Pleasure, reward value, prediction error and anhedonia

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Abstract

In order to develop effective treatments for anhedonia we need to understand its underlying neurobiological mechanisms. Anhedonia is conceptually strongly linked to reward processing, which involves a variety of cognitive and neural operations. This chapter reviews the evidence for impairments in experiencing hedonic response (pleasure), reward valuation, and reward learning based on outcomes (commonly conceptualised in terms of "reward prediction error"). Synthesizing behavioural and neuroimaging findings, we examine case-control studies of patients with depression and schizophrenia, including those focusing specifically on anhedonia. Overall, there is reliable evidence that depression and schizophrenia are associated with disrupted reward processing. In contrast to the historical definition of anhedonia, there is surprisingly limited evidence for impairment in the ability to experience pleasure in depression and schizophrenia. There is some evidence that learning about reward and reward prediction error signals are impaired in depression and schizophrenia, but the literature is inconsistent. The strongest evidence is for impairments in the representation of reward value and how this is used to guide action. Future studies would benefit from focusing on impairments in reward processing specifically in anhedonic samples, including transdiagnostically, and from using designs separating different components of reward processing, formulating them in computational terms, and moving beyond cross-sectional designs to provide an assessment of causality.

1. Introduction

Anhedonia is usually defined as a loss of interest or pleasure in previously rewarding activities. It is a cardinal symptom of depression and a core negative symptom in schizophrenia, and it is also often present in Parkinson's disease and other neurological disorders. Its clinical manifestation overlaps with several other symptoms, such as apathy, fatigue, anergia or avolition. Anhedonia is an important symptom to understand because it is associated with poor clinical outcomes: anhedonic patients are at higher risk for non-response to both psychological and pharmacological treatments (McMakin et al. 2012; Craske et al. 2016), established treatments may have little impact on anhedonia (Fig. 1), and there are no interventions specifically targeting this symptom (Argyropoulos and Nutt 2013). It is also associated with suicidal ideation independently of depression (Ducasse et al. 2018) and suicide within one year (Fawcett et al. 1990).

In order to develop effective treatments for anhedonia we need to understand the neurobiological mechanisms underlying it. This is complicated by the fact that anhedonia does not represent a unitary construct as its conceptualisation has evolved from "inability to experience pleasure" to "loss of interest or pleasure in previously rewarding activities", adding a motivational component. But experiencing pleasure and being motivated involve multiple distinct neurocognitive mechanisms, which may be differently affected in different patients, and may therefore require different treatments (Treadway and Zald 2011; Husain and Roiser 2018). To understand the neurobiology of anhedonia and develop targeted treatments, it is therefore important to deconstruct it into its component cognitive and neural processes.

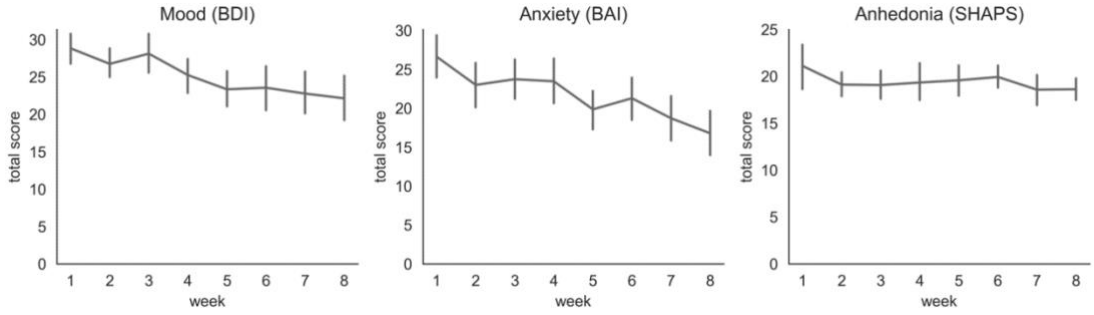

Fig. 1 Anhedonia is relatively unaffected by cognitive behavioural therapy, even as the broader spectrum of depressive symptoms improves; adapted from Nord et al. (2019). Weekly mood, anxiety, and anhedonia self-report scores, shown over a course of eight weeks of therapy. Error bars represent standard error of the mean. BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; SHAPS = Snaith-Hamilton Pleasure Scale

2. Anhedonia and reward processing

Cognitively, anhedonia can be conceptualised as a disruption in reward processing. Reward processing involves a variety of cognitive operations in which information about reward is used to guide behaviour. This includes: computing and making decisions based on reward value; anticipating reward; initiating and sustaining action necessary to obtain reward; experiencing hedonic response (pleasure); and learning based on reward outcomes (commonly conceptualised in terms of "reward prediction error"). Disruption to any of these processes (Fig. 2) could potentially drive anhedonia (Husain and Roiser 2018).

One of the main benefits of studying anhedonia through the conceptual framework of reward processing is that the cognitive and neural mechanisms of reward processing are relatively well understood (Berridge et al. 2009). Describing how the different subcomponents of reward processing are altered in anhedonia could help explain the mechanistic heterogeneity within this symptom and provide specific targets for treatment.

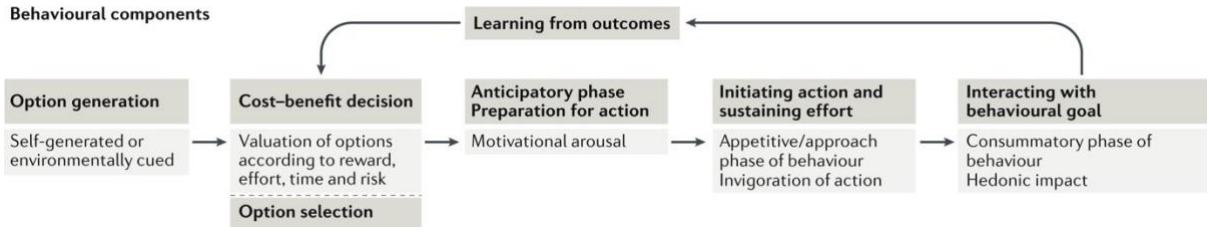

Fig. 2 Components of reward processing, disruption to any one of which could potentially drive anhedonia; adapted from Husain & Roiser (2018).

While some of these processes are relatively straightforward to measure, others can only be studied indirectly. The most common approaches are to use cognitive tests which engage them, or record physiological responses which they elicit (including functional neuroimaging and psychophysiology). More recently, computational accounts of different stages of reward processing have been developed (Dreher and Tremblay 2009). Such accounts express what happens at the different stages of reward processing in mathematical form, and allow us to exploit the full richness of data (for example, by capturing how responses change on a trial-by-trial basis during learning). Computational modelling additionally provides insight into processes that are not directly observable (for example, physiological correlates of reward prediction error).

While anhedonia is considered a transdiagnostic symptom (Husain & Roiser, 2018) and disrupted reward processing a transdiagnostic research domain (Insel et al. 2010), most

studies examined reward processing in case-control designs investigating individual disorders in which anhedonia is present (Halahakoon et al. 2020). Only a minority of studies focused on anhedonia specifically, attempted to measure anhedonia levels, included anhedonic subsamples, or studied anhedonia transdiagnostically (Lambert et al. 2018; Whitton et al. 2021). This chapter examines the evidence from these case-control studies in the context of depression (which form the largest body of literature) and schizophrenia, and highlights the studies which focused specifically on anhedonia.

3. Pleasure

The term anhedonia was classically understood as "inability to experience pleasure", but it is not clear that patients with anhedonia actually have attenuated hedonic responses.

3.1. Self-report questionnaires

The most common way to assess hedonic capacity in anhedonic individuals has been to use self-report questionnaires, such as the Snaith-Hamilton Pleasure Scale (Snaith et al., 1995), Temporal Experience of Pleasure Scale (Gard et al. 2006), Chapman's Physical Anhedonia Scale (Chapman et al. 1976), or—the most recently developed—Dimensional Anhedonia Scale (Rizvi et al. 2015). In these questionnaires, patients with depression, schizophrenia and other disorders consistently report diminished experience of pleasure compared to healthy controls (Watson & Naragon-Gainey, 2010). However, all these questionnaires ask patients to rate the degree of pleasure experienced from theoretical or imagined rewards. It is therefore difficult to ascertain whether lower scores really indicate a lower ability to experience pleasure, or the fact that the internal value of these imagined rewards is diminished (possibly due to a disruption in valuation processing, as discussed in the following section). Lower scores could also reflect recollection bias or general negative bias in depression, or cognitive impairments (Roiser and Sahakian 2013). The same limitations apply to qualitative studies, in which patients with depression (Watson et al., 2020) and schizophrenia (Gee et al. 2019) have reported lower experience of pleasure.

3.2. Ecological momentary assessments

Studies using ecological momentary assessments (EMA), asking people to rate their levels of enjoyment in response to various daily events several times a day, have generally found that depressed patients did not report lower reactivity to positive events, despite having higher scores of anhedonia on self-report questionnaires (Peeters et al. 2003; Bylsma et al. 2011; Thompson et al. 2012). One such study (Wu et al. 2017) did find lower levels of reported pleasure in patients with depression. However, this study assessed the experience of pleasure by asking participants which of the recently-reported activities they had been most looking forward to, and was therefore not necessarily an assessment of momentarily experienced pleasure but instead of recollection of anticipation.

Interestingly, in some EMA studies, patients with depression even reported *greater* brightening of mood following pleasant events than did healthy controls, after accounting for baseline mood (Peeters et al. 2003; Bylsma et al. 2011). This surprising and apparently paradoxical finding might be reconciled by studies finding that mood does not depend on rewarding outcomes *per se*, but is instead driven by the difference between expected and actual outcomes, in other words the prediction error (Eldar et al. 2016). Notably, in the above-mentioned EMA studies, depressed participants experienced fewer rewarding events. It is possible that they engaged in fewer rewarding activities because they valued them as less rewarding than did healthy controls—suggesting an impairment in valuation rather than hedonic capacity, as discussed below. However, when they did experience rewarding events, the 'in-the-moment' experience of reward may have been relatively normal, as suggested by

lab-based studies discussed below. Combined with more negative expectations, such preserved "in-the-moment" hedonic responses would correspond to greater prediction errors, resulting in greater improvement in mood than in healthy controls (albeit likely only transitory). If this explanation is correct, an important question is why reward values were not updated following the positive experience (which would suggest differences in some aspect of reward learning). Either way, the findings of these studies point to impairments in other components of reward processing than hedonic capacity.

3.3. Laboratory assessments

Laboratory assessments of pleasure have yielded similar results to EMA. Specifically, when patients were asked to report the pleasantness of various primary rewards presented to them in laboratory conditions (such as sweet tastes and pleasant odours, which are intrinsically rewarding without requiring learning; Rizvi et al., 2016), most studies found no differences between healthy controls and patients with depression (Amsterdam et al. 1987; Berlin et al. 1998; Swiecicki et al. 2009; Chentsova-Dutton and Hanley 2010; Dichter et al. 2010; Arrondo et al. 2015a) or schizophrenia (Berlin et al. 1998). Notably, even those studies which specifically examined patients with high levels of self-reported anhedonia (Chentsova-Dutton and Hanley 2010) or melancholic depression (Amsterdam et al. 1987)—who exhibit high levels of anhedonia by definition—did not identify any abnormality. This pattern of results is consistent with the notion that anhedonia, in contrast with its etymology and historical definition, is not associated with diminished ability to experience pleasure *per se*. Instead, lower levels of enjoyment reported by anhedonic patients on questionnaires may be better explained by disruptions in other components of reward processing.

However, the literature is not entirely consistent and there are some unresolved questions. Findings of no differences in pleasantness ratings are somewhat complicated by the observation that, while depressed patients did not differ from healthy controls in their pleasantness ratings of sweet tastes, they exhibited higher threshold for sweet taste perception (Berlin et al. 1998). This could suggest that while anhedonic patients experience pleasure to a similar degree to healthy individuals overall, they might need to accumulate more evidence to reach the same experience. This would also be consistent with some computational accounts of anhedonia, which have found lower drift rate (i.e., the speed of reaching decision threshold) in depression (Robinson & Chase, 2017).

3.4. Physiological responses

Few studies have attempted to measure hedonic reactions through physiological responses, or facial responses. One such study (Steiner et al. 1993) found that depressed patients responded to sweet tastes with muted and shorter facial expressions compared to controls (interestingly there was no difference for aversive tastes). There is also some evidence of lower physiological responses (such as heart rate changes) during the delivery of pleasurable stimuli in healthy individuals with high levels of self-reported anhedonia (Ferguson and Katkin 1996), but studies in clinically-defined anhedonic groups are lacking.

A parallel line of evidence comes from neuroimaging studies of responses to pleasant stimuli. McCabe et al. (2009) used fMRI to measure hemodynamic responses to pleasant stimuli (both picture and taste of chocolate) in patients with remitted depression. They found that despite giving the same ratings to the pleasant stimuli as healthy controls, the remitted depressed group showed attenuated hemodynamic responses to the stimuli in the ventral striatum, a region linked to reward responsiveness. However, because the stimuli were presented on screen and delivered at the same time, this study design does not allow anticipation and consummation of reward to be assessed separately. It is therefore possible that the blunted responses reflected lower sensitivity to anticipated reward or disruption in

some other component of reward processing. In a subsequent study (McCabe 2016), the researchers attempted to disentangle anticipatory and consummatory responses to pleasant stimuli by examining whether the neural responses parametrically varied with participants' pleasantness ratings, and how much they reported they "wanted to have them". Interestingly, hemodynamic responses in the ventral striatum in remitted depressed patients were parametrically modulated by the ratings of wanting, *not* pleasantness.

In summary, the extant literature does not provide strong evidence for lower hedonic experience or associated physiological responses in clinical anhedonia. However, definitive studies are lacking. Future studies should use designs that can disentangle hedonic responses from other components of reward processing because, as discussed in the next section, there is evidence that these subcomponents associate negatively with anhedonia.

4. Reward value

If the ability to experience pleasure is really intact in anhedonia, what might account for consistently reported lower levels of experienced pleasure in both self-report questionnaires and qualitative studies? One possible explanation is that the internal value assigned to potentially rewarding activities is decreased. Lower valuation would also lead to lower reward seeking, potentially explaining why anhedonic individuals exhibit lower interest and engage in fewer rewarding activities.

Reward value has been defined as "the subjective desire or preference for some quantity of one resource over another" (Redish et al. 2016), although several approaches to defining and measuring value exist, often with slightly different meanings (O'Doherty 2014). According to the neuroeconomics literature, value of a certain quantity of reward is determined by how much benefit an individual *expects* to derive from it (e.g. because it will elicit pleasure or cover a physiological or social need). This value can be discounted by the expected costs associated with obtaining the reward, the probability that the reward will occur, or length of time until the reward will be obtained (Zald and Treadway 2017). Reward value is a theoretical concept—as a latent construct it is not directly observable—but it can be inferred, either from behavioural (in particular, choices or reaction times) or physiological (in particular, neuroimaging) responses to potential or anticipated reward. Over the past decade an influential method of inferring reward value has been to use computational modelling (discussed in Chap. 24).

4.1. Behavioural studies

We can infer how much an individual values a reward based on how frequently they choose one reward over another; the costs they are willing to overcome to obtain it (by measuring e.g. how much physical effort or money they are willing to expend); or with how much vigour and speed they approach the reward. By varying reward magnitudes, we can also assess how sensitive individuals are to increasing rewards. Several behavioural tasks using such approaches have been developed and used to infer whether and to what extent individuals with depression and schizophrenia value rewards less than control participants. However, only a limited number of these studies have actually focused specifically on individuals with anhedonia, or indeed even included measures of anhedonia (Halahakoon et al. 2020).

Effort tasks In one group of tasks, such as the Effort Expenditure for Rewards Task (Treadway et al. 2009), which was reverse translated from prior animal studies (Salamone et al. 2016; see Chap. 17), or the Incentive-Force Task (Prévost et al. 2010), participants' valuation of rewards of various magnitudes is inferred from their willingness to engage in physical effort to obtain them. Several studies using such "value-based choice" tasks have found that, compared to healthy controls, people with depression and schizophrenia are less willing to expend greater effort for larger or more probable rewards. While in some studies

depressed participants expended less effort overall (Treadway et al. 2012; Hershenberg et al. 2016), in most studies participants with depression (Cléry-Melin et al., 2011; Yang et al., 2014; Zou et al., 2020) and schizophrenia (Barch et al., 2014; Chang et al., 2019; Fervaha et al., 2013; Gold et al., 2013; McCarthy et al., 2016; Treadway et al., 2015; Yang et al., 2021; Zou et al., 2020) did not differ from healthy controls in their overall willingness to expend effort; instead, anhedonic individuals were less willing to expend greater effort when the magnitude or probability of reward were high. Although some studies in depression (Yang et al., 2021) and schizophrenia (Docx et al. 2015) reported divergent results, overall the pattern is remarkably consistent (although this may be due in part to publication bias; Halahakoon et al., 2020).

Importantly, the degree of responsiveness to increasing potential reward was found to correlate negatively with self-reported anhedonia (Sherdell et al., 2012; Yang et al., 2014) or broader negative symptoms (Gold et al. 2013; Barch et al. 2014; Strauss et al. 2016; Moran et al. 2017), even in studies where there was no overall group difference (Sherdell et al. 2012; Strauss et al. 2016). This pattern suggests that lower valuation of increasing rewards is related to anhedonia specifically, rather than depression or schizophrenia *per se*. However, this interpretation is complicated by the fact that the association with self-reported anhedonia is not a universal observation (Cléry-Melin et al. 2011; Treadway et al. 2012; Fervaha et al. 2013; Hershenberg et al. 2016; Chang et al. 2019). One possibility is that divergent results are due to differences in the questionnaires used to assess anhedonia as some of them may measure a different construct than the effort tasks (Horan et al. 2006). Here, a useful alternative could be the recently developed Positive Valence Systems Scale (Khazanov et al. 2019), which measures the Research Domain Criteria's "positive valence systems" subdomain (Insel et al. 2010) and may relate to differences in effort valuation more closely.

Risk-taking tasks Lower ability of rewards to incentivise choices in depression and schizophrenia has also been observed, although less consistently, in risk-taking paradigms, such as the Cambridge Gambling Task (Rogers et al., 1999), in which reward value is indexed by the amount of money or points participants are willing to stake at different odds. Two prospective studies found that, compared to healthy controls, adolescents with depression failed to increase their stake when the odds of winning were very high (Forbes et al., 2007; Rawal et al., 2013). In other words, as in the effort-based paradigms, they were less incentivised by higher probability of reward. In one study, lower "reward seeking" was correlated with self-reported anhedonia and negatively correlated with the frequency of extracurricular activities (Rawal et al., 2013), and it predicted the onset of new depression after one year in both studies (Forbes et al., 2007; Rawal et al., 2013). However, a very large prospective study in adolescents, using the Cambridge Gambling Task, did not find strong evidence for lower reward seeking in depression (the association did not survive adjustment for gender), either cross-sectionally nor longitudinally (Lewis et al. 2021). Importantly, this study included a nationally representative sample, longer follow-up period and adjusted for a number of potential confounders, increasing confidence in this negative finding. Other studies using this task, performed in elderly patients with depression (Clark et al., 2011; Dombrovski et al., 2012) and adolescents with schizophrenia (MacKenzie et al. 2017) also failed to find any association. These inconsistencies may have arisen because the Cambridge Gambling Task conflates reward seeking with risk taking, which may not be altered in depression, and punishment avoidance, which is heightened in depression (Eshel and Roiser 2010), potentially masking associations. As such risk-taking paradigms may not be specific measures of reward valuation, and because of equivocal findings yielded by them, their interpretation remains tentative. Notably, though, when differences have been detected, the pattern of results has largely agreed with the findings from effort-based paradigms.

Reward bias tasks The above findings are complemented by evidence from tasks that assess the ability to develop "reward response bias", which have shown that patients with depression exhibit lower responsiveness to reward even when information is not explicitly provided. In these tasks, such as the Probabilistic Reward Task (Pizzagalli et al. 2005) and its adaptations (Aylward et al. 2020), correct responses to one stimulus are rewarded more frequently than correct responses to the other. When uncertain about which stimulus has been presented, healthy participants are more likely to respond as if the more frequently rewarded stimulus has been presented, termed the reward response bias. In several studies, individuals with depression have been found to be less likely to develop reward bias than control participants (Henriques and Davidson 2000; Pizzagalli et al. 2005; Pizzagalli et al. 2008; Vrieze et al. 2013; Aylward et al. 2020), suggesting that they are less sensitive to implicit reward information. Computational support for this interpretation was provided by a meta-analysis by Huys et al. (2013) (discussed in detail below). Some studies reported that lower reward response bias was associated with high levels of anhedonia or was specific to the melancholic subtype of MDD (Fletcher et al. 2015), and predicted poor antidepressant response (Vrieze et al. 2013). In a larger sample, Lawlor et al. (2020) did not find evidence of a lower reward bias in depression, but a subsequent meta-analysis by Halahakoon et al. (2020) nonetheless concluded that lower reward bias in depression is a consistent finding; moreover, its effect size was the largest of the reward processing impairments assessed in the meta-analysis. Interestingly, using computational analysis, Lawlor et al. (2020) showed that even in the absence of lower reward bias, participants with depression were slower to accumulate the evidence required to make decisions. This result does not necessarily contradict the notion of lower reward sensitivity in depression, but indicates that the mechanisms behind it may be more nuanced.

In contrast to depression, patients with schizophrenia have not been found to show lower reward response bias (Heerey et al. 2008; Barch et al. 2017). This could mean that reward valuation in schizophrenia might be impaired only when information about possible options is explicitly provided and requires conscious evaluation, while decision making based on implicit reward information is intact. Several authors (Culbreth et al., 2018; Strauss et al., 2014) proposed that apparent lower reward valuation in schizophrenia may therefore be due to impairments in executive function—well established in schizophrenia—specifically the ability to integrate and maintain reward value representations (see also Chap. 8). Such findings demonstrate that lower reward valuation may arise by different mechanisms in different patients across disorders (as discussed in the final section).

Response vigour tasks Another possible method to index reward value is to examine the vigour individuals are willing to expend, as opposed to choices (as assessed in the studies discussed above). However, there is little evidence that reward-related vigour is impaired in depression (Halahakoon et al. 2020), despite symptoms such as psychomotor slowing and fatigue.

In summary, although not all studies agree, there appears to be reasonably consistent evidence from a range of different behavioural paradigms that individuals with depression and schizophrenia value rewards less than healthy controls. In particular, stimuli associated with high probabilities and magnitudes of reward appear to incentivise their behaviour less. In depression, this has been confirmed and quantified by a recent meta-analysis of studies investigating behavioural differences in reward processing between individuals with depression and healthy controls (Halahakoon et al. 2020). However, the precise cognitive mechanisms underlying lower reward valuation in depression and schizophrenia remain to be

elucidated, and it remains unclear whether this is specific to anhedonia or relates to other symptoms present in depression and schizophrenia.

4.2. Neuroimaging studies

Complementing behavioural tasks, differences in reward valuation can be studied by measuring neural responses elicited by stimuli associated with reward. The most commonly-used neuroimaging paradigm is the Monetary Incentive Delay task (Knutson and Heinz 2015), which requires quick responses to cues in order to obtain associated rewards (typically monetary). Responses are required after a delay, which allows the separation of neural responses to anticipation and consummation. As summarised by several meta-analyses, mostly non-overlapping, numerous studies have found that individuals with depression (Zhang et al. 2016; Keren et al. 2018; Ng et al. 2019), schizophrenia (Leroy et al. 2020), and sometimes specifically with anhedonia (Arrondo et al. 2015b), exhibited lower hemodynamic responses during reward anticipation than did controls, particularly in the striatum, a region known to play a causal role in reward processing from animal experiments (Berridge et al. 2009). Most convincingly, this pattern was observed in a large longitudinal study in adolescents, where lower ventral striatum response during reward anticipation predicted anhedonia (but not low mood without anhedonia) in previously healthy adolescents two years later (Stringaris et al. 2015), in addition to cross-sectional associations.

While such findings are consistent with the hypothesis that anhedonia is driven by lower reward valuation, their interpretation is not entirely straightforward. First, lower responses were not always specific to reward anticipation or a single region within striatum: they were equally often (and sometimes only) observed following reward delivery and in both ventral and dorsal striatum, as well as other brain regions (Borsini et al. 2020). This pattern makes it difficult to ascertain whether they relate to reward valuation specifically or reflect a general alteration in reward processing. Second, because they used tasks not designed to capture behavioural differences, they were often not accompanied by differences in behaviour (here, the invigoration of responding with greater potential reward; Halahakoon et al., 2020; Nielson et al., 2021). This makes it difficult to interpret whether lower neural responses indicate impairment, compensation or relate to some group difference unrelated to reward processing (Robinson et al., 2013). Interestingly, in one study, striatal responses to reward correlated with EMA of positive affect immediately prior to scanning (Forbes, 2009). Third, as hemodynamic responses in striatum were often not specific to reward processing (Dombrovski et al., 2015), interpreting them as such may be a fallacious reverse inference (Poldrack 2006). Finally, as the tasks typically used in these studies did not require making any decisions (although there are exceptions; Huang et al., 2016), it is difficult to relate the neuroimaging findings to the behavioural literature where most differences were observed in decision making.

Despite the aforementioned limitations and inconsistencies, the behavioural and neuroimaging literatures largely agree and are consistent with lower reward valuation in anhedonia, at least when assessed within the context of depression and schizophrenia.

5. Learning and reward prediction error

One possible explanation for why rewards are valued less in anhedonia could be that individuals are less able to learn about them. According to reinforcement learning theory (see Chap. 19 on reinforcement learning and anhedonia), reward value is not static but can be updated following experience, using the difference between obtained and predicted reward, termed the reward prediction error. There is strong evidence that prediction errors drive reward learning, are represented in several brain regions (including the ventral striatum), and correspond to dopamine release in the ventral striatum (Bayer and Glimcher 2005; Steinberg

et al. 2013). It has been proposed that dysfunction in the way that reward prediction errors are computed or signalled in the brain could be one mechanism driving anhedonia. Being less able to compute or utilise prediction errors would lead to weaker internal representations of reward values, which might then manifest as lower interest in engaging in rewarding activities as well as lower anticipated pleasure.

Like reward value, reward prediction error is a latent construct that cannot be directly observed. However, parameters governing the influence of prediction errors can be estimated, by using computational models; and using the same models, physiological responses corresponding to modelled reward prediction errors can be measured.

5.1. Neuroimaging studies

Findings from neuroimaging studies using such an approach to examine reward prediction errors and anhedonia are inconsistent. While some studies reported lower reward prediction error signals in the ventral striatum in patients with depression and schizophrenia (Murray et al. 2008; Gradin et al. 2011; Ermakova et al. 2018; Kumar et al. 2018; Katthagen et al. 2020), other studies reported discrepant results (Culbreth et al., 2016; Rutledge et al., 2017). Problematically, the responses corresponding to reward prediction errors are typically not specific to a single region but distributed across prefrontal cortex, insula, hippocampus and striatum, and sometimes accompanied by differences in behaviour (in some studies, clinical participants exhibited lower exploration, slower reaction times, slower learning, worse choice accuracy or worse overall task performance), which complicates the interpretation of differences observed (Strauss et al. 2014). Overall, the idea that anhedonia is driven by attenuated reward prediction error signals is not convincingly supported by neuroimaging findings.

5.2. Behavioural studies

The evidence from behavioural studies is also mixed. By computationally analysing behavioural data from a reinforcement learning task, Chase et al. (2010) found that the learning rate, a parameter governing the extent to which prediction errors update value, negatively correlated with anhedonia in depressed participants, suggesting anhedonia is associated with impaired reward learning. A similar result in participants with depression was reported by Brown et al. (2021) who additionally found that the lower learning rate observed in depressed participants was normalised following successful cognitive-behavioural therapy. These findings are consistent with several other studies in which depression, including anhedonic depression, was associated with slower learning from rewarding outcomes (Must et al. 2006; Thoma et al. 2015; Kumar et al. 2018). However, discrepant findings have also been reported (Gradin et al. 2011; Rothkirch et al. 2017), and a meta-analysis of case-control studies of reinforcement learning in depression (Halahakoon et al. 2020) only identified a relatively modest effect size.

Problematically, in many of the tasks which are commonly used to measure reward learning, such as the Iowa Gambling Task (Bechara et al. 1994), it is difficult to separate reward learning and reward valuation. Given the consistent findings of impaired reward valuation in anhedonia, presented above, it is possible that what is ostensibly “learning” on these tasks could be driven by problems with valuation (making the subjective value of options more similar to one another).

Several studies which used computational approaches to analyse behavioural data from various reinforcement learning tasks provided support for this idea. By reanalysing behavioural data from the Probabilistic Reward Task (Pizzagalli et al. 2005), Huys et al. (2013) tested whether individuals with depression were less likely to develop a response bias because they value rewards less, or because they are less able to learn about reward. Using

computational models with separate parameters for reward sensitivity (in this model represented by the inverse temperature parameter, which influences the steepness of the softmax choice function—see Chap. 24 for a detailed explanation) and learning rate, the authors showed that anhedonia is specifically associated with lower inverse temperature, rather than lower learning rates, compared to healthy controls. Interestingly, a dopamine agonist drug, pramipexole, increased the development of reward bias by enhancing learning but *not* reward value, calling into question whether it would be an effective intervention to improve reward valuation and thereby anhedonia.

Similar conclusions came from a study by Gold et al. (2012) in schizophrenia, which analysed a different probabilistic choice task using computational modelling to understand the decisions of patients with schizophrenia following an initial learning phase. Participants with schizophrenia who had severe avolition (another negative symptom, related to anhedonia) did not seem to prefer stimuli that frequently yielded rewards over those associated with frequently avoiding losses (both of which outcomes would elicit positive prediction errors), suggesting an impairment in the representation of value. However, prediction error processing per se was apparently intact, as this group did prefer stimuli associated with frequent gains over those which yielded frequent losses.

Consistent with these findings, in an EEG study using a probabilistic learning task Cavanagh et al. (2019) reported that depression was associated with smaller reward positivity (an event-related potential elicited by rewards) and delta-band response, but this did not affect reward prediction error signals or lead to impaired reward learning; therefore the authors suggest that this may instead reflect lower reward valuation in depression.

Taken together, the evidence from the studies discussed in this section suggests that learning from rewarding outcomes is probably intact in anhedonia and that the impairments observed in anhedonic individuals may be, at least in part, explained by impairments in the representation of value.

6. Directions for future research

As discussed in the preceding sections, a growing body of literature has linked anhedonia to impaired reward processing, in particular decision making based on reward value. However, there are inconsistencies across behavioural paradigms, neuroimaging findings, and samples, which in some cases lack satisfying explanations, suggesting that our understanding of the mechanisms underlying the observed differences may be incomplete. This section outlines the key open questions and approaches which may help resolve them.

6.1. Characterising reward processing alterations using suitable paradigms and computational approaches

A key challenge for the field to move forward is to explain why anhedonic individuals value rewards less. They could be less sensitive to information about reward magnitude; they could perceive costs required to obtain rewards to be higher or discount reward values more dramatically; they could discount uncertain or delayed rewards more; they could perform integration of this information in a suboptimal way etc. Often, the paradigms used to study reward processing do not allow these processes to be easily dissociated, but it is important to do so, because different processes may suggest different causal pathways and treatment targets (Prévost et al. 2010; Husain and Roiser 2018).

A promising way to gain deeper insight into these issues is to computationally model the reward-related behaviour being studied, which allows a more fine-grained analysis of the behavioural responses recorded, as well as insights into processes which are not directly observable using traditional analyses. The usefulness of computational approaches for dissociating component processes of reward processing is exemplified by the studies by Huys

et al. (2013) and Gold et al. (2012) (discussed above), which suggested that impairments on reinforcement learning tasks may be driven by impairments in reward valuation and not learning.

Computational approaches have several other advantages which may help elucidate the mechanisms underlying altered reward processing more precisely (see Chap. 24). One notable advantage is that they can link behavioural and neuroimaging findings and help us understand what neuroimaging differences mean. Using this approach, Rutledge et al. (2017) showed that striatal hypoactivation in depression is unrelated to reward prediction error. Combining value-based choice tasks with computational modelling and neuroimaging may be a particularly fruitful endeavour (Forbes et al., 2020; Rupprechter et al., 2021).

6.2. Understanding heterogeneity across disorders using transdiagnostic assessments

Our understanding of altered reward processing as a mechanism of anhedonia is limited by the fact that most studies examine it within the context of diagnostic categories such as depression or schizophrenia, without focusing on specifically anhedonic individuals—many studies do not even assess anhedonia levels (Halahakoon et al. 2020). The assumption is that because anhedonia is a prominent diagnostic symptom of these disorders, the studied participants will be sufficiently anhedonic. However, the inherent heterogeneity of the diagnostic categories—some participants with the diagnosis of depression or schizophrenia may have no anhedonia at all—may mask important associations and lead to inconsistencies between studies (Müller et al. 2017). Future studies of reward processing impairments should focus on anhedonic individuals specifically, measure the presence, type and level of anhedonia using well-validated tools, and examine reward processing impairments as functions of these measures in addition to case-control comparisons.

Given the presence of anhedonia across disorders, transdiagnostic studies may be informative. Several recent studies comparing reward processing in different disorders (Culbreth et al., 2018; Lambert et al., 2018; Whitton et al., 2015; Yang et al., 2021) have yielded insights into the commonalities and differences in reward processing in different disorders. For example, it has been suggested that, in depression, lower willingness to expend effort for higher reward magnitudes may relate to lower reward sensitivity, whereas in schizophrenia it may be due to impaired ability to integrate and maintain reward value representations (Culbreth et al., 2018). In addition to such broad comparisons between disorders, it would be informative to examine whether there are dissociable patterns of reward processing impairments in anhedonic individuals irrespective of diagnostic classification. Computational approaches have been increasingly used to this end (Marquand et al. 2016; Husain and Roiser 2018).

6.3. Improving the validity and reliability of reward processing measures

As studying the components of reward processing relies either on self-report or requires inference from behavioural or physiological responses, it is important to make sure that these tools are psychometrically valid and reliable (Mkrtchian et al. 2021). Most of the behavioural paradigms used to assess reward processing are yet to be psychometrically validated or have varying test-retest reliability (Reddy et al. 2015). Furthermore, they have typically been developed to capture between-group differences but often perform less well in assessing individual differences, which is a problem that applies also to the computational analysis of reward-processing behaviour (Eckstein et al. 2021).

Another issue is that the behavioural paradigms used to assess reward processing typically rely on monetary rewards (Halahakoon et al. 2020). However, monetary rewards may not necessarily be valued equivalently across participants with different socioeconomic backgrounds, and there are well-known relationships between socioeconomic status and

incidence of psychopathology (Kessler et al. 1997). Studies using other types of reward, including social or primary rewards, would be informative. Researchers using monetary rewards should assess income levels and take this into account when performing analysis.

Self-report questionnaires have their own set of limitations. As mentioned above, they rely on conscious evaluation of hypothetical scenarios and are thus potentially affected by working memory impairments or a variety of different biases (such as recollection bias, anchoring effects and demand characteristics). These problems may explain why they are often not found to correlate well with behavioural and neuroimaging measures, or even with EMA (Gold and Strauss 2012; Moran et al. 2017). Future studies should nonetheless always include them and examine their associations with the observed findings, as self-reported questionnaires still capture important aspects of the subjective experience of anhedonia. However, researchers should take advantage of recent and well validated questionnaires (see Chap. 2), and these could be usefully complemented by EMA as well as assessments of psychosocial functioning.

6.4. Addressing causality with longitudinal and intervention studies

Nearly all work on reward processing and anhedonia has been cross-sectional (Halahakoon et al. 2020; Nielson et al. 2021). More longitudinal studies would help ascertain whether the association between disruptions in reward processing and anhedonia is casual and could therefore be used as a risk marker and target for intervention, including prevention. The existing longitudinal studies support the notion that disrupted reward processing is a causal factor in the development of anhedonia, but do not provide a completely consistent picture (Forbes et al., 2007; Lewis et al., 2021; Rawal et al., 2013; Stringaris et al., 2015).

Evidence of causality could also come from intervention studies, for example assessing whether direct manipulation of the reward system, e.g., pharmacologically or with deep-brain stimulation, alters reward processing and consequently improves anhedonia. There have been only a few intervention studies which focused specifically on the reward system and anhedonia, but the results to date are promising. For example, deep brain stimulation of the ventral striatum normalised its responses to reward and improved depression symptoms in one study (Bewernick et al. 2012). Similarly, ketamine was found to specifically improve anhedonia over-and-above general depressive symptoms, and the level of improvement was specifically correlated with increased in striatal metabolism (Lally et al. 2014) and normalisation of fronto-striatal connectivity (Mkrtchian et al. 2020).

7. Conclusion

This chapter has presented evidence that depression is associated with disrupted reward processing. In contrast to the historical definition of anhedonia, there is surprisingly limited evidence for impairment in the ability to experience pleasure. However, this is largely based on self-reports of pleasure in response to various pleasurable stimuli; definitive studies measuring neurophysiological responses to pleasure are lacking, particularly studies with designs that can disentangle hedonic responses from other processes such as anticipation. There is some evidence that learning about reward, and reward prediction error signals, are impaired in depression, but the literature is inconsistent. The strongest evidence is for an impairment in how reward value is represented and used to guide choices. Several computational accounts of these processes have also been proposed, which may facilitate our understanding of the specific cognitive mechanisms that underlie anhedonia. Future studies would benefit from focusing on impairments in reward processing specifically in anhedonic samples, including transdiagnostically, and from using designs separating different components of reward processing, formulating them in computational terms, and moving beyond cross-sectional designs to provide an assessment of causality.

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