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Attentional Bias Predicts Increased Reward Salience and Risk Taking in Bipolar Disorder

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ABSTRACT

BACKGROUND: There is amassing evidence that risky decision-making in bipolar disorder is related to reward-based differences in frontostriatal regions. However, the roles of early attentional and later cognitive processes remain unclear, limiting theoretical understanding and development of targeted interventions.

METHODS: Twenty euthymic bipolar disorder and 19 matched control participants played a Roulette task in which they won and lost money. Event-related potentials and source analysis were used to quantify predominantly sensory-attentional (N1), motivational salience (feedback-related negativities [FRN]), and cognitive appraisal (P300) stages of processing. We predicted that the bipolar disorder group would show increased N1, consistent with increased attentional orienting, and reduced FRN, consistent with a bias to perceive outcomes more favorably.

RESULTS: As predicted, the bipolar disorder group showed increased N1 and reduced FRN but no differences in P300. N1 amplitude was additionally associated with real-life risk taking, and N1 source activity was reduced in visual cortex but increased activity in precuneus, frontopolar, and premotor cortex, compared to those of controls.

CONCLUSIONS: These findings demonstrate an early attentional bias to reward that potentially drives risk taking by priming approach behavior and elevating reward salience in the frontostriatal pathway. Although later cognitive appraisals of these inputs may be relatively intact in remission, interventions targeting attention orienting may also be effective in long-term reduction of relapse.

Keywords: Accumbens, FRN, mania, N1, P300, Reward, Risk taking, Striatum

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Impulsive and risky decision making characterizes bipolar disorder as well as a variety of other psychiatric disorders, including addiction (1), attention-deficit/hyperactivity disorder (2), and antisocial personality disorder (3). Using functional magnetic resonance imaging (fMRI), we have previously shown that impulsivity and risk taking in bipolar disorder are related to a greater activation of frontostriatal regions in response to rewards (4). However it is not clear at what stage(s) of processing this bias manifests and, therefore, which stage(s) may be most amenable to intervention. Here we sought to further delineate attentional, motivational, and cognitive stages of processing in the same subjects, by using the superior temporal resolution of electroencephalography (EEG).

EEG is able to delineate several functionally, temporally, and spatially distinct components of the reward-based decision-making system, not yet dissociable by current fMRI techniques. Although there is considerable overlap among these components, they can be conceptualized as somewhat sequential and can be broadly defined by their sensory (indexed by N1), motivational (feedback-related negativity), and cognitive (P300) processes. Most studies of reward and impulsivity have focused on the performance-monitoring system, which generates error-related negativities (ERN) and feedback-related negativities (FRN). The FRN system performs an early evaluation of outcomes against predictions, with rewards eliciting a smaller FRN deflection than losses (5). This reduction in FRN has been theorized to be related to frontostriatal dopaminergic activity that superimposes a "reward positivity" at the same latency (6). In line with this, recent studies using combined EEG and fMRI have identified FRN sources in ventromedial prefrontal (7,8) and anterior cingulate (8,9) cortices, as well as in striatum (7,8,10). Furthermore, ventral striatum volume predicts FRN amplitude in response to rewards (11). Clinically, FRN amplitude correlated with the blunted fMRI activations of ventral striatum that were observed in depression, which also related specifically to anhedonia (12). Of relevance to bipolar disorder, differences in FRN measurements relate to impulsivity and reward sensitivity traits (13,14). Furthermore, this FRN performance-monitoring system mediates a stronger preference for rewards in hypomania (particularly immediate compared to delayed rewards) (15) and a reduced impact of losses (16), consistent with previous fMRI findings of abnormal reward-based decision-making in bipolar disorder (4,17,18,19).

Occurring immediately after the FRN, the processes that generate the P300 encode a more elaborated and conscious appraisal of the motivational significance of an outcome (20). In particular, this system may use evaluations from the performance monitoring processes to update future predictions in working memory, guide attention, and adjust ongoing behavior (21). Consistent with these diverse processes, a distributed network of sources has been identified across frontal, parietal, and temporal areas, including dorsal prefrontal

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cortex, precuneus, anterior and posterior cingulate, and supplementary and premotor areas (22,23). The reward-elicited P300 is also positively associated with trait reward sensitivity (24) and is more pronounced in euthymic bipolar disorder patients (25), possibly indicating a greater orienting of attention toward reward outcomes.

Recent evidence suggests that reward-related differences may also manifest earlier, in low-level visuosensory processing in extrastriate visual cortex, which generates the N1 component (15,26). Although originally thought to reflect purely sensory aspects of stimuli, it has been shown that this system is also influenced by attention (27) through prefrontal cortical inputs to visual cortex (28,29). This top-down influence explains how the N1 can be modulated by affect (30), as well as by more abstract aspects of motivational feedback, such as valence and delay (15). In addition, the last study demonstrated that these early sensory-attentional processes predicted steeper devaluing of delayed rewards evident in a nonclinical hypomania group. This provides initial evidence that early attentional processes, which precede the contribution of both the FRN and the P300 systems, contribute importantly to clinical impulsivity.

In the present study, people with euthymic bipolar disorder underwent simultaneous EEG–fMRI. To separate the attentional, motivational salience and cognitive appraisal stages from the EEG, we did not use the fMRI to constrain the EEG (but instead, used this in a separate analysis [see *Methods and Materials*]). The fMRI analyses, described elsewhere (4), revealed both a hyperactivation of the ventral frontostriatal network (including anterior cingulate and ventromedial prefrontal cortex) and an attentional bias toward risky rewards (in dorsal prefrontal cortex) compared to that in controls. Based on the view that activity in these ventral frontostriatal sources generates a reduced (i.e., more positive) FRN (6), we expected that the bipolar disorder group would show reduced FRN in this study. We also hypothesized that differences in these motivational processes would be influenced by earlier sensory-attentional inputs (c.f. 15). Based on this earlier work, we predicted that rewards (compared to losses) would elicit increases in N1 and its extrastriate cortical sources and that this effect would be more pronounced in the bipolar disorder group. Finally, in a later cognitive appraisal (P300), we expected that this group would show greater attentional focus on rewards, as well as on greater approach motivation, manifested by a more pronounced P300 for rewards and greater activity in dorsal prefrontal and premotor areas.

METHODS AND MATERIALS

Participants

Participants were 20 patients with bipolar disorder in remission and 20 controls matched for age, gender, and level of education [see Mason *et al*. (4)]. Data for one control subject was discarded due to technical failure. Briefly, diagnosis and remission of at least 2 months was confirmed using Structured Clinical Interview for DSM-IV Axis I Disorders (31). Current alcohol abuse and substance use were excluded. Participants in receipt of antipsychotic medication in the previous 6 months were also excluded to reduce the effect of medication on reward-related activations (32,33). Residual manic and depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale and 12-item Bech-Rafaelsen Mania Scale, respectively. Participants also completed the Domain-Specific Risk-Taking Scale (DoSpeRT) (34). Informed written consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

Task

Participants played a modified version of a previously validated Roulette task (35), described in detail elsewhere (4). Briefly, participants chose which of four colors to bet on, each of which had the same reward probability (25% or 75%), and bet size (£3 [$4.46 USD] or £9 [$13.37 USD]) was fixed for each trial. After they chose, there was an anticipation phase in which the Roulette wheel spun, followed by outcome (gain or loss [Figure 1]). Participants were instructed to respond within the fixed selection time and were informed that a random choice would be automatically made if a timely response was not issued. There were a total of 272 trials over eight 6-minute runs, with probability and stake being equally distributed across each run. Participants were informed that they would be paid the actual winnings from the task at the end of the experiment.

Data Collection and Preprocessing

Participants wore a [^{63}Ag]AgCl electrode EEG cap (Braincap MR; Brain Products GmbH, Gilching, Germany) with a sampling rate of 5000 Hz, later down-sampled to 250 Hz. Impedance levels at each electrode were below 5 kOhm (scalp) and 30 kOhm electrocardiograph at the time of entering the scanner. BrainVision analyzer 2.0 (Brain Products GmbH) was used for preprocessing and averaging. Steps taken to correct for scanner-related artifacts are reported in

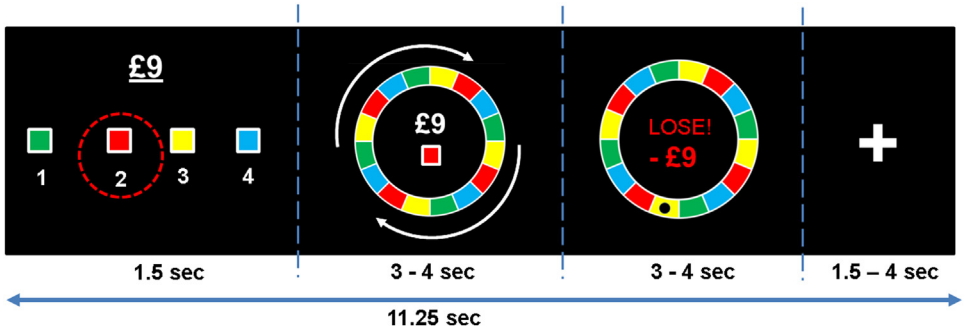

Figure 1. Participants made (9£ $1.49 [USD]) bets on which color would win in a Roulette gamble. The trial sequence consisted of three phases: appraisal/selection, outcome anticipation while the wheel spun, and outcome evaluation when the ball stopped on one of the colors, signifying delivery of the reward or loss.