Chapter 40

Reward processing and depression: Current findings and future directions

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List of abbreviations

BOLD	blood-oxygen-level-dependent
dACC	dorsal anterior cingulate cortex
EEG	electroencephalography
ERP	event-related potential
fMRI	functional magnetic resonance imaging
MDD	major depressive disorder
RDoC	research domain criteria
RewP	reward positivity
ROI	region of interest
SNc	substantia nigra pars compacta
VTA	ventral tegmental area

Introduction

Depressive disorders, including major depressive disorder (MDD) and persistent depressive disorder, are common and impairing. Worldwide, more than 300 million people suffer from depression (WHO, 2012) and depressive disorders are the leading contributor to the global disease burden (Ferrari et al., 2013). Over the past decade, dysfunction in neural processing of rewards has emerged as one of the most promising biological markers for the development of depressive disorders due to the role of reward processing in learning and in emotions central to depressive disorders. Despite this, depressive disorders are still defined by self-reported symptoms and behavior, and research has begun to focus on identifying the pathophysiology of the disorder. These findings have implications for etiological theories of depressive disorders while providing important targets for interventions.

In this chapter, we provide a selected review of theory and research on the association between reward processing and depression. Because adolescence is a critical period in the development of depressive disorders and understanding risk factors that predate the onset of psychopathology is crucial for understanding etiology, we review the reward-processing literature as it relates to depression in childhood and adolescence, as well as adulthood. Although we review behavioral studies, we emphasize studies using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). We also provide an overview of a more recent line of research examining the influence of stressful life events on the link between reward processing and depression. Finally, we provide suggestions for the direction of future research in the area of reward processing and depression.

Theory linking reward processing and depression

Theories suggest that the core symptoms of depressive disorders, especially anhedonia, arise from dysfunction in the processing of rewarding stimuli (Berrios, 1996). From an evolutionary perspective, rewards are a positive response to behavior that promotes survival. Much of the theoretical work focusing on the processing of rewarding stimuli have examined its role in learning via positive reinforcement; experiencing a reward increases the likelihood of engaging in that behavior again, whereas punishers (e.g., negative feedback or loss) contribute to learning by promoting behavioral withdrawal (Schultz, 2016). At a neural level, this is instantiated by phasic increases and pauses in dopamine release in the midbrain dopaminergic system (see Fig. 1) in response to rewards and punishers, respectively (Cox & Witten, 2019; Schultz, 2016). These dopaminergic responses encode a reward prediction error that reflects the difference in value between the expected and the experienced outcome, which drives reinforcement learning, with greater differences between anticipated and actual outcomes having a greater influence on learning (Schultz, Dayan, & Montague, 1997). Importantly, while the influence of positive prediction errors on learning behavior (e.g., increased likelihood of repeating the rewarded behavior) is well established, negative prediction errors are also encoded (Cox & Witten, 2019), with inhibition of dopamine neurons promoting extinction of previously conditioned responses (Chang et al., 2016) and

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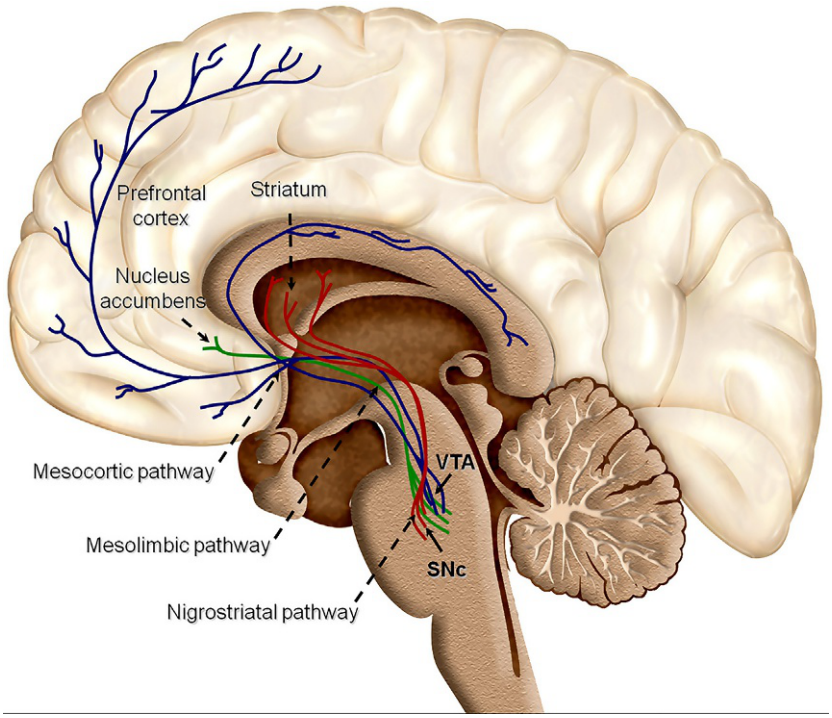

FIG. 1 Overview of the midbrain dopaminergic reward system. Dopamine neurons located in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) project to the striatum (caudate nucleus, putamen and ventral striatum, including the nucleus accumbens) and prefrontal cortex. *Figure reprinted with permission from Arias-Carrion, O., Stamelou, M., Murillo-Rodriguez, E., Menendez-Gonzalez, M., & Poppel, E. (2010). Dopaminergic reward system: A short integrative review*. International Archives of Medicine, 3, *24*. *https://doi.org/10.1186/1755-7682-3-24*.

TABLE 1 Reward-processing phases and associated depressive symptoms.

Reward phase	Definition	Depression symptoms
Reward learning	A type of reinforcement learning in which information about stimuli, actions, and contexts are used to predict outcomes. A reward-prediction error that reflects the difference in value between the expected and the experienced outcome is encoded and informs behavioral modification.	Depressed mood, anhedonia, hopelessness
Anticipation/prediction	Evaluation of an anticipated reward, including determination of expectation of obtaining that reward and how pleasurable it will be.	Anticipatory anhedonia
Decision	Integration of valuation of how important the reward is and how much effort will be required to obtain the reward.	Impaired decision-making
Action/effort expenditure	Implementation of a goal-directed behavior necessary to obtain a reward.	Fatigue, reduced energy
Consummatory/experience	Evaluation of how pleasurable or unpleasurable an obtained reward was.	Consummatory anhedonia

An overview of reward-processing constructs: reward learning, anticipation/prediction, decision, action/effort expenditure, and consummatory/experience.

reduction in the probability of repeating a previous action (Hamid et al., 2016). In the context of depression, dysfunction in the midbrain dopaminergic system in processing anticipation or receipt of rewards may contribute to a blunting of prediction error responses (Steele, Meyer, & Ebmeier, 2004), and an inhibited ability to learn from feedback.

Despite much of the theoretical work examining reward processing focusing on reward learning, there are numerous other aspects of reward processing which contribute to the development of depressive disorders. Table 1 integrates previous theoretical models (Kring & Barch, 2014; Rizvi, Pizzagalli, Sproule, & Kennedy, 2016) to provide an overview of aspects of reward processing, parsing reward processing into several constructs: reward learning, anticipation/prediction, decision, action/effort expenditure, and consummatory/experience. It is not yet evident how distinct

these reward constructs are, how dysfunction in different reward constructs influence one another, or whether each of these constructs contributes to deficits in reward learning. For example, deficits during the anticipation phase of reward processing may contribute to anhedonia via decreased motivation to engage in activities despite previous enjoyment, or through deficits in reward learning due to poor prediction of outcomes. Similarly, blunted response to reward during the consummatory phase may contribute to depressed mood or anhedonia through an inability to enjoy previously pleasurable activities via a diminished pleasure response, or through inaccurate reward prediction errors. Maladaptive reward learning may ultimately contribute to social withdrawal and reduced opportunities to experience potentially rewarding situations.

Reward processing and depression: A review of behavioral studies

Behavioral studies of adults suggest that individuals with, or at risk for, MDD demonstrate a hyposensitivity to rewarding stimuli. Individuals with MDD report less happiness in anticipation of a reward than nondepressed controls (McFarland & Klein, 2009), potentially reflecting approach-related deficits in the anticipation phase of reward processing. The Response Bias Probabilistic Reward Task is a signal detection task that rewards correct answers to one of the two stimuli three times more frequently than the other stimuli. Healthy subjects are more likely to learn to select the highly rewarded stimuli, whereas individuals with high levels of depression symptoms (Pizzagalli, Jahn, & O'Shea, 2005) or MDD (Pizzagalli et al., 2009) do not. Hierarchical drift-diffusion modeling of this task suggests that individuals with MDD respond more slowly and receive fewer rewards due to impaired ability to accumulate and incorporate evidence, not slowed perception or response (Lawlor et al., 2019).

Several investigations have also explored the role of maladaptive behavioral responses to punishment. Studies comparing adult MDD patients to matched healthy and psychiatric controls demonstrated that patients with MDD perform more poorly on cognitive tasks following an error (Elliott et al., 1996; Elliott, Sahakian, Herrod, Robbins, & Paykel, 1997). Additionally, only MDD patients demonstrated an increased conditional probability of error commission after an error on the previous trial. Consistent with theory implicating reward-learning deficits, these findings suggest that depressed individuals fail to incorporate negative feedback in order to improve future performance.

An ERP measure of reward processing

ERPs provide precise temporal resolution of electrophysiological recordings on the scalp in response to stimuli, thus providing a measure of neural activity on the order of milliseconds. The Reward Positivity (RewP; also called the Feedback Negativity [FN] and Feedback-Related Negativity [FRN]) is an ERP component scored as the neural response to gain minus loss. It is a positive deflection in the ERP signal occurring approximately 250–350 ms after feedback and is larger in response to gains (Proudfit, 2015). The RewP is frequently elicited through the use of forced-choice guessing tasks (see Fig. 2), and can be measured in response to both monetary and social rewards (Distefano et al., 2018). Importantly, reinforcement learning theory suggests that the RewP is generated in response to reward-prediction errors, with feedback indicating outcomes that are better or worse than expected evoking phasic increases and decreases in midbrain dopamine release, respectively (Holroyd & Coles, 2002). Evidence suggests that the RewP is correlated with fMRI BOLD activation in the striatum (Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011), and source localization studies indicate that the RewP is generated by the midbrain dopaminergic system (Foti, Weinberg, Dien, & Hajcak, 2011), supporting the theory that the RewP reflects individual differences in reward-related neural activity.

Reward processing and depression: A review of ERP studies

In children and adolescents, accumulating evidence suggests that the RewP is an important biological marker of risk for depression. In a study of more than 400 never-depressed 9-year olds, maternal history of depression, one of the best established risk factors for depression, was associated with a reduced RewP in offspring; moreover, this association was strongest for children with a severe maternal history of depression, and a maternal history of anxiety was not related to offspring RewP (Kujawa, Proudfit, & Klein, 2014). Additionally, the RewP is associated with depressive symptoms and episodes during childhood and adolescence. In an unselected sample of children aged 8–13, a blunted RewP was cross-sectionally correlated with increased self- and parent-reported depression, but not anxiety, symptoms (Bress, Smith, Foti, Klein, & Hajcak, 2012). A follow-up of this sample of children 2 years later also demonstrated that a reduced RewP predicted increased depression symptoms at the 2-year follow-up (Bress et al., 2012). Similarly, a study of 68 adolescent girls showed that a blunted RewP predicted increased depressive symptoms and depressive disorder onset (Bress, Foti, Kotov, Klein, & Hajcak, 2013). Furthermore, a study of 444 adolescent girls demonstrated that a blunted RewP prospectively predicted the first onset of depression and increased symptom severity 18-months later (Nelson, Perlman, Klein, Kotov, & Hajcak, 2016). Finally, a recent meta-analysis concluded that there is a significant moderate-sized effect of the RewP on depression among individuals under the age of 18 (Keren et al., 2018).

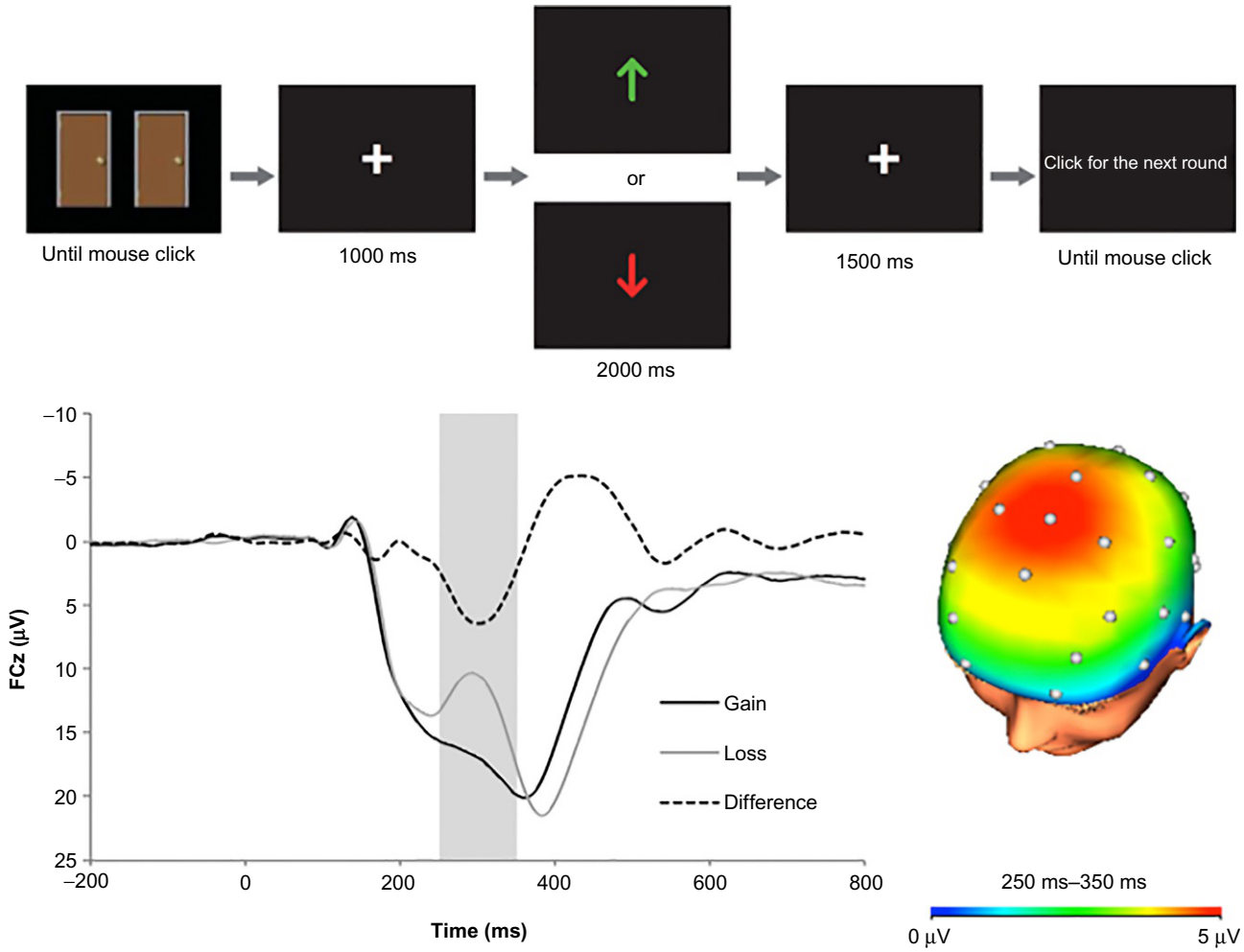

FIG. 2 The Doors Task and RewP waveform and scalp distribution. The *top portion* of the figure displays the Doors task, a forced-choice guessing paradigm frequently used to elicit the RewP. The *bottom left* and *right portions* of the figure are an example RewP waveform and scalp distribution, respectively. *Figure adapted with permission from Mackin, D. M., Kotov, R., Perlman, G., Nelson, B. D., Goldstein, B. L., Hajcak, G., et al. (2019). Reward processing and future life stress: Stress generation pathway to depression.* Journal of Abnormal Psychology, 128*(4), 305–314. https://doi.org/10.1037/abn0000427.*

Multiple studies have also demonstrated an association between the RewP and depression symptoms and status in adults (Foti, Carlson, Sauder, & Proudfit, 2014; Foti & Hajcak, 2009; Liu et al., 2014). However, the association between reward processing and depression is less consistent in adults than in youth. The same meta-analysis cited above found that although there is a significant effect of the RewP on depression, this effect was moderated by age and that the association between depression and the RewP was nonsignificant in adults (Keren et al., 2018). One explanation for this finding may be that, in adults, among whom neural development of the reward system is complete, the relationship between the RewP and depression is specific to melancholic depression, a subtype that is characterized by pervasive anhedonia and lack of reactivity to positive events. Indeed, one study examining the association between remitted depressive subtypes, healthy controls, and the RewP found an association between a blunted RewP and remitted melancholic depression, but showed that the magnitude of the RewP did not differ between the remitted non-melancholic depression and healthy control groups (Weinberg & Shankman, 2017).

Taken together, the RewP is associated with known risk factors for depression in children, adolescents, and adults. Among children and adolescents, evidence suggests that there is a moderate effect of the RewP on current and subsequent depression symptoms and episodes. There is also evidence of an association between the RewP and adults although findings are less consistent and may be specific to subtypes of depression, such as melancholia.

fMRI measurement of reward processing

An alternative method to ERPs that provides improved spatial resolution is fMRI. Reward-processing tasks in fMRI studies have frequently distinguished between the anticipation and

consummatory phases of processing. Studies utilizing fMRI methodology to study reward processing have typically focused on the midbrain dopaminergic reward system. Many of the current reward-processing studies have focused on activation in one or several of these regions and frequently score activity as the response on a rewarding condition or the response on a rewarding minus a control condition.

Reward processing and depression: A review of fMRI studies

Evidence from fMRI studies also suggests that reward-related deficits are a risk factor for depression, especially in children and adolescents. Several studies have demonstrated reduced activation in subcortical reward regions (e.g., dorsal and ventral striatum) in both anticipation and response to reward among offspring of depressed relative to nondepressed parents (Gotlib et al., 2010; Luking, Pagliaccio, Luby, & Barch, 2016; Olino et al., 2014; Sharp et al., 2014). Consistent with theory implicating negative prediction errors, several studies have also noted aberrant processing of loss-related stimuli being associated with depression risk (Gotlib et al., 2010; Luking et al., 2016).

Several fMRI studies have also identified an association between reward processing and concurrent depression symptoms and episodes during childhood and adolescence. One study of adolescents found that reduced striatal activity to receipt of reward was associated with depression symptoms (Forbes et al., 2010), while another demonstrated that blunted ventral striatal activation was associated with the presence of MDD in a sample of adolescent girls (Sharp et al., 2014). Importantly, studies have also demonstrated a prospective association between reward processing and depression in youth. A study of 77 adolescents found that blunted striatal activation in anticipation of rewards predicted subsequent depressive symptoms in boys and girls who were in the mid to late stages of puberty (Morgan, Olino, McMakin, Ryan, & Forbes, 2013). Additionally, a large community study of 1576 adolescents found that individuals with subthreshold and threshold MDD demonstrated reduced bilateral ventral striatal activation in anticipation of reward relative to healthy individuals. Furthermore, blunted striatal activation in anticipation of reward also predicted increased depression symptoms as well as diagnostic transition from no depression to subthreshold and from subthreshold to threshold depression at the 2-year follow-up (Stringaris et al., 2015). Finally, reduced bilateral ventral striatal activation was concurrently associated with the presence of anhedonia, and prospectively predicted the presence of both anhedonia and low mood at the 2-year follow-up, suggesting that these deficits might be especially relevant to melancholic depression, a subtype of depression characterized by anhedonia and lack of reactivity to positive events.

Findings examining the association between reward processing and depression in adults tend to be less consistent than those using child and adolescent samples. However, several of these studies have found a relationship between reward-processing abnormalities and depression. One such study (Pizzagalli et al., 2009) demonstrated that participants with MDD showed significantly weaker responses to gains in the left nucleus accumbens and the bilateral caudate, as well as reduced activation in anticipation of reward in the left posterior putamen, relative to control participants. Similar to some studies in children and adolescents, the authors also found reduced responses to monetary penalties in caudate regions among depressed participants. Importantly, these dorsal regions of the striatum are implicated in reward learning. Another study found that depressed adults exhibit decreased connectivity between the caudate and dorsal anterior cingulate cortex (dACC) in response to monetary gains, and increased connectivity between the caudate and a more rostral subregion of the dACC in response to monetary penalties (Admon et al., 2015). Furthermore, a study utilizing a reward learning task to examine the influence of reward-prediction errors on depression demonstrated that patients with depression exhibited reduced prediction errors in the striatum and midbrain compared to healthy controls and that the extent of signal reduction in the bilateral caudate, nucleus accumbens, and midbrain correlated with increased anhedonia severity (Gradin et al., 2011).

A recent meta-analysis reviewed fMRI studies investigating the association between anticipatory and consummatory reward processing and depression in both youth and adults. Analyses aggregating across youth and adult studies that employed a whole brain activation approach found significantly reduced activation in the bilateral caudate in depressed subjects relative to healthy controls when examining the reward feedback phase (Keren et al., 2018). The authors also analyzed studies that employed an ROI methodology. Depressed subjects demonstrated blunted activity during the anticipation phase bilaterally in the caudate and putamen, and moderation analyses suggest a stronger relationship among individuals under age 18. Results also suggested reduced activation during the feedback phase in the caudate, putamen, and globus pallidus for depressed relative to healthy subjects, but this effect was not moderated by age (Keren et al., 2018).

As a whole, these findings implicate reward-processing deficits in both the anticipation and consummatory phases in depression, and these abnormalities likely precede the onset of the disorder. Additionally, findings are stronger and more consistent among children and adolescents than adults. Although most studies focus on the processing of rewarding stimuli, loss-related deficits may also play a role in the development of depressive symptoms, especially in youth.

Life stress, reward processing, and depression

More recently, etiological models of depression have begun to examine the influence of life stress with regard to reward dysfunction and depression.

Auerbach and colleagues proposed three potential models in which reward processing and stress may differentially contribute the development of depression: a mediation model in which acute and chronic stress creates reward-processing deficits, subsequently resulting in potentiated depressive symptoms; a stress-generation model in which reward-processing dysfunction generates life stress that then influences subsequent depression; and a diathesis-stress model in which reward dysfunction and life stress interact to confer risk for depression (Auerbach, Admon, & Pizzagalli, 2014).

Pieces of the mediation model, including the influence of life stress on reward processing, have been examined separately in adults and, to a lesser extent, adolescents. Studies of adults have demonstrated that acute and chronic stress contributes to reward-processing deficits (Admon et al., 2012; Bogdan & Pizzagalli, 2006; Ossewaarde et al., 2011). Similarly, studies that have examined this association during adolescence found that life stress, including early childhood maltreatment, disrupts neural processing of reward (Admon et al., 2012; Casement et al., 2014; Novick et al., 2018; Vidal-Ribas et al., 2019).

There is also evidence that reward-processing deficits influence subsequent depression symptoms via stress generation. Consistent with the stress generation hypothesis (Hammen, 1991), a recent ERP study of a large sample of adolescents demonstrated that a blunted RewP predicted the generation of increased behaviorally dependent life stress 18-months later (Mackin et al., 2019). Additionally, this stress generation effect mediated the association between reward processing and subsequent depression symptoms. These findings are consistent with the reinforcement learning account of the RewP. A diminished RewP may indicate less efficient learning following feedback, resulting in continued engagement in maladaptive approach- or avoidance-related behaviors. Similarly, a recent fMRI study found that a blunted response to reward anticipation was correlated with increased stress reactivity at age 10 (Vidal-Ribas et al., 2019).

Finally, several studies have also found support for the diathesis-stress model in which reward dysfunction and life stress interact to confer risk for depression. Two large longitudinal ERP studies of children and adolescents demonstrated that a blunted RewP interacted with life stress to predict subsequent depression symptoms (Burani et al., 2019; Goldstein et al., 2019). In both cases, children with a blunted RewP who also experienced high levels of stressful life events had the greatest level of depression symptoms. Additionally, an fMRI study of 200 young adults found similar results; recent life stress interacted with ventral striatal activation such that individuals with blunted activation who experienced high levels of life stress reported the lowest levels of positive affect (Nikolova, Bogdan, Brigidi, & Hariri, 2012).

In sum, there is evidence supporting each of these models of reward-processing deficits, life stress, and depression. In our view, it is likely that all of these processes are occurring simultaneously. Fig. 3 proposes a theoretical model of how these processes may occur, ultimately resulting in depression.

Conclusion and future directions

In conclusion, theory and evidence from behavioral, ERP, and fMRI studies suggest that reward-processing deficits contribute to the development of depression. Deficits in reward processing are concurrently and prospectively associated with depression risk, symptoms, and episodes in children and adolescents, as well as adults. Additionally, recent evidence suggests that acute and chronic life stress play an important and multifaceted role in the relationship between reward processing and depression.

In order to advance this body of research, a number of future directions are likely to be fruitful. First, while theory and some preliminary evidence indicate that learning may be one of the mechanisms by which reward processing contributes to depression, the majority of reward processing and depression studies thus far have not utilized learning paradigms. An explicit examination of these paradigms

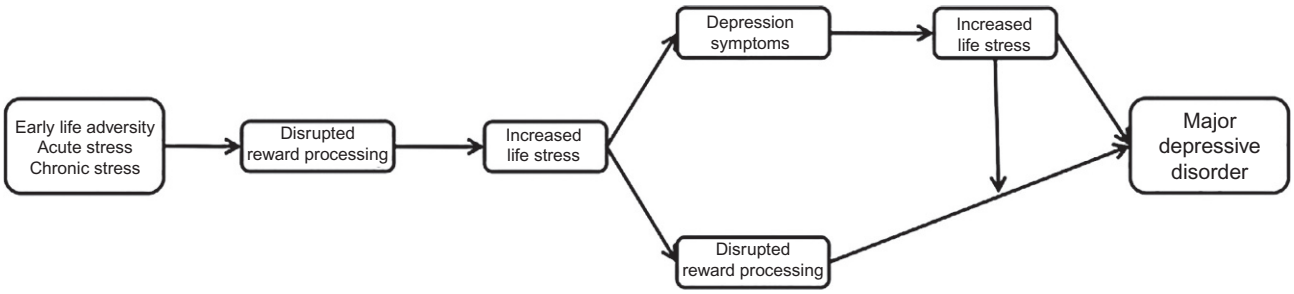

FIG. 3 Theoretical model of reward processing, life stress, and depression. Theoretical model outlining how life stress and reward processing may influence one another to confer risk for depression, including the influence of stress on reward processing, reward dysfunction in stress generation, and the moderating role of life stress.

would be useful for a better understanding of these relationships. Additionally, the majority of ERP and fMRI studies have examined monetary reward. Emerging evidence suggests that processing other forms of reward may be particularly salient to particular populations. For example, social rewards may be especially important during adolescence because it is a period characterized by social development. Future studies should continue to examine other forms of reward. Furthermore, a number of other important factors have not been examined, including the roles of sex and pubertal status. As the prevalence of depression increases more sharply in females than males after puberty, and the association between reward processing and depression appears stronger in youth than adults, reward-processing deficits may be particularly influential during the pubertal transition. Similarly, there are likely to be numerous other mediators and moderators that have yet to be fully examined, such as the presence of anxiety during childhood (Kujawa et al., 2014). Finally, while several investigators (e.g., Luking, Nelson, Infantolino, Sauder, & Hajcak, 2018; Mackin et al., 2019) have examined the processing of loss-related stimuli, the role of negative feedback has not been explored thoroughly. Considering that negative prediction errors are also encoded (Cox & Witten, 2019), and are an important RDoC construct (Cuthbert & Insel, 2013), this is an important area for future research.

Despite the evidence implicating reward-processing deficits in depression, there are several important caveats. First, reward processing only accounts for a small proportion of variance in depression. This is to be expected; effect sizes for biological markers of psychopathological disorders have been consistently small across disorders (Paulus & Thompson, 2019). This suggests that reward-processing abnormalities are only a small piece of understanding depressive disorders, and it is likely that more complex models that account for a larger number of small, and often bidirectional, effects between important variables, such as life stress, may be necessary to provide a more comprehensive account of the etiopathogenesis of depressive disorders. In the future, machine learning methods and identification more homogenous subtypes of depression or transdiagnostic phenotypes may prove beneficial in these areas.

Key facts of reward learning

- One of the primary roles of reward is to drive learning and influence behavioral modifications.
- Reward prediction errors are encoded by a dopaminergic response and drive reinforcement learning, with greater differences between anticipated and actual outcomes having greater influence on learning.
- Positive prediction errors occur when the outcome is better than expected, resulting in a phasic increase in dopamine release, thus increasing the likelihood of repeating the rewarded behavior.
- Negative prediction errors are encoded when outcomes are worse than expected and result in an inhibition of dopamine neurons that contributes to a reduced probability of repeating a previous action.
- Aberrations in reward processing may result in the generation of maladaptive positive and negative prediction errors, contributing to ineffective behavioral modifications, which lead to depression.

Summary points

- Dysfunction in neural processing of rewards has emerged as a promising biological marker of depression.
- One manner in which aberrant reward processing contributes to depression is through reward learning.
- Behavioral studies suggest that individuals with MDD demonstrate a hyposensitivity to rewarding stimuli, which contributes to deficits in reward-related decision-making.
- A blunted RewP in children and adolescents is correlated with depression risk, and is also concurrently associated with, and prospectively predicts, depression.
- A blunted RewP is also associated with depression in adults.
- Child, adolescent, and adult fMRI studies demonstrate reduced responsiveness in subcortical reward regions in both anticipation and response to reward are concurrently and prospectively associated with depression.
- The relationship between reward-processing deficits and depression appears to be stronger in children and adolescents than in adults.
- Life stress influences reward processing and moderates the association between reward processing and depression, while blunted reward processing predicts stress generation.
- Complex models that account bidirectional effects and depression subtypes may be necessary to provide a more comprehensive account of the etiopathogenesis of depressive disorders.

Mini-dictionary of terms

Anhedonia A core feature of depressive disorders marked by a reduced interest in appetitive stimuli, and/or diminished pleasure in response to stimuli previously considered rewarding or that others typically experience as rewarding.

Midbrain dopaminergic system Neurons project from the SNc and VTA to the striatum (caudate nucleus, putamen, and ventral striatum, including the nucleus accumbens) and the prefrontal cortex. This system is involved in motivation and reward-based learning, action selection, motor performance, working memory, and cognition.

Reward positivity (RewP) An event-related potential component reflecting neural sensitivity to reward that is scored as the neural response to gain minus loss.

Reward prediction error The difference in value between the expected and the experienced outcome, which is encoded by a dopaminergic response and drives reinforcement learning, with greater differences between anticipated and actual outcomes having greater influence on learning.

Stress generation hypothesis Risk factors for, and symptoms of, depression increase the likelihood that an individual will experience stressful life events in which their behavior contributed to the occurrence.

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