What Can Fear and Reward Learning Teach Us About Depression?

Katherine A. Collins and Daniela Schiller

Abstract The precise neural substrates of major depressive disorder (MDD) remain elusive, and FDA-approved antidepressants fail at least one-third of treatment-seeking patients. It is imperative, therefore, to identify novel research strategies to tackle the factors impeding progress. In this chapter we propose that the knowledge derived from computational investigations of associative learning might offer new insights into the neurobiology of MDD.

Keywords Associative learning · Reward learning · Fear learning/conditioning · Prediction error · Major Depressive Disorder (Mdd)

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K. A. Collins · D. Schiller (✉)
Mt. Sinai School of Medicine, New York, NY, US
e-mail: daniela.schiller@mssm.edu

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1 Introduction

The origins of depressive illness have been the subject of documented intellectual inquiry since Hippocrates wrote about melancholic disorders in approximately 400 BC (Hippocrates 1849). Since the serendipitous discovery in 1951, that a drug developed to treat tuberculosis appeared to induce improvements in mood, basic scientists and clinicians have been continuously engaged in investigations of the biological correlates of depression, employing a range of techniques at multiple levels of analysis, such as behavior, genetics, neuronal etc. Here we focus on the neural systems underlying cognitive process in depression (see Tables 1 and 3).

Despite the efforts of so many, current antidepressant interventions fail at least one-third of treatment-seeking patients (Rush et al. 2006). Moreover, the precise neural substrates of major depressive disorder (MDD) remain elusive. Those individuals who continue to suffer from the illness are both burdened by their own pain and can constitute a burden to their families and society. MDD is a leading cause of worldwide disability and is estimated to cost the United States alone over 80 billion dollars annually in workplace, medical and suicide-related mortality expenditures (Greenberg et al. 1990; World Health Organization 2012).

In this chapter we propose that studies of associative learning constitute one important untapped resource available to depression researchers. We begin by highlighting the characteristics of MDD that make it an illness so difficult to understand. We then describe how insights from fear and reward learning research can facilitate the interpretation of abnormal neural activity patterns in depressed patients, and inform the design and hypotheses of future investigations. Our aim is to encourage interdisciplinary collaboration that can accelerate the application of new insights about the pathophysiology of MDD in clinical settings.

2 Why do the Neural Mechanisms of Depression Remain Elusive?

In 1937 Papez proposed that, "the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus, and their interconnections constitute a harmonious mechanism which may elaborate the functions of central emotion, as well as participate in emotional expression" (Papez 1937). By offering evidence that affect is generated in the brain and is not a "magic product", Papez and his contemporaries set the stage for modern researchers to study mood disorders as a biological phenomenon. In the subsequent decades, scientists have tested several theories of depression's etiology (Table 1) and identified countless behavioral, neural, molecular, and genetic correlates of the illness. Given the bulk of data acquired, why do the precise neural mechanisms of depression remain elusive?

Table 1 Major Theories of Depression's Pathophysiology

Hypothesis	Example of supporting evidence
1. Monoamine: Deficits in monoamine neurotransmission can cause depression (Lehmann et al. 1958; Bunney and Davis 1965)	Drugs that modulate monoamine neurotransmission have antidepressant effects (Schildkraut 1967)
2. Cognitive: Automatic negative thoughts about the self, the world, and the future can cause depression (Blackburn 1986)	Depression patients reliably report more automatic negative thoughts than healthy volunteers (Hollon 1965; Beck et al. 1963)
3. Neurotrophic: Decreased expression of neurotrophic factors including BDNF can cause depression (Smith et al. 1995; Nibuya et al. 1995)	Stress exposure decreases, but antidepressants increase, hippocampal BDNF levels in animals (Duman and Monteggia 2006; Duman et al. 1997)
4. Glutamatergic: Dysfunction of the glutamatergic system can cause depression (Trullas and Skolnick 1990)	NMDA antagonists function as antidepressants (Sanacora et al. 2012)

MDD's complexity is one barrier to progress. The diagnostic criteria for MDD (Table 2) (American Psychiatric Association 2000) were developed in order to achieve reliability across clinicians and are not grounded in biology. They are so broad as to encompass a diverse set of patients. One patient may describe sadness, insomnia, weight loss, fatigue, and feelings of worthlessness. Another will report hyper-phagia, agitation, poor concentration, and suicidal ideation, complaining that she no longer enjoys any of her activities. A single individual, in addition, may describe different constellations of symptoms during different episodes of depression.

The diversity of depressive phenotypes makes it difficult to create a laboratory model of depression. Laboratory manipulations do not provoke a syndrome as durable and multifaceted as MDD. In the Velten Mood Induction Procedure, for instance, participants read self-referential statements that describe emotional ("I am worthless") and/or physical states ("I am listless") associated with MDD (Emmett 1968; Riskind et al. 1982). After completion, subjects not only report feeling more depressed, they also evince mild psychomotor retardation and find it easier to recall negative versus positive autobiographical memories (David 1983). These effects are transient, however, and participants do not describe changes in neurovegetative symptoms such as sleep, appetite, or energy.

Pharmacological models of depression have similar limitations. Acute tryptophan depletion is a procedure originally used in humans to test the hypothesis that abnormally low levels of serotonin trigger depression (Table 1) (Reilly et al. 1997). In this protocol, a nutritional supplement is used to temporarily reduce the bioavailability of tryptophan, serotonin's amino-acid precursor (Reilly et al. 1997). Tryptophan depletion changes sleep architecture in healthy volunteers so that it more closely resembles that observed in depression patients (Zimmermann et al. 1993; Voderholzer et al. 1998; Arnulf et al. 2002). It does not, however, reliably

Table 2 Major Depressive Disorder: Diagnostic Criteria

*History of at least one *major depressive episode* in the absence of a separate psychotic disorder
*No history of manic, hypomanic, or mixed episodes
Major Depressive Episode: Diagnostic Criteria
**Prevasive depressed mood and/or anhedonia lasting at least two weeks*
**At least 4 of the following symptoms:*
*Change in appetite or weight
*Insomnia or hypersomnia
*Psychomotor agitation or retardation
*Fatigue or loss of energy
*Feelings of worthlessness or excessive/inappropriate guilt
*Impaired concentration or indecisiveness
*Suicidal ideation
* All symptoms are pervasive
**Symptoms cause clinically significant distress or impairment*
*Symptoms are not associated with substance use, a medical condition, or bereavement

influence mood in healthy volunteers (Ruhe et al. 2007) and any impact is short-lived (Reilly et al. 1997).

More intense psychological or pharmacological challenges might induce a quorum of persistent MDD symptoms. Yet such experimental conditions would likely be unethical. Hence, it remains impossible to dissociate the neural states that precipitate depression from those that are secondary or caused by the illness, using laboratory experiments in healthy volunteers.

Scientists have developed several animal models of depression in an effort to compensate for the weaknesses inherent in human models (Table 3). Researchers can subject animals to extreme stressors in order to produce lasting behavioral change and use invasive techniques to probe depression's neurobiology. Unfortunately, the utility of these protocols is still undermined by the internal nature of MDD symptoms. Phenomena such as depressed mood, anhedonia, suicidal ideation, and feelings of worthlessness or helplessness lack reliable physiological or behavioral signatures (Meaney 2001). It is impossible to confirm the presence of parallel "symptoms" in animals. Instead, models and measures of animal "depression" are primarily selected because traditionally, their effects can be reversed by acute administration of monoaminergic antidepressants (Porsolt 1978). In the forced swim test, for instance, animals are placed in a cylinder of water. The time that passes before they stop struggling and become immobile is the measurement used to quantify "depression" severity. Animals who struggle the least are considered the most "depressed" because antidepressants such as imipramine and fluoxetine increase latency to immobility (Porsolt 1978).

In recent years, clinical research confirmed that monoaminergic medications rarely elicit meaningful improvement in patients until after one week to several months of treatment (Rush et al. 2006). This understanding triggered a surge of more complex models of MDD, which involve more chronic sources of stress. In the social defeat model, for instance, male mice repeatedly confront larger

Table 3 Animal Models and Measures of Depression (Yan et al. 2010)

A. Models

Model	Protocol	Behavioral and physiological changes	Strengths	Weaknesses
Forced Swim (Connor et al. 1997; Porsolt 1978)	Subject suspended in cylinder of water, time swimming is assessed. Less = depressed	Transient increase in stress hormones, transient reduction in immune function	Predicts drug efficacy, easy to replicate	Face validity, no other behavioral symptoms elicited, no durable effects
Tail Suspension (Kanda et al. 1993; Steru et al. 1985)	Subject suspended by tail, time struggling to escape is assessed. Less = depressed	Transient increase in stress hormones, catecholamines	Predicts drug efficacy, easy to replicate	Face validity, no other behavioral symptoms elicited, no durable effects
Learned Helplessness (Seligman 1972)	Repeated exposure to intense, unpredictable, and inescapable electric foot shock	Altered sleep, reduced body weight, energy, sexual activity, and locomotion; elevated levels of stress hormones	Rapid, easy to replicate, predicts drug efficacy	Symptoms not durable, requires repeated exposures
Chronic Mild Stress (Katz et al. 1981; Katz and Baldrighi 1982; Willner 1987, 1997)	Exposure to multiple innocuous but unpredictable stressors (e.g. light/dark reversal, temperature change, food deprivation, restraint) over an extended period of time (3 weeks or longer)	Gradual attenuation of sucrose preference, and coat deterioration, decreased sexual, aggressive, exploratory, and general locomotive behavior	Face validity, elicits many symptoms Durability: behavior changes lasts several weeks	Time-intensive, labor intensive, and difficult to replicate across laboratories. No changes in elevated plus maze or social interaction
Social Defeat (Berton et al. 2006)	Repeated exposure to larger more aggressive breeding animals. Initial contact is direct and the aggressor attacks the subject. Subsequently separated from aggressor by translucent	Reduced social interaction, attenuated sucrose preference, changes in stress hormones	Social nature of induction	Only used in male animals Durability depends on number of defeat sessions

(continued)

	barrier but visual, olfactory, auditory contact maintained.			
Maternal Deprivation (Plotsky and Meaney 1993; Meaney 2001; Ruedi-Bettschen 2004)	Pup separated from mother for extended periods of time during first two weeks after birth	Changes in stress hormone and catelcolamine systems, increased startle, suppressed feeding during novelty exposure, changes in hippocampal development	Face validity, elicits many symptoms Durability: behavior changes persist into adulthood	Time-intensive, variability across laboratories

B. Measures

B. Paradigm	Protocol	Quantification
Sucrose Preference	Subject given access to water with high sucrose content	Proportion of sucrose solution consumed out of all liquid consumed Less = depressed
Novelty-suppressed feeding (Dulawa and Hen 2005)	Subject given access to food that is placed under a bright light	Time until feeding commences Longer = depressed
Social interaction	Subject put in cage with other animals	Time spent interacting with others Less = depressed
Latency to Avoid/Escape Aversive Stimuli	Animals are trained to perform a specific behavior to avoid or terminate exposure to aversive stimulus	Time until escape behavior Longer = depressed
Coat change	Coat appearance and grooming are observed	Grooming score given for 7 body parts Less = depressed

aggressor mice (Berton et al. 2006). In the chronic mild stress model, animals endure innocuous stressors daily for three weeks (Steru et al. 1985; Dulawa and Hen 2005) and in maternal deprivation young pups are separated from their mothers during the first three weeks of life (Seligman 1972).

Animals subjected to these protocols indeed evince lasting behavioral and physiological changes that are reversed only with chronic antidepressant treatment (Yan et al. 2010; Dulawa and Hen 2005; Ruedi-Bettschen et al. 2004). Yet the translational value of these "symptoms" is still unclear. Animals who have completed either the chronic stress (Willner et al. 1987) or social defeat (Berton et al. 2006) paradigm, for example, consume less sugar-water than controls when given free access to both pure water and sugar-water. Attenuated sucrose preference is conceptualized as evidence of anhedonia because the animals show a lack of motivation to seek out an innately rewarding sensation. While this interpretation seems reasonable, there is still no evidence that reduced consumption of sweet foods is associated with anhedonia or depression severity in humans (Amsterdam et al. 1987).

As a group, animal models of MDD have limited face validity. While useful in drug screening and in illuminating the neural mechanisms of antidepressant action, it remains unclear how much insight they offer into the pathophysiology of human depression.

3 The Neurocircuitry of Depression

Neuroimaging studies of MDD patients find abnormalities in brain regions involved in evaluating the salience of stimuli, executive function (control of cognition), encoding and storing complex mental representations of contextual information, and value representation. Although different theories of MDD emphasize the importance of different brain structures (Murray et al. 2011; Mayberg et al. 1997; Mayberg 2003; Hamani et al. 2011), there is a consensus that these highly interconnected regions interact in an affective network, and that persistent dysfunction in its hubs may cause MDD (Fig. 1).

Mayberg and colleagues (Mayberg 2003; Hamani et al. 2011) proposed the "Limbic-Cortical Dysregulation Model", which posits that persistent imbalance between subcortical and cortical regions, influencing mood and arousal, results in MDD. A key correlate of pathology in this model is hyperactivity in the subgenual anterior cingulate cortex, a prefrontal region residing under the genu of corpus callosum. Drevets, Price, and Murray (Price and Drevets 2010; Murray et al. 2011) proposed an alternative model whereby abnormal signaling in the amygdala and a set of interacting prefrontal networks could produce depressive illness. These models do make some predictions about relationships between structure and symptoms, but they lack specificity. Drevets and peers, for instance, discuss how orbitofrontal dysfunction could contribute both to feelings of worthlessness/helplessness (self-concept) and anhedonia (Price and Drevets 2010; Murray et al. 2011).

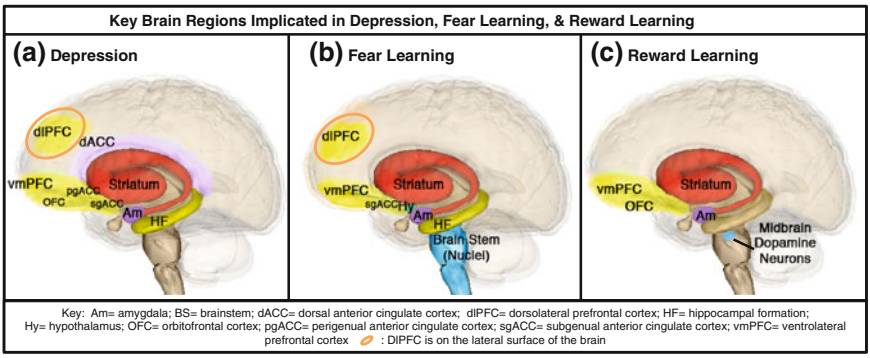

Fig. 1 Key brain areas implicated in depression, fear and reward learning. Note the substantial overlap

Below we describe knowledge hitherto of the neural mechanisms underlying core symptoms of MDD.

3.1 Salience Evaluation

Depressed individuals display excessive reactions to negative stimuli (e.g., sad faces) in the amygdala, insula, and dorsal anterior cingulate cortex (dACC) (Sheline et al. 2001; Siegle et al. 2002; Fu et al. 2004; Suslow et al. 2010; Victor et al. 2010; Hamilton et al. 2012). This triad is implicated in detection of salient events in the environment (Rangel and Hare 2010). In this framework, the amygdala orients the learner towards biologically relevant stimuli (Schoenbaum et al. 2011). The dACC activates the sympathetic nervous system in preparation for action (O'Doherty 2011). The insula mediates conscious awareness of changes in arousal and contributes to the intensity of the emotional experience (Schiller et al. 2008). With hyperactivity in these three regions, MDD patients may be more likely than healthy individuals to overestimate the salience of negative cues. They may also experience more robust physiological responses to aversive experiences. Network hypersensitivity to negative stimuli could underlie a bias towards perception and processing of negative information.

3.2 Executive Dysfunction

The dorsolateral prefrontal cortex (dlPFC) is involved in "executive" control of cognition, enabling deliberate regulation of attention. The dlPFC is recruited during activities that require working memory, planning, inhibition, mental flexibility, initiating action, and monitoring action (Ridderinkhof et al. 2004).

MDD patients evince less dlPFC activity than healthy controls when exposed to negative stimuli (e.g., sad faces), during working memory tasks, and when asked to deliberately modify their thoughts to attenuate or enhance an emotional reaction to a specific stimulus (Siegle et al. 2007; Johnstone et al. 2007; Joormann et al. 2011). dlPFC hypoactivity in depression might reflect an inability to control thought content (e.g., avoid focusing on aversive cues). dlPFC dysfunction would thus prevent patients from successfully employing a wide range of coping skills ranging from distraction to reframing (interpreting a situation in a new way in order to change related affect) (Delgado et al. 2008a, b; Schiller and Delgado 2010; Ochsner et al. 2002, 2004; Ochsner and Gross 2005; Kanske et al. 2010).

3.3 Representation of Context

The hippocampus is essential for contextual learning and encoding of episodic memories. MDD patients who have endured multiple episodes have significantly smaller hippocampi (Neumeister et al. 2005). MDD diagnosis is also associated with abnormal hippocampal recruitment during autobiographical memory recall (Young 2011). Specifically, depressed patients exhibit less activity in the left hippocampus and right parahippocampal gryus during memory recall while healthy volunteers display the opposite pattern. Such aberrations may underlie autobiographical memory impairment in depression. MDD patients tend to over-generalize their autobiographical memories, recalling fewer specific memories and fewer positive memories (Dalgleish et al. 2007; van Vreeswijk and de Wilde 2004; Sumner et al. 2010). Deficits in hippocampal function might impair the capacity to use historical and contextual information and to implement adaptive emotional responses.

3.4 Valuation and Choice

In response to rewards and stimuli that predict them, MDD patients evince hypoactivity in the striatum and orbitofrontal cortex (OFC) (Epstein et al. 2006; Pizzagalli et al. 2009; Smoski et al. 2009; Forbes et al. 2009; Robinson et al. 2011) regions that are also typically smaller in size in depressed versus healthy populations (Koolschijn et al. 2009; Kempton et al. 2011; Arnone et al. 2012). The medial portion of the OFC is a subdivision of the ventromedial prefrontal cortex(vmPFC), as are the subgenual and perigenual anterior cingulate cortices. In these cingulate vmPFC regions, individuals with MDD display smaller volumes but enhanced basal activity (see for review Drevets et al. 2008; Pizzagalli 2011) MDD patients who exhibit the greatest degree of elevation in baseline sub/perigenual activity are more likely than their peers to respond to a variety of antidepressant therapies (Mayberg 2003; Pizzagalli 2011). The striatum is involved in

value prediction; the OFC and vmPFC, in value representation. Their dysfunction may relate to the anhedonia commonly experienced by MDD patients.

4 What Can Fear and Reward Learning Tell Us About Depression?

Having established that depression neither lives in one brain region nor results from a deficit in a single type of information processing, how should the field proceed in its efforts to understand MDD? We believe that observing and characterizing in patients the precise patterns of neural activity during associative fear and reward learning might offer new insights into the neurobiology of the illness. In contrast to depression, fear and reward learning (Box 1) are emotional phenomena uniquely suited to research, and are highly conserved processes that are easy to elicit and assess in both human and non-human animals. What is more, the brain regions that evince dysfunction in MDD overlap significantly with those involved in fear and reward learning. By focusing our inquiry on the neural substrates of simpler emotional experiences mediated by the same neural structures, we may be able to identify and reliably reproduce experimental evidence of subtle abnormalities in affective information processing that contribute to depression. Our hypothesis is buttressed by recent fMRI studies of reward learning documenting only subtle (if any) differences in the behavior of MDD patients versus control subjects, but significant differences in corresponding changes in brain activity (Pizzagalli et al. 2009; Smoski et al. 2009; Robinson et al. 2011; Kumar et al. 2008). In the subsequent sections we describe how, by conducting additional studies of reward learning, and beginning to study fear learning in depression, we might learn more about the role of three key brain regions in MDD: the striatum, the amygdala, and the vmPFC.

BOX 1: Associative Learning

Basic fear and reward learning are complementary forms of associative learning, or classical conditioning (LeDoux 2000). During conditioning, the learner encodes a relationship between a sensory cue, such as a sound or a visual stimulus, and a biologically significant outcome, such as pain or food. Knowing this relationship improves the ability to predict, based on the sensory cue, the upcoming occurrence of the biologically significant outcome. After successful conditioning, the sensory cue alone elicits a behavior similar to the response originally triggered by the biologically significant outcome (e.g., preparing to escape at the sound of an alarm).

4.1 The Striatum

Sutton and Barto developed the temporal-difference learning model to describe reward learning (Sutton 1988; Sutton and Barto 1988) In their formulation, learning is a self-perpetuating cycle in which the learner uses information about past rewards to make predications about future rewards. If the reward is greater or lesser than expected, then the learner has made a prediction error, which serves to update the next prediction.

Dopamine cells in the ventral tegmental area and substantia nigra encode prediction errors. Their phasic firing rate increases robustly following the delivery of an unexpected reward (positive prediction error). After reward omission (a negative prediction error), firing is suppressed (McClure et al. 2003; O'Doherty et al. 2003). The striatum, which receives direct input from midbrain dopamine neurons (Haber and Knutson 2010), exhibits the same pattern of change (Delgado et al. 2008a, b; McClure et al. 2003; O'Doherty et al. 2003; Sutton 1988; Sutton and Barto 1988; Schultz et al. 1997; Kishida et al. 2011; Pagnoni et al. 2002).

MDD patients evince weak prediction error signaling in the striatum during reward learning (Kumar et al. 2008; Gradin et al. 2011), which is inversely correlated with anhedonia severity (Gradin et al. 2011). These findings suggest that deficits in prediction error signaling during reward learning might cause or contribute to anhedonia in depression. If weak striatal prediction error signaling during reward learning is a genuine biomarker of depressive anhedonia, it could become an important proxy for anhedonia in animal models of MDD. Monitoring prediction error signal, in addition, could constitute a novel method of tracking illness severity. Before exploring such practical applications, it is imperative that we confirm the relationship between anhedonia and prediction error signal strength by conducting new studies, or revisiting the data from completed studies. We must also determine if signal strength changes in patients as their capacity to experience pleasure fluctuates across episodes or in response to treatment.

Because the striatum also monitors prediction errors during aversive learning (Delgado et al. 2008; Kishida et al. 2011; Li et al. 2011) it will also be important to study fear conditioning in depression. Robinson et al. reported that depression patients show normal neural responses to punishment, tentatively suggesting that they will also display normal striatal prediction error signaling during fear conditioning. If this is the case we can conclude that MDD is characterized by a valence-specific, rather than generalized, deficit in associative learning.

4.2 The Amygdala

Amygdala reactivity to sensory cues is especially robust in two conditions: early in fear conditioning before the learner understands its relationship to the primary threat; and after trials in which it is not followed by the primary threat. Though this pattern is very similar to that observed in the striatum, computational analyses

reveal that amygdala and striatal responses to a given sensory cue during fear learning represent different types of information (Li et al. 2011; Kishida et al. 2011; Spoormaker et al. 2011; Kumar et al. 2008; Gradin et al. 2011). As previously described, striatal activity increases when the learner receives an unexpected reward or punishment, and decreases when an expected reward or punishment is omitted. Amygdala activity, in contrast, always increases in response to prediction error (Kishida et al. 2011; Kumar et al. 2008; Gradin et al. 2011; Harmer 1849) Amygdala and striatal responses to prediction errors also differ in their temporal pattern and magnitude.

The Pearce-Hall learning model more accurately predicts amygdala signaling during associative learning than the temporal difference model (Pearce and Hall 1980; Roesch et al. 2010; Li et al. 2011). According to Pearce and Hall (1980), surprise and uncertainty divert attention to novel or changing stimuli, resulting in reallocation of perceptual and cognitive resources thus accelerating learning. Consistent with this formulation, studies in animals (Roesch et al. 2012) and humans (Li et al. 2011) found that amygdala activity peaks early in learning, when the meaning of stimuli is unclear and they are not yet good predictors of reward or threat. As learning progresses and the rewards or punishment become more and more predictable, amygdala responses to the predictive stimuli wane, and attention supposedly returns to other processes. The amygdala thus allocates attention to stimuli that are uncertain in order to enhance learning.

In depression, the amygdala is hyperactive in response to aversive stimuli, which might result in a pervasive negative information processing bias (Calu et al. 2010; Roesch et al. 2010). It is possible that the amygdalae of depressed individuals do not accurately track the surprise associated with aversive cues, but persistently respond to negative stimuli as if uncertainty is high. Here we would expect to observe approximately equivalent increases in amygdala BOLD signal in response to both the primary threat and sensory cue throughout fear conditioning (a lack of habituation). MDD patients, as a result, would endure protracted periods of arousal whenever exposed to negative stimuli (whether the valence is innate or learned). Over time, the allostatic load conferred by excessive activation of the body's stress response systems might trigger depressive symptoms.

Alternatively, it is possible that the amygdala accurately tracks the surprise associated with aversive cues, but that the magnitude of the negative surprise signal is excessive. Here we would expect MDD patients to display excessive increases in amygdala activity when novel stimuli are presented early in conditioning, but a normal pattern of signal attenuation over time. They would therefore be predisposed to form durable negative associations after few, or even one (potentially stochastic) pairing of the primary threat with a novel sensory cue. The persistence of such a state in which an individual is constantly "overreacting", and quickly learning to expect aversive experiences, might engender feelings of hopelessness.

Lastly, it is possible that amygdala's sensitivity to surprise induced by threatening cues is different from the one induced by rewarding cues. In this case, perhaps a combination of hypersensitivity to negative and hyposensitivity to positive stimuli is required for moderate or severe depression. Alternatively, the

strength of amygdala responses to surprising aversive stimuli might correlate specifically with severity of depressed mood.

4.3 The vmPFC

Making sense of vmPFC dysfunction in MDD is especially challenging because of its complex cytoarchitecture and because of its complex role in many different mental processes (see Roy et al. 2012 for review). Drevets and colleagues (Drevets et al. 2008; Price and Drevets 2010; Murray et al. 2011) proposed that hyperactivity in a subregion of the vmPFC, the perigenual ACC, is the cause for the autonomic dysregulation observed in depressed patients. Pizzagalli, in contrast, emphasizes vmPFC's role during self-referential processing (Pizzagalli 2011) and postulates that the abnormal vmPFC signaling observed in MDD might correspond to excessive maladaptive rumination. Mayberg's Limbic-Cortical Dysregulation model (Mayberg 2003; Hamani et al. 2011) highlights the contribution of the perigenual and subgenual ACC, in dysregulation of executive function and autonomic and circadian systems, respectively. Studies of reward and fear learning describe specific possible roles for the vmPFC in value representation and fear inhibition. Below we discuss how these studies might provide insights about the link between vmPFC function and MDD.

4.3.1 Reward Learning and Value

As previously mentioned in Sect. 3.4, the vmPFC is engaged during value representation. In order to understand the role of the vmPFC in this process, it is necessary to revisit the temporal-difference learning model as discussed in Sect. 4.1 (The Striatum). There we described how this model conceptualizes reward learning as a self-perpetuating cycle with two components: generation of outcome predictions, and comparison of expected with actual outcomes. We described how midbrain dopaminergic projections to the striatum enable outcome comparison by encoding prediction errors. Studies of reward learning suggest that the vmPFC participates in generation of outcome predictions, representing and updating the value of the rewarding or aversive stimuli (Roy et al. 2012 for review; Maier et al. 2006; Schiller and Delgado 2010; Hare et al. 2009).

In this context, vmPFC dysfunction would not only impair associative learning, but also result in maladaptive decision-making. If MDD patients were unable to update the value of positive stimuli, they would struggle to recover from negative experiences. Experiencing rejection when applying for a job, for instance, might cause anyone to feel inadequate. Healthy individuals, however, would regain their confidence after being offered a position by another employer. An MDD patient, in contrast, might fail to recover even after receiving another job offer because of inability to generate updated predictions. Future studies of reward learning in

MDD should explore the pattern of vmPFC activity while manipulating the value of conditioned stimuli. It will also be necessary to study vmPFC function during fear conditioning to understand the effect of valence on value encodings. Such investigations will permit careful exploration of vmPFC value representation and updating in depression. If meaningful data emerges, they will also demonstrate how probing simple cognitive processes might resolve unique components of prefrontal dysfunction in MDD.

4.3.2 Fear Learning and Inhibition

One way to diminish fear is through extinction learning, when a fear conditioned stimulus is presented repeatedly without the negative outcome. This results in a new safety association, which the vmPFC could then retrieve in the appropriate context (Milad and Quirk 2002; Quirk et al. 2006; Delgado et al. 2008a, b; Seymour et al. 2004) Animal studies show that the vmPFC projection onto the amygdala can control its output and prevents the expression of conditioned fear during extinction (Milad and Quirk 2002; Quirk et al. 2003; Quirk and Beer 2006). Viewed in this light, the vmPFC hyperactivity documented in MDD might be understood as compensatory. It might reflect vmPFC's persistent effort to regulate excessive amygdala activation and the constant generation of negative emotions. It could also reflect inadequate structural or functional connectivity between the vmPFC and amygdala. Interrogating extinction learning in MDD patients might help narrow down the possible interpretations of vmPFC's role in depression.

5 Conclusions and Future Directions

In this chapter we propose that studies of associative learning in depressed patients could offer novel insight into MDD's pathophysiology. We argue that weak striatal prediction error signaling during reward learning could be a biomarker of depressive anhedonia; we draw attention to amygdala's role in allocating attentional resources to uncertain stimuli as a possible explanation for the bias toward negative information in depression; finally, we describe how the vmPFC's role in generation and representation of reward value and vmPFC-amygdala interactions in fear extinction might explain MDD patients' inability to modify negative learning and update future predictions based on novel information.

By considering what studies of associative learning in healthy volunteers have taught us about the roles of the striatum, amygdala, and vmPFC, we highlight the potential utility of conducting similar studies in depression. Understanding the role of these brain regions in associative learning provides an excellent reference as for what goes awry in depression. Examination across domains is an efficient way to

distill the basic function of a brain region, with which we can begin to predict the manifestation of this function across disorders.

We believe that collaboration between scientists who investigate associative learning and clinical researchers will advance scientific knowledge of depression's neural substrates. Given that currently available treatments fail one-third of patients, it will be important to take advantage of this untapped resource.

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