Dysfunctional reward processing in depression

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Anhedonia — diminished pleasure and/or decreased reactivity to pleasurable stimuli — is a core feature of depression that frequently persists after treatment. As a result, extensive effort has been directed toward characterizing the psychological and biological processes that mediate dysfunctional reward processing in depression. Reward processing can be parsed into sub-components that include motivation, reinforcement learning, and hedonic capacity, which, according to preclinical and neuroimaging evidence, involve partially dissociable brain systems. In line with this, recent findings indicate that behavioral impairments and neural abnormalities in depression vary across distinct reward-related constructs. Ultimately, improved understanding of precise reward-related dysfunctions in depression promises to improve diagnostic and therapeutic efforts in depression.

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Introduction

More than 40 years have passed since reduced reward function was first mentioned as a diagnostic criterion for depression [1]. Ever since, progress in three discrete lines of inquiry has deepened our understating of reward processing and highlighted the significant contribution of anhedonia to depression. First, following the conceptualization of reward processing as a broad psychological construct, impaired behaviors in depression have been characterized across distinct reward-related processes, including motivation, reinforcement learning, and hedonic capacity. Second, abundant preclinical and growing neuroimaging evidence has suggested that these separable reward-related psychological processes are supported by dissociable brain systems. Third, and most importantly, those efforts were driven by increased recognition that current treatments often fail to address anhedonia in depression. Taken together, the convergence of these three lines of evidence strongly suggests that a better understanding of dysfunctional reward processing in depression may aid clinical practice.

Dysfunctional reward-related behaviors in depression

Because the traditional definition of anhedonia emphasizes reduced pleasure, preclinical studies have often used the sucrose preference test as a measure of anhedonia-like behaviors in rodents. Similarly, early behavioral studies in humans compared the performance of depressed and healthy individuals in the 'sweet taste test', during which participants are asked to rate the pleasantness of different sucrose concentrations. Somewhat surprisingly, however, those studies consistently found equivalent pleasure ratings between depressed and healthy individuals [2,3]. In contrast to these null findings, more recent behavioral studies probing other reward-related constructs have highlighted impaired performance in depressed individuals. For example, unmedicated depressed individuals failed to develop a response bias toward a more frequently rewarded stimulus in a probabilistic task, indicating a deficit in reinforcement learning [4]. Such impairment was also found in healthy individuals with high levels of anhedonia and euthymic individuals with a history of depression [5,6•]. A meta-analysis of six studies that implemented a probabilistic reward task concluded that depression, as well as sub-clinical anhedonia in healthy cohorts, was specifically associated with reduced reward sensitivity rather than impaired learning *per se* [7]. More recently impaired reward learning was demonstrated in both medicated and unmedicated depressed individuals relative to controls [8]. Interestingly, medication was found to reduce learning from negative feedback but had no effect on depression-related impairments in learning from positive feedback [8].

Motivation is another reward-related behavioral construct that has been recently investigated with regard to depression. The 'effort expenditure for rewards task' (EEfRT) was specifically designed to quantify motivation by involving a series of trials during which participants may choose to expend more or less effort (number of button presses) for the opportunity to win varying amounts of monetary rewards. In this task, depressed individuals were less willing to expend effort for rewards than controls, and were also less able to effectively use information about the magnitude and probability of rewards to guide their choice behavior [9•]. This finding was recently replicated using a task in which effort was operationalized as the strength with which participants squeezed a handgrip [10]. Interestingly, in this latter study, depressed

individuals' ratings of perceived effort increased for high rewards as if they subjectively felt that they tried harder yet objectively failed to do so [10]. Similarly, depressed but not healthy individuals exhibited a dissociation between how much they liked an image and the amount of effort (clicking on a moving square) they were willing to exert in order to view it [11]. Collectively, these findings suggest that anhedonia in depression is not expressed by reduction in pleasure *per se*, but rather by an impaired ability to modify behavior as a function of positive reinforcement, as well as by dissociation between pleasure and the amount of effort invested in order to achieve it.

Neural network underlying dysfunctional reward processing in depression

Neuroscience aims to identify the neural substrates associated with specific emotional/cognitive processes, thus allowing a mechanistic explanation of behavior. Within the reward domain, influential discoveries have emerged from the work of Schultz (1998), who used single cell recordings in primates to link a highly localized neural operation with a specific reward-related behavior [12]. Specifically, Schultz showed that the receipt of an unpredicted reward was associated with increased firing rate of dopaminergic (DA) neurons in the midbrain and striatum (the largest recipient of midbrain DA projections), resulting in increased phasic DA release in these regions. In contrast, when an expected reward was omitted, firing in DA neurons was suppressed. Most importantly, learning that an auditory tone predicted subsequent reward was accompanied by DA neuronal firing in response to the predictive tone, but not the (now expected) reward [12]. Since then, extensive evidence has accumulated from preclinical studies implementing self-stimulation, pharmacological, physiological, and behavioral manipulations to expand our understanding of midbrain-striatal (i.e., meso-limbic) DA reward signaling [13••,14]. Similarly, human neuroimaging studies have used [^{11}C]-labeled raclopride positron emission tomography (PET) scans, in which displacement of the tracer can be taken as an indirect demonstration of endogenous DA release, to demonstrate striatal DA release in healthy individuals in response to monetary rewards [15], and while listening to pleasurable music [16].

The well-established role of the striatum in reward processing has guided functional magnetic resonance imaging (fMRI) studies to explore putative differences in striatal function between healthy and depressed individuals in response to specific reward-related processes, such as anticipation versus consumption of monetary reward [17,18], sight and flavor of primary reward (i.e., food) [19], motivation to obtain reward [20], and reinforcement learning [21]. Interestingly, hypo-function of striatal regions in depression was a common finding across all different reward-related processes, implicating striatal hypo-function as a major neural mediator of dysfunctional

reward processing in depression. Moreover, the excellent spatial resolution of fMRI enabled to identify regionally specific striatal alterations that may mediate distinct aspects of dysfunctional reward processing in depression. Specifically, reduced activation of the three striatal nuclei — nucleus accumbens, caudate, and putamen — was associated with impaired pleasure, reward learning, and reward prediction in depression, respectively (see [22••,23] for extensive reviews). These human imaging findings mirrored animal data that have highlighted functional localization within the striatum by showing separable striatal 'hotspots' for pleasure versus motivation [24].

Although findings implicating various striatal regions in MDD have been influential, current models of reward circuitry suggest that reward processing involves a cortical-striatal network, in which frontal brain regions also play important roles, in particular the orbital frontal cortex (OFC) and anterior cingulate cortex (ACC) [25]. Consistent with this, a recent PET study demonstrated that engagement in a reward learning task was accompanied by DA release in the OFC and ACC in healthy volunteers [26]. In depression, fMRI has been used to link reward-related impairments to cortical-striatal connectivity abnormalities. For example, Heller *et al.* (2009) found that the inability of depressed individuals to sustain positive affect was coupled with both reduced cortical-striatal connectivity and blunted striatal activation [27]. Similarly, by analyzing task-specific changes in striatal functional connectivity, a recent study demonstrated that depression was characterized by context-dependent abnormal striatal connectivity with the dorsal ACC (dACC). Specifically, relative to healthy controls, depressed individuals exhibited stronger striatal-dACC connectivity in response to monetary losses, but weaker striatal-dACC connectivity in response to monetary gains [28•]. Of note, a baseline composite score of these two connectivity metrics predicted 36% of the variance in changes of depressive symptoms after an eight-week treatment [28•].

A growing number of studies are beginning to recognize the role of the lateral habenula, a small structure located at the posterior end of the thalamus, within the neural reward circuitry. Matsumoto and Hikosaka (2007), who used a similar setup of single cell recording in primates as Schultz [12], were the first to report habenula involvement in reward processing by demonstrating that habenula neurons are excited by target predicting no rewards and inhibited by a reward-predicting target [29]. This response pattern, which is opposite to that of midbrain DA neurons, was interpreted as suggesting that the lateral habenula contributes to reinforcement learning through inhibitory action on midbrain DA neurons [29]. More recently and specifically relevant to depression, lesions of the lateral habenula [30] and attenuation of midbrain-habenula signaling [31] were found to reduce depression-like behaviors in rat models of depression. In humans, depression was associated with

smaller habenula volume [32], and acute administration of antidepressant was found to reduce glucose metabolism in the habenula [33•].

Finally, recent evidence also implicates neurotransmitters other than DA in reward processing, including gamma amino butyric acid (GABA), glutamate, serotonin, and oxytocin. In particular, animal studies have demonstrated that the rewarding properties of social interactions require the coordinated activity of oxytocin and serotonin in the ventral striatum [34•]; blockade of glutamate uptake in the frontal cortex can produce anhedonia [35]; and finally, habenula inhibition on midbrain DA neurons is partly mediated via glutamatergic and GABA-ergic release [36•]. In humans, recent studies have associated depression with reduced serotonin receptor binding potential in the striatum [37], as well as reduced glutamate [38] and GABA [39] concentration in the prefrontal cortex, with the latter study implicating reduced GABA specifically in anhedonic depression. Collectively, these findings highlight promising pathways that go beyond monoaminergic dysfunction as potential treatment targets for depression.

Clinical implications

Currently up to 60% of depressed patients fail to respond to treatment [40]. Notably, common treatments (e.g., selective serotonin reuptake inhibitors, SSRIs) often do not address reward-related symptoms in depression, such as loss of pleasure, interest, or energy [41•], and, in some cases, might even worsen them [42]. Conversely, explicitly encouraging patients to engage in rewarding activities during treatment has been found effective in alleviating depression [43], potentially by affecting striatal response to reward [44]. Therefore, increased attention to dysfunctional reward processing within the therapeutic process may improve clinical outcomes. In fact, depressed patients report that their remission is linked to reinstatement of positive feelings such as optimism and self-confidence [45•].

Clearly, a considerable gap still needs to be bridged before the body of work reviewed above could be used to directly guide clinical procedures. Nevertheless, neuroimaging evidence has already informed deep brain stimulation (DBS), an invasive neurosurgical procedure for highly treatment-resistant patients in which electrodes are implanted in specific brain regions. Interestingly, DBS targeting core reward circuitry regions such as the ventral striatum [46] and lateral habenula [47] provided significant symptomatic improvement in these severely depressed and highly refractory patients. The clinical relevance of reward dysfunction was further demonstrated by recent findings that blunted reward learning [48] and abnormal cortical-striatal connectivity [28•] predicted antidepressant treatment outcome in depression. Taken together, accurate identification of specific reward-related dysfunctions and their neural underpinnings holds promise for individually tailored localization of DBS

targets and treatment selection. Finally, altered response to reward was recently demonstrated even in young healthy individuals who are at risk for depression by virtue of their mothers' history of depression [49], suggesting that improved understanding of dysfunctional reward processing may also facilitate identification of depression vulnerability.

Conclusion

Dysfunctional reward processing is central to the pathophysiology of depression, yet its exact manifestation and pathophysiology vary across specific reward-related constructs. Substantial preclinical and clinical evidence has implicated a distributed network of brain regions and pathways in reward processing, with dopaminergic signaling in the striatum playing a major role in these processes. Ultimately, improved understanding of precise depression-related dysfunctions in reward processing, as well as their mediating neural pathways, may aid both diagnostic and therapeutic efforts required to address current unmet needs associated with this prevalent disorder.

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