Review

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The neurobiology of anhedonia and other reward-related deficits

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Anhedonia, or markedly diminished interest or pleasure, is a hallmark symptom of major depression, schizophrenia and other neuropsychiatric disorders. Over the past three decades, the clinical definition of anhedonia has remained relatively unchanged, although cognitive psychology and behavioral neuroscience have expanded our understanding of other reward-related processes. Here, we review the neural bases of the construct of anhedonia that reflects deficits in hedonic capacity and also closely linked to the constructs of reward valuation, decision-making, anticipation and motivation. The neural circuits subserving these reward-related processes include the ventral striatum, prefrontal cortical regions, and afferent and efferent projections. An understanding of anhedonia and other reward-related constructs will facilitate the diagnosis and treatment of disorders that include reward deficits as key symptoms.

Introduction

> *For it is then that we have need of pleasure, when we feel pain owing to the absence of pleasure.* Epicurus (341–270 B.C.) [1]

Anhedonia, or loss of interest or pleasure in all or almost all activities, is a prominent symptom of many neuropsychiatric disorders, most notably major depressive disorder (MDD) and schizophrenia (see Glossary) [2]. Greek philosophers, such as Epicurus, contemplated the nature of pleasure (and the absence of pleasure) over 2000 years ago. Today, however, reward-related deficits experienced by individuals with MDD, schizophrenia and other neuropsychiatric disorders involve more than just an absence or loss of pleasure. Anhedonia is a core feature of reward deficits because the capacity to feel pleasure is a critical step during the normal processing of rewards. However, having the motivation to seek out pleasurable experiences and making appropriate decisions based on those previous experiences are important processes that are equally, if not more in some cases, disturbed in individuals with MDD or schizophrenia. Deficits in these reward processes are often inappropriately labeled under the umbrella of anhedonia. The current preclinical and clinical literature regarding the neural bases of the various aspects of reward processing, and the contribution of deficits in these reward processes to the clinical symptom of anhedonia, is reviewed here.

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A brief history of anhedonia

Anhedonia as a psychopathological symptom was first noted in the early 19th century. Haslam, who documented the first complete study of a psychiatric patient in 1809 (suffering from schizophrenia), noted a 'neglect [of] those objects and pursuits which formerly proved sources of

Glossary

Anhedonia: markedly diminished interest or pleasure in all, or almost all, activities

Avolition: a reduction or difficulty in the ability to initiate and persist in goal-directed behavior; lack of motivation.

Chapman Physical and Social Anhedonia Scales (CPAS/CSAS): self-report anhedonia scales that differentiate between physical (eating, sex) and social (expressing feelings and interacting with people) pleasures.

Deep brain stimulation (DBS): clinical procedure involving surgical implantation of stimulating electrodes in discrete brain sites in humans, such as the subgenual cingulate cortex, ventral striatum, inferior thalamic peduncle and lateral habenula. Subsequently, continuous stimulation of these brain sites is used to treat depression, particularly treatment-resistant depression.

Diagnostic and Statistical Manual of Mental Disorders (DSM): standard classification of mental disorders published by the American Psychiatric Association and used by mental health professionals, including clinicians and researchers, in the USA.

Effort Expenditure for Rewards Task (EEfRT): human experimental task used to assess motivation and effort-based decision making.

Fawcett-Clark Pleasure Capacity Scale (FCPS): self-report anhedonia scale that measures the intensity of pleasurable responses with some components of anticipatory pleasure.

International Classification of Diseases (ICD): the international standard diagnostic classification of diseases and other health problems published by the World Health Organization for epidemiological and health management purposes.

Intracranial self-stimulation (ICSS): experimental animal procedure used to assess brain reward function. This procedure involves surgical implantation of stimulating electrodes into discrete brain sites that are part of brain reward systems. Brief electrical stimulation of these brain sites is extremely rewarding for rats and allows direct assessment of brain reward function. Please note that ICSS in experimental animals differs from DBS in humans in that: (i) ICSS involves the delivery of brief (msec) electrical pulses whereas DBS is on continuously for months or longer; (ii) ICSS is delivered on performance of an operant response by the experimental animal subject (thus the term self-stimulation) whereas DBS does not involve a discrete operant response by the patient; and (iii) according to historical and anecdotal reports, ICSS involves brief stimulation of brain sites that lead to intense feelings of pleasure in humans, whereas DBS may alleviate depressive symptoms but is not associated with intense feelings of pleasure and euphoria. The latter may be due to the discrete versus continuous nature of ICSS compared to DBS.

Snaith-Hamilton Pleasure Scale (SHAPS): self-report anhedonia scale that measures hedonic responses across four domains: interests and pastimes, social interaction, sensory experience, and food and drink.

Temporal Experience of Pleasure Scale (TEPS): self-report anhedonia scale that distinguishes between consummatory and anticipatory anhedonia.

Trait anhedonia: anhedonia that is present in non-clinical populations or precedes the onset of psychiatric illness. Assessment of trait anhedonia in human subjects without a neuropsychiatric illness allows the dissociation of neural processes that are specific to anhedonia from confounding factors associated with the onset and progression of neuropsychiatric illnesses that include anhedonia as a symptom.

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delight and instruction' [3]. The term *anhedonie* was later introduced by the French psychologist Ribot in 1896 to describe the counterpart to analgesia in his patients, for whom 'it was impossible to find the least pleasure' [4]. Nonetheless, the term anhedonia was subsequently seldom used to describe general signs of apathy or indifference that were often considered part of a myriad of behavioral abnormalities characterizing disorders such as schizophrenia. In 1956, Rado offered a contradictory view, that the inability 'to experience such pleasures [and] lacking the drive to pursue rewarding activities' was an inherited *predisposition* to schizophrenia [5]. Meehl corroborated this view and listed anhedonia as one of four cardinal features of schizophrenia [6]. By 1976, Chapman and colleagues devised the Chapman Physical and Social Anhedonia Scales (CPAS/CSAS) to test and confirm the hypotheses of Rado and Meehl that are widely used today in their revised forms as diagnostic tools [7].

With regard to depression, Klein is largely credited for providing a similarly influential hypothesis that 'a sharp, unreactive pervasive impairment of the capacity to experience pleasure or to respond affectively to the anticipation of pleasure' is a central feature that predicted the prognosis and treatment of endogenomorphic depression [8]. By 1980, this definition of anhedonia was condensed to 'loss of interest or pleasure in usual activities' and was designated as one of two essential features of MDD in the Diagnostic and Statistical Manual (DSM) III [9], and the term anhedonia was later introduced as a negative symptom of schizophrenia in DSM-IV. The World Health Organization International Classification of Diseases (ICD) 10 does not list the term anhedonia, but rather 'loss of interest and pleasurable feelings' as a non-essential symptom of depressive episodes [10]. In addition to mood disorders and schizophrenia, anhedonia is common among patients with Parkinson's disease (PD) [11], substance use disorder (particularly during withdrawal) [12], Alzheimer's disease (AD) [13] and eating disorders [14].

Reward deficits beyond anhedonia

There are numerous published studies documenting the neurobiological changes associated with MDD, schizophrenia and other neuropsychiatric disorders characterized by anhedonia, but relatively few that specifically examined the presence or severity of anhedonia. Considering that MDD and schizophrenia are characterized by various symptoms, it is unlikely that the neural circuits mediating anhedonia are also involved in, for example, hallucinations or feelings of guilt. Thus, it is challenging to link single genetic and neural mechanisms to such complex behavioral disorders. Recently, there has been increased focus on an understanding of the neurobiology of specific behavioral dimensions such as hedonic capacity that are altered in psychiatric patients [15–20]. It is hypothesized that individual behavioral processes (or symptoms) are more likely than diagnostic categories to be linked to specific biological components, and that an understanding of the biological underpinnings of specific behavioral disruptions will facilitate the treatment of disorders that include such symptoms. This approach is consistent with research in experimental animals in which typically the neurobiology of specific behavioral processes is assessed [20].

Importantly, the term anhedonia does not adequately capture the complex and multifaceted reward-related deficits observed in neuropsychiatric disorders. Besides the specific loss of an ability to experience pleasure, deficits in other discrete reward-related processes can lead to behaviors that may be interpreted as a loss of interest or pleasure. For example, individuals may lack the ability to: (i) anticipate or predict expected rewards; (ii) associate relative values and costs with rewards; (iii) determine the effort required to obtain rewards; (iv) integrate this information to decide whether it is worthwhile to obtain rewards; or (v) become motivated to perform the necessary actions to obtain rewards. Deficits in any of these processes may preclude an individual from engaging in goal-directed actions for rewards, regardless of whether or not the reward is perceived as pleasant once obtained. Research in experimental animals has forged ahead in this regard by exploring behaviors distinctly related to pleasure, valuation, anticipation, motivation and decision-making.

Assessments of anhedonia in humans and experimental animals

Traditional subjective self-report measures of anhedonia assess the ability to experience pleasurable events. In these assessments, individuals respond to statements such as 'I would enjoy being with my family or close friends' [Snaith-Hamilton Pleasure Scale (SHAPS)]. The preclinical analogs to these anhedonia scales, and the procedures most commonly used to assess depression-like behavior in rodents, are the sucrose intake and preference tests, whereby decreased intake of or preference for a sweet sucrose solution (relative to water) reflects an anhedonic state, it is argued (Table 1). There are concerns, however, regarding this interpretation because of confounding motivational effects due to food or water restriction during testing and the unreliability of the procedure among laboratories [21]. Notably, individuals with MDD do not differ in their preference for sweet solutions over water compared to healthy controls [22,23]. Furthermore, self-report assessments of anhedonia are only moderately associated with depression severity [24]. These results suggest that either (i) sucrose intake or preference is not a valid procedure for modeling human anhedonia, and/or (ii) human anhedonia does not just involve decreased hedonic capacity.

Indeed, in the case of schizophrenia, it has become apparent that reward deficits involve more than just anhedonia [25–27]. In some cases, the ability to experience pleasure may even remain intact. Rather, schizophrenia appears to be associated with inappropriate valuation of rewards, particularly when patients are required to generate and maintain internal representations of rewards not immediately available [28]. For example, schizophrenia patients heavily discount the value of future rewards compared to control subjects. Furthermore, motivation to engage in goal-directed actions is impaired in schizophrenia patients [29]. Consequently, decision-making is compromised, because it is based on inappropriate reward representations and impaired motivation. Each of these reward-related processes is mediated by discrete neural circuits (discussed below). Thus, the neurobiological mechanisms of hedonic experience are not necessarily involved in other reward deficits

Table 1. Reward deficits and their neural mediators: from experimental animals to humans

Reward deficits	Anhedonia assessments in animals	Anhedonia assessments in humans	Circuits and neural mediators
Consummatory	Sucrose intake or preference	CPAS/CSAS[a], SHAPS[a], FCPCS[a]	• NAc, ventral pallidum, OFC • μ opioid, $GABA_A$, endocannabinoid receptors
Anticipatory	Positive–negative contrast	TEPS[a]	• ACC, OFC, mPFC, basal ganglia, thalamus, hypothalamus
Motivational	Effort-based tasks (e.g. progressive ratio, concurrent choice, ICSS)	EEfRT[b]	• VTA to NAc dopamine • Amygdala μ opioid receptors • vmPFC to NAc glutamate • ACC • Lateral hypothalamus
Learning		Response Bias Probabilistic Reward Task[b]	• Dorsal basal ganglia (caudate) • ACC

[a]Self-report questionnaire.

[b]Behavioral assessment.

displayed by individuals with MDD and schizophrenia, and this highlights the need for clinical measures that assess multiple reward-related deficits (Box 1).

Dissecting the circuits of anhedonia and other reward-related deficits

The majority of studies in humans to assess the neurobiology of anhedonia have involved MDD or schizophrenia patients, although we could extrapolate that the same circuits are likely to be involved in anhedonia exhibited in other neuropsychiatric disorders, such as PD and AD. Although anhedonia in clinical populations is primarily defined by subjective responses to self-report questionnaires, these purported measures of anhedonia may also reflect deficits in other reward processes, such as motivation, valuation and decision-making, that are implicitly assessed by these scales. Studies in experimental animals have probed neural markers of these discrete reward processes, and these can be compared with imaging studies of anhedonic humans. Thus, the neurobiology of anhedonia, as generally defined in clinical populations, may correspond to the neurobiology not just of anhedonia, but also of other discrete reward-related processes that are more clearly defined in experimental animal procedures.

Pleasure: ventral striatum and orbitofrontal cortex

The ventral striatum and orbitofrontal cortex (OFC) contribute to experiences of pleasure. In particular, μ opioid and endocannabinoid receptors in the nucleus accumbens (NAc) and ventral pallidum mediate hedonic perception of rewards, such that activation of these receptors enhances the affective response for highly palatable rewards such as sucrose [30,31]. Activation of $GABA_A$ receptors in the NAc is also known to regulate the affective response to sucrose [32]. Human neuroimaging studies suggest that subjective assessments of pleasure are also mediated by the OFC [33], although it is unclear whether the OFC mediates the perception of pleasure or rather codes for pleasure (e.g. by assessing relative reward value; see below) [31]. Activity of the ventral striatum and OFC is decreased in anhedonic individuals with MDD [34] or schizophrenia [35], although it is debated whether schizophrenia is associated with impaired reward valuation and motivation rather than decreased hedonic capacity [25–28]. Importantly, the NAc and OFC are involved in other reward-related processes that are possibly disrupted in individuals broadly classified as anhedonic (see below).

Reward valuation, cost–benefit analysis and decision-making: prefrontal cortex

Deficits in many areas of the prefrontal cortex (PFC) have been implicated in anhedonia. In schizophrenia patients, self-reported anhedonia severity was negatively correlated

Box 1. Constructs related to anhedonia: novel clinical assessments of discrete reward-related processes

Clinical measures have been developed to assess reward processes beyond hedonic capacity, such as anticipation, motivation and reinforcement learning. The TEPS is a self-report measure designed to distinguish between consummatory and anticipatory anhedonia [129]. Consummatory probes include statements such as: 'I appreciate the beauty of a fresh snowfall'; anticipatory probes include statements such as: 'I look forward to a lot of things in my life'. In animals, anticipatory and consummatory effects can also be distinguished. For example, positive–negative contrast effects probe anticipation and reward valuation in rodents. When presented consistently with a sucrose solution of a set concentration, rodents display an exaggerated increased or decreased response when suddenly presented with a sucrose solution of higher or lower concentration, respectively, in anticipation of the original concentration [70].

Motivation and effort-based decision-making is assessed with a procedure recently developed by Zald and colleagues called Effort Expenditure for Rewards Task (EEfRT). This task probes motivational deficits using an objective, laboratory-based procedure [102]. Using EEfRT, trait anhedonia was negatively correlated with willingness to expend effort for rewards. Effort-based tasks are commonly used in animal studies. A concurrent choice task assesses whether animals choose a larger reward requiring more effort over a smaller reward requiring little effort. Operant response on a progressive ratio schedule of reinforcement assesses motivation, whereby animals must emit exponentially greater effort to continue receiving rewards [58].

Pizzagalli and colleagues designed the Response Bias Probabilistic Reward Task, an objective, laboratory-based procedure to assess deficits in reinforcement learning [101,130,131]. In this task, individuals with MDD or healthy individuals that either (i) have high trait anhedonia, (ii) are exposed to an acute stressor or (iii) are administered a dopamine autoreceptor agonist to lower dopamine levels fail to develop a biased response over time for the more frequently rewarded of two stimuli; this reflects an inability to allow reinforcement history to alter subsequent responses for rewards.

One particular advantage of the latter two tasks is that they do not rely on subjective verbal responses from participants, which can be limited by their ability to recall or relate to subjective experiences [132]. Rather, the tasks are based on existing rodent procedures or may be readily developed for use in animals.

with OFC, ventromedial (vm) PFC and dorsolateral (dl) PFC activity [35,36]. In healthy individuals, trait anhedonia was negatively correlated with rostral anterior cingulate cortex (ACC) [35,37] and dlPFC [36] resting activity, and vmPFC gray matter volume [38]. Similarly, opioid-dependent subjects and healthy individuals showed negative correlations between anhedonia severity and activity in the ventral ACC, dlPFC and anterior regions of the PFC [39]. However, there is also evidence of increased vmPFC activity in individuals with high levels of trait anhedonia [34,40]. Increased vmPFC activity was observed in healthy subjects, whereas decreased vmPFC is limited to schizophrenia patients [34–36,40]. Thus, it is possible that vmPFC structure and function are altered after progression of schizophrenia. Furthermore, distinct vmPFC subregions may differentially regulate aspects of reward processing in different populations that cannot be discretely visualized with current imaging techniques. Indeed, multiple studies reported contradictory results reflecting increased [41,42] and decreased [43,44] activity of the subgenual PFC (corresponding to the ventral ACC) in depressed individuals. Interestingly, deep brain stimulation (DBS) of the subgenual PFC alleviated depression symptoms in treatment-resistant depressed individuals [45], although it is unclear whether anhedonia was affected by this treatment. It also remains unclear whether the mechanisms underlying DBS of this brain region involve inhibition or excitation of neural activity.

Research in experimental animals indicates that the OFC codes the absolute value of rewards, along with the relative value compared to other rewards [31,46]. Determination of reward value is based on the hedonic perception of the reward and the costs and benefits associated with obtaining that reward. Thus, insufficient valuation of rewards may be misinterpreted as a decreased hedonic capacity using traditional self-report measures. The ACC, which receives input from the OFC, determines the effort required to obtain rewards [47]. Dorsal ACC neurons encode previous reward outcomes that guide future decisions [48]. Accordingly, ACC lesions result in preferences for low-cost–low-reward compared to high-cost–high-reward choices [49–51]. Reward value and effort information are then processed by the anterior vmPFC and dlPFC, which are responsible for decision-making based on reward values and effort calculations of multiple choices to promote goal-directed behavior [47]. The decision to choose a particular reward based on cost–benefit analyses incorporating reward value, effort requirement and reinforcement history leads to goal-directed action. Impairment of this circuit would result in abnormal reward valuation, abnormal calculation of the effort required, or deficits in decision-making for optimal reward-based actions, each of which could be mistaken for anhedonia, or loss of pleasure.

Prediction, anticipation and motivation: ventral tegmental area, amygdala and ventral striatum

Investigation of the neurobiological bases of anhedonia has traditionally centered on the neurotransmitter dopamine and the mesolimbic circuit consisting of dopaminergic projections from the ventral tegmental area (VTA) to the ventral striatum, including the NAc. In addition, there are dopaminergic projections from the substantia nigra to areas such as the dorsal striatum, also called caudate putamen. The latter dopaminergic projections may also be involved in anhedonic responses, particularly in individuals suffering from Parkinsonism, which is characterized by gradual degeneration of the substantia nigra dopaminergic projections. In humans, anhedonia severity, but not depression severity *per se*, was negatively correlated with ventral striatal activity in response to pleasant stimuli [34,35,52], monetary rewards [37] and positive words [53]. Furthermore, self-reported anhedonia was negatively correlated with ventral striatal gray matter and caudate volume [40,54], but not with NAc volume in unmedicated MDD subjects [54]. Moreover, the severity of Parkinsonian symptomatology is negatively correlated with motivational arousal responses to appetitive food images [55]. In addition, microstructural abnormalities were found in the VTA of MDD patients compared to controls [56]. The severity of abnormalities did not correlate with anhedonia, although anhedonia may have been inadequately probed with one question on the Inventory of Depressive Symptomatology – Self Report. Thus, decreased activity and/or volume of the ventral and dorsal striatum may contribute to anhedonia in affected and healthy individuals.

Research in experimental animals indicates that although dopamine does not mediate the perception of pleasure [57], it is associated with prediction or anticipation of and motivation to obtain rewards [58]. Although administration of addictive drugs that increase synaptic dopamine levels leads to feelings of euphoria in humans [59], it is unclear if this dopamine release mediates hedonic arousal. It is well established that dopamine projections from the VTA to the ventral striatum fire in response to unpredicted rewards [60]. Subsequently, dopaminergic neurons fire in response to cues that predict rewards. Thus, it is hypothesized that one role of dopamine is to transfer positive incentive value from the reward to the cue that predicts the reward [57]. Conversely, when predicted rewards are not presented, dopamine firing is blunted [60]. Hence, ventral striatal dopamine regulates the prediction and anticipation of rewards, two mechanisms responsible for basic reinforcement learning [61]. With regard to motivation, studies have shown that dopamine depletion or antagonists in the NAc of rats decrease responses for large rewards requiring greater effort to obtain, but increase responses for smaller rewards requiring less effort [62]. Similarly, dopamine lesions decreased responses for rewards requiring five, but not one, successive responses [63]; indicating that NAc dopamine is necessary to elicit responses for rewards when the effort required is increased [64]. In human imaging studies, the appearance of food that was unavailable for consumption elicited an increased striatal dopamine response in fasting subjects, which points to a role for dopamine in motivated behavior and anticipation of reward [65].

Psychostimulant withdrawal results in numerous symptoms of MDD, including anhedonia [12]. Incidentally, psychostimulant withdrawal decreases NAc dopamine levels in rodents [66] and induces reward deficits as measured by: (i) elevations in reward thresholds in intracranial self-stimulation (ICSS) of the posterior lateral hypothalamus (Figure 1a,b; [67,68]); (ii) increased avolition in the

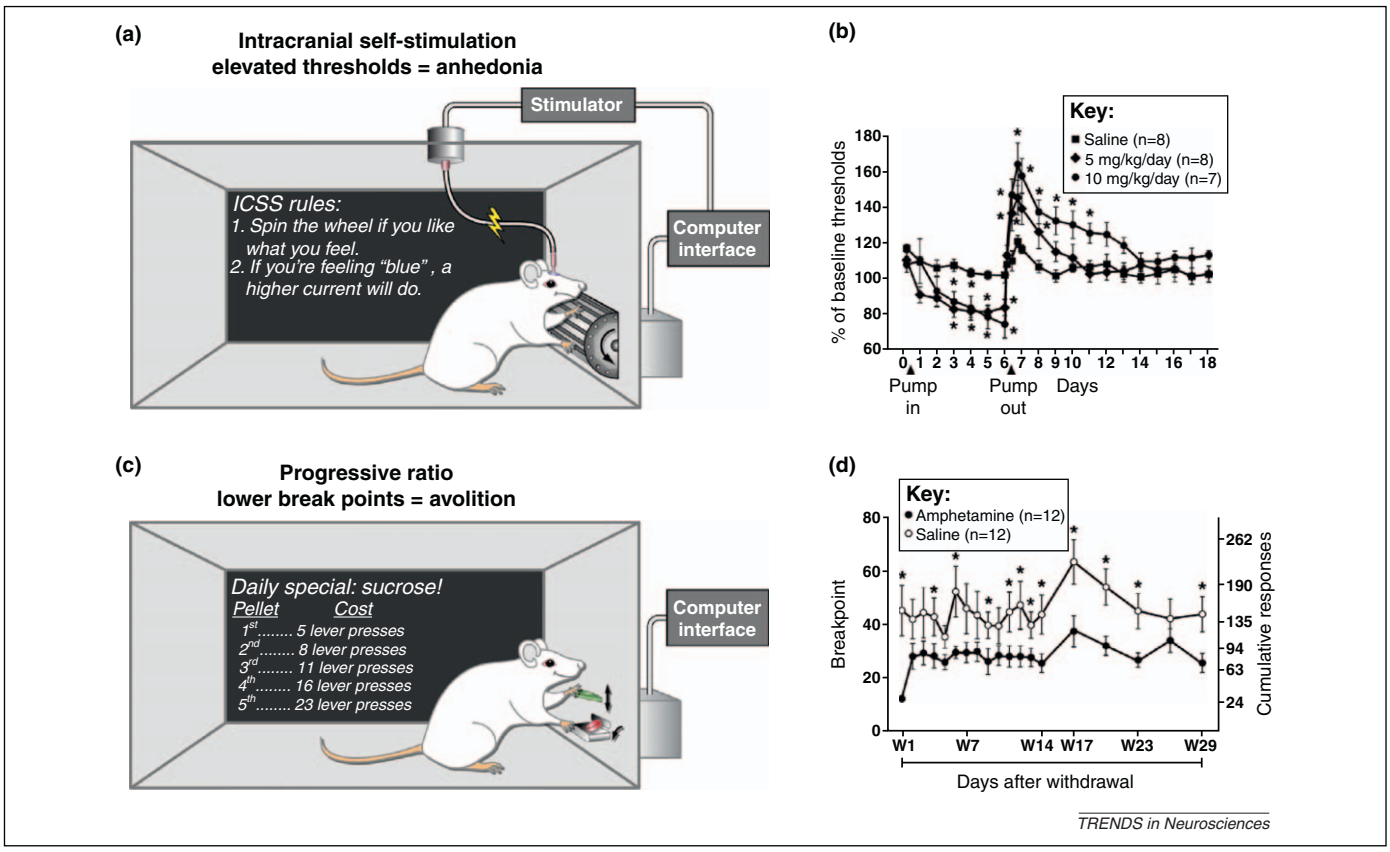

Figure 1. Examples of contemporary measures of anhedonia and reward-related deficits in experimental animals. (**a**) ICSS can be used to assess brain reward function. Self-stimulation of parts of the brain reward circuitries (e.g. lateral hypothalamus) is positively reinforcing at certain current intensities. The current intensity is systematically increased and decreased to determine the threshold that will support self-stimulation. Elevations of this reward threshold indicate that an increased current intensity is required to elicit a behavioral response, reflecting anhedonia. (**b**) Withdrawal from chronic amphetamine exposure elevates reward thresholds (i.e. anhedonia) for up to 5 days in rats [103]. Pump in/out indicates initiation/termination of amphetamine exposure using subcutaneous osmotic minipumps. (**c**) Responses to a palatable reward (e.g. sucrose pellets) on a progressive ratio schedule of reinforcement can be used to assess motivation to obtain rewards. Animals must perform an operant response (e.g. lever press) at an exponentially increasing rate to obtain each subsequent sucrose pellet. Eventually, animals will cease to respond as the response requirement to obtain a single pellet demands too much effort, termed the break point. A decrease in break points is an indication of avolition, or decreased motivation to obtain the reward. (**d**) Withdrawal from chronic amphetamine exposure (10 mg/kg per day for 7 days) decreases break points for a sucrose pellet for up to 29 days in rats [70]. Reproduced, with permission, from **(b)** [103] and **(d)** [70].

progressive ratio test (Figure 1c,d; [69,70]); and (iii) increased successive negative contrast effects, where withdrawing rats respond significantly less than controls when presented with a sucrose solution of a lower concentration than anticipated [71]. Treatment with the norepinephrine/dopamine reuptake inhibitor bupropion, an atypical antidepressant, attenuated withdrawal-induced ICSS threshold elevations in rats [72]. Thus, deficits in dopamine neurotransmission in the ventral striatum may impair reinforcement learning and increase avolition, whereby unconditioned or conditioned rewards fail to stimulate responses to obtain those rewards. Again, this may be incorrectly interpreted as decreased hedonic capacity if anticipation or motivation is not specifically assessed. In this regard, it should be noted that whereas bupropion increases striatal dopamine in rats [73], clinically therapeutic doses do not increase striatal dopamine or dopamine transporter occupancy in humans [74,75]. Thus, it is important to determine whether bupropion indeed improves motivation or anticipation of rewards, irrespective of its general antidepressant properties, in depressed patients. Two separate groups used DBS of the ventral striatum/NAc to relieve patients with otherwise treatment-resistant depression [76,77]. DBS of this region attenuated depression severity in half of the patients, with treatment responders showing a corresponding decrease in anhedonia [77]. Again, it is unclear whether DBS altered ventral striatal dopamine activity or whether stimulation of this region indirectly affected the function of other regions that mediated the change in anhedonic symptoms.

Among other functions, the amygdala is involved in the evaluation of rewards [78–81]. Opioids in the basolateral amygdala (BLA) partly mediate the incentive properties of rewards. Infusion of the μ opioid antagonist naloxone into the BLA attenuated the increased response for sucrose during food deprivation, without affecting palatability for sucrose [82]. In addition, optogenetic inhibition of glutamatergic projections from the BLA to NAc decreased motivated responses for sucrose [83]. These observations suggest that along with NAc dopamine, opioid and glutamatergic activity in the BLA is necessary for motivated behavior. In schizophrenia patients, increased self-reported anhedonia severity was associated with decreased bilateral amygdala activation in response to stimuli with a positive emotional valence [52]. Again, anhedonia was assessed using the CPAS and thus it is unknown whether changes in amygdala activity specifically represent avolition.

Constructing the circuits for anhedonia, anticipation, valuation, decision-making and avolition

Although distinct neural regions code for separate reward processes, the circuits connecting these regions allow an individual to: (i) sense a pleasant stimulus; (ii) compute reward value and associated costs; (iii) determine effort requirements to obtain that stimulus; (iv) decide to obtain that stimulus; and (v) anticipate and increase motivation to obtain that stimulus (Figure 2). The hedonic perception of rewards is mediated primarily by endogenous opioid, GABA and endocannabinoid systems in the NAc, ventral pallidum and OFC. The OFC and ventral striatum receive inputs from sensory cortices and calculate the reward values. The OFC then projects reward value information to the ACC to incorporate costs, benefits and reinforcement history to determine the effort required for different possible actions. The ACC sends projections to the anterior vmPFC and dlPFC, which are involved in decision-making based on reward value, effort and reinforcement history regarding future actions. Glutamatergic efferents relay this information to the NAc, which receives dopaminergic and glutamatergic inputs from the VTA and amygdala, respectively; these provide incentive salience properties and increase motivation to carry out the goal-directed action planned in the PFC. Indeed, there is focus on glutamate because of its putative antidepressant properties [84,85]. Ketamine, an NMDA receptor antagonist, produces rapid antidepressant effects and it is hypothesized that these are partly mediated by increased glutamatergic signaling via AMPA receptors [86] (see also [87] in this Issue). In animal studies, disruption of glutamatergic signaling between the mPFC and NAc or administration of an AMPA receptor antagonist in the NAc shell resulted in avolition for rewards [32]. Furthermore, nicotine-withdrawal-induced elevations of ICSS thresholds were exacerbated by a decrease in glutamatergic activity and, conversely, were attenuated by an increase in glutamatergic activity [88]. Disruption in any of these circuits can lead to different types of reward deficits. For example, blocking of (i) dopaminergic transmission from the VTA to NAc, (ii) opioid signaling in the BLA, (iii) ACC activity, or (iv) glutamate transmission from the vmPFC to NAc each decreased motivation for a large reward.

The circuit presented here probably represents an incomplete view of the neurobiology mediating different aspects of anhedonia and other reward-related deficits. Indeed, additional neurotransmitter systems regulate various reward processes (Table 2). The multiple reciprocal connections between different PFC subregions, as well as reciprocal connections with the NAc, VTA, amygdala and hippocampus, probably play an important role in regulating the behavioral response to rewards. For example, decreased neurogenesis in the dentate gyrus reduced sucrose preference in mice [89] and reversed the therapeutic effects of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), on separation stress-induced anhedonia in nonhuman primates [90]. Serotonin (5-HT) originating from the midbrain raphe nuclei (RN) also regulates reward processing and anhedonic behaviors. For example, chronic treatment with SSRI antidepressants increased ventral striatal activity in humans [91] and sucrose preference in mice [92]. Interestingly, agomelatine, an antagonist of 5-HT_{2C} receptors, also increased sucrose preference in mice [92] and improved SHAPS anhedonia scores in MDD patients [93]. 5-HT_{2C} receptors inhibit NAc dopamine release, and antidepressant treatment increases striatal dopamine levels by decreasing 5-HT_{2C}-mediated dopamine inhibition [94]. Furthermore, fluoxetine treatment combined with a 5-HT_{1A} antagonist that rapidly elevates 5-HT levels in forebrain structures reversed psychostimulant withdrawal-induced anhedonia in rats [67].

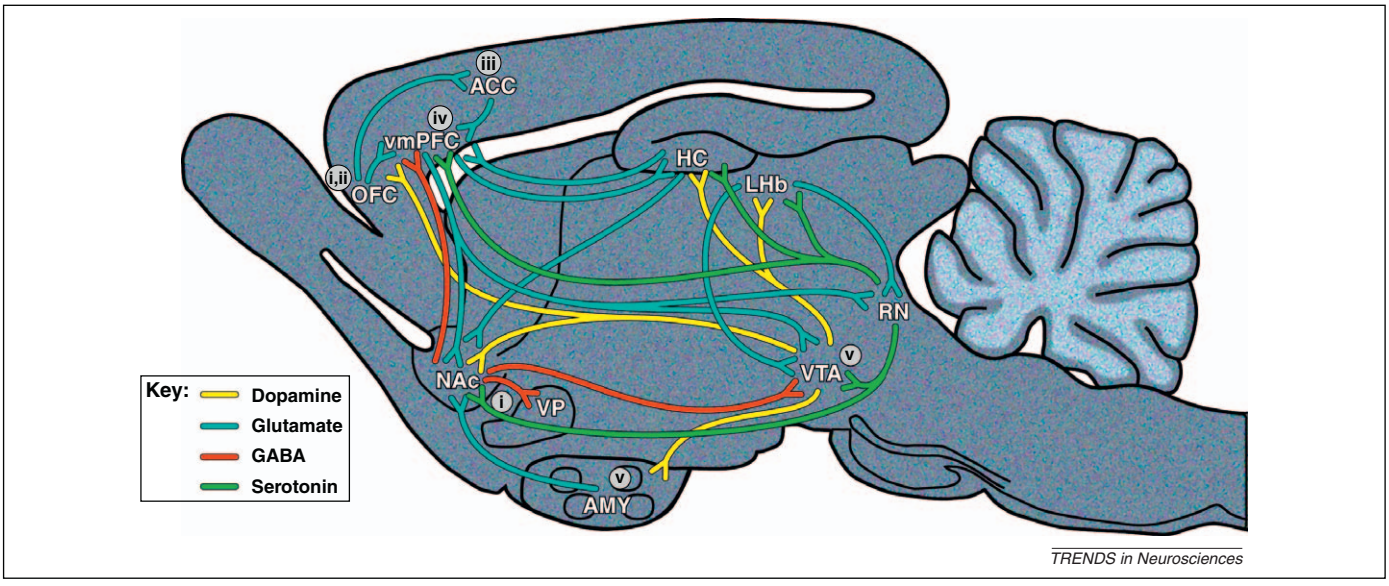

Figure 2. Simplified model of a rodent brain illustrating the neural circuitry of anhedonia and other reward-related deficits. (i) The nucleus accumbens (NAc), ventral pallidum (VP) and orbitofrontal cortex (OFC) mediate the perception of pleasure. **(ii)** The relative reward value of the pleasant stimulus is computed by the OFC. **(iii)** The effort required to obtain the stimulus is computed by the anterior cingulate cortex (ACC). **(iv)** The ventromedial prefrontal cortex (vmPFC) is involved in the decision to engage in goal-directed activity to obtain the pleasant stimulus. **(v)** The ventral tegmental area (VTA) and amygdala (AMY) are responsible for increasing anticipation and motivation to carry out the goal-directed activity. Additional brain areas that interact with these circuits also play crucial roles in reward-related behaviors. Decreased neurogenesis in the hippocampus (HC) may lead to anhedonia and prevent the reversal of anhedonia by SSRI treatment. SSRI treatment, which purportedly has antidepressant effects by increasing 5-HT activity from the raphe nuclei (RN), increases striatal activity and sucrose preference, and reverses drug-withdrawal-induced anhedonia. Deep brain stimulation of the LHb, which purportedly leads to disinhibition of mesolimbic dopamine and RN 5-HT circuits, has antidepressant effects.

Table 2. Effects of gene knockouts in mice on measures of natural reward

Knockout[a]	Increased anhedonia	Decreased Anhedonia	No Effect
Dopamine			
Tyrosine hydroxylase	Decreased initiation of sucrose intake [104]		No effect on sucrose preference [104]
D1 dopamine receptor	Decreased ICSS response, and decreased fixed and progressive ratio response for sucrose [105,106]		No effect on sucrose intake or preference [105]
D2 dopamine receptor	Decreased progressive ratio response for food [107]		No effect on ICSS responding [108]
D3 dopamine receptor			No effect on sucrose intake [109]
Dopamine transporter		Increased intake and positive bias for sucrose [110,111]	
Serotonin			
Serotonin transporter	Decreased sucrose intake [112]		No effect on sucrose intake or preference [110,113]
Serotonin 1A receptor		Increased sucrose preference [114]	
Norepinephrine			
Norepinephrine transporter			No effect on sucrose intake [110]
Glutamate			
Glutamate transporter EAAT1; AMPA receptor GluA1 subunit			No effect on sucrose preference [115,116]
GABA			
$GABA_A$ receptor α1 subunit	Decreased sucrose intake [117]		
$GABA_A$ receptor α3 subunit	Increased negative contrast [118]		No effect on sucrose preference [118]
$GABA_A$ receptor α5 subunit			No effect on sucrose intake [119]
$GABA_A$ receptor γ2 subunit	Decreased sucrose intake [120]		
Opioid			
μ opioid receptor	Decreased progressive ratio responding for food or sucrose [121]		
β-Endorphin/enkephalin	Decreased progressive ratio responding for food [122]		No effect on sucrose or saccharin preference [122]
Preprodynorphin	Decreased saccharin preference [123]		
Cannabinoid			
Cannabinoid 1 receptor	Decreased sucrose intake and preference [124]		
Oxytocin			
Oxytocin		Increased sucrose intake [125]	
Oxytocin receptor			No effect on sucrose intake [126]
Cytokine			
Interleukin 6		Increased sucrose preference [127]	
TNF alpha receptor 2		Increased sucrose intake [128]	

[a]Abbreviations: EAAT, excitatory amino acid transporter; TNF, tumor necrosis factor.

The lateral habenula (LHb) may also play an important role in reward processes given its reciprocal connections with the VTA and RN. LHb neurons inhibit dopaminergic and 5-HT cells in the VTA and RN, respectively [95]. Consequently, DBS of the LHb, purported to inhibit LHb activity and disinhibit dopamine and 5-HT activity, has antidepressant effects, although it should be noted this was in a single case study [96]. Other regions have also been implicated, such as the insula and precuneus/medial parietal cortex, according to imaging studies of anhedonic individuals [35,36,39,40]. The anterior insula encodes the subjective value of rewards [97] and representations of interoceptive effects of rewards [98]. Furthermore, the parietal cortex encodes reward values relative to other available options [99]. Future integration of these reciprocal connections and identification of additional structures will provide a more comprehensive neural framework with which to investigate reward-related deficits.

In particular, the advent of DBS has provided a new and promising treatment for otherwise refractory depression and has promoted our understanding of the neurobiology of depression and other neuropsychiatric disorders. For example, DBS of the subgenual PFC [45], ventral striatum [76,77], inferior thalamic peduncle [100] and LHb [96] each has antidepressant effects. Unfortunately, with the exception of one study [77], anhedonia was not specifically

assessed and we can only speculate whether these brain regions are involved in anhedonia or depression *per se* based on current DBS studies.

Concluding remarks and future considerations

The focus on neurobiological markers of specific behaviors, rather than entire disorders, has led to significant advances in our understanding of anhedonia and related reward deficits in neuropsychiatric disorders. One advantage for clinical researchers is that preclinical research has provided a wealth of information regarding the neurobiology of reward-related processes, from perceiving pleasure to coding reward value, assessing costs and benefits, learning from prior reinforcement, evaluating effort, and making decisions that lead to action. Each process is regulated by specific neural circuits. Therefore, an improved understanding of which processes are disrupted in individuals with MDD, schizophrenia or PD may offer guidance regarding which neural processes to target with treatments. To this end, translational measures incorporating different aspects of reward processes are needed from clinical and preclinical researchers. Two excellent examples are from the laboratories of Pizzagalli [101] and Zald [102], both of whom developed objective laboratory-based procedures that are used to detect the influence of reinforcement history and motivation, respectively, in human subjects (Box 1). That these tasks are objective and not based on verbal reports makes them ideal for adaptation for experiments in laboratory animals.

Given what is known about the sophisticated nature of reward deficits in neuropsychiatric disorders, it would be beneficial to limit the term anhedonia to describe only deficits in hedonic capacity and to incorporate additional terms to describe other aspects of reward-related processes that are compromised in neuropsychiatric disorders (i.e. avolition; deficits in anticipation or prediction, valuation, reinforcement learning and decision-making). Consequently, it is necessary to expand the clinical and preclinical tools used to investigate discrete reward-related processes and their underlying neurobiology.

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