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MOOD DISORDERS (E BACA-GARCIA, SECTION EDITOR)

Presentation and Neurobiology of Anhedonia in Mood Disorders: Commonalities and Distinctions

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Abstract

Purpose of Review To focus on the clinical and behavioral presentation of anhedonia in mood disorders, as well as the differences and commonalities in the underlying neurocircuitry.

Recent Findings Evidence suggests that depression is characterized by hypofunction of the reward system, while bipolar disorder manifests dysregulation of the behavioral activation system that increases goal-directed reward behavior. Importantly, strong evidence does not exist to suggest significant differences in anhedonia severity between depressed unipolar and bipolar patients, suggesting that there are more nuanced fluctuations in reward processing deficits in bipolar patients depending on their state. Both euthymic unipolar and bipolar patients frequently report residual reward dysfunction, which highlights the potential of reward processing deficits that give rise to the clinical symptom of anhedonia to be trait factors of mood disorders; however, the possibility that therapies are not adequately treating anhedonia could also explain the presence of residual symptoms.

Summary Reward processing represents a potential diagnostic and treatment marker for mood disorders. Further research should systematically explore the facets of reward processing in at-risk, affected, and remitted patients.

Keywords Major depressive disorder · Bipolar disorder · Anhedonia · Reward processing · Neuroimaging

Introduction

Anhedonia and other reward circuit abnormalities have been described across many psychiatric and neurological disorders, including major depressive disorder (MDD), bipolar disorder (BD), schizophrenia, attention deficit hyperactivity disorder, and substance abuse disorders [1–3]. Traditionally, anhedonia has been defined as "the inability to feel pleasure" [4; see 5 for review]. However, recent neuroscientific research on reward processing has brought about a collective effort to understand, redefine, and conceptualize anhedonia [6]. Anhedonia exists on a spectrum of reward circuit abnormalities ranging from hyperhedonia (reward circuit hyperactivation) to anhedonia (reward circuit deficit) [5]. Understanding anhedonia on a spectrum, and how it manifests differently across disorders, may help guide treatment for a range of symptomology as well as therapeutic development [7, 8, 9•]. This review will focus on the clinical and behavioral presentation of anhedonia in mood disorders, as well as the differences and commonalities in the underlying neurocircuitry.

Clinical Presentation of Anhedonia in MDD vs. BD

Clinical reports of anhedonia symptom manifestation do not support the presence of significant differences among MDD, bipolar disorder I and II (in depressed state) [10–12]. However, in a clinical sample of 291 unipolar, BD I and II patients, unipolar depressed patients exhibited greater severity of anhedonia [13]. In contrast, among youth with ADHD, those with BD reported more severe anhedonia than those with unipolar depression [14]. It is not clear from these data whether significant or non-significant differences remain after controlling for overall depression severity. Furthermore, one

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study controlling for demographic characteristics demonstrated higher anhedonia in euthymic/remitted mood disorder patients compared to healthy controls, with a lack of difference between MDD and BD [15]. The authors reported that approximately 20–25% of patients reported residual anhedonic symptoms. Although clinical presentations of depressive episodes are similar in BD and MDD, the underlying cause of anhedonia may be quite different [16•]. However, it is important to consider the implication of the last episode before remission in BD as residual symptoms can last for an extended period of time after remission [17].

Importantly, whether anhedonia represents a state or trait in mood disorder patients is still not established. Among MDD inpatients, anhedonia scores remained stable over 7 months despite recovery in 75% of patients [18]. This is consistent with later findings in another observational study in chronic MDD patients, where anhedonia did not change over 1 year, irrespective of reductions in depressive symptoms [19]. Additionally, evidence suggests dysregulation in the trait behavioral activation system (BAS), which reflects the movement toward a desired stimulus or activity, is a vulnerability factor for BD [20]. In parallel, Quilty and colleagues [21] reported BD patients scored higher on behavioral activation than MDD patients. In the BAS/reward hypersensitivity model of BD, Alloy and Abramson [22] proposed that stable reward hypersensitivity exists in BD, while negative or positive experiences (i.e., obtaining the desired reward or not) can lead to both manic (reward attained) and depressive (reward not attained) symptoms. Thus, this model of BD suggests state fluctuations occur due to BAS "overreaction" in response to positive or negative outcomes during goal pursuit [22]. Nusslock and colleagues [23] instead suggested that while the BAS over-activation model likely holds true during mania, it is unlikely that reward circuit hyperactivation is responsible for major depressive episodes.

Interpretation of the above data as a trait factor should be done with caution as it is unclear whether anhedonia is related to the failure of treatment in targeting or exacerbating this symptom. This can be gleaned from evidence showing that anhedonia is a predictor of non-response to conventional antidepressants that primarily target serotonin [24, 25]. However, some aspects of anhedonia may be present as a trait when unaffected youth are considered. For example, low reward seeking in unaffected youth with a family history of MDD was a predictor of depression onset 1 year later [26]. Additional prospective research is necessary to address this issue. The lack of the ability of clinical tools utilized in the above studies to resolve different aspects of anhedonia is also a limitation that hinders the quantification and understanding of differences in anhedonia across mood disorders.

Anhedonia Reflects a Reward Circuit Deficit

Measuring anhedonia as simply a decrease in pleasure significantly impacts accurate assessment and does not account for the various facets of reward processing that can give rise to anhedonia. To aid in the illustration of this process, a model modified from Kring and Barch [27] outlines that reward processing begins by assigning rewarding value to a stimulus, otherwise known as a "reward association" [28]. Based on this model, once this association has been made, one can then have interest in a reward, be able to anticipate it, as well as have motivation and expend effort to obtain it, ultimately leading to the experience of consummatory pleasure. Integrating information from past reward experiences to guide future behavior is also necessary for maintaining accurate stimulus-reward associations. For example, if the stimulus is rewarding only in certain contexts, the reward association must be updated with this feedback. Notably, while this overall process is presented as a linear one for ease of understanding, the facets may occur in parallel or in a different order (e.g., anticipation of a reward itself induces consummatory pleasure).

Having reviewed the facets of reward processing, it is clear that, in practice, the clinical symptom of "anhedonia" has often focused on consummatory pleasure; however, a deficit in any facet of the reward experience could potentially give rise to anhedonia [28]. The most common clinical tools do not resolve anhedonia at this level, and as such, behavioral tasks have provided more nuanced information about reward processing and its neurobiology across mood disorders.

Behavioral and Neurobiological Reward Processing in MDD and BD

There have been many studies on the neurocircuitry of reward processing that overall highlight the ventral tegmental area (VTA), caudate, putamen, ventral striatum—with a focus on the nucleus accumbens (NAc), prefrontal cortex (PFC), orbitofrontal cortex (OFC), and the amygdala as key brain areas involved in reward processing [3, 5, 29–32]. However, it is difficult to develop a concrete model of reward circuit dysfunction in depression or bipolar disorder due to the multi-faceted nature of reward and the heterogeneity of both mood disorders. An additional layer of complexity is added by the large degree of variability in person-to-person performance on behavioral reward tasks. For example, Misaki and colleagues found a large degree of NAc response variability during a reward task, even in the healthy control group [33]. Much of our knowledge on reward circuits comes from functional magnetic resonance imaging (fMRI) studies conducted during behavior tasks designed to target specific facets such as anticipation or reward outcome (Table 1).

Table 1. Comparison of MDD and BD reward processing behaviour and associated neurocircuitry

Disorder		Reward Behaviour	Neurocircuitry	Literature
MDD	Remitted	↓Reward response bias ↓Reward learning	↓Inferior frontal gyrus activity during loss outcomes	Whitton et al. [1] Dichter et al. [3] Schiller et al. [34]
	Depressed	↑Expectation of negative outcomes ↑Risk avoidance ↑Prediction error ↓Reward learning	↓Striatal (left NAc, bilateral caudate) response during gain outcomes ↓OFC during reward learning ↓Connectivity between PFC and striatum when processing pleasant stimuli	Ubl [35] Sherdell et al. [36] Smoski et al. [37] Gradin et al. [38] Whitton et al. [39] Pizzagalli et al. [40] Rothkirch et al. [41] Young et al. [42]
BD	Euthymic	↑Risk behavior (vs. controls)	↑Striatum and OFC during reward anticipation	Adida et al. [43] Nusslock et al. [23]
	Manic	↑Risk behavior (vs. controls) ↑Goal striving & motivation		Adida et al. [43] Nusslock et al. [44] Abler et al. [45]
	Depressed	↑Risk behavior (vs. controls) ↑Sensitivity to punishment (vs. euthymic & manic)	↓PFC, striatum during reward processing	Adida et al. [43] Redlich et al. [16]

ACC anterior cingulate cortex, *MDD* major depressive disorder, *OFC* orbitofrontal cortex, *PFC* prefrontal cortex, *rs* resting state, *SHAPS* Snaith Hamilton Pleasure Scale, *VS* ventral striatum

Anticipation and Outcome of Reward

Evaluation of anticipation of reward in MDD has yielded conflicting neurobiological findings. Some studies have found decreased striatal activity that normalizes with antidepressant treatment [46, 47], while others have found no difference in striatal activity [3]. Interestingly, there are several reports of reward network hyperactivation in depressed and remitted depression patients compared to healthy controls during anticipation, particularly in frontal and limbic regions [3, 48]. In contrast, reward outcome (e.g., loss or gain of a monetary reward) in depressed patients reveals dampened striatal and ventral striatal activity during the outcome phase of receiving a monetary reward [39, 40] that correlates with the severity of anhedonia [49]. Reduced striatal and ventral striatal response in MDD patients during this task may be partially due to reduced reactivity in the striatal dopamine network, decreased striatal volume, or genetic variants decreasing expression of dopamine receptors [40, 50]. Furthermore in response to outcome, remitted depressed patients still demonstrate decreased orbitofrontal cortex activity compared to healthy controls, suggesting that there may be an anticipatory hyperactivation and an outcome hypoactivation in depression [3]. Additionally, considering the oribitofrontal cortex is important for reward valuation, these data suggest that depressed patients continue to devalue reward even in remission. Interestingly, Kumar et al. [51] found that adding a "stress" paradigm while healthy controls completed a monetary reward task resulted in a blunted striatal response to gains. Perhaps stress is a vulnerability factor in depression that could be shifting brain activation patterns toward an anhedonic phenotype during reward processing [52].

Similar to some findings in depressed patients, anticipation in BD appears to reflect a hyperactive state compared to healthy controls even in remission. Several studies have reported increased activation in euthymic BD (mostly BD-I) in either the striatum, amygdala, orbitofrontal cortex, or anterior cingulate cortex [23, 53, 54, 55]. However, there is a conflicting finding of decreased ventral striatal activity and connectivity to the anterior prefrontal cortex [56]. Another study in remitted BD-I showed increased ventral striatum-oribitofrontal cortex connectivity during reward receipt and decreased ventral striatum-medial prefrontal cortex connectivity following reward omission [57]. The

authors conclude that the enhanced orbitofrontal connectivity after reward receipt is related to elevated evaluation of reward even in remission, which is in contrast to remitted depressed patients.

The majority of the studies conducted in BD and reward processing include euthymic patients or those with BD-I. One study in manic patients revealed increased orbitofrontal activity in response to reward gain and decreased activity associated with increasing loss, while healthy controls demonstrated the opposite effect [58]. Counteracting the proposition that BD reflects a general reward system hyperactivation, Satterthwaite and colleagues [59•] demonstrated that in those with BD-depression and unipolar depression, severity of depression was a significant contributor to reduced activation in the ventral striatum, anterior cingulate cortex and insula. However, increased resting-state reward connectivity was observed in BD compared to unipolar depression. Furthermore, in BD-II and BD not otherwise specified patients, there was also decreased striatal activity during anticipation compared to healthy controls [60]. A head-to-head comparison of BD-I and BD-II revealed increased anticipatory ventral striatal activity in BD-II compared to BD-I [61]. Taking a graph theory approach to connectivity, Manelis and colleagues [62] observed anticipation of loss was characterized by bottom-up frontal-striatal connectivity in MDD, and more sparse connectivity in BD that lacked fronto-striatal connections. In contrast, anticipation of wins was characterized by dense connectivity of frontal-striatal and frontal-lateral regions in BD, and sparser bottom-up frontal-striatum connectivity in MDD. These data imply that, in response to gains, there is a hyperfunction in BD and hypofunction in MDD, while the opposite holds true for losses. It also highlights the complexity of evaluating reward processing function in such heterogeneous disorders.

Reward Expectation

Expectation or the signal associated with inaccurate reward prediction is strongly mediated by dopaminergic nucleus accumbens activity [see 63 for review]. In the few studies done in MDD, the prediction error signal is typically blunted [38, 64]. However, Rothkirch et al. [41] found unmedicated MDD patients and controls had similar levels of activation in the ventral striatum and anterior insula when engaging in reward learning tasks; however, reduced prediction error signal in the orbitofrontal cortex was observed in patients. Moreover, prediction error signals in the medial orbitofrontal cortex and ventral striatum were negatively correlated with anhedonia severity. Subclinical hypomanic patients also demonstrate a stronger prediction error signal irrespective of the value of a reward, suggesting an enhanced perception of reward and an inability to discriminate reward value in a manic state [65].

Reward Learning: Building a Response Bias and Integrating Negative Feedback

Response bias tasks are designed to measure the ability of a subject to develop a stimulus-reward association and adjust choices to the more rewarded stimulus. It is also important to integrate feedback on whether a reward continues to be a reward. During a depressive episode, patients may be less motivated to seek pleasure [35]. Interestingly, MDD patients demonstrate a blunted reward response bias even in remission [1, 3], suggesting a continued inability to learn when a stimulus is rewarding. Adida et al. [43] investigated reward learning and risk behavior in bipolar patients using the Iowa Gambling Task (IGT) and found that BD patients selected riskier cards than controls during euthymic, depressive and manic states. However, the depressed BD group demonstrated a marked increased sensitivity to the punishment deck and avoided it more so than the other groups, whereas manic patients were less likely to care about low magnitude losses in favor of potentially large rewards. Although bipolar patients may demonstrate an overall increased risk behavior, differences in decision making still exist across the three BD states. MDD patients tend to be more concerned with avoiding risk than winning money in the IGT, and as a result can occasionally perform better than controls by using a strategy of 'not losing' rather than 'gaining' [37]. However, the literature suggests that the degree of risk aversion and reward learning deficits differ between MDD patients and BD patients. Those with BD are more clearly characterized by a risk-seeking/impulsive phenotype [66, 67, 68] and individuals with MDD are hypersensitive to negative feedback [69, 70], which can persist into remission [71].

At-Risk Youth: A Case for Trait Factors for Mood Disorders

Interestingly, children of BD and MDD parents seem to have reward circuit abnormalities prior to onset of any psychiatric conditions. Manelis et al. [72] demonstrated that offspring of bipolar parents had decreased ventrolateral PFC connectivity during a reward task. However, children at high risk for mania demonstrated less activation in the pregenual cingulate during anticipation and, consistent with the BD euthymic patient data, increased activation in the orbitofrontal cortex when receiving rewards [73•]. Age-related changes in reward function among pediatric BD patients have also been noted [74]. Adolescents 13–19 with BD had decreased activation in frontal regions, including the dorsolateral prefrontal cortex, during anticipation of reward. While healthy adolescents demonstrated an age-related decrease in activity in other frontal areas important for cognitive control, BD adolescents exhibited an age-related increase in activity, suggesting changes in development during adolescence. In the context of MDD, Kujawa

et al. [75] found that children from mothers who suffered from MDD were less reactive to rewards than losses, signifying blunted reward responses may begin in adolescence or childhood. Overall, these findings speak to the possibility of anhedonia being a "trait" at least in a subsample of patients.

In summary, it is clear that evaluating the behavioral performance and neurobiology of reward processing is quite complex. The standing theory is that BD reflects hyperactivation of the reward system while depression manifests hypofunction, but data from BD depressed patients challenges this assertion, and suggests that the picture may be more associated to the valence of episode (e.g., depressed or manic). Reward processing deficits appear to be present in high-risk youth for BD and MDD, as well as early on after illness onset. This implies that there is at least some aspect of reward function that represents a trait of the disorder, especially considering the deficits can persist with remission. While there is inconsistency that remains in the data, potentially due to the small sample sizes and differences in methods and sample characterization, the brain regions affected are consistent. In particular, the ventral striatum and orbitofrontal cortex were frequently reported in the above studies, which may be related to deficits in reward expectation and valuation, where BD patients overvalue and MDD patients undervalue reward.

Current Limitations and Future Directions of Anhedonia Research

Currently, there are a number of issues that limit the applicability of anhedonia research across mood disorders. Reward circuit function is very complex and includes clinical symptoms, brain circuitry, molecular, and genetic processes. The Research Domain Criteria (RDoC) has highlighted the importance of implementing a trans-diagnostic approach to psychiatric research [76]. However, attempting to establish clear reward circuitry deficits across diagnoses will be a challenge given the inherent heterogeneity among patients themselves [33].

There also continue to be discrepancies in the literature regarding the "state" or "trait" nature of anhedonia. Thus, it may be beneficial to abandon this dichotomous categorization and accept anhedonia as a construct existing along a spectrum which is highly influenced by affective state, while also being underpinned by stable circuitry abnormalities that arise prior to onset of diagnosis. However, understanding state and trait aspects of reward function could significantly advance our ability to predict at-risk groups, relapse, and treatment strategy. Importantly, a state or trait reward deficit may not have the exact same underlying neurobiology. Further systematic research in unaffected high-risk youth and longitudinal studies would help to tease apart these issues, along with utilizing more sensitive clinical tools to measure anhedonia and assessing more than one facet of reward processing in a single study.

The role of neurotransmitters in reward processing is an under-studied area [77]. Past depression research has focused heavily on dopaminergic pathways; however, it is clear that other systems are also involved like the glutamate, GABA, and opioid systems as well as inflammatory processes [28, 78–80]. In fact, dopamine may be more important for anticipatory and high reward-high effort activities as well as outcome evaluation [81, 82]. The opioid system, in particular, may underlie aspects of consummatory pleasure [83], but very little research on humans has been conducted to date due to a lack of widespread in vivo measurement capabilities. Based on preclinical research, kappa opioid receptor antagonism has relevance in the treatment of reward-related function [84]. Further study of neurotransmission and opioid circuitry in humans will be necessary to bring greater clarity to the reward circuit and help identify other novel pharmacotherapies targeting anhedonia.

On the methodological side, current behavioral tasks only hone in on specific aspects of reward, while most clinical scales do not incorporate our current understanding of reward function and focus on consummatory pleasure [see 28 for review]. Consequently, there is much to be explored here. In order to develop a more cohesive model of reward processing, it is necessary to conduct more than one behavioral task in order to understand how the facets work together and independently. Furthermore, developing clinical tools (e.g., scales) that are proxies for the behavioral and neurobiological processes underlying anhedonia are important for translation of biology to the clinic.

Finally, there is substantially less research on bipolar patients during an MDE than manic episodes. This trend in research has placed the focus on reward circuit *hyperactivity* in BD when in reality these patients suffer from a wide range of affect including depression and anhedonia. Furthermore, research on euthymic bipolar patients often disregards the pre-euthymic state. There has been evidence to show significant residual symptoms exist in BD for extended periods of time [17]. Neglecting to control for pre-euthymic state will impact future findings regarding reward processing in BD.

Conclusion

As one of the two key symptoms of an MDE, anhedonia has been the subject of research efforts to better understand, redefine and conceptualize mood disorders. Future advancement in this area will benefit from a refining of its definition as a clinical symptom on the reward circuit spectrum, the creation of a more comprehensive and widely adopted set of behavioral tasks that assess multiple facets of reward, and an increase in the study of neurotransmitters (such as endogenous

opioids). This increased attention to the study of anhedonia will help to refine methodology and produce more robust data of whether anhedonia is a viable avenue for biomarker research.

Compliance with Ethical Standards

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