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MOOD AND ANXIETY DISORDERS (C HARMER, SECTION EDITOR)

Can Understanding Reward Help Illuminate Anhedonia?

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Abstract

Purpose of Review The goal of this paper is to examine how reward processing might help us understand the symptom of anhedonia.

Recent Findings There are extensive reviews exploring the relationship between responses to rewarding stimuli and depression. These often include a discussion on anhedonia and how this might be underpinned in particular by dysfunctional reward processing. However, there is no specific consensus on whether studies to date have adequately examined the various sub-components of reward processing or how these might relate in turn to various aspects of anhedonia symptoms.

Summary The approach to understanding the symptom of anhedonia should be to examine all the sub-components of reward processing at the subjective and objective behavioural and neural levels, with well-validated tasks that can be replicated. Investigating real-life experiences of anhedonia and how these might be predicted by objective lab measures is also needed in future research.

Keywords Reward · Anhedonia · Depression · Ventral striatum · Mood disorders · Stress

Introduction

Depression is defined as a negative emotional state that affects daily life, ranging from unhappiness and displeasure to extreme sadness and pessimism. In accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, the diagnosis of depression necessitates five or more symptoms within a 2-week period [1]. Anhedonia is the loss of interest and pleasure during depression and is one of the two main diagnostic criteria alongside low mood [1]. Even though anhedonia is one of the most important components of depression, the behavioural and neurobiological basis of anhedonia is not completely understood [2•, 3]. In this respect, the main purpose of this review is to discuss anhedonia in relation to reward processing as studies on the neurobiology of depression [4, 5] suggest that anhedonia is related to dysfunction in the brain's reward pathways [6] which in turn, therefore, may be a potential target for treatment development.

Why Is It Important to Understand the Symptom of Anhedonia Better?

The term anhedonia was first used in 1896 to describe reduced hedonic capacity by Théodule-Armand Ribot [7]. Although historically anhedonia has been mainly described as a 'loss of pleasure', studies reveal other components such as reduced desire, expectation, motivation, and enjoyment of reward [8•]. Further, even though anhedonia is frequently considered as a specific symptom for depression [2•, 7], it is also a common symptom of many neuropsychological disorders [9•], such as schizophrenia [10], Parkinson's disease [11], and substance abuse [12]. In a recent meta-analysis [13], it has been emphasized that there is a strong relationship between anhedonia and suicidal thoughts, and studies suggest anhedonia increases the risk of suicide [14•, 15, 16]. Furthermore, in relation to treatment, anhedonia is the strongest predictor, among all depressive symptoms, of increased time to remission [17] and reduced response to serotonergic treatment [8•]. Therefore, it is imperative to increase our understanding of anhedonia so that we can not only alleviate depression

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symptoms and prevent relapse but also possibly help reduce suicide risk.

How Might Understanding Reward Illuminate the Symptom of Anhedonia?

There are many theories as to what might cause anhedonia, such as stress [18, 19], genetic variations [20••], and dysfunction in brain activity [21, 22]. The brain's response to reward during depression is of interest in relation to understanding the causes of anhedonia [23] as it is thought that anhedonia comes about by dysfunctional reward mechanisms in the brain [24]. Seeking out reward is vital for human survival, and eating, drinking, and mating are basic physiological needs [25, 26]. However, reward processing involves more than one neuropsychological component such as 'liking', defined as a hedonic sensation; there is also 'wanting', thought of as the motivation to get a reward, and there is also 'learning' how we learn and make decisions to get rewards. Each of these components plays an important adaptive role in initiating, maintaining, and modifying our behaviour [27]. The neurobiology of reward has already been widely reviewed [28]; in summary, neuroimaging and neural recording studies have found that rewards ranging from sweet taste to intravenous cocaine, winning money, or a smiling face activate many brain structures, including orbitofrontal cortex, anterior cingulate and insula, and subcortical structures such as nucleus accumbens, ventral pallidum, ventral tegmentum, and mesolimbic dopamine projections and the amygdala [29–37]. Thus, neural differences in these systems may be underpinned by variations in dopamine, and reviews suggest that anhedonia might be improved by modulating changes in the mesolimbic dopamine system, which in turn could increase motivation and reactivity to reward [38]. However, dopamine is not the only neurotransmitter involved in reward and pleasure and rather the opioid, endocannabinoid, and GABA-benzodiazepine neurotransmitter systems are important for generating pleasurable reactions [3, 4, 39]. As the symptom of anhedonia itself is also multidimensional with various components that each might be contributing to various aspects of the experience, more work is needed on a detailed examination of the sub-components of reward processing in relation to anhedonia and brain function. Whether it is the desire/expectation for reward or the effort to reach reward or the consummatory response upon receiving a reward that is the main dysfunction during anhedonia, is not yet clear [8•, 40, 41••].

It is suggested that stress can disrupt reward processing [19], and preclinical work shows that physical stress (e.g. foot shock) decreases consummatory behaviour in rats (decreased saccharine consumption) [42] and exploratory behaviour [43, 44]. Similarly, acute social stress by means of social defeat in rats leads to a decrease in reward-seeking behaviour [45]. In humans, studies have found that an interaction between recent life stress and ventral striatal (VS) reactivity predicted self-reported positive affect (PA), such that higher levels of life stress were associated with lower PA for participants with relatively low, but not for those with high, VS reactivity. Interestingly, this work suggests that even in the face of stress, those with high VS activity may be protected against vulnerability to low positive mood precipitated by stressful life events [46]. Furthermore, Corral-Frias and colleagues [47] showed that individual differences in neural responses to reward may confer vulnerability to stress-related psychopathology. They found that as activation in the VS of individuals exposed to early life stress (ELS) decreased, the risk for anhedonia increased [47]. However, the authors point out that more work needs to be done to elucidate the relationship between stress and anhedonia in more detail; for example, it is not known which types of stress lead to changes in motivation and reward processing at the molecular and neural levels [19]. Further studies in humans have found that ELS is associated with reward dysfunction, as evidenced by blunted activation during both reward anticipation in the dorsal striatum [48, 49] and reward receipt in the ventral striatum [50–52]. Studies have also found that the stress of active military service, for example, was related to reduced VS activation during reward receipt [53] while the stress of a physical cold pressor has been found to decrease activation to monetary reward in the dorsal striatum and orbitofrontal cortex in healthy adults [54]. In an effort to examine patterns of reward function before and after acute stress, a study by Kumar and colleagues showed reduced activation in the putamen and caudate during reward receipt following stress relative to no stress, suggesting that stress can elicit anhedonic-like activation patterns [55]. Taken together, most studies to date have assessed reward processing in adults but have not always clearly differentiated the effects of stress on the sub-components of reward processing. Further, it is important for future work to investigate how stress and reward processing interact in young people at increased risk of depression, to identify risk factors early that might be targets for treatment.

Family and twin studies have been used to examine genetic links with symptoms such as anhedonia [56, 57]. For instance, Liu and colleagues [56] compared the reward sensitivity of a group of healthy individuals with no family history of depression and another group of first-degree relatives of depressed patients. Compared with the control group, relatives of patients with major depression who themselves had subclinical depressive symptoms displayed a blunted reward bias which was associated with anhedonia. Relatives without symptoms displayed largely intact motivational processing on both self-report and experimental measures [29]. In another study examining twins, responses to an objective behavioural measure of hedonic capacity (reward responsiveness), it was found that hedonic capacity and perceived stress are indeed

heritable with substantial shared additive genetic contributions [30]. The authors also pointed out that replications in larger samples are needed. Accumulating research suggests that genetic differences conferring relatively increased subcortical DA or reduced cortical DA signalling (via either receptor availability or synaptic clearance) are associated with enhanced reward-related neural activation and behaviour [58]. This supports the notion that anhedonia might therefore have a genetic component. Yet most research on the genetics of reward processing have yet to establish how the various *sub-components* (anticipation vs motivation vs consummation) of reward processing might confer genetic risk [58]. Therefore, more work needs to be done on how to examine if one sub-component or a combination of them confers risk differently, in different people. Taken together, it is possible that anhedonia might be precipitated by various factors such as stressful life events, genetic variations, and/or neural dysfunction. Knowing more about the mechanisms underpinning anhedonia could help us detect early signs and thus help us develop preventative strategies and improved treatments.

The Link Between Anhedonia and Reward Processing in Depression

To date, the neurobiology of reward deficits in depression have been well documented in adults [59, 60] and more recently in adolescents [61–64]. In summary, studies report mostly decreased responses to the anticipation and outcome of reward (money) in regions like the ventral striatum, caudate, the dorsolateral and medial prefrontal cortex (PFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and amygdala [61, 65]. Striatal regions are often reported as negatively correlating with anhedonia and subjective positive affect in depression [9•, 66]. Yet as mentioned above, the sub-components of reward processing are not always explicitly examined in studies of reward and it has been argued that using the receipt of monetary rewards in tasks cannot capture adequately consummatory hedonic responses as the money is not actually received during the study (on each trial) and money is itself a secondary reinforcer [6, 41••]. In an attempt to examine the various sub-components of reward processing in relation to anhedonia, we have employed a task that uses both primary and secondary reinforcers. Our tasks also separate out anticipation from motivation using effort and anticipation from consummation using taste. We recently found using this that adolescents with depression symptoms have blunted neural responses during the anticipation, effort, and consummation of rewarding and aversive stimuli [67, 68]. This work is of interest as it shows how anhedonia is related to all the sub-components of reward processing but also to blunted aversion processing. This data is novel and interesting as it provides evidence for motivational deficits in those at increased risk of clinical depression and that motivational deficits need not be just to reward but could affect how one acts to avoid aversion.

As mentioned above, learning about rewards is also important if we are to optimally direct our behaviour towards gaining rewards. Previous research suggests that anhedonia and depression are related to impaired reward learning, on both the behavioural and the neural levels [38, 69]. Computational models have been used to examine learning about rewards and specifically used to examine how prediction error signalling is related to reward learning deficits in depression. A prediction error (PE), in simple terms, is calculated by subtracting the prediction value (how strongly a given cue is associated with positive or negative outcomes) from the outcome value. Finally, the prediction value is updated by adding the prediction error, multiplied by a learning rate. Studies find that medicated depressed subjects have reduced reward PE encoding in the ventral and dorsal striatum, the midbrain, and the hippocampus [70]. Further studies find that self-reported depression scores in unmedicated individuals negatively correlate with decreased reward PE encoding in the ventral striatum [71]. Interestingly, not all studies measure anhedonia and of those that do, the sub-components are not always measured, e.g. anhedonia scores, using the Snaith Hamilton Pleasure Scale (SHAPS), in unmedicated depressed individuals were found to negatively correlate with reward PE signals in the medial OFC [72]. However, the SHAPS measures only hedonic tone and not anticipatory of motivational aspects of anhedonia. Further, most studies to date have not related their findings to real-life experiences of anhedonia. In an attempt to address this, we recently found that adults with high depression symptoms compared to those with low symptoms spend higher amounts of time in negatively perceived real-life situations and that this was predicted by lower learning rates in our social reward learning task (using Facebook likes as a reward) using computational modelling [73••]. These findings support the idea that deficits in learning may negatively affect the quality of everyday life experiences and that impaired ability to use reward feedback to appropriately update future actions may lead to suboptimal real-life experiences. It therefore would be of interest in future work to examine how we can use objective measures of the various sub-components of reward processing, i.e. reward learning, reward anticipation, motivation, and consummation, to predict real-life rewarding interactions and therefore risk of anhedonia in young people. As it has been suggested that anhedonia may be a possible biomarker for depression (57) as it seems to predate depression and persist into recovery [74], examining young people before they have clinical depression and how they respond to reward in a dimensional fashion across the spectrum would be beneficial [24, 67].

Further understanding of the neural functions underlying reward could then allow the testing of the effects of antidepressant treatments on reward function in line with

anhedonia's potential as a biomarker tool [75]. In this context, a recent qualitative analysis by Cao and colleagues [76] examined the therapeutic efficacy of pharmacological treatments on measures of anhedonia in adults with MDD. They reported that a significant number of antidepressants do have beneficial effects on anhedonic symptoms as well as depressive symptoms [5, 76]. Interestingly, the authors also state that therapies targeting melatonergic receptors and circadian rhythm imbalances are more direct targets for treating anhedonia while drugs like ketamine may be faster acting on anhedonia due to their direct effect on mitochondrial energy metabolism. The authors also point out that future studies should aim to evaluate the comparative efficacy of different pharmacological agents on measures of anhedonia and that measures of function and quality of life should also be investigated.

Although perhaps less often studied, there is also growing evidence for the effects of psychological treatments on anhedonia. Behavioural activation (BA), for example, works by increasing engagement with reinforcers within the environment and overcoming avoidance [5]. Recent promising findings in adults show that greater pre-treatment anhedonia severity in a monetary reward processing task [77] and decreased neural functional connectivity, in a positive emotion upregulation task [78], are predictive of response to BA treatment. Further, BA is thought to be more cost effective and more acceptable to young people who are depressed than other psychotherapies [79], but it is still not effective for everyone. Therefore, increased understanding of reward processing and how it underpins the symptom of anhedonia could also allow the development of more effective psychological treatments for depression.

Conclusion

Studies to date have elucidated the reward system in both animal and human neural systems and behaviours. Reviews have described the role of the reward system in depression and those at risk of depression. However, there is still not a clear understanding of how the sub-components of reward processing might underpin the symptom of anhedonia in depression or in those at risk of depression. Further, it is still not clear how the everyday experiences of anhedonia relate back to the objective measures of reward processing used in lab experiments. Therefore, going forward, more needs to be done to map the subjective experience of anhedonia with the behavioural and neural measures of reward processing if we are to find new targets for intervention and treatment strategies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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