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The Atypical Neural Processing of Reward in Bipolar Disorder

Yiran Yuan[1,a,*]

[1]*Beijing No.35 High School, Beijing, China*
a. a84363960@tzc.edu.cn
**corresponding author*

Abstract: There are still many unanswered questions regarding bipolar disorder among researchers. Understanding the characteristics of a particular area and neuroeconomics can aid in a more thorough examination of reward dysfunction and the reward process. Because changes in reward are undoubtedly one of the most prevalent signs of psychopathology in humans, researchers try to understand the prevalence of these diseases as well as the importance of reward in the manifestation of these conditions. Research indicates that different biological entities with comparable phenotypic symptoms make up bipolar illness. Finding the primary and secondary rewards connected to the functioning resting-state of bipolar illness patients' brain circuits is the goal of another investigation. On the other hand, using a reward task that begins with the expectation and consumption of rewarding and nonrewarding outcomes and progresses through fixation point, target, and outcome screen, researchers hope to better understand the connections between healthy individuals and BD patients' reward processing and striatal responses. This review can provide some suggestions to the development of prevention and intervention programs for individuals at risk of BD.

Keywords: Bipolar Disorder, neural processing, reward processing, stress.

1. Introduction

In psychopathology, abnormal reward processing has a feature that transdiagnostic. Nowadays, because almost any similar case which has a little bit difference are diagnosed as bipolarity, it shows limitations in articulating integrate opinion on bipolar disorder [1]. As a result, considering different aspects of reward processing and neuroeconomics field that can aid to understanding reward process. To better understand reward dysfunction, researchers need to find characteristics of specific region, like hedonics, reward anticipation, facilitation and so on [2]. In recent years, there has been a "unified field theory" of diseases that begin early in life, get worse with time, and involve neurodevelopmental problems such as bipolar illness that are associated to functional abnormalities. Several research investigations have already indicated a number of processing impairments that may cause different kinds of selective modifications in reward-related behavior. These investigations addressed signaling from positive prediction errors, cost variables and reward dysfunctional weighting, (mal)adaptive scaling and anchoring, and concluding valuation systems. Moreover, cellular research has shown that fast shrinkage of brain regions is required for cognitive function and mood regulation; as a result, bipolar disorder is associated with disturbance of glial-neuronal interactions. In the euthymic state, sometimes referred to as drive inflammatory activation, the body will revert to normal in accordance

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with modifications in the hypothalamic-pituitary-adrenal axis. Research also shows that both the manic and depressed stages of the illness, inflammation rises, and hyperactive microglia are present in bipolar individuals. In conclusion, etiology and onological state cannot be combined by a single gene, pathway, or aberrant brain activity to produce complete knowledge. Researchers therefore strive to explore the possibility that this perspective could lead to the discovery of other related forms of bipolar disease and have a major impact on treatment outcomes, which is why researchers need to expand and enhance treatment.

Repeated mood episodes, no matter how small, have been shown in epidemiologic studies to cause significant volumetric changes in the brain that are linked to impairment in numerous functional domains. Research indicates that bipolar disorder is a destructive and violent syndrome. Researchers now know that neuropsychological deficiencies consistently maintain that patients with the illness are in a euthymic state. Regretfully, rather than precisely defining causal pathways, the existing diagnostic criterion for bipolar disorder only relies on descriptive nomenclature [1]. Furthermore, the current pharmaceutical therapies suffer from worsening metabolic conditions. Additionally, negative effects impair cognition in those who already struggle in this area. Consequently, difficulties associated with treatment and polypharmacy often result in less-than-ideal treatment adherence. Thanks to advancements in genetics, neuroimaging, biochemistry, and other fields, bipolar disease may now be seen from various angles. Finally, a deeper understanding of the neurobiological distinctions across bipolar subtypes is necessary to enhance treatment success and minimize adverse effects. According to studies, there are several biological entities that make up the diagnostic entity known as bipolar disorder, all of which share comparable phenotypic characteristics. Improved knowledge of the connection between the phenotypic signs of bipolar illness and microscopic and macroscopic brain abnormalities (such as modifications in cellular and subcellular signaling) should result in less disruptive and more successful treatment approaches. Because the sickness is diverse in terms of both hereditary and neurological makeup, researchers are attempting to investigate probabilistic relationships between the pathophysiological bases and clinical presentations of the illness.

Take into account the frequency of these diseases as well as the importance of reward in the manifestation of these conditions [2]. It is arguable that one of the most prevalent signs of psychopathology in humans is reward modification. These symptoms might potentially be a factor in the comorbidity of the two mental illnesses. This is because a variety of distinct disorders are listed as having similar symptoms in the official diagnostic standards. Furthermore, because the formation and appearance of various forms of psychopathology are fundamentally impacted by comparable or related reward processing problems. These days, scholars try to establish a conceptual framework for reward abnormalities and to summarize the existing understanding of reward processing in psychopathology. Particularly, they are drawn from the emerging domains of neuroeconomics and behavior. Recent research has yielded novel insights into the mechanisms involved in decision-making and valuation.

2. The Complications of Reward Processing in BD

2.1. Reward Processing in BD and At-Risk Populations

This study looks at how reward prediction errors in the prefrontal brain of bipolar illness patients and their family members progress abnormally [3]. It is believed that differences in impulsiveness and pleasure-seeking impact how the brain interprets rewards, predicts mistakes, and links susceptibility in families. The study uses a financial card game to compare functional magnetic resonance imaging (fMRI) data from BD patients and their unaffected first-degree relatives with those from healthy people. Studies look at how the prefrontal cortex, ventral striatum, and midbrain behave differently

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while predicting errors or valuing rewards. Because of this, the prediction error signal is reduced in the ventrolateral prefrontal cortex and the supplementary motor area in both BD patients and their unaffected relatives. In comparison to healthy controls, there is no correlation observed between the dorsal anterior cingulate cortex prediction error signal and the out-of-scanner motor inhibition measure in patients with BD and their unaffected relatives. As expected, the study finds that prefrontal inhibitory control deficits are linked to reward processing anomalies in BD patients. However, insufficient planning movement activation seems to suggest a connection to the family history of BD patients.

The first 10 volumes of each subject were removed in order to reduce the impacts of magnetization disequilibrium and participant acclimation to the scanning noise. Spatial realignment was therefore omitted for head motion correction (mean head motion,) greater than 0.2 mm/degree [4]. The 17th slice was used as the reference for slice time calculations. Following the removal of one patient from the BDM group from the statistical analysis, there was no significant difference between the two groups' numbers of outlier volumes. The composite average and maximum assessments of head motion did not differ between the two groups. Following this, each patient's segmented, high-resolution T1-weighted anatomical images were registered to their fMRI scans, and regression analysis was performed on the signals originating from their cerebral spinal fibers and white matter. After normalization, an isotropic, 6-mm full-width at half maximum Gaussian kernel was used to spatially smooth the fMRI images. Ultimately, respiratory and cardiovascular noise was eliminated using temporal band-pass filtering and detrending.

This work investigates the relationship between the resting-state function of brain circuits and main and secondary rewards affected by bipolar disorder. There are sixty BD patients in this study; twenty-one of them have depressive episodes (BDD), and the remaining forty have manic episodes. When BD patients' secondary reward circuit is compared to that of normal participants, researchers find that rsFC at the orbitofrontal cortex and left ventral striatum is smaller. Additionally, rsFC shows a lowest level in BDD and a highest level when situated between the OFC and right striatum, or amygdale in BDM. Researchers use resting-state functional connectivity (rsFC) to calculate participants' interest-wise analyses area. These findings suggest that BD patients may exhibit unusual patterns of rsFC at these locations during second reward and in relation to their mood states.

A monetary incentive delay (MID) task is one in which participants are aware that, upon completion of the training session, they will receive a monetary reward [5]. Participants in the task are thus presented with five distinct amounts of money (500,100), including the option to gain no money at all (0,{0}) or lose some money (-100). In addition to one trial where participants are prompted to press a button to indicate success, there is another with no incentive or feedback (0). The crossbar will be presented after a configurable delay of 1500–2000 ms, during which participants must wait. After that, they pressed a button to react for varying lengths of time (between 100 and 700 ms) to a white target square. To keep participant hit rates between 60 and 70 percent, researchers modified the target square's presentation duration based on each participant's performance. For instance, the target's display length was decreased by 30 ms if participants "hit" it in all except the "0" or "[0]" trials over the last three trials. With the exception of "0" or "[0]" trials, people's time to "miss" the target was increased by 30 milliseconds if they failed to do so on two or more trials. Participants can view comments regarding their task performance following each trial. Participants that perform well will receive financial compensation as a reward. Each cue was delivered ten times during the task's two runs of fifty trials, with the cues' order being pseudo-random each time. Before the initial run, there will also be a quick practice run. Using a 7-point Likert scale, participants evaluated the level of tension and joy connected with each reward at the conclusion of each run. A higher score indicated a higher level of stress or joy.

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Few studies explore the difference of reward system abnormalities in remitted states, however, in this study by using functional MRI in Monetary Incentive Delay task. In this research there are 65 patients in total. 33 of them are BD patients, 32 of them are MDD patients, 33 of them are healthy controls [6]. Researchers also test the difference between the dimensional effect of depression in brain and normal condition. As a result, researchers found out BD patients decreased activation a lot in anterior cingulate cortex, anterior insula (AI) and putamen, when there is reward compared to healthy people. MDD patients have decreased lots of activation in AI and brainstem. There are serious trend-level differences in BD patients and MDD patients in right brainstem. In this study shows there are difference depression effect on reward system between BD patients and MDD patients. To conclude, in future studies the reward system may should distinct MDD and BD patients' depressive phase.

There is a study to distinguish healthy youth at bipolar disorder familial risk and youth at a major depressive disorder familial risk to find out their neural correlations of reward processing. That is because youth at BD-risk and MDD-risk have characteristics of abnormal reward processing. By comparing 45 healthy participants, 41MDD-risk, and 40 BD-risk through the MID Task in monetary game to find out their activation and connectivity. In the study, it focusses behavioral and clinical outcomes in around 2.08 to 6.66 years by MID task. Researchers find that BD-risk have lower activation in cerebellum when compare to HC and MDD-risk. In monetary gain games, researchers use region-of-interest(ROI) analyses in ventrolateral prefrontal cortex, thalamus, putamen seeds and nucleus accumbens. To BD-risk, MDD-risk has higher connection in left-superior temporal gyrus, thalamus, cerebellum, left middle frontal gyrus, by psychopathological interaction analyses. When there is reduced thalamic activation in reward process with decrease in prosocial behavior and increase impulsivity, researchers then can distinguish familial risk for BD with MDD familial risk indicated that social dysfunction during adolescence.

2.2. A Developmental Perspective

Studies have shown that it is effective in identifying abnormal expected value (EV) and reward prediction error (RPE) signals in people with BD [7]. There were three steps in each of the 48 trials in this exercise: guessing, anticipation, and outcome phase. Players must click the button to indicate whether they thought the value of the card that will be shown later would be higher or lower than three or five seconds during each guessing phase. Then, a sign showing an upward, downward, or no arrow will be displayed and will jitter for a few seconds to indicate the probability of winning, losing, or nothing changing during the waiting period. A feedback screen with three distinct dollar symbols will therefore appear after the real number on the card (500 ms) appears. The dollar symbols are a green dollar symbol with an upward-pointing arrow (500 ms) indicating gain (6 DKK), a red dollar symbol with a downward-pointing arrow (4.5 DKK), or a yellow circle indicating no change (0 DKK). Consequently, anticipating a loss will result in a loss outcome (i.e., loss trials) or a no change outcome (i.e., relief trials); on the other hand, anticipating a victory will result in a win outcome (i.e., win trials) or a no change outcome (i.e., disappointment trials). The trials were randomised, with twelve appearances for each condition. They won't share information or exert influence. The exercise took seven minutes overall since the intertrial intervals were jittered with a fixation cross (0.5–1.5 s). A practice task was completed by participants before the scan. They had no idea that after the fMRI procedure, they had been paid a set amount of 30 DKK ($4.5).

The study is used to explore the special path of reward processing in bipolar disorder patients. Researchers invited both remitted BD patients and healthy people (HC) for a card guessing task and test by fMRI. 41 BD patients and 36 HC will be tested again after 16 months to explore the relation of neuronal response to reward and compute influence of mood relapse [8]. As a result, patients have lower RPE than normal people signal in ventrolateral prefrontal cortex (vlPFC) and decrease EV signal in occipital cortex, which means feature of dysfunctional reward-based learning or habituation.

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Some patients normalize EV signal over time, which means normalization of reward anticipation activity. HC has decreased in RPE signal which patients do not show. There are still some limitations, fMRI scan needs to reflect varied of process from primary to diagnosis of BD patients' illness duration, follow -up time and medication status, but fMRI cannot do that now.

This study for the first time explored bipolar disorder patients' longitudinal brain activation changes when there are win and loss anticipation to find out their special anticipatory processing. Researchers chose 34 depressed and euthymic BD-I patients and 17 healthy people to participate in study. By using fMRI six months begin and after researchers find out when healthy participants predicting possible money loss their right lateral occipital cortex reduce activity in longitudinal. Subthreshold hypo/mania symptoms are elevated in 12.5% of BD patients at baseline as abnormal longitudinal patterns of neural activity. Overall, there is likely a correlation between increased negative emotional arousal and increased occipital brain activity when bad outcomes are anticipated. That is because BD patients cannot learn and realize money loss is less than money gain. BD patients also cannot have less emotional arousal for at least 6 months.

2.3. Stress as a Relevant Factor

Processing reward under stress is likely to be different compared to without. Use a modified version of the Trier Social Stress Test (TSST) in this study to measure psychosocial stress. Fifty minutes after the start of the TSST, the incentive task was completed in the MRI scanner. The reward task in this study starts with the expectation and intake of both nonrewarding and rewarding outcomes. It then moves through the target, the outcome screen, and the fixation point. During the target presentation, participants were to hit a button as quickly as they could, regardless of the type of cue. This trial was marked as a hit if the button was touched within the allotted time.

This study explored the connect of healthy people and BD patients' reward processing and striatal responses [9]. Stress has influenced BD patients 'mood episodes and healthy participants' reward processing system which depend on time to distinguish. In the study, after stress researchers using fMRI to test participants' brain responses when there is reward processing for 50 minutes. They also set up two prerequisites for the participants: the Trier Social Stress Test and the no-stress condition. In healthy individuals, ventral striatal responses and cortisol levels increase in response to stress or reward outcomes. BD participants will also increase cortisol levels when they feel stress. To conclude, there is no difference between participants when they are feeling stress but there is difference between participants with their ventral striatal to reward outcome. This study first shows when BD patients recover from stress, how change reward processing and reduce neural flexibility of hedonic signaling. Let more researchers realize the susceptibility to environmental challenges.

3. The Effectiveness of Intervening the Reward System in BD

In order to examine neural activity during reward or loss and expectation, the study's reward task required participants to complete two event-related card-guessing games in eight minutes each. Twelve possible outcomes (16 for a loss, 12 for a win, and 12 for neutral) were included in each of the two blocks' trials, and the reward expectancy regressor was calculated from all of the trials. To guarantee that every participant felt their performance influenced the outcome, trials were given in pseudorandom order, with 75 minutes removed for a loss and one dollar awarded for a win. In fact, each trial's outcome was predetermined, with $6 won.

This study is unique in that the anode was extracephalic (EC), located on the contralateral shoulder, was stimulated [10]. During the 16.5-minute reward task, transcranial direct current stimulation (tDCS) was used, with a 30-second ramp up at the beginning and a 30-second ramp down at the end. Participants will receive a constant 1 mA current while they are in fMRI. One week apart, participants

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underwent two counterbalanced scans: the first used the F7-EC montage, which targets the left vlPFC as previously described, and the second used the CP1-EC montage, which targets the left somatosensory cortex. The participants in each group had the two scans in a counterbalanced order to reduce the possibility of practice effects on behavioral and brain interest measures. Participants also didn't know the order of the montage. The left somatosensory cortex serves as the investigation's control region. This is due to the fact that cathodal tDCS over the left vlPFC, as opposed to cathodal tDCS over the left somatosensory cortex, produced a more concentrated and potent electric field at (and current flow to) the left vlPFC, according to earlier research using eurotargeting. Somatosensory cortex tDCS has minimal effect on vlPFC and subcortical areas.

The effects of targeted cathodal transcranial current stimulation on bipolar disorder patients' reward systems are investigated in this study. The purpose of the research is to determine whether cathodal tDCS affects left vIPFC functional and activity linkages to other regions in bipolar disorder patients as well as healthy people. Consider how tDCS impacts, not the control area, but the left vIPFC's reward system and hypo-/manic episodes. Participants in a card-guessing game monitor brain activity associated with expectancy, reward, and loss perception. They are made to believe that the result is determined by how well they do, yet this is untrue. Every week, the participants will get two scans, one of which will focus on the left vIPFC and the other on the left somatosensory cortex. Selecting the left somatosensory cortex as the control region will guarantee that the cathodal tDCS over the left vIPFC have a stronger and more concentrated electric field than those over the left somatosensory cortex. To avoid confusion about the possible montage, affect result, two scans across their order and calculations made before and after each scan using the Positive and Negative Affect schedule are required. Left BA24, right BA24, and left BA32 are impacted by this, since cathodal tDCS over left vIPFC are less active than left somatosensory cortex. Post-scan affect is reduced after cathodal tDCS over left vIPFC by controlling other parameters, compared to left somatosensory cortex.

4. Conclusion

Bipolar disorder participants showed the difference between reward system activation and major depressive disorder participants in the monetary incentive delay task. And researchers have already known that both BD patients and their unaffected relative's lower prediction error signal in different regions. Thus, researchers found that BD patients reward processing have related deficits in inhibitory control of prefrontal regions. There is also a study that showed there are probably unusual patterns of rsFC at OFC and LVS in second reward and different mood states of BD patients. One of the research's results show there is no different between participants when they feel stress but has difference between participants with their ventral striatal to reward outcome, when BD patients in recovery of stress how change reward processing and reduce neural flexibility of hedonic signaling and more researchers realize the susceptibility to environmental challenges. There is one study distinguishing healthy youth at bipolar disorder familial risk and youth at a major depressive disorder familial risk to find out their neural correlations of reward processing. There probably have connection with familial vulnerability to BD patients. Also, BD patients must have a feature of dysfunctional reward-based learning or habituation. Some patients' normalization of EV signal over time, which means normalization of reward anticipation activity, but there are still need more studies. What's more, BD patients cannot learn and realize money loss are less than money gain and cannot have less emotion arousal in short time. Furthermore, a card-guessing game is used to evaluate brain activity associated to expectation and earning rewards or losses in a study examining the impact of focused cathodal transcranial current stimulation on the reward system in bipolar disorder patients. Overall, by adjusting for other variables, post-scan effect was found to be lower after cathodal tDCS over left vIPFC than over left somatosensory cortex.

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