Reward and Punishment Processing in Depression

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Depression is a complex and heterogeneous disorder whose cause is poorly understood. Theories on the mechanisms of the disease have often focused on either its neurobiology or its cognitive and behavioral manifestations. Recently, studies exploring how depressed patients process reward and punishment have linked these two facets together. It has been suggested that individuals with a dysfunction in a specialized network of brain regions are unable to exploit affective information to guide behavior. Deficits in this ability might predispose such individuals to develop depression, whereas subsequent restoration of this ability—whether through pharmacological or behavioral treatments—might enable recovery from the disorder. Here we review behavioral, neuroimaging, and computational findings relevant to this hypothesis. There is good evidence that depressed patients exhibit abnormal behavioral responses to rewards and punishments and that these tendencies correspond to aberrant function in frontostriatal systems modulated by the monoamine systems. Furthermore, computational studies have generated testable predictions for how these neural signaling and neurochemical abnormalities might contribute to the symptoms of depression. Combining these approaches—as well as molecular and behavioral work in animals—provides great promise for furthering our understanding of this common and debilitating disease.

Key Words: Behavior, computational, depression, feedback, neuroimaging, reinforcement

Depression is a leading cause of morbidity and mortality worldwide. Fifteen percent of people will develop depression over their lifetimes, making it a greater burden to health than angina, arthritis, asthma, and diabetes (1). Currently the fourth leading cause of disability, it is projected to become the second by 2030 (2).

Although low mood is the traditional hallmark of depression, anhedonia (reduced interest or pleasure) and cognitive dysfunction are equally integral to the disorder (3,4). The diagnostic criteria for Major Depressive Disorder (MDD) include such cognitive symptoms as indecisiveness and diminished concentration (5), and laboratory tasks have demonstrated depression-related deficits in attention, memory, and psychomotor speed (4). Furthermore, cognitive dysfunction forms a core aspect of many psychological models of MDD, from Seligman's learned helplessness model (6) to Beck's cognitive model (7). These theories have initiated the development of cognitive therapies, which are a common and effective route to combat depression.

The cognitive deficits in depression are most striking in the context of affective information processing. Emotionally "hot" tasks, which test responses to positively or negatively valenced stimuli, provoke more robust differences between MDD patients and healthy individuals than do "cold" tasks (e.g., motor function) (4). These behavioral findings fit with convergent neuroimaging evidence suggesting that the same brain regions that function abnormally in depressive patients (e.g., orbitofrontal cortex [OFC], medial frontal cortex, ventral striatum [VS], amygdala, and hippocampus) (3,8) are critical for reinforcement processing (9). Taken together, these results suggest that imbalances in a distinct network of regions, particularly those innervated by monoamines, disrupt patients' ability to process affective stimuli. This disruption could in turn lead to symptoms of depression (Appendix 1). Such a two-stage process—in which neural abnormalities lead to impaired cognitive function, which then predisposes individuals to depression—complements recent theories of antidepressant drug action (10,11).

To bear out these cognitive hypotheses, it is necessary to show that depressed patients have difficulty with reinforcement learning and decision-making and that this difficulty corresponds with abnormalities in reward-related brain systems. In this non-exhaustive review, we discuss selected evidence for these claims. We start with behavioral results, focusing on tasks in which patients are given reward or punishment during task performance. We then examine human neuroimaging studies that complement the animal neurobiology literature (12), probing the neural correlates of these behavioral effects. Finally, we review computational modeling work, which has begun to provide a compelling account for the neural signals underlying depressed individuals' behavior.

Behavioral Studies

It has long been recognized that depressed patients suffer from cognitive impairments in addition to low mood (6). A number of paradigms have been used to probe patients' ability to process information in the context of reward or punishment. Two major conclusions have emerged from this literature: that depressed individuals show maladaptive responses to punishment (negative feedback) and hyposensitive responses to reward (positive feedback).

Maladaptive Response to Punishment

Among the first observations in the literature on cognitive function in depression was that patients—as predicted by models of learned helplessness (6)—show dysfunctional responses to negative feedback. Beats *et al.* (13) asked depressed patients and control subjects to perform the Tower of London planning task. The groups completed easy problems equally well, but for difficult problems, depressed patients required more steps than did control subjects. Importantly, the depressed group was not simply worse at planning; regardless of difficulty, both groups answered the same number of problems perfectly. However, once patients made an error on a trial, their performance deteriorated rapidly, which the authors termed a "catastrophic response to perceived failure" (13).

A number of subsequent studies confirmed this abnormal response to negative feedback (14–16), although not every study showed the effect (17). The deficit was shown to correlate with the severity of depression (14) and to be specific to depressed patients

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and not patients with schizophrenia, Parkinson's disease, or brain lesions (15). Although all of these patient groups performed worse overall than control participants, only depressed patients showed an increased conditional probability of making an error, given an error on the previous trial. Furthermore, remitted depressed patients continued to show an abnormal response to negative feedback, even though their overall task performance had improved (15), providing further evidence that this deficit is not simply secondary to poor overall performance.

In line with Beck's psychological theory of depression (7), one interpretation of these findings is that perceived failure on a task could trigger further failure-related thoughts, interfering with subsequent performance. Thus, patients could be hypersensitive to punishment. An alternative interpretation, however, is that depressed patients simply failed to use negative feedback to improve future performance (15,18), which might provide the impression of punishment hyposensitivity. Holmes and Pizzagalli (19) found that, after errors, a population of participants with high scores on the Beck Depression Inventory (BDI) adjusted their responses significantly less than those with low scores. Such a failure in posterror performance adjustments could reflect underlying deficits in motivation or performance monitoring or a generally blunted response to reinforcement rather than hypersensitivity.

Other studies have examined whether abnormal response of depressed patients to negative feedback depends on whether that feedback is accurate or misleading. With a task that required participants to ignore occasional misleading negative feedback, Murphy *et al.* (20) found that MDD patients performed as well as control subjects after accurate (informative) feedback but were more sensitive to misleading (uninformative) negative feedback. This finding was recently replicated (21). In other words, whether depressed patients are oversensitive to punishment or unable to use it to facilitate performance might depend on the type of punishment. In a dynamic and often inconsistent world, a tendency to exaggerate the importance of uncertain or misleading information could lead to a perceived lack of control, which could then bias future actions and cause a cycle of "learned helplessness" (6).

In sum, depression seems to be characterized by maladaptive responses to negative feedback. Depending on the task, patients can either perform worse after punishment (demonstrating increased sensitivity) or fail to perform better (demonstrating blunted responses to reinforcement). These observations fit with psychological theories of the disorder, which argue that depressed patients exhibit abnormally negative attitudes and assumptions and tend to distort environmental information to confirm these biases (7).

Hyposensitivity to Reward

In addition to maladaptive reactions to aversive stimuli, depressed individuals exhibit blunted responses to rewarding information, possibly representing a deficit in the approach-related or appetitive system (22). For example, McFarland and Klein (23) asked participants to rate their mood before and after a block of puzzles where correct performance was rewarded with money or the avoidance of physical punishment (60 sec with their hand placed in a freezing cooler). The authors found that depressed participants were significantly less happy than healthy control subjects when anticipating reward, despite no difference in anxiety to anticipated punishment.

What is the effect of this reduced approach system on behavior? Henriques *et al.* (24,25) asked participants to perform a memory task with three conditions: one where correct responses were rewarded, one where incorrect responses were punished, and one without reward or punishment. To examine their results, the authors employed signal detection theory, which provides orthogonal measures of sensitivity (the ability to remember stimuli) and response bias (the general tendency to respond "yes" or "no"). Although participants with low BDI scores liberalized their response bias in the reward condition, thus maximizing their earnings, subjects with high BDI scores (24) or MDD (25) maintained a conservative bias, representing indifference to reward.

More recently, Pizzagalli *et al.* (26,27) used similar signal-detection techniques to explore the responsiveness to reward of depressed patients. They designed a task in which correct responses to one target were three times more likely to be rewarded than correct responses to another target. Healthy individuals developed a strong preference for the highly rewarded stimulus, whereas participants with high BDI scores (26) and MDD (27) did not, a deficit that correlated with depressive symptoms (26). These results suggest that depressed patients are less able to modulate behavior according to prior reinforcements.

It is important to note that, although these studies demonstrate the presence of reward-processing deficits in depressed individuals, they cannot show whether such deficits are causal. However, both recovered depressive subjects (28) and girls whose mothers were depressed (29) have shown impairments in identifying emotional expressions. Similarly, recovered depressive subjects have shown blunted neural responses to positive stimuli, even when their subjective ratings of such stimuli matched those of control subjects (30). These results, along with pharmacological studies that have dissociated changes in reward processing from changes in mood (31,32), hint at an underlying abnormality in affective processing that could confer vulnerability to depression, although further research is needed in this area.

The results reviewed in the preceding text suggest that depressed individuals respond abnormally to both punishments and rewards, although some contradictory findings have been reported. These tendencies might cause or exacerbate their depression. In particular, if individuals are unable to adapt their behavior in response to reinforcements, they might experience fewer rewards and more punishments, in a self-maintaining vicious cycle. In the next section, we discuss the possible neural substrates of these abnormalities.

Neural Mechanisms

Monoamine Function

It has been recognized for more than 40 years that agents that increase monoamine levels alleviate some of the symptoms of depression (33). This serendipitous finding led to the hypothesis that a deficiency in monoamine neurotransmitters is at the root of the disease (34). Although there are significant limitations to this hypothesis, there is now broad consensus that each of the three major monoamines—serotonin, norepinephrine, and dopamine—might contribute to the symptoms of depression (35,36).

In parallel, a large body of literature has linked the function of these monoamines to reinforcement processing. In particular, manipulating serotonin levels through either tryptophan depletion (e.g., 31,37) or selective serotonin reuptake inhibitor (SSRI) administration (e.g., 38) changes how healthy individuals respond to rewards and punishments, independently of changes in mood (for review, 11). Furthermore, decades of research—from intracranial self-stimulation in rats to single-cell recording in monkeys and neuroimaging in humans—have demonstrated a

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