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Where's the Fun in That? Broadening the Focus on Reward Function in Depression

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In the search for the neural substrates of depression, some recent work has suggested that the disruption of reward processing occurs as part of the essential pathophysiology of the disorder. Depression has long been conceptualized as a disorder of dysregulated positive affect and unusual reward processing (1), and affective neuroscience findings have begun to support this perspective. Research on reward represents a shift away from a focus primarily on aspects of depression related to negative affect and threat processing. More important, this research direction could offer the potential to develop treatments that target reward-related circuits and thereby offer hope to those who exhibit dysfunction in those circuits.

The literature on reward functioning and depression is not without its contradictions, however, and much remains to be understood. Three approaches are relevant for elucidating the role of reward processing in depression: 1) taking a developmental perspective; 2) developing ecologically valid, consistent measurement techniques; and 3) identifying interindividual variability in reward functioning to improve treatments.

To summarize the current literature, research in several areas indicates that dysregulation in the processing of rewards—or stimuli that inspire behavior and reinforce it after it occurs—could play a pivotal role in affective, behavioral, and physiologic aspects of depression. Phenomenologically, people with depression experience dampened positive affect and reduced motivation, and they engage less frequently in behavior likely to lead to the achievement of goals or experience of pleasant emotions. Anhedonia, which reflects difficulty with anticipating and enjoying pleasant events, is commonly experienced, with up to 76% of adolescents with major depressive disorder reporting the symptom (2). Behaviorally, during the anticipation or receipt of reward, adolescents and adults with depression exhibit difficulty applying a flexible approach to making decisions or responding under varying conditions.

Depression has been linked to disrupted signaling in the dopamine neuromodulatory system, which plays an important role in reward-related affect and behavior through projections from the midbrain to the striatum and prefrontal cortex. Specifically, animal research, postmortem studies, pharmacologic studies of response to psychostimulants, and studies of receptor binding all point to the possibility of reduced dopamine transmission in depression (3). Similarly, animal studies manipulating brain-derived neurotrophic factor in dopamine pathways further implicate the dopamine system in depression-relevant behaviors (4).

Physiologic findings on reward processing in depression have not been consistent, partly because methods differ widely and are rarely compared directly. Some studies have reported

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that people with depression exhibit reduced brain reactivity to rewarding stimuli in the striatum, a region traditionally associated with pleasant mood. However, results have differed in terms of direction of depression effects, methods used to measure reward processing, and brain regions where differences are evident. Paradigms employed include physiologic (e.g., functional magnetic resonance imaging tasks) and pharmacologic challenges (e.g., dopaminergic probes). Physiologic paradigms focus on various experiences, including decision making, responding under time pressure, receiving performance feedback, viewing words or pictures, and recalling autobiographical events. In addition to the striatum, the brain regions in which depression effects are reported for reward functioning include the orbito-frontal cortex, anterior cingulate cortex, and amygdala. Until consistency of methods improves, it will be difficult to draw conclusions about the presence and extent of reward dysfunction in depression.

A Developmental Perspective

Developmental frameworks may be especially valuable to understanding the role of reward processing in depression. Adults suffering from depression have often experienced an onset of the disorder during adolescence. As such, understanding the role of reward dysfunction in the onset and course of depression—and the potentially associated fluctuations in reward functioning in depression at different points in the life span—is likely to be critical to elucidating the role of reward-related differences in adult depression. As noted, depression typically begins during adolescence, and there is evidence that altered behavioral responding to reward is a predictor of future depression in adolescents (5). Altered reward processing might be traitlike, existing before the onset of depression or persisting between episodes, as illustrated in the article by Hasler and colleagues in the current issue. Their finding that catecholamine depletion elicits slower reward-related behavior in adults with a history of depression still raises questions about the conditions under which reward processing is disrupted. And despite this important finding, it is not clear that reward dysregulation occurs throughout the course of depression. One intriguing possibility raised by behavioral studies is that reward dysregulation may be more characteristic of early episodes of depression than later episodes (6). Because early episodes also tend to correspond to earlier points in the life span, it is worth asking whether disruption of reward processing is more closely related to the onset or early maintenance of depression than to later recurrence.

Indeed, greater vulnerability to reward dysregulation may occur as part of the development of neural reward systems during adolescence. Developmental processes during adolescence have been postulated to be important to the dramatically increased incidence of depression during early to mid adolescence, with the development of the dopamine system and the prefrontal cortex claimed both to support social and affective changes and to make failures in achieving social goals particularly devastating to adolescents' mood, with possible implications for dysregulated dopamine signaling (7). In adolescents at risk for affective disorders, this process could potentially trigger the onset of depression. Yet because the dopamine system undergoes changes during typical adult development, including receptor reductions, changes in patterns of reward-related brain function, and shifts in the association between midbrain and prefrontal activation (8), it is important to ask whether these typical changes also influence reward regulation in depression.

Selecting Reward Stimuli

We have much to learn about which types of rewards elicit reduced responding in depression. The context of reward can be a critical determinant of the response, as demonstrated by behavioral economics findings that factors such as delay and effort influence the strength of reward responding. Reward paradigms used in depression research tend not to manipulate such

factors, and although studies have focused on money, pleasant pictures, or words as rewarding stimuli, little work has addressed the processing of other, potentially more meaningful types of reward. Social rewards are a particularly important class of rewards in depression—and in human functioning generally—yet we know little about the dysregulation of neural response to social stimuli. Loss of a romantic relationship is a typical triggering event for first episodes of depression (9), and social withdrawal occurs frequently in depression. Social stress is commonly used for inducing depression-like behavior in rodent research. In this issue, findings by Dillon and colleagues indicate that maltreatment early in life can have consequences for subjective and physiologic aspects of adult anhedonia. Although reduced social experiences can limit opportunities to experience rewards, it is also possible that in depression, reward responding is less sensitive to social stimuli. Monetary reward is understandably more straightforward to study and can be linked to cross-species findings. However, without examining the rewards that are most critical to human functioning, we may be missing a chance to understand the mechanisms and extent of reward dysfunction in depression. On a similar note, it will be important to gain enough insight into the brain's reward systems to understand how their functioning might differ in response to different classes of rewards in depression.

Reward Responding and Treatment

In addition to the *which* question of reward dysfunction in depression—that is, which types of reward elicit differences between depressed and healthy people—we need to understand more about the *how much* question. How much do individual differences in degree of reward responding distinguish subgroups with depression or predict differential treatment response? Variability in the capacity to respond to reward, hinted at by variability in reward-related brain function, behavior, and subjective experience, could be relevant to the wide and often unpredictable variability in response to treatment. Perhaps lower responding to reward indicates less overall likelihood of improving with treatment, poor suitability for certain types of treatments, or greater chance of recurrent or chronic course. This knowledge could greatly improve our success in treating depression.

Could treatments for depression be tailored to reward responding? Treatments have not generally been guided by the affective neuroscience of reward in depression. Current psychosocial treatments for depression have begun to target reward explicitly through behavioral activation, scheduled pleasant events, or savoring of positive experiences, and these could increase exposure to rewarding stimuli and subjective experience of reward. Pharmacologic approaches to depression have putative reward targets, including enhancing dopamine signaling—by blocking dopamine removal or reuptake or by preventing degradation of dopamine—and inhibiting norepinephrine reuptake and thereby increasing prefrontal dopamine levels. Furthermore, animal research indicates that reward-motivated, low-frequency behavior is sensitive to multiple classes of antidepressant medication (10), which could reflect effects involving enhanced reward sensitivity. Most recently, deep-brain stimulation has been applied to ventral striatal functioning in adults with treatment-resistant depression (11). Still, an unexplored area for improving reward responding in depression is treatment inspired by neuroimaging and behavioral findings. Perhaps reward-processing training could be developed to encourage initial and sustained response to salient rewards or to decrease the overregulation or dampening of that response.

In all, efforts to understand the functioning of reward-related brain systems may offer important new insights into depression, including a better understanding of its etiology, development, and pathophysiology, and may lead to more effective and targeted treatments. The development of these treatments could, in turn, have implications for preventing onset, improving functioning, and ameliorating course in depression.

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