Reward processing dysfunction in major depression, bipolar disorder and schizophrenia

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Abstract

Purpose of review—This article reviews the recent literature on reward processing dysfunction in major depression, bipolar disorder and schizophrenia, with a focus on approach motivation, reward learning, and reward-based decision-making.

Recent findings—Emerging evidence indicates the presence of reward processing abnormalities across all three disorders, supporting a transdiagnostic approach. In particular, findings are consistent with a role of abnormal phasic striatal dopamine signaling, which is critical for reinforcement learning, efficient mobilization of effort to obtain reward, and allocation of attention to reward-predictive cues. Specifically, reward-related striatal signaling appears blunted in major depression and the negative symptoms of schizophrenia, elevated in bipolar (hypo)mania, and contextually misallocated in the positive symptoms of psychosis. However, whether shared or distinct pathophysiological mechanisms contribute to abnormal striatal signaling across the three disorders remains unknown.

Summary—New evidence of reward processing abnormalities in major depression, bipolar disorder and schizophrenia has led to a greater understanding of the neural processes associated with symptomatology common across these conditions (e.g., anhedonia). Dissecting various subcomponents of reward processing that map onto partially different neurobiological pathways and investigating their dysregulation in different psychiatric disorders holds promise for developing more targeted, and hopefully efficacious treatment and intervention strategies.

Keywords

Introduction

In recent years, efforts focused on understanding and treating reward-related dysfunction in psychiatric disorders have grown substantially. This has reflected the confluence of several currents, including significant preclinical advancements in understanding the neurobiology of approach-related behavior and a growing recognition that impairments in reward-related

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processes are insufficiently addressed by current treatments (1). As a result, numerous studies have sought to test the presence of reward circuit dysfunction in clinical populations that exhibit alterations in motivation and/or hedonic responses. Moreover, as the field has increasingly eschewed categorical diagnostic boundaries in favor of symptom dimensions, there has been a parallel rise in studies seeking to identify transdiagnostic neural markers of reward processing dysfunction that may transcend disorders as distinct as major depressive disorder (MDD) and schizophrenia.

Central to this effort has been the recognition that "reward processing" does not represent a unitary construct nor does it rely on a singular biological circuit. There are many distinct aspects subsumed under the term "reward processing," including motivation, salience, anticipation, pleasure, and satiety. In this critical review, we summarize recent advancements that support this transdiagnostic view of reward processing abnormalities in depression, bipolar disorder and schizophrenia, and offer recommendations for future studies.

Major Depressive Disorder: Reconceptualizing Anhedonia

Anhedonia has long been considered a cardinal feature of depression (e.g., (2)). However, contrary to the traditional conceptualization of anhedonia, recent reviews have highlighted inconsistent evidence for "loss of pleasure" in depression (3, 4). Critically, on prototypical tests of consummatory pleasure (e.g., the sweet taste test) individuals with depression report normative ratings of hedonic responses (4). In contrast, recent studies probing motivation, reinforcement learning, and reward-based decision making have uncovered a more nuanced understanding of reward processing dysfunction in depression.

MDD, particularly in the presence of anhedonia, is characterized by a reduced ability to modulate behavior as a function of rewards (5, 6). This reduction in reward responsiveness appears to persist after remission (7) and has been found to predict MDD chronicity despite antidepressant treatment (5). Interestingly, reduced reward responsiveness has also been found in healthy participants following a pharmacologically-induced attenuation of phasic dopaminergic signaling (6). Collectively, these findings indicate that depression is characterized by an inability to modulate behavior in response to intermittent rewards, possibly due to blunted phasic dopaminergic signaling critically implicated in reward learning.

In addition to reinforcement learning, dopamine has been strongly implicated in appetitive behaviors (e.g., reward anticipation) and effort-based reward-related decision making. Based on mounting evidence of dopaminergic abnormalities in depression (3), one could expect that depressed individuals show blunted reward anticipation and willingness to exert effort in order to obtain rewards. Recent findings are consistent with these hypotheses. First, using the Effort Expenditure for Rewards Task (EEfRT or "effort") – a task that requires subjects to choose between a potential low-effort, low-reward outcome vs. a high-effort, high-reward outcome – Treadway and colleagues reported that individuals with MDD were less willing to exert physical effort to obtain potentially larger rewards. Relative to controls, MDD subjects also used information about reward magnitude and probability less effectively in

order to guide their decisions (8). Second, relative to healthy adolescents and adolescents with externalizing disorders, adolescents at increased risk for depression (due to a family history of MDD) showed reduced reward seeking in a gambling task, the magnitude of which predicted depressive symptoms, MDD onset, and diminished engagement in extracurricular activities one year later (9).

In light of this behavioral evidence, and owing to preclinical data emphasizing the role of dopamine-rich mesocorticolimbic pathways (including ventral and dorsal striatal regions) in reinforcement learning, abnormalities in this circuitry might be hypothesized in MDD. Consistent with this notion, depressed adults showed reduced putamen activation during reward anticipation as well as reduced caudate, nucleus accumbens (NAcc), and dorsal anterior cingulate (ACC) activation to partially unpredictable rewards (10). Recent findings indicate that ventral striatal (VS) blunting might constitute a risk factor for depression. Specifically, reduced reward-related VS activation has been described in never-depressed youth at increased risk for MDD due to a family history of depression (e.g., (11)), is evident even when accounting for (subclinical) depressive symptoms (12), and has been found to predict increases in depressive symptoms over two years among adolescents (13). Furthermore, reduced feedback-related negativity (FRN) amplitude – an event-related potential (ERP) deflection thought to originate from reward prediction error-related activity in the dorsal ACC and striatal regions – predicted first-onset of MDD in a 2-year follow up among never-depressed adolescent girls (14).

Complementing these data are recent observations that reward-related striatal and cingulate abnormalities might be exacerbated by disease burden. Accordingly, during performance of an instrumental reinforcement task involving selection of stimuli probabilistically linked to rewards, NAcc, ACC, and ventromedial prefrontal cortex (vmPFC) activation during acquisition of reward contingencies was greatest among healthy controls, intermediate in individuals facing their first major depressive episode (MDE), and lowest in individuals with recurrent MDD (> 3 prior MDEs and illness duration of at least 5 years) (15).

In sum, when integrating these lines of evidence, it appears that blunted processing of incentive salience, incentive motivation, and reinforcement learning (and associated NAcc and ACC hypoactivation) might be potent precursors of MDD. However, when these abnormalities are worsened by recurrences and emerge coupled with abnormalities in regions implicated in coding the hedonic value of stimuli (e.g., vmPFC), these disruptions might lead to more tenuous anticipatory reward-related associations, and ultimately anhedonic symptoms (see also (15)).

Bipolar Disorder: An Emerging Picture of Reward Hypersensitivity

A focus on the sequelae of dysfunction in reward-related dopamine signaling has given rise to the notion that (hypo)mania may in part result from a state of hyperdopaminergia. This theory was driven by early observations that dopamine agonists induce mania-like behavior in non-clinical individuals (16), but compelling support has emerged from recent research showing that dopamine agonists exacerbate reward learning abnormalities – such as a

preference for high-risk, high-reward choices – in euthymic individuals with bipolar disorder (BP) (17).

Recent electrophysiological and neuroimaging studies corroborate this hypothesis, showing that (hypo)manic symptoms are associated with heightened reward-related activation in brain regions with high dopamine receptor density. An ERP study examining FRN deflection (an indirect index of prediction-error-related dopamine signaling) to rewards of varying temporal proximity found that differences in FRN amplitude to immediate versus delayed rewards was greater in hypomania-prone compared to non-hypomania-prone individuals (18). Similarly, evidence of abnormally elevated activity within the VS during reward anticipation (19), reward consumption (19), and to reward-predictive cues (20) has been found in BP. A failure of prefrontal regions to effectively down-regulate VS responses has also been observed (21), and regions that integrate reward-relevant information from limbic and prefrontal regions, such as the vmPFC, evidence a bias towards VS inputs (20).

An important translational study suggests that increased dopamine bioavailability in BP may arise due to depletions in dopamine transporter (DAT), which would result in increased dopamine levels. Thus, mice that have chronic or acute DAT depletion show increased rates of switching to high-risk high-reward choices on the Iowa Gambling Task, similar to those observed individuals with BP (22). This finding aligns with earlier evidence of lower DAT availability in the dorsal caudate of untreated individuals with BP (23), indicating that dopaminergic abnormalities in BP may result from aberrant dopamine reuptake mechanisms.

Several key reward circuit abnormalities have also emerged that remain persistent in BP across different mood states, and set it apart from MDD. First, heightened activation in the left ventrolateral PFC (vlPFC) during reward anticipation has been found in depressed BP type I (BPI) individuals compared to controls and individuals with MDD (24). Left vlPFC activation has been associated with heightened arousal during processing of salient emotional stimuli (25), therefore heightened activation in this region may reflect increased anticipation-related arousal in BP. Second, the effects of dopamine are mediated in part by their influence on glutamatergic (Glu) signals originating in the medial and vmPFC regions (26), and two recent meta-analyses of studies using magnetic resonance spectroscopy found that individuals with MDD (27) and individuals with BP (28) show decreased and increased levels of brain Glu, respectively. Importantly, increases in Glu or ratios of glutamate/glutamine have been found in BP across states of mania (29), depression (30) and euthymia (31), indicating that glutamatergic abnormalities may contribute to trait-level differences in reward responding between BP and MDD.

Possible differences in reward processing across the bipolar subtypes have also recently come to light. Self-report data have shown that BPI mania variability was associated with reward consumption and anticipation scores on the Behavioral Inhibition and Approach scales (BIS/BAS), whereas BP type II (BPII) depression variability was associated with reward anticipation scores (32). A similar distinction was found in a recent imaging study showing that abnormalities in reward consumption-related activation were more prominent in BPI, whereas abnormalities in reward anticipation-related activation were more prominent in BPII (19). Given that anhedonia is most closely linked with abnormalities in reward

anticipation rather than consumption (e.g., 33), a primarily anticipation-related impairment in BPII may explain the pervasiveness of depression in BPII relative to BPI.

Taken together, recent findings suggest that reward processing abnormalities in BP may arise due to elevated activity within the dopamine-rich VS, and left vlPFC during reward processing. Although there is strong evidence for the role of excessive dopamine bioavailability in BP, these abnormalities may be state-dependent, and therefore may not represent the primary pathophysiology of the disorder. Instead, abnormalities in levels of neurotransmitters that contribute to reward processing abnormalities across mood states, such as Glu, may represent a trait marker of BP-related reward dysfunction.

Schizophrenia: Growing Support for the 'Aberrant Salience' Hypothesis

For over fifty years, dopamine circuitry has been postulated as a primary pathology in schizophrenia. The current iteration of the "dopamine hypothesis" of schizophrenia (34) posits that positive and negative symptoms results from irregular (as opposed to enhanced or reduced) dopamine release that may ascribe 'aberrant salience' to irrelevant stimuli (resulting in positive symptoms) while failing to appropriately respond to meaningful reward cues (resulting in negative symptoms).

Supporting this hypothesis, a recent meta-analysis of positron emission tomography (PET) studies using a dopamine precursor radioligand ($[F^{18}$ or $C^{11}]$-dopa) – an index of dopamine synthesis capacity – found that binding was substantially up-regulated in psychosis (35). In addition to this evidence for a global increase in striatal dopamine availability, fMRI has been used to evaluate striatal responsivity during paradigms known to elicit dopamine burst-firing, such as trial-and-error learning. A number of imaging studies have highlighted associations between aberrant striatal responses and propensity for positive psychotic symptoms (34). Most critically, recent work has demonstrated both a blunting of neural prediction errors to contextually relevant cues (36) as well as behavioral evidence for *enhanced* prediction error learning for irrelevant stimuli (37). Collectively, these findings suggest that salience attribution mechanisms used to optimize the allocation of attentional resources are impaired in schizophrenia, and that such impairments are partially mediated by elevated striatal dopamine availability and altered striatal function.

Support for the aberrant salience model is also found in studies of negative symptoms in schizophrenia. Such symptoms typically involve reduced affective expression, decreased motivation, and self-reported reductions in pleasurable experiences, and can be similar in clinical presentation to anhedonic and fatigue symptoms of MDD. Strikingly, despite self-reports of low positive affect and pleasurable experience on trait and symptom inventories, individuals with schizophrenia frequently show normative affective ratings in response to positively valenced laboratory stimuli (38). This discordance between self-reported trait pleasure and momentary pleasure suggests that negative symptoms may not reflect a primary deficit in the capacity for hedonic experience, but rather a difficulty in representing rewarding experiences accurately (39) – a deficit that is consistent with disruptions in dopamine circuitry (40).

To test this hypothesis, recent work in schizophrenia has examined effort-based decision-making – a process that is highly sensitive to striatal dopamine levels. In animals, blockade of striatal signaling via either dopamine receptor agonist or dopamine terminal lesions induce a behavioral shift away from larger or more preferred rewards that require extra effort to obtain (41). Based on these studies, one might expect that negative symptoms in schizophrenia are associated with reduced striatal dopamine, however this is contradicted by evidence for elevated striatal dopamine discussed above. Importantly, the aberrant salience hypothesis reconciles this apparent conflict with its prediction that individuals with schizophrenia should not necessarily exhibit less willingness to work than controls, but rather, show deficient allocation of effort in terms of maximizing reward. Consistent with this hypothesis, three separate studies have found that individuals with schizophrenia did not exhibit an overall reduction in effort expenditure (as has been shown in individuals with MDD), but consistently failed to select the high effort option at times when it was most advantageous to do so (42–44). Additionally, this effect was most pronounced in individuals with negative symptoms (42), and related to goal-directed activity in daily life (44). Finally, a recent ecological-momentary-assessment study found that individuals with schizophrenia often failed to exert effort in pursuit of pleasurable activities, despite reporting that they anticipated enjoying the activities more than controls (45). These findings suggest that individuals with schizophrenia are unable to mobilize effort effectively, which is likely due to inadequate dopamine release to appropriate (high reward) trials.

In sum, recent evidence from behavioral paradigms, molecular imaging and fMRI studies converges in supporting a model of aberrant salience wherein excessive striatal dopamine release in response to meaningless or irrelevant stimuli may drive positive symptoms of psychosis. In contrast, blunted dopamine firing patterns critical for motivated responding to incentives may underpin negative symptoms of the disorder.

Future Directions: Transdiagnostic Mechanism or Equifinality

As summarized above, symptoms associated with altered reward processing share similar substrates across different disorders, supporting a transdiagnostic approach. On the basis of such evidence, it can be tempting to conclude that common pathological mechanisms must be at play. For instance, both MDD and schizophrenia are characterized by a reduced willingness to expend effort, both show blunted VS responses during reward anticipation, and both show reduced prediction error signaling to rewards. Despite such similarities, it must be noted that there are many distinct pathological mechanisms that could result in alterations to striatal signaling (often referred to as 'equifinality'), and it is not necessarily the case that similar symptoms reflect similar pathologies (46). Consequently, although transdiagnostic assessments may be valuable in identifying macrocircuits that need further investigation, similarities in neural responding during laboratory tasks should not outweigh the substantial differences in clinical presentation across these disorders. At their best, what symptom-focused transdiagnostic studies can provide is the opportunity to uncover new dimensions in symptom presentation that are not immediately evident to the clinically-trained eye, but nevertheless possess reliable behavioral and neural correlates.

Conclusion

Reward processing abnormalities are central to the pathophysiology of major depression, bipolar disorder and schizophrenia, and mounting evidence points to cross-diagnostic dysfunction in reinforcement learning, effort-based reward-related decision making, and allocation of attention to reward-predictive cues. As transdiagnostic study designs increasingly compare distinct patient groups with common symptoms, the identification of shared and unique biological mechanisms will continue to improve, which is a prerequisite step towards the development of improved prevention and treatment strategies.

Acknowledgments

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Key points

- Major depression is characterized by blunted processing of incentive salience, incentive motivation, and reinforcement learning likely resulting from blunted phasic dopamine signaling, and these abnormalities are emerging as potential precursors of MDD.

- Although there is strong evidence for the role of excessive dopamine bioavailability in BP (hypo)mania, these abnormalities may be state-dependent, and as a result, may not represent the primary pathophysiology of the disorder.

- Research converges in support of a model of aberrant salience in schizophrenia, wherein excessive striatal dopamine release in response to meaningless or irrelevant stimuli may drive positive symptoms of psychosis, whereas an absence of dopamine firing critical for motivation may underpin negative symptoms of the disorder.