) for each block of the PRT using the following formulae:

$$\text{Response bias: } \log b = \frac{1}{2} \log \left(\frac{Rich_{correct} * Lean_{incorrect}}{Rich_{incorrect} * Lean_{correct}} \right)$$

$$\text{Discriminability: } \log d = \frac{1}{2} \log \left(\frac{Rich_{correct} * Lean_{correct}}{Rich_{incorrect} * Lean_{incorrect}} \right)$$

To compute response bias and discriminability for cases that had a zero in the formula, .5 was added to every cell in the matrix [27]. Mean accuracy (hit rates) and RT in response to rich and lean stimuli were also computed.

Scalp Data. Electroencephalography was recorded using a 128-channel Hydrocel Geodesic Sensor Net system (Electrical Geodesics, Inc, Eugene, Oregon) and sampled at 250 Hz (bandwidth, .1–100 Hz; impedances <100 kΩ) referenced to the vertex electrode (Cz) at acquisition. Data processing occurred offline using BrainVision Analyzer 2.0 (Brain Products GmbH, Gilching, Germany). Blinks, horizontal eye movement, and electrocardiogram were removed using independent components analysis [28], and corrupted channels were interpolated using a spherical spline interpolation [29]. Data were re-referenced to the average reference and filtered (.1–30 Hz). Epochs were extracted from −250 ms to 1050 ms around presentation of reward feedback following correct identification of the rich stimulus (segments from lean stimulus trials were not used because of the low number of usable segments). Epochs were visually inspected, had remaining artifacts removed, were baseline-corrected (−250 ms to 0 ms), and were averaged. Additional information about the artifact rejection criteria used is presented in Supplement 1.

The time-domain ERP elicited in response to reward feedback was decomposed using temporospatial PCA with the ERP PCA Toolkit [30]. In accordance with prior guidelines [31], temporal variance in the averaged ERP waveforms was first examined using temporal PCA and Infomax rotation. Based on the resulting scree plot, 12 temporal factors were retained for rotation. Spatial distributions of these factors were examined using spatial PCA and Infomax rotation, with a separate spatial PCA being conducted for each temporal factor; five spatial factors were retained for each temporal factor. We focused analyses on the PCA components that showed a timing and topography most consistent with a possible RewP. There were three such components: Temporal Factor 4/Spatial Factor 1 (TF4/SF1), Temporal Factor 4/Spatial Factor 2 (TF4/SF2), and Temporal Factor 6/Spatial Factor 1 (TF6/SF1).

Source Localization

Low-resolution electromagnetic tomography (LORETA) [32] was used to estimate the intracerebral current density in a priori ROIs. The LORETA solution space was restricted to gray matter and hippocampus in the Talairach atlas and was divided into 2394 voxels (7 mm³). The ERP time window of interest for the LORETA analyses was chosen as the global field power peak occurring 200–300 ms following reward feedback. The global field power peak is reference-free and was computed as the spatial SD of the brain electrical field; it

reflects brain activity across the entire scalp. In the present study, we extracted mean activity around the global field power peak (248 ± 20 ms) following receipt of reward feedback.

Current density was analyzed using an ROI approach. The ROIs were defined based on two independent meta-analyses of fMRI studies examining neural activity in response to reward [21,22]. Given that LORETA has lower spatial resolution than fMRI, it was not always possible to identify a LORETA voxel that exactly matched the peak reported in the fMRI meta-analyses. To circumvent this issue, a LORETA cluster was defined such that its center of gravity was closer to the fMRI coordinates than any single LORETA voxel, as done in prior work [33]. In cases in which the two meta-analyses identified slightly different peak coordinates for the same regions, individual LORETA clusters were defined using the above-outlined strategy, and the mean center of gravity of the two clusters was calculated. A LORETA "meta-cluster" was defined in which the center of gravity was closest to this mean. When defining the LORETA clusters, two parameters were emphasized: 1) minimization of the distance between the fMRI peak coordinates and the LORETA ROI center of gravity and 2) similarity of size between the LORETA cluster and the ROI size in the fMRI meta-analyses. The LORETA voxels that contributed to each ROI are listed in Supplement 1. The ROI analyses were carried out using SPAMALIZE (http://brainimaging.waisman.wisc.edu/~oakes).

Statistical Analyses

Behavioral Data. Response bias and discriminability were analyzed using group (control, rMDD) × block (block 1, block 2) analysis of covariance, entering mean BDI-II score (averaged across sessions) as a covariate (see Results). For accuracy and RT, a second within-subjects variable stimulus (rich, lean) was added.

PCA Factors. A group (control, rMDD) × PCA factor (TF4/SF1, TF4/SF2, TF6/SF1) analysis of covariance was used to determine whether there were differences in the mean amplitude of the scalp-recorded PCA factors after controlling for BDI-II scores.

LORETA ROIs. For each ROI, an analysis of covariance with group as the between-subjects factor was used to determine whether there were group differences in levels of reward-related neural activity within the LORETA ROIs after controlling for BDI-II scores.

RESULTS

Sample

The PRT data of 34 control subjects and 26 rMDD subjects met quality control criteria. Demographic and clinical characteristics are shown in Table 1. Although the mean BDI-II scores for both groups were well below clinical threshold, the rMDD group had significantly higher scores at screening and at the time of electroencephalography recording. These two BDI-II scores were averaged, and the mean score was used as a covariate in all subsequent analyses.

Table 1. Demographic and Clinical Characteristics

	Control Subjects ($n = 34$)	rMDD Subjects ($n = 26$)	Test Value	p Value
Female, Number (%)	23 (67.6)	19 (73.1)	$\chi^2 = .21$	.65
Age, Years	29.8 (10.9)	30.6 (14.0)	$t = -.25$	.81
Years of Postsecondary Education	4.6 (2.4)	4.5 (2.1)	$t = .24$	.81
BDI-II Total Score	.9 (1.9)	2.0 (1.8)	$t = -2.25$	.03
Number of Prior MDEs	NA	2.3 (1.6)		NA
Time in Remission, Months	NA	23.4 (13.4)		NA
Past Comorbidities, Number (%)	0 (0)	8 (30.8)[a]		

Values are mean (SD) unless otherwise indicated (%).

BDI-II, Beck Depression Inventory-II; MDEs, major depressive episodes; rMDD, remitted major depressive disorder.

[a]Substance-related ($n = 8$), posttraumatic stress disorder ($n = 2$), panic disorder ($n = 1$); three participants had two of these past comorbidities.

Behavioral Data

Response Bias. A trend-level group $\times$ block interaction emerged ($F_{1,57} = 3.33$, $p = .07$, $\eta_p^2 = .06$) (Figure 1A), indicating that groups tended to differ in their reward learning (Figure 1B). Bonferroni-corrected follow-up tests showed that the response bias of healthy control subjects increased significantly from block 1 to block 2 ($p = .002$) but did not differ across blocks for rMDD participants ($p = .72$).[1]

Discriminability. There was no group $\times$ block interaction or main effect of group for discriminability (all $ps > .05$), indicating that response bias findings were not due to group differences in task difficulty.

Results from analyses of secondary variables (accuracy and RT) are presented in Supplement 1.

Scalp ERP Data

The ERP data for five healthy control subjects and four rMDD subjects were discarded because of excessive noise artifacts, leaving a final sample of 29 control subjects and 22 rMDD subjects with usable ERP data. Figure 2 shows how the original ERP waveforms at frontocentral and parietal sites were decomposed into temporospatial factors using PCA analysis. In addition to the waveforms with morphologies consistent with the RewP, for completeness, Figure 2 also shows waveforms for earlier (<200 ms) and later (>300 ms) components.

A significant group $\times$ PCA factor interaction emerged [$F_{2,96} = 4.16$, $p = .047$, $\eta_p^2 = .08$]. Bonferroni-adjusted post hoc tests showed that group differences emerged for factor TF4/SF2 ($p = .03$). This positive-going centroparietal PCA factor peaked 294 ms following reward feedback and was blunted in the rMDD group relative to controls.

LORETA Data

Eight ROIs were chosen from the fMRI meta-analyses and used in LORETA analyses. Table 2 and Figure 3C show the coordinates and spatial extent of the ROIs defined. For reference, Figure 3A and B shows the ROIs from the meta-analyses from which our LORETA ROIs were defined. Specifically, Figure 3A displays significant clustering for regions with greater fMRI blood oxygen level–dependent activation for more rewarding outcomes in the meta-analysis by Bartra et al. (21). Figure 3B shows the activation likelihood estimation map highlighting the brain regions most consistently activated by monetary rewards in the meta-analysis by Sescousse et al. (22). Analyses showed a main effect of group for the ACC meta-cluster ($F_{1,48} = 4.92$, $p = .03$, $\eta_p^2 = .09$) and the pregenual ACC (pgACC) cluster ($F_{1,48} = 4.87$, $p = .03$, $\eta_p^2 = .09$). For both clusters, reward-related neural activity was diminished in the rMDD group relative to the control group. Furthermore, reduced activity in the ACC meta-cluster ($r = .46$, $p = .001$, $n = 51$) and the pgACC cluster ($r = .42$, $p = .002$, $n = 51$) correlated with poorer reward learning on the PRT (Figure 4).

We also examined associations among the LORETA ROIs and the TF2/SF4 PCA factor. Consistent with the centroparietal scalp topography of this factor, a significant positive correlation emerged between its amplitude and reward-related activity in pre-SMA ($r = .32$, $p = .02$, $n = 51$). Furthermore, activity within pre-SMA was associated with increased activity in both ACC clusters (ACC meta-cluster, $r = .46$, $p = .001$, $n = 51$; pgACC, $r = .34$, $p = .01$, $n = 51$) and a trend toward increased overall response bias on the PRT ($r = .27$, $p = .056$, $n = 51$). Additional correlations involving measures of depression chronicity are presented in Supplement 1.

DISCUSSION

The goal of this study was to examine the neural processes underpinning reward learning in individuals with rMDD relative to control subjects with no history of depression. Although abnormalities in reward learning have been suggested as a trait-like characteristic of MDD (7), the neural mechanisms associated with reward learning deficits in individuals with rMDD remain unclear. Results showed that in contrast to healthy control subjects, individuals with rMDD had a tendency toward poorer modulation of behavior based on prior reward contingencies. This behavioral impairment was mirrored by blunted neural responses to reward feedback (as indexed by scalp-recorded ERPs) and reduced reward-related activation in the ACC (estimated using LORETA). Collectively, these findings suggest that reward learning impairments observed in acute MDD persist into full remission and that these impairments may be attributable to abnormalities in the neural substrates that support reward feedback monitoring.

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[1]When comorbidities in the rMDD group were taken into account, we found that both rMDD subsamples failed to show a significant increase in response bias from block 1 to block 2 of the PRT ($p = .88$ for subjects with past depression only; $p = .34$ for subjects with a comorbidity), indicating that effects did not differ according to comorbidity status.

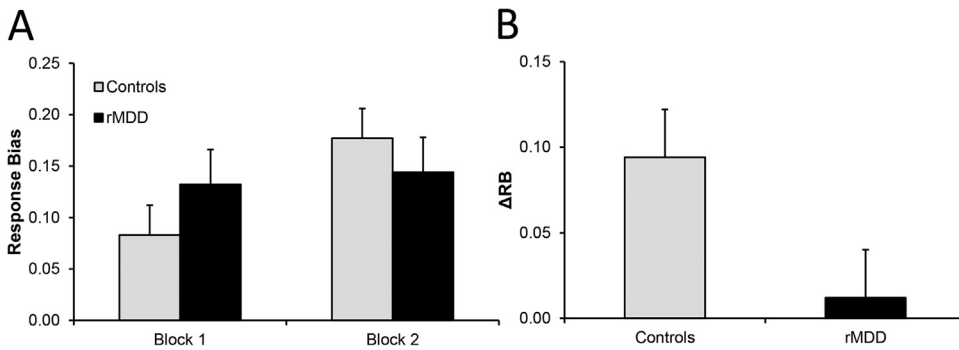**Figure 1.** Group differences in **(A)** response bias and **(B)** reward learning (ΔRB = Response Bias [Block 2] − Response Bias [Block 1]). ΔRB, change in response bias; rMDD, remitted major depressive disorder.
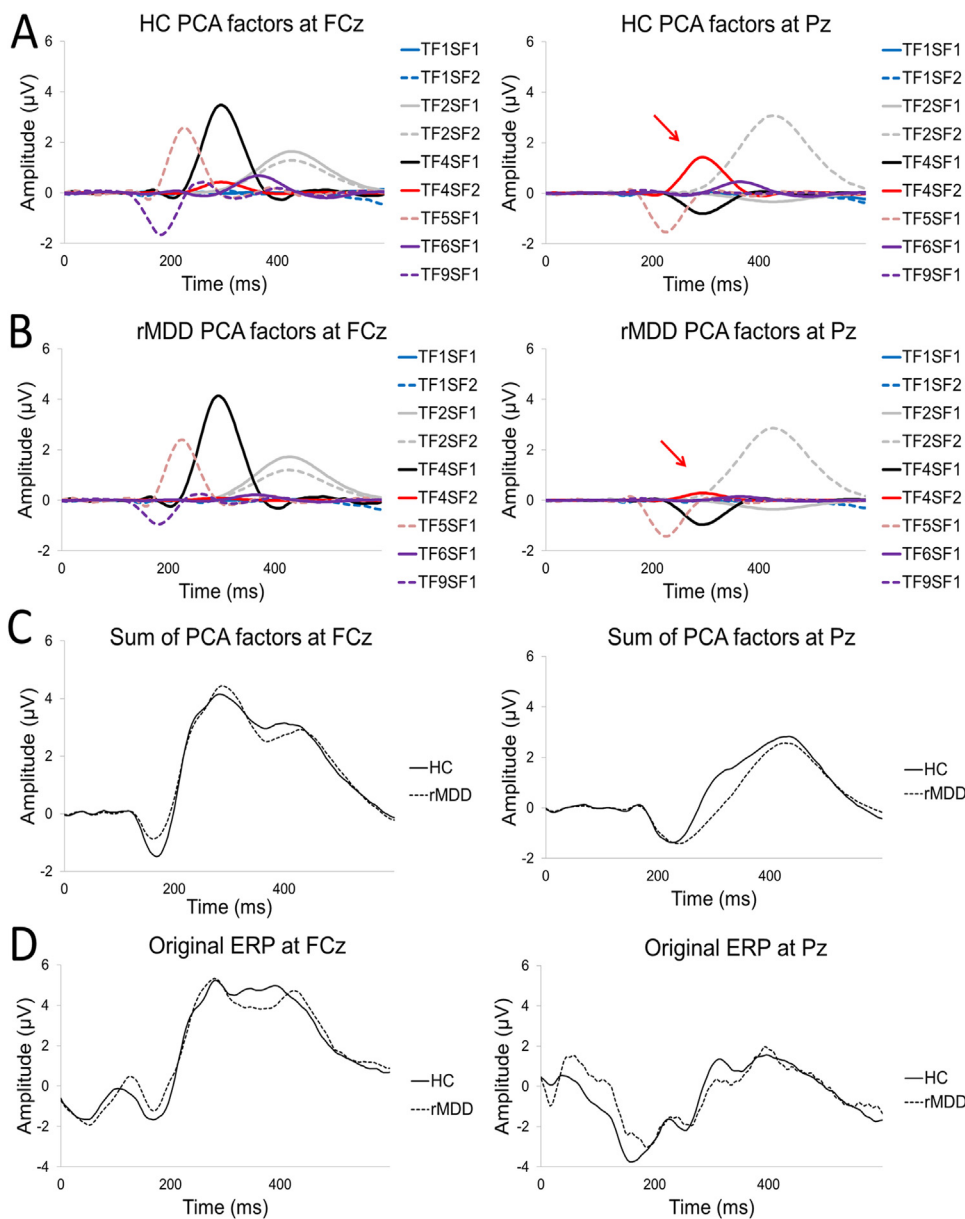

Figure 2. Individual principal components analysis (PCA) factors in the healthy control (HC) **(A)** and remitted major depressive disorder (rMDD) groups **(B)**, sum of all PCA factors **(C)**, and the original event-related potential (ERP) waveforms **(D)**. Panels on the left are at the frontocentral site (FCz), and panels on the right are at the parietal site (Pz). Arrows indicate PCA factor TF4/SF2, which was significantly reduced in the rMDD group relative to the HC group.

Table 2. Regions of Interest Entered in the Analyses

Region	ROI Source	Side	fMRI Meta-analyses[a]			LORETA Approximation[b]			Voxels	Vector[c]
			x	y	z	x	y	z		
Posterior OFC	Sescousse	Left[d]	−25	35	−18	−25.75	34.50	−16.50	4	.90
vmPFC	Bartra	Middle	2	46	−8	1.20	46.40	−8.80	5	.89
	Sescousse	Right	12	60	0	12.75	60.75	−.75	4	1.06
	Meta-cluster	Middle				6.98	53.58	−4.78	5	
pgACC	Sescousse	Middle[e]	−5	38	7	−5.33	38.00	8.00	3	.33
ACC	Bartra	Middle	−2	28	28	−1.25	29.25	27.25	4	1.46
	Sescousse	Right	8	36	24	8.67	35.67	24.33	3	.75
	Meta-cluster	Middle				3.71	32.46	25.79	4	
PCC	Bartra	Middle	−4	−30	36	−3.00	−32.00	36.00	3	2.24
	Sescousse	Middle[e]	1.33	−34.67	26.67	1.67	−34.33	29.00	3	.47
	Meta-cluster	Middle				−.67	−33.17	32.50	3	
Pre-SMA	Bartra	Middle	−2	16	46	−1.25	15.25	46.50	4	1.06
Anterior Insula	Bartra	Right	32	20	−6	32.00	20.50	−6.00	2	.50
	Sescousse	Right	36	22	−6	35.50	20.50	−6.00	2	1.58
	Meta-cluster	Right				33.75	20.50	−6.00	2	
Anterior Insula	Bartra	Left	−30	22	−6	−31.00	20.50	−6.00	2	1.80
	Sescousse	Left	−28	16	−8	−27.50	17.00	−9.50	2	1.12
	Meta-cluster	Left				−29.25	18.75	−7.75	3	

ACC, anterior cingulate cortex; fMRI, functional magnetic resonance imaging; LORETA, low-resolution electromagnetic tomography; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; pgACC, pregenual anterior cingulate cortex; pre-SMA, pre–supplementary motor area; ROI, region of interest; vmPFC, ventromedial prefrontal cortex.

[a]Coordinates reported in Bartra et al. (21) (positive effects of subjective value on blood oxygen level–dependent imaging) and Sescousse et al. (22) (monetary reward meta-analysis).

[b]Mean coordinates of LORETA center of gravity of the cluster minimizing the distance (vector[c]).

[c]Distance (in mm) between LORETA approximation and fMRI coordinates.

[d]Averaged over two left regions.

[e]Averaged over right and left regions.

Consistent with predictions and with our prior work (7), individuals with rMDD showed poorer ability to modulate behavior as a function of reinforcement, as evidenced by a reduction in reward learning on the PRT. Although the group × block interaction for response bias fell just below significance in the current study, this is possibly due to the smaller sample size, as our prior significant effects were observed in a larger sample of 37 control subjects and 47 rMDD subjects (7).

Prior work using the PRT has shown evidence of similar impairments in response bias development in individuals with acute MDD (3) and individuals with high depressive symptoms (25), and further studies point to disruptions in reward-related phasic dopaminergic signaling as a potential source of this impairment. Specifically, blunted response bias has been observed after administration of a low dose of the D_2/D_3 agonist pramipexole [which is assumed to reduce phasic dopaminergic signaling via dopaminergic autoreceptor stimulation (34)] and after a laboratory-based stressor hypothesized to interfere with phasic dopaminergic signaling (35). Deficits on the PRT have also been found to improve in acutely depressed (36) as well as remitted depressed (37) individuals who smoke, putatively because nicotine increases phasic dopaminergic firing (38,39). These separate lines of evidence provide support for the hypothesis that the blunted response bias observed in our rMDD sample may reflect a trait-like dysfunction in phasic dopaminergic signaling that persists beyond depression remission.

In line with blunted response bias, individuals with rMDD evidenced reduced modulation in the ERP waveform at PCA factor TF2/SF4, which was a positive-going component that peaked at 294 ms following receipt of reward feedback. The polarity and timing of this factor suggest that it most likely captured variance attributable to the RewP. Prior research indicates that the RewP varies in accordance with mesolimbic reward circuit activity elicited during early evaluation of outcomes against predictions (40). Consistent with the hypothesized role of mesolimbic deficits in depression (41), previous studies have found reductions in RewP amplitude (as measured by FRN amplitude changes under win vs. loss conditions) in individuals with acute MDD (17,18). Our findings extend this work by showing that RewP amplitude is also present in asymptomatic individuals who are in complete remission from depression. Importantly, the RewP factor could be distinguished from another positive-going, slower wave component (TF2/SF2) that peaked at 426 ms, which likely captured variance associated with the P300. Taken together, these findings indicate that reward learning deficits in individuals with rMDD may be linked to deficits in neural responses to reward feedback occurring at the point in neural processing where the value of reward feedback is evaluated against internal predictions.

Our LORETA analyses clarified that the rMDD group had reduced reward-related neural activation in the ACC. Specifically, we found reduced activity to reward feedback in the
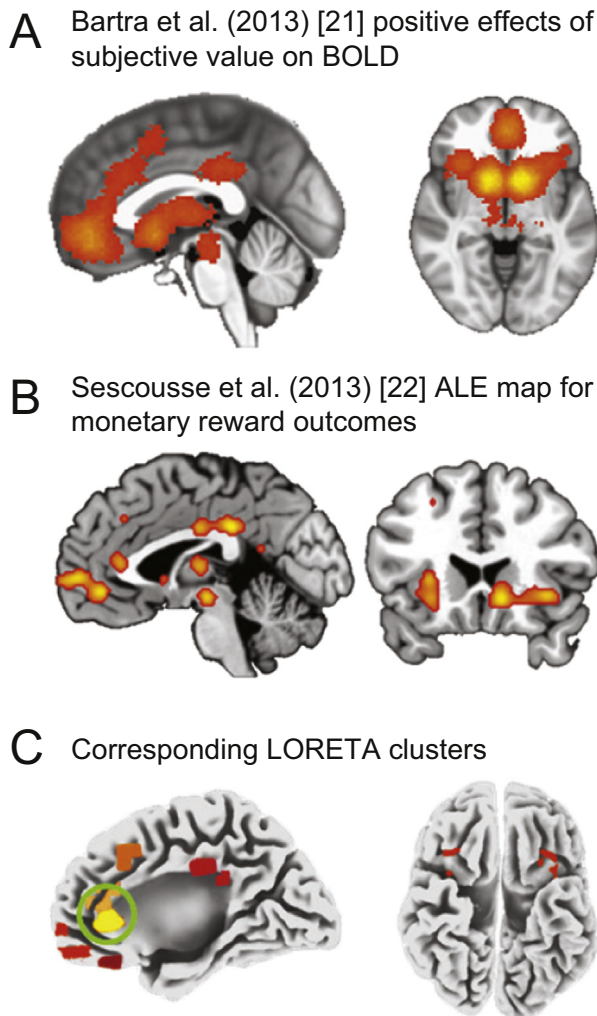
A   Bartra et al. (2013) [21] positive effects of
subjective value on BOLD

B   Sescousse et al. (2013) [22] ALE map for
monetary reward outcomes

C   Corresponding LORETA clusters

Figure 3. Bartra *et al.* (21) whole-brain meta-analysis showing significant clustering of regions with greater blood oxygen level–dependent (BOLD) activity in response to reward outcomes **(A)**, Sescousse *et al.* (22) activation likelihood estimation (ALE) map for monetary reward outcomes **(B)**, and the low-resolution electromagnetic tomography (LORETA) clusters defined in the current study **(C)** with regions showing reduced activation in the remitted major depressive disorder group (anterior cingulate cortex and pregenual anterior cingulate cortex) circled in green.

ACC and the pgACC clusters (21,22), which was associated with poorer behavioral reward learning. These findings align with prior evidence of reduced ACC activity during reward anticipation in individuals with MDD (42) and the role of these regions in reward learning (43), particularly in experimental settings requiring integration of reinforcement history over time (20). These findings extend prior work by showing that reward processing deficits in individuals with rMDD 1) arise very early in the course of information processing and 2) involve disruption in an area (the ACC) that forms action-outcome associations for the purpose of guiding goal-directed behavior.

In addition to the involvement of the ACC, we found that reduced RewP amplitude and poorer overall response bias were linked to lower reward-related activity in pre-SMA.

Reduced activity in pre-SMA was also associated with blunted activity in the two ACC clusters. Although directionality cannot be inferred from these correlations, one possible explanation for this relationship is that it captures the interactive effects of disruption in reward processing originating in the striatum and ACC. Specifically, during reward learning, striatal reward signals project to the ACC, and pyramidal neurons in the ACC then project to the primary and supplementary motor areas (44), putatively transforming motivation and cognitive inputs into preparatory actions. It is possible that in individuals with reduced reward-related ACC activity (e.g., individuals with rMDD), there may be a disruption in the reward-outcome representations necessary for the development of preparatory motor responses in pre-SMA, which causes reward learning deficits.

Additional studies are needed to confirm this speculation and address the limitations of the current work. First, the predictive validity of reward feedback monitoring deficits in identifying risk for relapse in rMDD needs to be examined. Although blunted RewP has been found to predict MDE onset in adolescent girls (10), it is unclear whether it has sensitivity and specificity in identifying individuals who subsequently develop recurrent depression and who may warrant targeted preventive intervention. Second, LORETA analyses did not correct for multiple comparisons (as the ROIs were defined a priori), and these findings await independent replications. Third, the design of the reward task used in the current study precludes the assessment of ERP difference waves that capture processing of reward versus nonreward (e.g., penalty) feedback. Finally, we examined responses elicited only during reward receipt and not during reward anticipation; this is an important area for future research because evidence indicates that reward anticipation may be blunted in acute MDD (45) but intact in rMDD (46,47). Specifically, although Dichter *et al.* (46) found blunted neural responses to reward outcomes in rMDD, reward-related hyperactivation within the pgACC emerged during reward anticipation. This finding was interpreted as evidence of relatively greater neural resources needed to represent the value of anticipated rewards in individuals with rMDD. Similarly, although individuals with rMDD have been shown to have reduced ventral striatal responses to pleasant stimuli (e.g., the smell of chocolate), differences in the subjective wanting of these stimuli have not been found (47). Taken together, findings of normative reward anticipation but blunted responses during reward outcome in rMDD indicate that vulnerability to depression may be characterized by reductions in hedonic capacity, whereas acute MDD may be associated with deficits that extend to the "wanting" of rewards. Future longitudinal studies are needed to confirm this conjecture.

In conclusion, the current findings extend our understanding of depression by showing that reward learning impairments observed in acute MDD persist into remission and that these impairments are accompanied by abnormalities in the neural processes that support reward feedback monitoring, particularly processes involving the ACC. These findings provide a basis for future longitudinal research to assess whether abnormalities in these neural systems can identify individuals with rMDD at risk for relapse who may benefit from targeted preventive intervention.
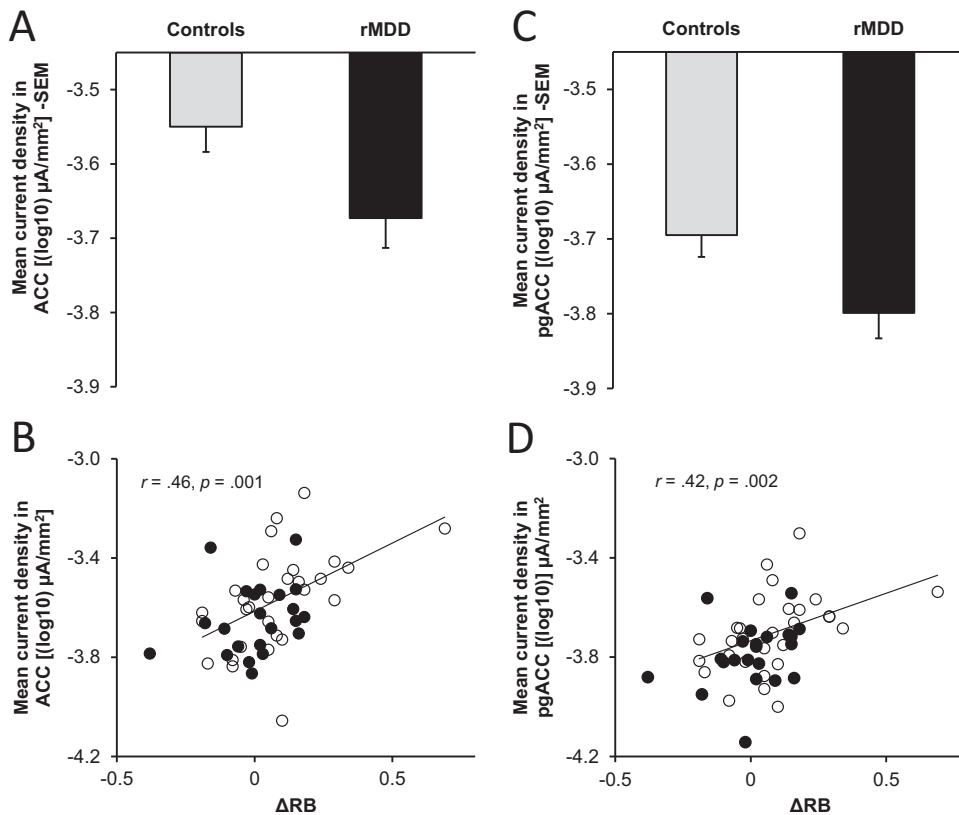
Figure 4. Group differences in reward-related mean current density in the anterior cingulate cortex (ACC) meta-cluster **(A)** and the pregenual anterior cingulate cortex (pgACC) cluster **(C)** and correlations between mean current density in these regions and reward learning (change in response bias [ΔRB]) **(B, D)**. In **(B)** and **(D)**, correlations remain significant after removing the control subject with the highest ΔRB. On the y axis, numbers are negative because of the log10 transformation.

ARTICLE INFORMATION

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Received Sep 17, 2015; revised Sep 28, 2015; accepted Sep 28, 2015.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.bpsc.2015.09.007.

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