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REVIEW ARTICLE

Cognitive emotional processing across mood disorders

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While impairments in cognitive emotional processing are key to the experience of mood disorders, little is understood of their shared and distinct features across major depressive disorder (MDD) and bipolar disorder (BD). In this review, we discuss the similarities and differences in abnormal emotional processing associated with mood disorders across the cognitive domains of perception, attention, memory, and reward processing, with a particular focus on how these impairments relate to the clinical profile of the disorders. We consider behavioral and neuroimaging evidence, especially that of the growing consensus surrounding mood-congruent biases in cognition, in combination with state- and trait-related characteristics in an attempt to provide a more comprehensive and translational overview of mood disorders. Special consideration is given to the shared phenomenon of mood instability and its role as a potential transdiagnostic marker across the prodrome and maintenance of mood disorders.

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Introduction and Background

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are a major cause of disability worldwide, affecting social and occupational functioning, quality of life, and mortality rates.[1] It is estimated that 21% of adults in the US will experience a mood disorder at some point in their lives,[2] and the most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5[3]) has further expanded the guidelines for mood disorders in order to account for the complexities in their symptomatic profiles.

While clinically mood disorders such as MDD and BD are predominantly characterized by subjective emotional symptoms—such as lowered mood and anhedonia in the case of MDD, and lowered mood and mania in the case of BD—a breadth of recent research, aided by developments in neuroscience, has begun to elucidate the cognitive underpinnings of such disorders. It is the presence of these cognitive symptoms, ranging from difficulties in sustained attention, learning, and memory to decision-making and reward processing, together with the recurring nature of such disorders, that likely magnify its wider effect on quality of life and economic burden. Cognitive deficits in these domains are reported across the disorders, regardless of severity of illness, and are often also modulated by pharmacological treatments, such as antidepressants and mood stabilizers. For example, while little is still understood of the mood stabilizing mechanism of action of lithium, the first-line pharmacological treatment for BD, it has been shown to have both detrimental effects on cognition in BD[4] and neuroprotective properties affecting memory performance and capacity in degenerative neurological diseases.[5]

Therefore, in this review, we will focus on describing and consolidating evidence of the mechanisms underlying cognitive processing in mood disorders. Interactions with mood symptoms, such as depression, anhedonia, and mania, will be discussed in order to provide a more comprehensive overview of the phenotypic nature of mood disorders. This should aid us in further understanding the interplay between cognition and affect, a process that is garnering attention as a potential target for therapeutic intervention.[6]

Classic Theories of Cognitive Processing

Since the 1950s, the idea that distorted or maladaptive cognition is key to the development and maintenance of mood disorders has gained momentum. For instance, Beck's[7] theory proposes that negative schemas about the

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self, the environment, and the future are core to the proliferation of MDD. For those who are vulnerable to depression, these schemas are thought to develop early on in life and become activated as a result of negative life events. Due to the ingrained and reinforced nature of these schemas, they are also considered to distort cognitive processing by influencing attention and memory, particularly encoding and retrieval of negative information.[8]

The hopelessness theory[9] built on this idea of negative schemas and life events in explaining the development of depression by emphasizing the role of negative inferential styles and attributions. The theory suggests that those with depressive symptoms have an increased tendency to attribute negative events to negative causes that are stable and global, a tendency to assume that only negative consequences will occur from such an event, and a tendency to attribute those causes and events to their own self-worth. Taken together, it proposes that depression results from expectations that negative events will occur and that nothing can be done to change them. This further combines some of the more clinical symptoms of MDD, such as anhedonia and feelings of worthlessness, into this particular cognitive processing style.

Hot and Cold Cognition

Building on these classic theories of cognitive processing in mood disorders, recent research has begun to draw distinctions between "hot" and "cold" cognition, or more precisely, how emotional state has a direct link to the way in which information is processed in mood disorders. Traditionally, "hot cognition" refers to cognitive processing on tests that result in an emotional response, for example, by viewing emotionally salient stimuli, or by receiving feedback that influences emotional state. "Cold cognition," thus, represents the opposite—cognitive processing in the absence of emotionally salient responses or stimuli.

It is important to note that both are key in everyday cognitive processing in healthy individuals, but is also of particular concern when considering their role in cases of psychopathology, such as in mood disorders. In particular, it is often noted how tests that do not include emotional stimuli or emotionally responsive feedback, and so are otherwise "cold," can be turned "hot" in participants with MDD and BD[10,11] based on their latent vulnerability to negative cognitive styles or schemas. This not only combines the classic theories of cognitive processing in mood disorders (eg, Beck's theory and the hopelessness theory) but also begins to elucidate how a combination of both bottom-up and top-down processes can be distorted in MDD and BD.

Cognitive Emotional Processing

In line with these developments, recent theories have emphasized the importance of interactions between cognitive and emotional systems,[11,12] and proposed that these interactions are implicated in both the prodrome and maintenance of mood disorders. Thus, cognitive emotional processing works as a cyclic system: cognitive factors, such as our interactions with the environment and the process by which we make decisions, are influenced by emotional context, or our emotional state, and vice-versa. This system is key to human behavior and experience[13] and aids us in forming appropriate responses to our environment, some of which have strong evolutionary bases (for example, stress and fear). This processing is also fundamental in forming social and moral responses, be it in terms of determining how we interact with our loved ones or in allowing us to behave altruistically with strangers. It then follows that impairments in such a processing style can lead not only to the clinical and cognitive symptom profile of mood disorders, but also the social and moral difficulties that patients often experience.

While we all interact with our environment in such a manner, the varying degrees with which we do so and the consequences that can arise from distortions in such processing are vital to understand. Mood disorders are at the core of this. In order to fully appreciate the contribution of such processing to the etiology and maintenance of mood disorders, the current review aims to consider the behavioral and neural underpinnings of cognitive affective processing in relation to MDD and BD, with a particular focus on mood instability as a transdiagnostic marker.

Major Depressive Disorder (MDD) and Bipolar Disorder (BD)

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*[3] outlines both MDD and BD as disorders with their own distinct clinical profiles. BD, both types I and II, is characterized by periods of mania, to varying degrees, in addition to depression, and it is this core difference that sets the two apart. Contrasts in their core cognitive profiles are also often emphasized, with BD being more closely associated with impairments in decision-making and impulsivity, resulting in changes in reward processing.[14]

However, MDD and BD share many symptomatic similarities, the clearest of which is the presence of depressive episodes. This contributes to clinical overlap, whereby BD is often misdiagnosed for MDD.[15] Depressive episodes usually present initially in the course of BD and are often experienced more saliently than manic or hypomanic episodes.[16] They are also both highly

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heritable, such that first-degree relatives of those with BD also have an increased risk of developing MDD.[17] This more complex intertwined nature of the disorders, particularly in the shared case of depressive episodes, is also reflected in some of their more "cold" cognitive symptoms, for instance, in consistent findings of impairments in working memory and attention in MDD and BD[18] related to the depressive symptom criteria of a "diminished ability to think or concentrate."[3]

Owing to the shared mood and cognitive symptom profile of MDD and BD, researchers have begun to investigate trait-related cognitive effects across the disorders. These trait effects of cognitive processing during periods of remission, or euthymia, rather than specific state effects that are manifested specifically during periods of depression or mania, are in line with the Research Domain Criteria (RDoC) movement toward focusing on the transdiagnostic and translational mechanisms that span such related mental disorders, involving both objective behavioral and neuroimaging methods.[19] Such methods enable us to better capture the complex nature of MDD and BD, which is often hindered by a strict focus on distinct clinical diagnostic classifications, and allows us to fully consider and appreciate the phenomenon of mood instability in contributing to cognitive affective processing across mood disorders.

Mood Instability

Mood instability, or rapid oscillations of intense affect, with difficulty in regulating these oscillations or their behavioral consequences,[20] is a prominent feature of a range of mental disorders, particularly MDD and BD. Mood instability has been highlighted as a risk factor for the development of these disorders and is thought to characterize their longitudinal course, particularly for BD.[21] While the clinical significance of this instability is now recognized—owing to its inclusion in the DSM criteria for various mood and related disorders, and its association with comorbid difficulties such as alcohol misuse, neurotic symptoms, and suicidal ideation,[20] little is understood of the cognitive implications and underlying neural mechanisms of mood instability. Its position as a transdiagnostic tool, nevertheless, can aid us in comparing and contrasting the presence of cognitive affective processing in MDD and BD, particularly by considering the similarities and differences in their underlying behavioral and neural mechanisms.

Disruptions in Cognitive Affective Processing

Face processing and attentional biases

Owing to the fact that individuals with depression experience major difficulties in their social interactions, tests involving facial expressions of emotion are some of the most powerful and ecologically valid ways of investigating cognitive processing.[22] According to Ekman and Friesen,[23] 6 basic facial expressions can be recognized: happy, sad, fearful, angry, disgust, and surprise; and these are pertinent across species and cultures. Across a range of experimental studies using these stimuli, MDD patients have been consistently shown to exhibit a negative bias,[24] such that they tend to recognize and focus significantly more on negative emotional expressions (eg, sadness or anger) or less on positive facial expressions (eg, happiness). In line with the clinical symptoms of rumination and in combination with a tendency to hold negative schemas and expectations, Bradley, Mogg, and Lee[25] suggest that individuals with MDD are both biased toward perceptually recognizing negative information, especially that of facial expressions, and have greater difficulties in disengaging once this information has become the focus of their attention.

In line with this, Gotlib et al[26] demonstrated a depression-relevant negative attentional bias in a sample of MDD patients and healthy controls. When presented with a dot probe task incorporating happy, sad, and neutral faces, individuals with MDD selectively attended to the sad faces above and beyond controls and participants diagnosed with generalized anxiety disorder (GAD). The authors particularly noted here that the negative attentional biases observed were specific to sadness, an emotion specific to depression, and not other types of negative stimuli, explaining this bias in cognitive affective processing as a characteristic of MDD. Similar results have also been reported by other studies of facial expressions by Gotlib and colleagues,[26–28] utilizing the dot-probe task as well as other tests of attention and memory including the emotional Stroop task and self-referential encoding and incidental recall task (SRET), and in comparisons of MDD depressed individuals with individuals recovered from a depressive episode and those with a diagnosis of other axis I disorders (eg, social phobia).

While a breadth of behavioral studies have found evidence for this negative attentional bias toward mood congruent sad faces in MDD, studies of the particular attentional mechanisms involved have been less consistent. Duque and Vázquez[29] aimed to clarify these mechanisms further by testing to see if such a negative bias is observed in both the orienting and maintenance of attention, using an eye-tracking technique to complement their face processing task. While further confirming the presence of a negative attentional bias to mood congruent sad faces, the authors also reported a bias in the maintenance of gaze or attention, over orientation. This finding lends further empirical support to the idea that once individuals with MDD focus on negative

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information, they experience particular difficulties in disengaging from it.[25]

This consistent finding of negative attentional biases in MDD toward sad facial expressions leads us to question whether the same mechanism is also in play in BD, and whether such bias is modulated by specific mood episodes. While this area of inquiry has been less researched in BD, some studies have found evidence for a similar mood congruent bias. For example, Lembke and Ketter[30] found that participants with BD mania were significantly impaired at recognizing negative facial expressions, including fear, sadness, anger, and disgust, and that the recognition of sad faces inversely correlated with their mania symptoms severity, such that their ability to recognize sadness became more impaired as they experienced more manic symptoms. While this positive bias seems to follow on from the idea of mood congruent cognitive processing of emotional faces in mood disorders, results in mania have not always been so consistent. Gray et al[31] found a result similar to MDD in that BD depressed participants showed a decreased sensitivity to happy faces and increased bias toward sadness. They did not, however, find evidence of a mood congruent positive bias in the perception of emotional faces in their sample of manic patients.

Drawing from evidence of mixed results in BD mood episodes, an investigation of cognitive processing of facial expressions during periods of euthymia may help to elucidate the particular trait-related mechanisms at play. In a study by Harmer et al,[32] euthymic BD participants were reported to show preferential recognition and perception of facial expressions of disgust, with no other differences in processing of other facial expressions reported. While this can also be viewed as adding to the premise of negative attentional biases in mood disorders, other results in euthymia have not been so consistent. For instance, while Venn et al[33] reported a statistical trend toward lower recognition of fear in their patients, they and Vaskinn et al[34] more generally found no significant difference between BD patients and controls in their measures of sensitivity to facial expressions of emotion, suggesting the absence of a specific trait-like bias in emotional perception and attention in BD. Martino et al,[35] however, furthered the trend reported earlier[33] by confirming a lowered recognition of fearful facial expressions in their larger sample of BD I and II euthymic patients.

While the differing nature of facial expression paradigms, such as a simple recognition task, a dot-probe task, or a facial morphing task, is often provided as an explanation for inconsistent findings, it is important to note that many of the participants included in these studies, as with most studies investigating euthymia, were medicated. As lithium is known to influence cognition and cognitive processing more generally, it is both difficult to control for this in face processing tasks during euthymia, and to interpret the results as being a characteristic trait marker of cognitive affective processing in BD. Nevertheless, in Bilderbeck et al's[36] study of medicated BD patients, a mood stabilizing effect of both lithium and dopamine antagonist (antipsychotic) medication was found whereby medicated patients showed reduced recognition of angry facial expressions compared to those who were mediation-free, as well as an inverse modulation of happy face recognition by increasing depressive symptoms. Therefore, this study is of particular value in highlighting the complexities of studying medicated euthymia considering the cognitive implications of such therapeutic agents.

Affective Go/No Go tests of attentional biases

In addition to face processing tasks, there are a number of other neuropsychological paradigms used to investigate attentional biases. The Affective Go/No Go task is a classic example that requires both a response to an emotional target stimuli and suppression of response to irrelevant emotional distractors. Thus, the task requires the participant to discriminate between relevant and irrelevant information and shift attention based on this outcome, employing the use of perception, attention, and executive functions.

As with the results from tasks of facial expressions of emotion, Murphy et al[37] reported that MDD patients were impaired in their ability to shift attention between differentially valenced information, such that they were slower in responding to happy but not sad stimuli. While this further confirmed the presence of negative attentional biases in MDD, it is important to note that the majority of participants were medicated. However, Erickson et al[38] confirmed this in their sample of unmedicated MDD patients by finding that their participants responded more quickly to sad words than happy words, and also made more emission errors when responding to happy words.

The evidence in BD, again, has not been so conclusive. Murphy et al[37] also employed the same Affective Go/No Go task in a sample of BD manic patients and found that they were faster at responding to positive words compared to negative words, supporting the notion of a mood congruent attentional bias. Rubinsztein et al,[39] however, found no such bias to happy or sad words in their sample of remitted or euthymic BD patients. In García-Blanco et al's[40] study of mood congruent attentional biases across the different episodes of BD, they found support for a negative attentional bias during depressive episodes, a positive attentional bias during manic episodes, and no mood congruent bias during euthymia. While this supports the idea of mood congruent biases in mood disorders, the

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presence of conflicting results in other tasks of attention, especially in the case of BD, leads us to question whether more robust methods, utilizing complimentary behavioral paradigms (eg, face processing tasks) and neuroimaging techniques, can help to clarify the particular mechanisms by which cognitive affective processing in relation to attention in mood disorders operate.

Memory and related biases

Building on the literature for mood congruent biases in attentional processing, research has also looked into the effect of emotional stimuli in tests of memory, particularly of verbal memory recall and retention. Tests using more "cold" forms of memory processing, for example the California Verbal Learning Test (CVLT), have found impairments in the recall of information, but not in retrieval and retention, in MDD.[41] The picture has not been so clear in BD, with a range of studies and meta-analyses reporting heterogeneous results,[42] with differing profiles of impairments in individuals with a diagnosis of BD I and BD II,[43] suggesting a modulation of impairment by symptomatology and illness severity. While the participants in these studies are usually in the euthymic phase of the disorder, they are also more likely to be medicated. Nevertheless, impairments in verbal recall memory have also been found in first-degree relatives of participants with BD,[44] suggesting that this impairment could form part of a core trait-related cognitive profile of the disorder.

Delving into this further, BD depressed individuals are known to show a greater degree of impairment in learning and memory recall than individuals with MDD.[45,46] Combining this with the idea of mood congruent biases in the recognition of, and attention toward, information—especially emotionally valenced information—suggests that the disorder may involve disruptions in the encoding and consolidation of memory, attenuated by the presence of affective biases and current mood state. Support for this is also provided by evidence of persistent memory deficits in BD euthymic individuals.[47] While further research is needed to fully elucidate the mechanisms of cognitive emotional processing in relation to memory in BD in order to understand whether the mood congruent biases that are present during attention are applicable over the memory deficits reported in "cold cognition," contributions from the MDD literature can help.

As with negative attentional biases, depressed individuals are reported to have a tendency toward remembering more negatively valenced information compared to controls.[48] This was further demonstrated in a study by Harmer et al,[49] which looked at the presence of negative affective biases in antidepressant-administered MDD patients across facial recognition, attention, and memory. Not only did those in the placebo group show reduced recognition of positive facial expressions of emotion, as well as a negative attentional bias, they also had significantly reduced memory for positive self-relevant personality adjectives. Providing support for the neuropsychological model of antidepressant action, this study also showed a reversal in these biases toward negative information, over and above any subjective change in mood, in their sample of MDD patients administered the antidepressant agent reboxetine. Thus, while also providing support for the presence of emotional biases in memory in MDD, this study also points to the importance of cognitive affective processing in being a core target for treatment in mood disorders.

Reward processing

Compared to the research into emotional biases in attention and memory in mood disorders, reward processing is a relatively understudied area of cognitive emotional processing. Nonetheless, it is an area that is garnering precedence due to its close association with many of the clinical symptoms of both MDD and BD, and the potential for sophisticated neuroscientific and computational methods to be applied. For instance, anhedonia, or "markedly diminished interest or pleasure … in activities," is a core clinical symptom of MDD and suggests an impairment or dampening in reward processing. Similarly, elevated mood and impulsivity associated with manic symptoms and episodes in BD also points to disruptions in reward processing, albeit perhaps in a differing direction and to varying degrees. The mechanisms by which reward processing differs in mood disorders is important to understand, as disturbed reward processing can lead to harmful social consequences (for example, excessive impulsivity and irrational decision-making, particularly in BD) and also predict response to treatment.[50]

In line with the presence of negative affective biases in other cognitive domains in MDD, depressed individuals are often reported to show a hypersensitivity towards negative feedback, for example punishment,[51] and hyposensitivity towards positive feedback, for example responses to reward.[52] This maladaptive response to punishment is thought to be reflected in a blunted ability to respond to feedback information.[53] For instance, in Holmes and Pizzagalli's[54] study, individuals with high levels of depressive symptoms were less able to adjust their performance and increase their accuracy following negative performance feedback on a range of cognitive tasks. Murphy et al[55] furthered this by attempting to elucidate the mechanisms of feedback that may hinder cognitive performance for those with MDD. In their

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probability reversal and spatial working memory tasks, they found that individuals with MDD showed impaired performance after negative, but misleading, feedback but that their performance was no more disrupted compared to controls following negative, but accurate, feedback. While these findings stress the importance of context in mediating maladaptive responses to feedback, the hypersensitivity to negative feedback and disrupted ability to modify behavior in such cases reflect a perceived lack of control or motivation in MDD, tying in with classic theories of cognitive processing in mood disorders, such as the hopelessness theory.

Pizzagalli and colleagues have also shown that individuals with both an increased vulnerability to MDD[54] and those with a diagnosis[52] were less able to learn about rewarding stimuli, and thus were less able to use this information to guide their subsequent behavior in their reward processing task. This impairment, along with those of maladaptive responses to negative feedback, are also reported to correlate positively with symptom severity, as well as present in first-degree relatives and recovered individuals,[56] suggesting that such disruptions in reward processing are core and pervasive features of cognitive affective processing in MDD.

Quite unusually for the area of cognitive emotional processing in mood disorders, which has often favored the study of MDD, reward processing is a cognitive domain that has been studied more so from a BD perspective. In line with findings of greater impulsivity in individuals with BD during manic phases, researchers have found a strong connection between manic patients and responsiveness to rewarding stimuli, which can then go on and influence decision-making. Following on from the literature in MDD, BD depressed individuals are also shown to have a hypersensitivity toward negative feedback, such that they were less able to modify their response to negative task feedback compared to controls.[57] A similar response to negative feedback has also been reported in manic BD patients,[58] lending support to the hypothesis that impairments in cognitive affective processing in mood disorders may be directly linked to a "catastrophic response to perceived failure"[11]—a hypothesis which brings together the clinical symptoms of mood disorders and the related predictions that classic theories of cognitive processing make based on these, such as Beck's theory and the hopelessness theory, in order to contextualize such deficits in processing.

Further research has attempted to clarify the distinct processes that may contribute to altered decision-making and reward processing in BD. In their comparison of BD manic and MDD patients, Murphy et al[59] found that the 2 groups were markedly slower at making choices on a probabilistic reward processing task and also earned significantly fewer points based on the reward learning information provided in the task. They suggest that these first-line results provide further support for cognitive emotional processing deficits in mood disorders, particularly in the executive functioning domain of set-shifting. However, when delving into the decision-making process further, the researchers also noted how manic patients were more likely to make detrimental choices leading to early termination of blocks, or "losing the game," compared to MDD depressed patients, as well as tending to select the choice associated with a lower probability of reward, indicating an impairment in learning about optimal reward information. Thus, it seemed that not only were manic patients poorer at making optimal decisions, they were also more willing to engage in risk-taking behavior when making these decisions, compared to both MDD patients and controls.

Again, while these results begin to highlight some of the cognitive impairments reported in mood disorders in the domain of reward processing, the fact that such impairments are modulated by mood episode and symptom severity points to the idea that these may be state-like characteristics of the disorders. A closer examination of the mechanisms at play during euthymic phases of BD should therefore aid us in understanding the trait-related features of the disorder, with the hope of describing the clinical symptoms of anhedonia during depression, and hyperhedonia, or excessive pleasure-seeking behavior, during mania and their relation to cognitive affective processing in further detail. Pizzagalli et al[60] set out to study this in their sample of euthymic BD patients by testing whether BD is characterized by an impairment in the ability to adapt behavior in response to changing reward, accounting for trait-related features that can be applicable across distinct mood episodes. In their probabilistic reward task, they found that euthymic patients were slower at selecting, and less likely to select, the more frequently rewarding stimuli, suggesting an impairment in response bias toward rewarding information, as well as decreased ability to learn and integrate information about reward over time. While this impairment was exacerbated by residual anhedonic symptoms in the sample, alluding to a similar pattern of diminished learning and negative attentional biases, the suggestion of impairments in learning over time, again, highlights underlying difficulties in executive function. Taken together with the interesting, yet inconclusive, evidence of cognitive emotional processing in other domains such as attention and memory, particularly in BD but also across mood disorders, such findings lead us to examine the neural mechanisms that may modulate and underpin these disorders.

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The Neural Underpinnings of Cognitive Affective Processing

As highlighted above, a discussion of the neural underpinnings of cognitive affective processing, via neuroimaging techniques such as magnetic resonance imaging (MRI), may help us to better understand the shared and distinct features of mood disorders. Generally, abnormalities are usually found in limbic structures, including the amygdala and hypothalamus, and in regions of the prefrontal cortex (PFC), including the orbital and medial prefrontal cortex (OMPFC), as well as various connections between the two[61] across both MDD and BD, accounting for most major mood-related symptoms.

In MDD, patients are reported to have increased activation in the amygdala, orbitofrontal cortex (OFC), and prefrontal cortex (PFC) when showing an attentional bias toward negative facial expressions.[62] As well as being involved in emotional processing and executive functions such as attention—linking the two together—disruptions in these regions and circuits are also thought to increase the risk of developing the disorder.[63] Other researchers have also reported increased activation in limbic areas, such as the hippocampus, insula, and anterior cingulate cortex (ACC), during the processing of negative facial expressions,[13,64,65] modulated by symptom severity, which emphasizes how the emotional component of the information is intrinsically related to cognitive processing in MDD. However, results in MDD have not always been so conclusive, with some studies failing to see increased amygdala responses to facial expressions,[66] while others have found differing patterns of activation in tasks engaging both attention and memory of facial expressions.[67,68] Methodological differences, including task instructions and the cognitive domains required, have been proposed as potential explanations for such differing results, and also suggest the need for more stringent investigations.

Increased activation in limbic regions during face processing tasks has also been reported in BD. In their systematic review and meta-analysis of the neural correlates of emotional processing in BD and MDD, Delvecchio et al[69] argued that increased limbic engagement, particularly involving the parahippocampal gyrus and amygdala, formed part of the core phenotype of cognitive affective processing of facial expressions in mood disorders, but that clear distinctions in other regions existed. For instance, BD, but not MDD, was associated with reduced activation in the ventrolateral PFC, an area known to be implicated in inhibitory control. As difficulties with inhibition, particularly within manic episodes, is a core feature of the disorder, this suggests that processing in this region and its associated circuits is specific to the experience of BD.[70,71] In a similar fashion, increased activation in the thalamus, particularly the pulvinar, was found to be associated with BD rather than MDD, while processing negative facial expressions. As this particular "higher order" region is known to have various cortical connections,[12] it has been proposed that overamplification toward emotionally salient information helps to explain the difficulties in fluctuating mood in BD, while the suppression of activation in the same region during the processing of positive facial expression in MDD points to the dampening of reactivity towards positive information associated with depression.[72]

A combination of connections between these cortical, striatal, and thalamic regions are thought to be intrinsically related to reward processing in mood disorders. According to research in MDD, patients show a decrease in activation in the ventral striatum in response to rewarding stimuli, compared to healthy controls, and this deactivation is known to be modulated by an increase in anhedonic symptoms.[73] Increased activation in the caudate nucleus, a structure of the striatum, is reported in BD when processing rewarding stimuli, including happy facial expressions during manic episodes.[69,74] This is in line with research that has shown distinct abnormalities in the function, size, and shape of the basal ganglia,[74–77] a region that encompasses the striatum and is known to be particularly implicated in reward processing, with connectivity to PFC regions and the amygdala. Taken together, reward learning and processing is known to involve cortico-striatal learning systems, such as those discussed here, in combination with prefrontal regions of executive control. While there is still a need for further neuroimaging research in this area in order to parse out the particular neural contributions, findings of disruptions in these areas across the domains of perception, attention, and memory of affective information combine to further inform us of the behavioral impairments noted in reward processing across mood disorders, and the distinct mood-related mechanisms which may modulate the severity and direction of impairment within the disorders.

Mood Instability and Cognitive Affective Processing

The wide-ranging, yet often inconclusive, evidence of cognitive affective processing in mood disorders leads us to further consider differences in processing outside of distinct mood episodes, that is, trait-related characteristics. Given that studying patients during periods of episodic recovery or euthymia can be confounded by medication status and residual mood symptoms, the phenomenon of mood instability—which is known to both predispose an individual to mood disorders and persist during the course of the disorder[78]—is of

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particular interest. For this reason, it follows that the relationship between mood instability and cognition, especially that of cognitive affective processing, should be investigated.

Little has yet been researched in the cognitive domains of perception, attention, and memory; however, the relationship between mood instability and reward processing has gained recent attention. Owing to the fact that reward-processing differences are particularly noticeable across mood disorders and employ learning, memory, and executive functions across time, its relationship with mood instability is of value for the similar reason that mood instability reflects fluctuations in affect across a longitudinal temporal scale. Recent research by Eldar and Niv,[79] for example, has shown a bidirectional relationship between emotional state and the perception and valuation of rewards and outcomes. In their task involving slot machines and an emotion-impacting wheel of fortune (WoF) draw, the researchers found that a large, unexpected outcome in the draw affected both emotional state and subsequent reward perception in the same direction in their group of individuals showing high levels of mood instability. This positive feedback loop, whereby unexpectedly winning a relatively large sum at chance on the WoF draw resulted in a positive bias in mood and subsequent decision-making, was not observed in control participants who otherwise showed stable mood. Utilizing computational modeling techniques, the researchers noted how such biasing also worked to result in mood destabilization, thus proposing mood instability as a result of a disruption in the relationship between emotional state and perception of reward.

Eldar et al[80] furthered this idea of a bidirectional relationship between mood and reward by proposing that mood is both affected by discrepancies in reward outcomes and expectations, and that mood works to bias the way we perceive outcomes and learn to make decisions based on these outcomes. Therefore, mood is proposed to reflect the "overall momentum of recent outcomes," such that biases work to account for environmental contingencies.[80] As demonstrated by Eldar and Niv[79] above, this interaction can become dysfunctional in the case of mood instability, contributing to the development and maintenance of mood disorders. While the presence of a similar pattern of cognitive and affective processes employing computational modeling techniques has not yet been investigated in MDD and BD, mood instability's standing as a prominent feature of the disorders and the clinical symptoms of anhedonia, hyperhedonia, and mania—implicating changes in reward processing—suggest the importance of this bidirectional relationship. By combining these methods of investigation in mood instability and cases of psychopathology, future research can begin to clarify the particular mechanisms at play that both cut across and differentiate between MDD and BD.

In a recent systematic review of mood instability, Broome et al[81] found impairments in cognitive processing reflecting increased distractibility, decreased recognition of and sensitivity to facial expressions, and increased attention toward highly salient or intense negative facial expressions (eg, anger and disgust). They also reported increased limbic engagement, particularly in the amygdala, suggesting a similar pattern of behavioral and neural activity to that often reported in MDD and BD. However, the researchers emphasized how the studies to date did not investigate mood instability in isolation, rather as a feature of a psychiatric diagnosis such as attention deficit hyperactivity disorder (ADHD), borderline personality disorder (BPD), or mood disorders, and so it becomes difficult to decipher whether the differences reported are diagnostically specific or relevant to the transdiagnostic phenomenon of mood instability. Future research should, thus, consider mood instability in the prodrome of mood disorders, in combination with clinical groups and healthy controls, in order to fully elucidate the shared and distinct features of cognitive affective processing.

Conclusion

Results from studies of cognitive affective processing, across the domains of perception, attention, memory, and reward processing, and in both MDD and BD, highlight the complex phenotypic profile of mood disorders. While research, both behavioral and neurobiological, has often pointed to shared trait-related characteristics, for instance, the presence of negative biases in both MDD and BD euthymic states, particular state-related features, such as residual anhedonic symptoms, and the administration of antidepressant or mood stabilizing medication, can present as confounds. The phenomenon of mood instability is specifically suggested as a transdiagnostic marker, owing to its standing as both a longitudinal indicator of vulnerability to psychopathology and a predictor of illness severity and functional outcome[78] across diagnostic categories.

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REFERENCES:

1. Mental disorders. World Health Organisation (WHO). 2017. http://www.who.int/mediacentre/factsheets/fs396/en/
2. Harvard Medical School. *National Comorbidity Survey* (*NCS*). 2007. https://www.hcp.med.harvard.edu/ncs/index.php
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
4. Roiser J, Farmer A, Lam D, *et al*. The effect of positive mood induction on emotional processing in euthymic individuals with bipolar disorder and controls. *Psychol Med*. 2009; **39**(5): 785–791.
5. Vo TM, Perry P, Ellerby M, Bohnert K. Is lithium a neuroprotective agent? *Ann Clin Psychiatry*. 2015; **27**(1): 49–54.
6. Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *Br J Psychiatry*. 2009; **195**(2): 102–108.
7. Beck AT. Depression. Clinical, experimental and theoretical aspects. *J R Coll Gen Pract*. 1969; **18**(87): 249.
8. Dozois DJA, Beck AT. Cognitive schemas, beliefs and assumptions. In: Dobson KS, Dozois DJA, eds. *Risk Factors in Depression*. San Diego: Elsevier; 2008:119–143.
9. Abramson LY, Metalsky G, Alloy L. Hopelessness depression: a theory-based subtype of depression. *Psychol Rev*. 1989; **96**(2): 358–372.
10. Scheurich A, Fellgiebel A, Schermuly I, Bauer S, Wolfges R, Muller MJ. Experimental evidence for a motivational origin of cognitive impairment in major depression. *Psychol Med*. 2008; **38**(2): 237–246.
11. Roiser J, Sahakian BJ. Information Processing in Mood Disorders. In: DeRubeis RJ, Strunk DR, eds. *The Oxford Handbook of Mood Disorders*. Oxford University Press; 2016.
12. Pessoa L, Adolphs R. Emotion processing and the amygdala: from a "low road" to "many roads" of evaluating biological significance. *Nat Rev Neurosci*. 2010; **11**(11): 773–783.
13. Elliott R, Zahn R, Deakin JFW, Anderson IM. Affective cognition and its disruption in mood disorders. *Neuropsychopharmacology*. 2011; **36**(1): 153–182.
14. Christodoulou T, Lewis M, Ploubidis GB, Frangou S. The relationship of impulsivity to response inhibition and decision-making in remitted patients with bipolar disorder. *Eur Psychiatry*. 2006; **21**(4): 270–273.
15. Ghaemi SN, Sachs GS, Chiou AM, Pandurangi AK, Goodwin K. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *J Affect Disord*. 1999; **52**(1–3): 135–144.
16. Hirschfeld RMA. The mood disorder questionnaire: its impact on the field [corrected]. *Depress Anxiety*. 2010; **27**(7): 627–630.
17. McGuffin P, Katz R. The genetics of depression and manic-depressive disorder. *Br J Psychiatry*. 1989; **155**(3): 294–304.
18. Harvey PD. Cognitive impairments in major depression and bipolar disorders. *Psychiatry (Edgmont)*. 2007; **4**(1): 12–14.
19. Insel T, Cuthbert B, Garvey M, *et al*. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010; **167**(7): 748–751.
20. Marwaha S, Parsons N, Flanagan S, Broome M. The prevalence and clinical associations of mood instability in adults living in England: results from the Adult Psychiatric Morbidity Survey 2007. *Psychiatry Res*. 2013; **205**(3): 262–268.
21. Henry C, Mitropoulou V, New AS, Koenigsberg HW, Silverman J, Siever LJ. Affective instability and impulsivity in borderline personality and bipolar II disorders: similarities and differences. *J Psychiatr Res*. 2001; **35**(6): 307–312.
22. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *J Pers Soc Psychol*. 2003; **85**(2): 348–362.
23. Ekman P, Friesen W V. Constants across cultures in the face and emotion. *J Pers Soc Psychol*. 1971; **17**(2): 124–129.
24. Beck AT, Rush J, Shaw BF, Emery G. *Cognitive Therapy of Depression*. 1st ed. Guildford Press; 1979.
25. Bradley BP, Mogg K, Lee SC. Attentional biases for negative information in induced and naturally occurring dysphoria. *Behav Res Ther*. 1997; **35**(10): 911–927.
26. Gotlib IH, Krasnoperova E, Yue DN, Joormann J. Attentional biases for negative interpersonal stimuli in clinical depression. *J Abnorm Psychol*. 2004; **113**(1): 127–135.
27. Gotlib IH, Kasch KL, Traill S, Joormann J, Arnow BA, Johnson SL. Coherence and specificity of information-processing biases in depression and social phobia. *J Abnorm Psychol*. 2004; **113**(3): 386–398.
28. Joormann J, Gotlib IH. Selective attention to emotional faces following recovery from depression. *J Abnorm Psychol*. 2007; **116**(1): 80–85.
29. Duque A, Vázquez C. Double attention bias for positive and negative emotional faces in clinical depression: evidence from an eye-tracking study. *J Behav Ther Exp Psychiatry*. 2015; **46**:107–114.
30. Lembke A, Ketter TA. Impaired recognition of facial emotion in mania. *Am J Psychiatry*. 2002; **159**(2): 302–304.
31. Gray J, Venn H, Montagne B, *et al*. Bipolar patients show mood-congruent biases in sensitivity to facial expressions of emotion when exhibiting depressed symptoms, but not when exhibiting manic symptoms. *Cogn Neuropsychiatry*. 2006; **11**(6): 505–520.
32. Harmer CJ, Grayson L, Goodwin GM. Enhanced recognition of disgust in bipolar illness. *Biol Psychiatry*. 2002; **51**(4): 298–304.
33. Venn HR, Gray JM, Montagne B, *et al*. Perception of facial expressions of emotion in bipolar disorder. *Bipolar Disord*. 2004; **6**(4): 286–293.
34. Vaskinn A, Sundet K, Friis S, *et al*. The effect of gender on emotion perception in schizophrenia and bipolar disorder. *Acta Psychiatr Scand*. 2007; **116**(4): 263–270.
35. Martino DJ, Strejilevich SA, Fassi G, Marengo E, Igoa A. Theory of mind and facial emotion recognition in euthymic bipolar I and bipolar II disorders. *Psychiatry Res*. 2011; **189**(3): 379–384.
36. Bilderbeck AC, Atkinson LZ, Geddes JR, Goodwin GM, Harmer CJ. The effects of medication and current mood upon facial emotion recognition: findings from a large bipolar disorder cohort study. *J Psychopharmacol*. 2017; **31**(3): 320–326.
37. Murphy FC, Sahakian BJ, Rubinsztein JS, *et al*. Emotional bias and inhibitory control processes in mania and depression. *Psychol Med*. 1999; **29**(6): 1307–1321.
38. Erickson K, Drevets WC, Clark L, *et al*. Mood-congruent bias in affective Go/No-Go performance of unmedicated patients with major depressive disorder. *Am J Psychiatry*. 2005; **162**(11): 2171–2173.
39. Rubinsztein JS, Michael A, Paykel ES, Sahakian BJ. Cognitive impairment in remission in bipolar affective disorder. *Psychol Med*. 2000; **30**(5): 1025–1036.
40. García-Blanco AC, Perea M, Livianos L. Mood-congruent bias and attention shifts in the different episodes of bipolar disorder. *Cogn Emot*. 2013; **27**(6): 1114–1121.
41. Kizilbash AH, Vanderploeg RD, Curtiss G. The effects of depression and anxiety on memory performance. *Arch Clin Neuropsychol*. 2002; **17**(1): 57–67.

https://doi.org/10.1017/S109285291800130X Published online by Cambridge University Press

42. Bourne C, Bilderbeck A, Drennan R, *et al*. Verbal learning impairment in euthymic bipolar disorder: BDI v BDII. *J Affect Disord*. 2015; **182**:95–100.
43. Sole B, Bonnin CM, Torrent C, *et al*. Neurocognitive impairment across the bipolar spectrum. *CNS Neurosci Ther*. 2012; **18**(3): 194–200.
44. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord*. 2009; **113** (1–2): 1–20.
45. Wolfe J, Granholm E, Butters N, Saunders E, Janowsky D. Verbal memory deficits associated with major affective disorders: a comparison of unipolar and bipolar patients. *J Affect Disord*. 1987; **13**(1): 83–92.
46. Burt T, Prudic J, Peyser S, Clark J, Sackeim H. Learning and memory in bipolar and unipolar major depression: effects of aging. *Neuropsychiatry Neuropsychol Behav Neurol*. 2000; **13**(4): 246–253.
47. Martínez-Arán A, Vieta E, Colom F, *et al*. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disord*. 2004; **6**(3): 224–232.
48. Mogg K, Bradley BP, Williams R. Attentional bias in anxiety and depression: the role of awareness. *Br J Clin Psychol*. 1995; **34**(Pt 1): 17–36.
49. Harmer CJ, O'Sullivan U, Favaron E, *et al*. Effect of acute antidepressant administration on negative affective bias in depressed patients. *Am J Psychiatry*. 2009; **166**(10): 1178–1184.
50. Uher R, Rutter M. Basing psychiatric classification on scientific foundation: problems and prospects. *Int Rev Psychiatry*. 2012; **24** (6): 591–605.
51. Elliott R, Sahakian BJ, Herrod JJ, Robbins TW, Paykel ES. Abnormal response to negative feedback in unipolar depression: evidence for a diagnosis specific impairment. *J Neurol Neurosurg Psychiatry*. 1997; **63**(1): 74–82.
52. Admon R, Pizzagalli DA. Dysfunctional reward processing in depression. *Curr Opin Psychol*. 2015; **4**:114–118.
53. Steele JD, Kumar P, Ebmeier KP. Blunted response to feedback information in depressive illness. *Brain*. 2007; **130**(9): 2367–2374.
54. Holmes AJ, Pizzagalli DA. Task feedback effects on conflict monitoring and executive control : relationship to subclinical measures of depression. *Emotion*. 2011; **7**(1): 68–76.
55. Murphy FC, Michael A, Robbins TW, Sahakian BJ. Neuropsychological impairment in patients with major depressive disorder: the effects of feedback on task performance. *Psychol Med*. 2003; **33**(3): 455–467.
56. Eshel N, Roiser JP. Reward and punishment processing in depression. *Biol Psychiatry*. 2010; **68**(2): 118–124.
57. Roiser JP, Cannon DM, Gandhi SK, *et al*. Hot and cold cognition in unmedicated depressed subjects with bipolar disorder. *Bipolar Disord*. 2009; **11**(2): 178–189.
58. Minassian A, Paulus MP, Perry W. Increased sensitivity to error during decision-making in bipolar disorder patients with acute mania. *J Affect Disord*. 2004; **82**(2): 203–208.
59. Murphy FC, Rubinsztein JS, Michael A, *et al*. Decision-making cognition in mania and depression. *Psychol Med*. 2001; **31**(4): 679–693.
60. Pizzagalli DA, Goetz E, Ostacher M, Iosifescu DV, Perlis RH. Euthymic patients with bipolar disorder show decreased reward learning in a probabilistic reward task. *Biol Psychiatry*. 2008; **64**(2): 162–168.
61. Price JL, Drevets WC. Neural circuits underlying the pathophysiology of mood disorders. *Trends Cogn Sci*. 2012; **16**(1): 61–71.
62. Wagner V, Müller JL, Sommer M, Klein HE, Hajak G. [Changes in the emotional processing in depressive patients: a study with functional magnetoresonance tomography under the employment of pictures with affective contents]. *Psychiatr Prax*. 2004; **31**(Suppl 1): S70–72.
63. Price JL, Drevets WC. Neurocircuitry of mood disorders. *Neuropsychopharmacology*. 2010; **35**(1): 192–216.
64. Anand A, Li Y, Wang Y, *et al*. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. *Biol Psychiatry*. 2005; **57**(10): 1079–1088.
65. Lee BT, Seok JH, Lee BC, *et al*. Neural correlates of affective processing in response to sad and angry facial stimuli in patients with major depressive disorder. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2008; **32**(3): 778–785.
66. Gotlib IH, Sivers H, Gabrieli JDE, *et al*. Subgenual anterior cingulate activation to valenced emotional stimuli in major depression. *Neuroreport*. 2005; **16**(16): 1731–1734.
67. Roberson-Nay R, McClure EB, Monk CS, *et al*. Increased amygdala activity during successful memory encoding in adolescent major depressive disorder: an FMRI study. *Biol Psychiatry*. 2006; **60**(9): 966–973.
68. Hamilton JP, Gotlib IH. Neural substrates of increased memory sensitivity for negative stimuli in major depression. *Biol Psychiatry*. 2008; **63**(12): 1155–1162.
69. Delvecchio G, Fossati P, Boyer P, *et al*. Common and distinct neural correlates of emotional processing in bipolar disorder and major depressive disorder: a voxel-based meta-analysis of functional magnetic resonance imaging studies. *Eur Neuropsychopharmacol*. 2012; **22**(2): 100–113.
70. Cerullo MA, Adler CM, Delbello MP, Strakowski SM. The functional neuroanatomy of bipolar disorder. *Int Rev Psychiatry*. 2009; **21**(4): 314–322.
71. Chen CH, Lennox B, Jacob R, *et al*. Explicit and implicit facial affect recognition in manic and depressed states of bipolar disorder: a functional magnetic resonance imaging study. *Biol Psychiatry*. 2006; **59**(1): 31–39.
72. Rottenberg J, Gross JJ, Gotlib IH. Emotion context insensitivity in major depressive disorder. *J Abnorm Psychol*. 2005; **114**(4): 627–639.
73. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci Biobehav Rev*. 2010; **35**(3): 537–555.
74. Abler B, Greenhouse I, Ongur D, Walter H, Heckers S. Abnormal reward system activation in mania. *Neuropsychopharmacology*. 2008; **33**(9): 2217–2227.
75. Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder : a review of neuroimaging findings. *Mol Psychiatry*. 2005; **10**(1): 105–116.
76. Strakowski SM, Adler CM, DelBello MP. Volumetric MRI studies of mood disorders: do they distinguish unipolar and bipolar disorder? *Bipolar Disord*. 2002; **4**(2): 80–88.
77. Hwang J, Lyoo IK, Dager SR, *et al*. Basal ganglia shape alterations in bipolar disorder. *Am J Psychiatry*. 2006; **163**(2): 276–285.
78. Broome MR, Saunders KEA, Harrison PJ, Marwaha S. Mood instability: significance, definition and measurement. *Br J Psychiatry*. 2015; **207**(4): 283–285.
79. Eldar E, Niv Y. Interaction between emotional state and learning underlies mood instability. *Nat Commun*. 2015; **6**:6149.
80. Eldar E, Rutledge RB, Dolan RJ, Niv Y. Mood as representation of momentum. *Trends Cogn Sci*. 2016; **20**(1): 15–24.
81. Broome MR, He Z, Iftikhar M, Eyden J, Marwaha S. Neurobiological and behavioural studies of affective instability in clinical populations: a systematic review. *Neurosci Biobehav Rev*. 2015; **51**:243–254.

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