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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

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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,

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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 $\pm$ 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