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Affective biases and their interaction with other reward-related deficits in rodents models of psychiatric disorders

Lucy R. Lewis^a, Abigail Benn^c, Dominic M. Dwyer^a, Emma S. J. Robinson^{b*}.

^aSchool of Psychology, Tower Building, Cardiff University, Park Place, Cardiff, United Kingdom, CF10 3AT.

^bSchool of Physiology, Pharmacology & Neuroscience, Biomedical Sciences Building, University of Bristol, University Walk, Bristol, United Kingdom, BS8 1TD.

^cUniversity of Oxford, Department of Experimental Psychology, Tinsley Building, Marsden Road, Oxford, OX1 3TA

lewislr@cardiff.ac.uk

Abigail.benn@psy.ox.ac.uk

dwyerdm@cardiff.ac.uk

emma.s.j.robinson@bristol.ac.uk *corresponding author.

Abstract

Major depressive disorder (MDD) is one of the leading global causes of disability. Symptoms of MDD can vary person to person, and current treatments often fail to alleviate the poor quality of life that patients experience. One of the two, core diagnostic criteria for MDD is the loss of interest in previously pleasurable activities, which suggests a link between the disease aetiology and reward processing. Cognitive impairments are also common in patients with MDD, and more recently, emotional processing deficits known as affective biases have been recognised as a key feature of the disorder. We consider affective biases in the context of other reward-related deficits and examine how affective biases associated with learning and memory may interact with the wider behavioural symptoms seen in MDD. We discuss recent developments in how analogues of affective biases and other aspects of reward processing can be assessed in rodents, as well as how these behaviours are influenced in models of MDD. We subsequently discuss evidence for the neurobiological mechanisms contributing to one or more reward-related deficits in preclinical models of MDD, identified using these behavioural assays. We also consider how the relationships between these selective behavioural assays and the neurobiological mechanisms for affective bias and reward processing could be used to identify potential treatment strategies.

Keywords

Depression; Animal models; Affective bias; Reward processing

1. Introduction

Depression is currently the leading global cause of disability [1]. According to the DSM-5, clinical depression or major depressive disorder (MDD) is a serious mood disorder characterised by the presence of several symptoms including low mood, diminished interest

or pleasure in almost all activities, slowness of thought processes/physical movements, and a diminished ability to think or concentrate [2].

This latter symptom may relate to two types of cognitive dysfunction experienced by patients with MDD, affective biases and cognitive deficits [3]. In this review, we focus on affective biases, which refer to how emotional or 'affective' states alter different cognitive processes. These biases can influence multiple cognitive domains including learning, memory and decision-making [4]. Affective biases have also been linked to the development of other symptoms of the disorder, suggesting some inter-relationship between negative affective biases and depressed mood, amotivation, anhedonia etc. [5]. It has been suggested that cognitive impairments that do not directly involve emotional/affective stimuli could still be linked to affective biases, for example, greater sensitivity to negative feedback from cognitive tasks or reduced positive associations during cognitive tasks involving rewards could lead to changes in goal-directed behaviour and motivation to perform the task [4].

Although descriptive accounts and more formal diagnoses of depression have been made for some centuries [6], it is only more recently that the idea of heterogeneity in depressed populations has been addressed. An individual patient can have a number of symptoms but not share a single one with another patient, even though they are diagnosed with the same disorder [7]. Despite this, treatments are not personalised to match the symptoms present in each patient, partly because we do not yet have a full understanding of the neurobiology underlying symptoms individually. Differences in the neurobiology of components in reward processing are becoming increasingly recognised [8], some of which can match to symptoms seen in MDD patients, and MDD can be seen as a disorder of reward processing [9]. Thus, in order to understand the neurobiological mechanisms of this complex disorder, we need to analyse the individual reward-related symptoms of MDD, for which reliable animal models and translational behavioural assays are essential.

Current animal models of depression appear to demonstrate face validity in relation to behaviours comparable to distinct symptomology defined by the DSM criteria of MDD, including impairments following exposure to chronic stress, a major risk factor for depression [10, 11]. Whilst these behavioural assays (discussed in section 3) show good validity in terms of stress-induced behavioural deficits and are sensitive to some antidepressant treatments, how well they recapitulate the human condition, and hence can demonstrate translational validity, has been questioned [12, 13]. Recently, the idea that affective biases can be modelled in animals and provide a more translational approach to studying MDD in non-human species has emerged. The nature of the animal experiments has meant that such behaviours are often seen as biases in processing of reward-related stimuli, which has led us to consider the wider deficits in MDD, particularly anhedonia and the loss of motivation for previously rewarding activities [9, 14, 15].

Reliable behavioural assays in animal models can help to parse the underlying neurobiological mechanisms of these deficits, as well as how they interact, and provide clear targets for treating individual symptoms [8]. Traditional behavioural assays have focused on symptoms of behavioural despair/learned helplessness, in which MDD patients are conditioned to experience negative events such that they give up trying to escape such situations [16]. In

rodents, this is often measured with the forced swim test (FST) for both mice and rats, or the tail suspension test (TST) for mice. Inescapable shock is also described as a method to induce learned helplessness [17] and has been used to induce a depression-like phenotype in animals with evidence for both vulnerable and resilient populations [18, 19]. In the FST, rodents are placed into an open container of water for a short period of time and their behaviour is recorded [20]. The animal swims around the container and attempts to escape, but eventually they stop moving and stay immobile. The time taken for the animal to become immobile can be used to measure this theory of learned helplessness. Pharmacological studies with pro- and anti-depressants have helped to validate this assay, with immobility time reducing with pro-depressants such as stressors, and increasing with typical antidepressants (see [21, 22] for a full review). The TST works on a similar principle, where mice are suspended by their tail so cannot escape. Immobility time is again used as a marker of learned helplessness [23].

Although widely used in both fundamental biology research and drug development, the validity of these methods has been questioned, particularly given evidence of a number of false positive and false negative findings [23-25], and a lack of sensitivity to atypical antidepressants [26]. Impairments in immobility time is observed in some, but not all, disease models where risk factors for MDD have been used (for a full review of animal models of depression, see [27]). For example, the FST and TST are generally sensitive to stress-related manipulations, but deficits are not reliably observed in immunomodulatory or early life adversity interventions [28-31]. Recent arguments against the validity of such measurements include suggestions of anthropomorphising natural rodent survival and adaptation mechanisms [29], as well as the possibility of changes in motor function underlying these behaviours [32]. Although these methods are some of the most commonly used to measure depressive phenotypes and can, in some cases, be used to screen novel psychotropic drugs, they cannot be said to accurately model 'depressive phenotypes' that would be seen in patients (for detailed reviews see [33, 34]).

This review will focus on direct assays of reward-related deficits which can be translated to symptoms often seen across patients with MDD. As anhedonia, the reduced ability to experience pleasure, is a core symptom of MDD, the most commonly used assay of reward-related deficits in rodents aims to model this symptom in the sucrose preference test (SPT), in which overall consumption of a rewarding solution containing sucrose in comparison to plain water is measured as a choice test [35]. This method has been used for decades as one of the go-to measurement of depressive-like behaviours and reduced sucrose preference has commonly been assumed to indicate consummatory anhedonia [11, 36]. However, it is important to note, there are many limitations in the current assays of reward deficits in animal models. For example, the direct link between sucrose preference and anhedonia has been questioned over the years [13, 14, 37-40]. While a reduced hedonic reaction to sucrose would be expected to lower sucrose preference, it should also be noted that general consumption of reward relies highly on being motivated to attain it, and choice tests require intact cognitive processes to learn where the rewarding solution is. Thus, it cannot be concluded that differences in overall consumption of sucrose or sucrose preference specifically reflect hedonic deficits alone. This highlights the importance of improving current assays of depressive-like phenotypes such that they specifically measure the symptoms they

are claimed to, and can therefore be used to parse differences in the underlying neurobiological mechanisms of this complex psychiatric disorder.

It can be difficult to reliably separate reward-related deficits given their interactions, and measurements of anhedonia in rodent models are often focused on consummatory behaviours, which may not capture the possibility that patients also experience anticipatory anhedonia [41, 42]. However, recent developments in our work investigating affective biases in putative models of depression has revealed some interesting and novel behavioural differences which could provide new insights into these questions.

In this review, we aim to highlight the importance of dissociating symptoms of MDD with more sensitive behavioural assays in rodent models, and discuss the findings to date which have used these methods. Further, we will summarise these findings to describe the potential neurobiological underpinnings of reward processing deficits relevant to symptoms of MDD. As affective biases are a key symptom of MDD and novel, translatable methods have recently begun to be described, this review will focus on these recent developments, as well as how these biases may be dissociable from, but also interact with, other reward-related deficits.

2. Affective biases in MDD

Impairments in cognitive processes such as executive function, attention, learning and memory and decision-making have been shown to be core features in patients with MDD [43]. Such impairments can be separated based on whether they involve dysfunctional processing of emotional information (“hot”), for example faces displaying different emotional expressions, or dysfunctional processing of information *without* emotional influences (“cold”), for example verbal learning (see Roiser & Sahakian 2013 for a full review [44]). Patients with MDD show significant impairments in the processing of both “hot” and “cold” stimuli, with some “cold” processing deficits proposed to result from negative emotions developed from feedback in the tasks [44]. This concept of “hot” stimuli processing can also be applied to reward-related stimuli, given that rewards have emotional value [4].

Early theories of cognitive dysfunction in MDD note that negative stimuli and events are more salient to patients compared to healthy individuals, attributed to a negative self-schema caused by past experiences, which can lead to biases in processing their environment [45]. These ‘cognitive’ biases can influence learning and memory, for example, patients often demonstrate increased recall of negative stimuli compared to positive stimuli [46], and learn to assign negative connotations to ambiguous stimuli, whilst healthy individuals would show more positive associations [47, 48]. This processing bias induces negative expectations of future events, and can alter other cognitive domains such as decision making and judgement [49, 50]. In addition to enhanced negative processing biases, patients with MDD show reduced biases toward positively valenced stimuli including reduced recognition or interpretation of positive emotions, decreased memory for positively associated words and blunted responses to rewards [51, 52]. Studies have also shown that acute antidepressant treatment can enhance positive biases in healthy volunteers and patients with MDD [53-55]. For a more detailed discussion of the proposed relationship between affective biases and

mood disorders, and the neuropsychological hypothesis of antidepressant action see Harmer, Duman and Cowen 2017 [56].

A task frequently used to specifically measure reward processing biases in humans is the 'Response Bias Probabilistic Reward Task' [57]. Here, subjects are presented with two ambiguous stimuli to which they must discriminatively respond to gain a reward. The correct identification of one stimulus is more frequently rewarded, so the expected response of healthy subjects would be to develop a bias for responding to the more frequently rewarded stimulus, thus demonstrating intact learning and decision-making about reward-related stimuli. Patients with MDD consistently show an impaired response bias to the more frequently rewarded cue when the reward is not present, compared to healthy controls [58-61]. This suggests depressed patients have impaired learning and decision-making biases for "hot" stimuli, i.e. stimuli with emotional value.

More recent theories of these deficits have argued that emotional processing biases are not solely a result of negative past experiences, but are also driven by aberrant neurobiological mechanisms. Such mechanisms are thought to involve environmental and/or genetic factors altering the normal transmission of monoamines [4], which have long been hypothesised to play a role in depression [62]. This dysfunctional monoamine transmission may then induce negatively biased expectations, and so it has been suggested these play a causal role in the development and treatment of depressive symptoms [63, 64].

Evidence for this latter theory comes from studies demonstrating that emotion and reward processing biases are present in individuals at risk of depression, but not yet demonstrating other symptoms [65-67], as well as patients in remission [68]. Some studies have also shown that negative processing biases can predict future diagnoses of MDD [69-71], and can be correlated with measures of anhedonia [58], whilst the presence of depression in other disorders has been associated with deficits in reward learning biases [72]. Finally, monoaminergic antidepressants are shown to reduce negative and induce positive affective biases prior to changes in mood [64, 73], suggesting affective states influenced by monoamine transmission works in a bottom-up approach to alter processing of rewarding stimuli leading to mood changes [74].

These findings may indeed suggest a relationship between affective biases and the development of other symptoms of depression. However, as mentioned previously, the symptomology of MDD is highly heterogeneous, and some evidence suggesting negative biases can be ameliorated through specifically treating other symptoms of depression [75].

2.1. Relationship between affective biases and other reward-related deficits

For the purposes of this review, reward-related deficits are categorised into three mechanisms of processing involving hedonic responses ('liking'), motivation ('wanting'), and learning (including anticipation of reward and decision-making capability) [76]. A lack of consistent evidence for the traditional view of consummatory anhedonia in MDD patients has led to a re-conceptualization of the term 'anhedonia' to refer to an "impaired ability to pursue, experience and/or learn about pleasure" [77], suggesting anhedonia is not a deficit only in 'liking' but additionally encompasses 'wanting' and learning. Although the recognition

of heterogeneity in patients indicates anhedonia might seem to include these three aspects, but they may not be seen all at the same time, nor all within the same individual.

Evidence suggests these three aspects are inter-related. As mentioned previously, affective biases are argued to precede other symptoms of MDD including anhedonia and motivational deficits. In contrast, formal psychological models of learning suggest that reward value determines the degree and strength of learning about reward [78]. Thus, an under-valuation of reward, perhaps by reduced hedonic experience, could impair learning about affective stimuli. Similarly, motivationally-relevant cues for rewards are shown to modulate cognitive processes such as attention in healthy mice, but not transgenic schizophrenia models [79]. Thus, even though affective bias may influence other symptoms in some cases, the interaction between hedonic experience, motivation, and learning may be multifaceted.

Although there are potential interactions between reward-related deficits, it is unlikely that they can be reduced to any single cause or set of causes. Patient symptoms are highly heterogeneous; there can be elements of reward processing which are intact whilst other aspects are dysfunctional. In animal models, combining behavioural assessments of individual aspects has identified dissociations between the presence of anhedonia and negative affective bias following pro-depressant treatments [80]. Models of schizophrenia have also been shown to display reduced positive bias for a greater reward value [81], whilst other studies show they do not show anhedonia-like deficits [82]. In addition, pharmacological agents have been identified as specific to influencing either 'wanting' or 'liking' separately, or in opposite directions [83]. This indicates mechanisms underlying hedonic experience, motivation and learning can be separated, implying that – while they may interact – reward-processing deficits are not monolithic, and each needs to be investigated individually.

3. Reward-related deficits in rodents

A major aim for developing tests that can dissociate different symptoms of clinical depression in animal models is to apply them to understanding the neurobiological mechanisms underpinning these symptoms and elucidate the causes behind this disorder. Initial theories of the neurobiological underpinnings of MDD suggest symptoms are caused by a deficiency in monoamine levels or neurotransmission in the central nervous system, mainly evidenced by understanding the mechanisms of antidepressants [84]. However, the low success rate in treating MDD has led to developments of more recent theories which encompass a range of potential causal mechanisms, such as stress-induced neurotrophic deficits [85, 86] and aberrant glutamatergic and GABAergic transmission [87]. There are also several different risk factors which contribute to the development of MDD, suggesting a number of possible biological and genetic causes of the disorder [14].

Here, we discuss three major types of reward-related deficit and the behavioural assays used to measure these deficits in both patients and rodent models of MDD. We then describe our current understanding of the neurobiological substrates that might be underpinning these behaviours from using pharmacological and psychological manipulations, with the aim of elucidating some distinct, and some interacting, neurobiological mechanisms contributing to these reward-related deficits.

3.1. 'Cognitive' Impairments

Given that impairments in different cognitive domains are a major component of MDD in patients, it is unsurprising that many assays have been developed to capture these impairments in rodents. Rodents where a disease model is induced using manipulations based on relevant risk factors have been shown to develop impairments in multiple types of learning and memory, ranging from working memory to associative learning (see [88]) with examples summarised separately below.

3.1.1. *Associative learning*

Pavlovian associations between a neutral stimulus and an unconditioned stimulus (i.e. reward) are well known to be formed with repeated pairings [89], and can be strengthened with greater reward value or altering expectation of reward through prediction error [78]. Instrumental associations are formed between a neutral stimulus requiring a response to produce a reward [90]. Dysfunctional associative learning has been linked to the development of depression, with patients often demonstrating impairments in positive reward associations [91].

Instrumental learning for reward-related stimuli in rodents typically involve tasks of lever pressing or nose poking to trigger the release of a reward. In one study, rats were trained to press a lever for delivery of a sucrose solution. Healthy rats produce progressively more lever presses as the number of training days increase, indicating they are learning the stimulus-response association, and rodent models of depression have been shown to display a reduced/slower improvement [92].

Many Pavlovian associative learning tasks in rodents involve fear conditioning, for example, Darcet *et al* [93] trained mice to associate being placed in a conditioning chamber once with a foot shock. Models of depression such as the chronic corticosterone model display reduced freezing time when re-introduced in to the chamber, suggesting reduced fear conditioning strength. However, since reward-related deficits are a core component of depression symptoms, reward-related associative learning tasks have also been developed.

In similar, contextual Pavlovian association tasks, Papp *et al* [11] demonstrated that healthy rodents show a greater preference for the environment in which several types of rewards were presented to them, indicating a learned conditioned place preference (CPP). However, models of chronic unpredictable stress showed reduced CPP, indicating they had reduced Pavlovian associative learning of reward-related contextual environments.

Xu *et al* [94] trained rats to enter a magazine for a sucrose reward, then paired the presence of a blue light with the delivery of this reward (stimulus-outcome association). They found that the chronic corticosterone rat model of depression did not demonstrate an increased number of magazine entries as would be expected with improved learning compared to controls, indicating that some models of depression display impaired reward-related associative learning.

3.1.2. *Rodent behavioural assays of affective bias*

The influence of emotional cues on cognitive function is a major area of depression research [95] and the reward neuro-circuitry has been heavily linked to disrupted cognition in MDD [96]. Thus, changes in processing of rewarding stimuli is an important aspect to investigate when assessing rodent models.

As mentioned previously, the Response-Bias Probabilistic Reward Task (PRT) is used in patient populations to assess biases in reward processing, and as a result of this a translational method for rodent models has been developed [97]. Rats were trained to discriminate between two auditory stimuli, each of which would require a specific operant response to gain a reward. They were then presented with similar tones, and correct discriminative responses to one tone would be reinforced with a reward more frequently than correct responses to the other tone. Like in patient studies, healthy rats develop response biases toward the stimulus more frequently rewarded, indicating a clear positive response bias.

Alternatively, the probabilistic reversal learning task (PRL) has also been developed, which assesses alterations in decision-making to positive and negative feedback, enabling detection of changes in reward sensitivity [98]. In this task, rats are trained to nose poke in an illuminated hole for a reward, and then presented with two illuminated holes in which one was more frequently reinforced. The two holes' probability of reward was then reversed following eight consecutive correct choices in the more frequently rewarded hole. In a validation experiment, it was shown that altering serotonin levels differentially influenced the ability to shift decision-making following reversal (i.e. cognitive flexibility), win-stay behaviour (i.e. reward sensitivity) and lose-shift behaviour (i.e. negative feedback sensitivity). These findings are similar to observations in healthy humans [99], and sensitivity to negative feedback is enhanced in depressed patients [100].

Emotional decision-making biases in humans can be measured by the affective Go/No-Go task, where subjects are presented with positive or negative stimuli, e.g. images, to which they are required to respond. They are also required to withhold responding to distractor stimuli. Depressed patients display attentional biases for negative stimuli in this task [101], and also tend to show a bias toward withholding responses with negative outcomes [102].

Decision making and interpretation biases induced by affective biases in rodents can be measured by the judgement bias task (JBT) [103]. Rodents are trained to produce one response to the presentation of a positive stimulus, and a different response to the presentation of a negative or less positive stimulus. Rodents hypothesised to have a positive affective state display a bias whereby ambiguous stimuli are more likely to elicit the response trained to the positive stimulus. In contrast, rodents in a negative affective state exposed to the same ambiguous stimuli display a bias to responses trained to the negative stimulus [104-107]. Thus, their judgements and/or interpretations of stimuli can be altered by changes to their affective states. A novel version of this task has also been developed which utilizes rodent natural investigative behaviours rather than lever pressing, which recapitulate similar effects of affective state manipulations on judgement bias [108]. Further, recent studies have evaluated translational human versions of this task, which link negative biases with pathological anxiety [95, 109, 110].

More recently, the affective bias test (ABT) has been developed to address the gap in assessing learning and memory impairments driven by affective biases (for full reviews of the ABT see [4, 12, 74]). In this task, rodents associate a particular digging substrate with a reward and a different substrate with no reward (figure 1a). Rodents hypothesised to have a pharmacologically induced positive affective state during the presentation of one reward-paired substrate will demonstrate a bias toward that substrate in a choice test with a different reward-paired substrate in which their affective state was not manipulated (neutral). In contrast, rodents in a negative affective state will show bias toward the neutral reward-paired substrate. [80, 111]. Thus, biases in reward-related learning and memory can be influenced by affective states and such biases can be modelled in rodents.

This task has also been modified to investigate the effects of long-term affective state manipulations, for example chronic drug treatments or environmental stressors on reward learning and the ability of an animal to develop a bias towards a cue previously associated with a higher value reward. In the modified ABT (mABT, figure 1b), rodents are given pairing sessions to learn the association between one digging substrate and a high value reward (i.e.

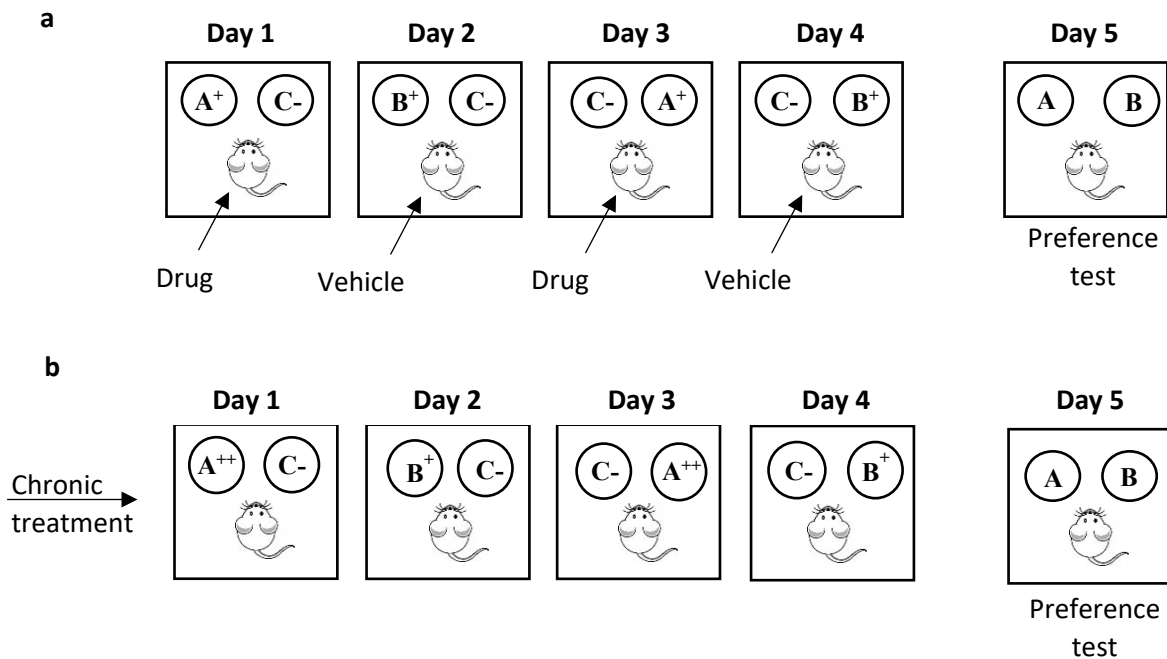


Figure 1. Method overview of the original affective bias test (ABT, a) and the modified ABT (mABT, b).

In the ABT, rodents undergo four pairing sessions of an affective state-manipulating drug with one type of digging substrate (A) or a vehicle with another type (B). A⁺ and B⁺ are both rewarded with one reward pellet, but are presented alongside a 'blank' substrate with no reward (C). On a preference test day, they are given the choice between A or B to investigate with random reinforcement. If their affective state at the time of learning about A was positive, they display a preference for A, and vice versa show a bias for B if their affective state was negative at the time of learning about A.

In the mABT, rodents undergo a chronic affective state manipulation via drug treatment or environmental factors, then are given four pairing sessions with one digging substrate containing two reward pellets (A⁺⁺) or another substrate containing one reward pellet (B⁺), each presented alongside C. Rodents with a neutral affective state display a preference for A during the choice test compared to B. If the chronic manipulation is proposed to induce a positive affective state, this preference for A will increase, whilst if the manipulation is proposed to induce a negative affective state, rodents will show reduced or no preference for A.

two reward pellets), and another digging substrate with a low value reward (i.e. one reward pellet). A healthy animal develops a bias toward the substrate associated with the higher valued reward when presented with a choice between the two previously paired substrates, i.e. a reward-induced positive bias. In contrast, rodents in a putative negative affective state display no or reduced bias for the higher valued reward [80]. Thus indicating that a negative affective state can alter reward-related learning and memory. Important for this discussion, these same animals did not show consistent impairments in SPT or PR tasks suggesting this reward-learning deficit is not mediated by the same underlying neurobiology as reward consumption and motivation, and does not result from a change in either of these aspects of reward processing [80].

Some theories of associative learning suggest it is an automatic, mechanistic process which does not involve higher-order cognition, although it is argued that this is true for smaller animals like rodents but human learning involves more complex expectancies of reward [112]. The loss of reward-induced positive bias that is observed in the mABT could reflect deficits in expectancies and anticipation of reward, given that this task requires animals to use more complex cognitive processes involving recalling prior experiences of reward-related stimuli, modulate decision making and stimulate a directed behaviour [80].

3.1.3. Neurobiological substrates of affective bias

In humans, reductions in monoamines including serotonin, dopamine and noradrenaline have been linked to impaired reward learning [113], and negative processing biases of rewarding stimuli [114-118], whilst serotonergic receptor antagonists negatively shift affective processing biases [119]. In remitted MDD patients, depletions in monoamines can trigger symptom relapse and changes in emotional processing [120, 121] without directly influencing mood [122], suggesting this generates a potential vulnerability for developing depressive symptoms. This is in line with theories of affective bias preceding changes in mood.

In rodents, pharmacological manipulations have been used to identify potential neurochemical factors and neurobiological pathways in affective processing biases (see table 2 for a list of example evidence, for a detailed review see [74]). Taking the main affective bias assays in turn, administration of D2/D3 agonists expected to decrease dopamine signalling are shown to impair reward bias in rats using the PRT described in 3.2.2 [97], which matches findings in humans using the original task [123]. Psychosocial stress also impairs reward bias in both species with the PRT [124, 125].

Using the JBT, the number of studies investigating neurobiological mechanisms are still limited but do suggest involvement of monoamines (dopamine and 5-HT, although data for 5-HT is mixed and may depend on acute versus chronic treatment) and the endocannabinoid system in inducing positive interpretation biases [126, 127]. The benzodiazepine inverse agonist and, interestingly, noradrenaline re-uptake inhibitors induce a negative bias following acute treatment [127]. Further, psychosocial stress induces negative interpretation biases [107] whilst environmental enrichment enhances positive biases [128].

Negative learning and memory biases have been found in the ABT with acute antagonism of the endocannabinoid system, along with psychosocial stress, whilst drugs of abuse do not

influence biases [111], indicating the affective state manipulation drives altered learning and memory bias, not simply activation of the dopamine reward system. Monoamine depletors, such as tetrabenazine, and several immunomodulators are also shown to induce negative biases in the ABT [80]. Furthermore, chronic treatment with interferon-alpha (IFN- α) or retinoic acid reduced reward-induced positive biases in the mABT compared to vehicle treated controls, whereas consummatory behaviour in the SPT was unaffected by these treatments [80]. IFN- α is used to treat viral diseases, such as hepatitis C, and has been associated with the development of depressive symptoms in patients receiving this treatment [129]. Similarly to findings in the ABT, hepatitis C patients receiving this treatment present negative biases in processing of emotional facial expressions, though these biases did not correlate with depression ratings [130].

Taken together, these current findings suggest that affective biases in learning and memory are influenced by several biological pathways including altered monoamine transmission, immunomodulators and stress. Findings in the ABT and JBT using conventional and rapid-onset antidepressants (discussed in section 4) suggest that the formation of affective biases may be mediated by the amygdala region, while recall of these biases are mediated through higher cortical and hippocampal regions [106, 131]. These regions can then input to the limbic reward pathway suggested to play a role in other reward-related behaviours [132, 133]. Neurobiological studies have linked the amygdala to the formation of an affective bias and the medial prefrontal cortex linked to recall of this bias [131]. Comparison with other reward behaviour assays, such as the SPT, suggest the neurobiological mechanisms underpinning affective biases are, in some cases, separate from other reward-related deficits such as consummatory anhedonia.

3.2. Hedonic experience

There are three main domains of reward-related impairments observed in MDD patients. Deficits in the consummatory hedonic experience derived from rewards, or consummatory anhedonia, are most often measured in animal models, in contrast to anticipatory anhedonia.

3.2.1. Rodent behavioural assays of consummatory anhedonia

As mentioned previously, the most common method claimed to assess consummatory anhedonia-like behaviour in rodents is the sucrose preference test (SPT) [35], however there are several limitations with using this test to isolate anhedonia from other reward-related deficits, discussed in section 1 of this review. In patients the 'sweet taste test' (STT) has been used to assess consummatory anhedonia, whereby they are given varying concentrations of sweet solutions and rate their pleasantness/liking on a self-report scale [134]. Although anhedonia is repeatedly reported in patients with MDD, self-reported hedonic experience to sweet solutions appears unaltered [135, 136], which could suggest measuring consumption of sweet solutions is additionally not an accurate measure of anhedonia in patients. However, it could also be argued that subjective self-report measurements are not reliable methods to assay this symptom of MDD. Further, knowing that patients with MDD are highly heterogeneous in which symptoms they present, more sensitive methods that can reliably isolate consummatory anhedonia from other reward-related deficits are needed.

To address some issues with measuring consummatory anhedonia, more selective methods have been developed (for more detailed reviews see [13, 137]). One emphasised by Berridge and colleagues assesses the natural orofacial reactions to the taste of rewarding or unpleasant solutions. Rodents display certain categorical facial expressions when tasting pleasant or unpleasant solutions, and the frequency of these reactions can reflect hedonic experience and thus are used in studying the neurobiological mechanisms underpinning the hedonic processing of reward [138].

Another selective measure of objective consummatory behaviour can be taken from the microstructure of licking. Rodents drink in bouts consisting of multiple licks separated from other bouts by longer pauses, and the average number of licks within these bouts (lick cluster size, LCS) has a positive monotonic relationship with increasing concentrations of sucrose, independent of changes in consumption [139]. This LCS measurement is reduced by sensations of pain or nausea [140, 141], and our group have also shown this can be reduced in a chronic corticosterone models of depression (Unpublished; [142]), thus suggesting licking microstructure can be influenced by negative events and could be used to assay anhedonia-like phenotypes in rodents.

Although these methods of assessing consummatory anhedonia in rodents has been refined and optimised, and orofacial reactivity has been compared to similar facial expressions produced by new born infants, it is still open to question how translatable these are to patient symptomology. As discussed previously, there is little evidence showing blunted or altered taste reactivity to sweet tastes in depression [135, 143]. Instead, impaired consummatory anhedonia has been found following self-reported pleasure ratings [144, 145], alongside deficits in anticipatory anhedonia. This apparent difference could reflect a number of factors, including difficulties in objectively measuring consummatory behaviour in humans whose patterns of eating/drinking are presumably more complex than that of rodents, or that the majority of human studies use more monetary rewards than the natural rewards of food and water [41]. Nevertheless, reduced LCS and reduced orofacial reactions to sucrose solutions in rodents represent a functional analogue of anhedonia (i.e. a reduced response to normatively rewarding events), regardless of the subjective experience itself [13]. That said, it is important to acknowledge that these simple measures of consummatory behaviour may not reflect the complexity of hedonic experience in humans.

3.2.2. Neurobiological substrates of anhedonia

Traditional views of the neuropharmacology of anhedonia in MDD suggested that dopamine was a core mediator of this reward process, given evidence that dopaminergic receptor antagonists appeared to inhibit ICSS and CPP learning [146, 147], as well as reducing sucrose preference in the SPT [148]. More recently, the application of more sensitive analyses of hedonic experience suggest that consummatory anhedonia is not influenced by dopaminergic neurotransmission. Instead, these earlier assessments of 'anhedonia' did not appropriately dissociate motivational processes from 'liking', and dopamine plays a greater role in incentive salience than hedonic experience of reward [149-151]. While dopaminergic manipulations can influence selective consumption-based assays of hedonic responses - for example, Peciña *et al* [152] report taste reactivity responses to be influenced by the administration of

dopamine antagonists – the effects are seen either after multiple sessions or late in extended test sessions. This implies the effects of dopamine on hedonic reactions is indirect and may rely on interactions with other reward processing aspects, such as learning [13].

Furthermore, some studies investigating alteration of serotonergic neurotransmission have also found no effect on lick cluster size (LCS), though inhibition does appear to reduce overall consumption whilst activation enhances consumption [153, 154]. However, Galistu *et al* [155] demonstrate that the atypical antipsychotic Clozapine does increase LCS without influencing overall consumption. Since Clozapine is believed to work through multiple neurotransmitter pathways including serotonin and dopamine it could be suggested that some monoaminergic transmission is involved in hedonic experience, however, their discussion of findings compared to previous research has ruled out the possibility of 5-HT₂ receptors and dopamine involvement in this process from clozapine's multiple potential mechanistic actions.

Opioid receptor stimulation in the nucleus accumbens (NAc) and ventral pallidum (VP) increase positive hedonic orofacial reactions to reward [156, 157]. Lick microstructural analysis has been less consistent in reporting opioid contribution to hedonic experience, with many studies showing direct stimulation with opioid agonists/antagonists does not affect LCS [158, 159]. Based on the evidence in orofacial reactivity studies, it is suggested there are different 'hotspots' in the brains reward system that mediate different aspects of reward processing. As such, opioid stimulation in specific regions such as the rostradorsal NAc shell enhance hedonic reactions to reward [160], whilst in different regions opioid stimulation enhances motivation/incentive salience [161, 162], which could explain contradictory findings with less specific opioid stimulation.

Benzodiazepines, GABA_A receptor agonists, have additionally shown to increase orofacial reactions to rewarding solutions, without affecting aversive reactions to a bitter solution [163]. Increased LCS following benzodiazepine administration has also been shown using lick microstructure analysis [164]. Evidence that blocking opioid receptors can attenuate the effects of benzodiazepines on hedonic reactions suggests the mechanisms by which benzodiazepines work in hedonic experience may involve opioid neurotransmission [165]

Recent studies in our group have shown distinct effects on hedonic responses following treatment with IFN- α and corticosterone, both known to induce negative affective biases in the ABT (Unpublished work; [142]). We found that chronic IFN- α treatment did not affect LCS in rats using microstructural analysis of licking, supporting findings from previous SPT data [80, 166]. IFN- α also does not alter the rate of sucrose pellet self-administration [167] or brain stimulation reward thresholds [168], suggesting its effects on depressive symptoms are not related to hedonic experience or sucrose preference.

We did find that chronic corticosterone treatment significantly reduced LCS in rats, supporting previous SPT data [169-171]. Further, psychosocial stress has consistently resulted in reduced reward sensitivity as indicated by the SPT [11, 35, 172], but there has been very limited investigation of psychosocial stress with more selective measures of hedonic experience (although see [13]).

These findings suggest that consummatory hedonic experience can be influenced by limited neurobiological mechanisms, which include stress and opioid transmission, but potentially does not directly involve immunomodulatory cytokines or monoaminergic neurotransmission. However, many of these studies investigate the pharmacological actions on general hedonic experience, but not in the alleviation of impairments, thus it cannot be firmly concluded what interaction these neurobiological substrates have on hedonic experience without more in-depth investigation.

3.3. Motivation

A third major component of reward processing deficits in depressed patients involves motivation for reward. For many years motivational processes and hedonic experience have been confounded when assessing clinical populations, potentially contributing to the difficulty in assessing consummatory anhedonia, as typical self-report measures would not adequately separate 'wanting' from deficits in 'liking' [83]. Motivational processes integrate the biological need for a reward, and learning and memory of a reward-associated stimulus to drive goal-directed actions to gain the reward [173].

3.3.1. Rodent behavioural assays of motivational deficits

One rodent assay that has been used for several decades to investigate the neurobiological basis of anhedonia is intracranial self-stimulation (ICSS) [174]. Electrodes are surgically implanted in specific regions of the limbic system, such as the ventral tegmental area (VTA), such that activation of the area was achieved by the rodent self-stimulating the electrodes through responding on a manipulandum. Levels of anhedonia would be scored through altering the reward stimulation frequency and assessing how much rodents would respond to higher or lower frequencies. Models of anhedonia were suggested to show reduced responding to lower frequencies compared to healthy rodents, and the major neurobiological pathway thought to be involved in mediating ICSS were dopaminergic [175-177]. However, this task is now more associated with motivational processing, rather than hedonic experience [14, 178, 179], through measuring willingness to work for a reward. It could also be argued that changes in responding to reward frequencies may reflect alterations in motor activity, especially given dopamine's role in motor function [180], however, the discrete-trial current threshold version of the ICSS task has been developed to reduce the sensitivity of this task to motor impairments [176, 181].

Another commonly used method for examining motivation for reward in rodents is the progressive ratio (PR) task, in which the number of lever presses required to obtain a fixed reward progressively increases, and motivation is assessed as their 'breakpoint', i.e. at what level of effort required will they stop responding [182]. Humans with motivational deficits show dysfunctional dopaminergic transmission [183, 184] and similarly, disrupted dopaminergic systems in rodent models impairs motivation in the progressive ratio task [182, 185, 186] suggesting translational neurobiological mechanisms underpinning behaviours in the PR task. However, in animal models of depression or schizophrenia there has been a lack of consistent deficits observed in PR tasks [187-189]. There are several limitations of using PR tasks to represent motivational deficits (see [190]) including difficulty in dissociating between

motivational or motor impairments, whilst some might also argue PR tasks could be influenced by habitual responding or impulse control deficits [185]. See Salamone [184, 191] for detailed discussions of a behavioural economics approach suggested to overcome some of these limitations with PR tasks, which is beyond the scope of this review.

Reward motivation deficits are common in patients with MDD [178, 192] and translational behavioural assays for these impairments have been developed for humans and animal models. In patients, methods such as the computer game-based 'Effort Expenditure for Rewards Task' (EEfRT) [193] have been employed to measure such motivational impairments. Here, subjects have a choice between participating in a low difficulty task (requiring 30 button presses in 7 seconds) for a smaller monetary reward or a higher difficulty task (requiring 100 button presses in 21 seconds) for a greater monetary reward, thus subjects are required to use a greater amount of effort to gain a higher value reward. Some studies using this task have shown a decreased amount of effort expenditure to gain the higher valued reward in both healthy people with higher ratings of anhedonia [42, 193] and with clinical MDD [194, 195], and some evidence suggests these impairments in the EEfRT are predicted by greater levels of anticipatory anhedonia [42, 196].

The effort-related choice paradigm task is directly comparable to the EEfRT, in which rodents are given a choice between pressing a lever several times (most commonly a fixed ratio 5 schedule) to gain one high value reward, or easily accessing low value lab chow from a bowl in the operant chamber [197]. Thus, like the EEfRT, they are required to produce a greater amount of effort to gain a higher value reward, and effort-related choice tasks can assess alterations in motivation for reward as well as decision-making behaviours.

3.3.2. Neurobiological substrates of motivational deficits

As mentioned previously, motivation and effort have become increasingly recognised as a process requiring an intact dopaminergic system (see [198-200] for detailed reviews). Dopamine antagonists and agonists are widely reported to reduce or increase instrumental responding for rewards respectively [197, 198, 201]. Studies have also shown that levels of dopamine neurons in the ventrolateral striatum following neurotoxic ablation with 6-hydroxydopamine positively correlated with number of lever press responses in an operant task [201], indicating dopamine transmission in the reward pathway plays a role in mediating incentive instrumental responding. Though, there is some contrasting evidence suggesting a lack of instrumental response changes following acute dopamine antagonist treatment, but rather dopaminergic signalling influenced Pavlovian reward learning [202].

The progressive ratio task can be interpreted as measuring the amount of effort rodents are willing to put in to gain a reward, indicating their level of incentive motivation for such rewards. This task has thus been used to further indicate involvement of dopamine in maintaining a high effort for gaining reward [186], as well as opioids [203]. Both dopamine and opioid treatment have additionally shown to increase incentive salience for Pavlovian associated reward cues, indicating they are involved in multiple types of associative motivation for reward [132].

More in-depth investigations of dopamine's role in motivational processing demonstrate that manipulators do not affect general food consumption, and in the effort-related choice task, antagonist-treated rodents will demonstrate greater preference for freely available chow than the reward requiring operant response [182, 197]. This suggests dopamine mainly interacts with the instrumental response requirement, that is, initiating and maintaining effort for retrieving reward, rather than appetite [204]. Studies in psychiatric patients for whom amotivation is a common symptom support these findings using an effort-based reinforcement task, demonstrating a correlation between behaviour in this task and striato-orbitofrontal connectivity which is predominantly a dopaminergic pathway [205].

Similar findings to dopamine antagonism in the effort-related choice paradigm have been shown with agonists of adenosine A2A receptors in the NAc [206, 207], which are believed to interact with dopamine and dopaminergic receptors in the neostriatal region. Muscarinic acetylcholine receptor agonists too suppress effortful behaviour for reward and enhance easy access chow consumption when administered to the NAc core only [208]. Injections of GABA_A receptor agonists in the VP reproduce this low-effort effect in an FR5 vs chow protocol [209], yet when injected to the NAc shell these agonists have no effect on progressive ratio behaviour [203].

Alternately, serotonergic pathways do not appear to play a role in effort-choice/motivational processes. Denk *et al* demonstrated that treatment with a tryptophan hydroxylase inhibitor did not affect performance of rats in a T-maze task given a choice between climbing a barrier to gain a high valued reward or entering an obstacle-free arm to gain a low reward, whereas those treated with a dopamine receptor antagonist showed reduced effort [210]. Similarly, Izquierdo *et al* reproduced this lack of effect of the tryptophan hydroxylase inhibitor on the same task, but found that instead rats showed an impaired reversal learning, suggesting the serotonergic system may be more involved in cognitive reward processing [211]. However, it has been shown that an antagonist for serotonin 2C receptors can enhance instrumental responding in a progressive ratio task and increase effort for greater reward in the effort-related choice paradigm [212]. Given that antagonism of these receptors increase dopaminergic firing from the ventral tegmental area and NAc, it is thought that this underlying mechanism involves dopamine signalling more than serotonin itself.

These recent developments in uncovering the psychopharmacology of effort-related choice behaviour highlight a specific network of neurotransmitters that interact and target NAc and VP regions to regulate motivational processing of reward.

3.4. Summary

The challenge of reliably measuring and dissociating reward processing deficits has been highlighted through inconsistencies in reporting and treating patient symptoms. Assays often used in patients do not effectively differentiate between multiple reward-related components that may be disrupted, and as a result, treatments have had poor efficacy. Developments in rodent assays of reward-related deficits are beginning to reveal dissociable behaviours specifically linked to separate domains of reward processing. Important to this discussion is data for the same manipulations inducing dissociable effects on different measures of reward, as illustrated in figure 2. Here, and in Stuart *et al* [80], chronic

pharmacological treatments were shown to induce a deficit in reward-induced positive biases with no effect in the SPT. We have also undertaken a pilot study to investigate reward learning using a lever press task where chronic IFN- α treatment had no effect, further supporting our conclusions that the effects seen in the modified ABT are specific.

Findings in these more sensitive pre-clinical behavioural assays have revealed complex neurobiological pathways that may be involved in reward processing and their associated deficits in disease. Although hedonic value, motivation and reward-related cognition all contribute to the arising behaviour, animal studies are revealing that important differences underlie these behaviours. From recent studies, monoaminergic and GABAergic neurotransmitter pathways have been identified as playing a role in mediating affective biases and motivational processing, while consummatory hedonic experience appears to be mediated more by opioid transmission with some overlapping GABAergic effects. Notably, several forms of stress induction negatively influence all three aspects of reward processing, whilst immunomodulatory manipulations do not influence current measures of consummatory anhedonia, but do modify affective biases. Neuro-circuit analyses are also starting to reveal the distinct neural circuits underlying these behaviours [131].

From the evidence to date, we can support the hypothesis that distinct neurobiological mechanisms may underpin reward-related learning and memory deficits in models of MDD, as well as mechanisms involved in incentive motivation arising from the re-activation of reward-associated memories, compared to hedonic experience [74]. However, there are still some overlaps and interactions between these processes which indicate they are not entirely separate, thus, heterogeneity seen in patients may arise from differences in aberrant neurobiological changes, along with different environmental and genetic factors. Further, issues with clinical assessments remain, in particular relating to hedonic experience. Development of human tasks that can similarly dissociate between these different aspects of reward processing would be valuable both in terms of understanding the relationship between these deficits and disease symptoms, but also to enhance the translational validity of rodent models [178].

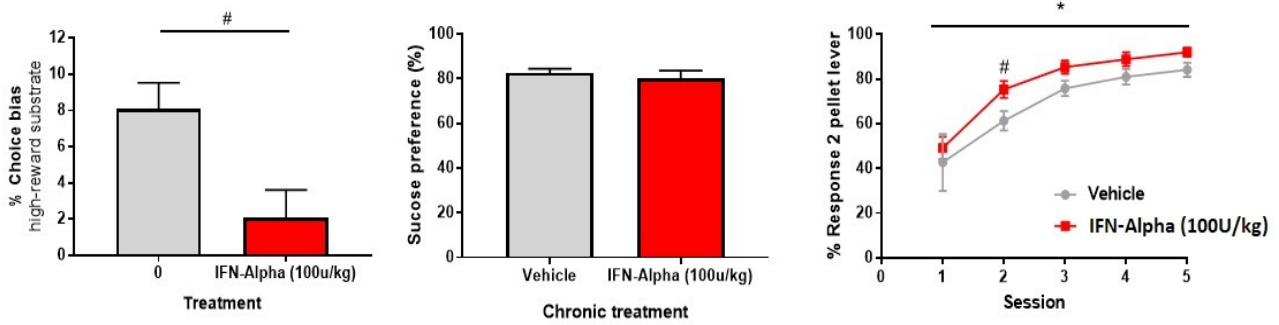


Figure 2. Specific affective bias deficits with chronic interferon-alpha (IFN- α) treatment.

Chronic interferon-alpha (IFN- α) treatment induces a deficit in reward-induced positive bias (panel A) but has no effect on sucrose preference (panel B). The data shown in panel A and B are from the same animals which received a 14-day treatment with IFN- α (100u/kg, i.p. once daily) or control and then tested in the modified affective bias test and a 1% sucrose preference test (data taken from Stuart et al., 2017). In a separate cohort of rats ($n=6$ per group) a preliminary study using a lever press task failed to show any deficit in learning to associated one lever with a higher value reward (panel C, data unpublished, Benn et al). In this pilot studies, animals were first trained using a continuous reinforcement schedule where each lever was presented on alternate days until they were consistently responding with >50 lever presses/session. Animals were then switched to a protocol where both levers were presented and responses paired with either a one or 2 pellet reward (left or right lever press was paired with the higher value reward, counter-balanced across animals). IFN- α treatment (14 days, once daily, dosing before testing) failed to induce any learning deficit with the animals treated with IFN- α showing a higher rate of acquisition (main effect of Session $F(2.4, 24.1) = 19.95$, $p < 0.001$ and Group $F(1, 10) = 8.32$, $p = 0.016$ but no Grp*Session $F(2.4, 24.1) = 0.56$, $p = 0.607$). Although only a small scale pilot experiment, these data do support our hypothesis that the deficits seen in the m-ABT are related to the ability to use reward information to guide behaviour when the current information available is ambiguous. During the choice test, rats must rely on their prior knowledge to make a decision about which substrate to choose as the reinforcement schedule is randomised for this phase of the task. In the sucrose preference test and lever press task, the information about reward value is available throughout the task and animals do not show the same impairment.

Reward-related deficit	Rodent Behavioural Assay	Key References	Human Behaviours
Apathy / Amotivation	Effort-Related Choice Tasks Progressive Ratio Behavioural Economic Approach Intracranial self-stimulation (ICSS)	Salamone <i>et al</i> [197] Randall <i>et al</i> [182] Salamone <i>et al</i> [184] Olds & Milner [174] Carlezon Jr & Chartoff [179]	Effort Expenditure for Rewards Task (EEfRT) [193] <i>Key findings:</i> MDD patients show reduced effort expenditure [194]. Effort expenditure is predicted by levels of anticipatory anhedonia [42, 196]
Consummatory Anhedonia	Sucrose preference test Orofacial reactivity Lick Microstructural Analysis	Willner <i>et al</i> [35] Pecina & Berridge [157] Davis [139] Dwyer [13]	Sweet Taste Test [134] Orofacial reactivity in new born infants [213] Subjective self-report ratings. [145]
Cognitive /Affective Bias	Affective Bias Test Judgement Bias Test Response-Bias Probabilistic Reward (PRT) Probabilistic Reversal Learning (PRL)	Hales <i>et al</i> [12] Stuart <i>et al</i> [111] Harding <i>et al</i> [103] Mendl <i>et al</i> [104] Der-Avakian <i>et al</i> [97] Bari <i>et al</i> [98]	Go/No-Go task [101] Back-translated Judgement Bias Task [109] Response-Bias Probabilistic Reward [57, 58] Probabilistic Reversal Learning [214, 215]

Table 1. A summary of key behavioural assays for measuring reward-related deficits in rodents.

Reward-related deficit	Example Psychopharmacological Effects	Key References
Apathy / Motivation	<p>Dopamine and opioid administration <i>enhances</i> incentive motivation/effort for reward, not general food intake.</p> <p>Stimulation of adenosine A2A and acetylcholine muscarinic receptors in the NAC core <i>reduces</i> incentive motivation/effort for reward.</p> <p>GABA_A agonists in the VP <i>reduces</i> incentive motivation/effort for reward.</p>	<p>Salamone <i>et al</i> [184, 197, 201]; DiFeliceantonio & Berridge [132]; Morales <i>et al</i> (Review) [216]</p> <p>Zhang <i>et al</i> [203]; Font <i>et al</i> [206]; Mingote <i>et al</i> [207]; Nunes <i>et al</i> [208]</p> <p>Farrar <i>et al</i> [209]</p>
Consummatory Anhedonia	<p>Opioids enhance consummatory hedonic reactions to both rewarding and unpalatable solutions.</p> <p>GABA_A receptor agonists, i.e. benzodiazepines, increase positive orofacial reactions to rewarding solutions but not aversive, and increase LCS when analysing lick microstructure.</p> <p>Chronic corticosterone treatment reduces LCS, and both chronic corticosterone and psychosocial stress reduce sucrose preference in the SPT.</p>	<p>Peciña & Berridge [156, 157]; Berridge & Krangelbach [137]; Castro & Berridge [160].</p> <p>Berridge & Treit [163]; Pittman <i>et al</i> [164].</p> <p>Unpublished data, Cardiff University; Zhao <i>et al</i> [170]; Willner <i>et al</i> [35]; Papp <i>et al</i> [11]</p>
Affective Bias	<p>Decreased dopamine signalling through D2/D3 agonist administration, and psychosocial stress, impairs reward bias in the PRT in humans and rats.</p> <p>Enhanced endocannabinoid, serotonergic and dopaminergic stimulation, and environmental enrichment induces positive judgement biases in the JBT.</p> <p>Noradrenergic stimulation and psychosocial stress induce negative judgement biases in JBT.</p> <p>In the ABT, negative biases are induced by acute treatment with: endocannabinoid antagonists, GABA_A receptor agonist (FG7142), retinoic acid, monoamine depletors (tetrabenazine), corticosterone immunomodulators (lipopolysaccharide, IFN-α). Positive biases induced by social enrichment.</p> <p>In the mABT, negative biases are induced by chronic treatment with IFN-α and retinoic acid.</p>	<p>Pizzagalli <i>et al</i> [123]; Der-Avakian <i>et al</i> [97]</p> <p>Bogdan & Pizzagalli [124]; Der-Avakian <i>et al</i> [125]</p> <p>Kregiel <i>et al</i> [126]; Rygula <i>et al</i> [127]; Brydges <i>et al</i> [128]</p> <p>Hales <i>et al</i> [107].</p> <p>Stuart <i>et al</i> [80, 111];</p> <p>Hales <i>et al</i> (review) [12]</p> <p>Robinson (review) [74]</p>

Table 2. A summary of example psychopharmacological evidence in behavioural assays of reward-related deficits in rodents.

4. Antidepressant actions and implications for treatments

Current treatments for MDD are limited in their robustness, with one third of patients remaining unresponsive following several courses of antidepressant and psychological therapies [217], and current antidepressants have limited impact on reward processing deficits such as anhedonia [218]. To improve treatment efficacy, valid animal models appropriately reflecting the behavioural and neurobiological impairments seen in patients are essential for testing novel therapies. Here, we will discuss some of the current literature describing potential mechanisms of action of antidepressants, as shown in the more sensitive behavioural assays discussed previously, and related to our updated knowledge of the neurobiological substrates underpinning such behaviours.

Aberrant monoamine neurotransmission has been implicated in the development of affective biases. Typical antidepressants tend to target these systems and have been shown to reverse negative affective processing biases and enhance positive biases in patients [219], as well as healthy subjects [55]. Similarly, this has been shown with various atypical antidepressants that involve some manipulation of monoaminergic pathways [53]. Some of the most commonly prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs), which have been shown to increase reward learning in patients [54]. The effects of monoamine-targeting antidepressants on other aspects of reward processing deficits is much less consistent, often having little effect on motivational deficits and anhedonia in MDD patients [15, 220]. Though, patient studies on antidepressant actions in motivation tasks such as the EEfRT, along with translational assays of anhedonia, are limited, but recent theories suggest dopamine-targeting antidepressants should be used in combination with SSRIs to enhance the motivational deficits of depression [221].

In animal models, studies have shown that reward preference deficits following chronic stress seen in the SPT can be reversed with typical antidepressant treatments [35, 222, 223], while there is limited pharmacological evidence for antidepressant effects in the more sensitive methods of anhedonia discussed previously. Dopamine enhancing drugs not typically prescribed as antidepressants have shown to reverse amotivational shifts in the effort-related choice task in rats [224], whilst serotonin-targeting typical antidepressants do not [225], supporting the specific role of dopamine in motivational processing. However, studies where tetrabenazine is used to induce a deficit have shown subsequent reversal with monoaminergic antidepressants [225].

However, serotonergic modifying antidepressants are shown to enhance positive reward sensitivity and learning in the PRL task [98]. Various monoaminergic and atypical antidepressants also enhance positive affective biases in the ABT [80, 111, 226, 227] (see figure 1 and [74] for a recent overview of antidepressant actions). The recent development of these tasks mean no studies, to our knowledge, have yet investigated the effects of these antidepressants on reversing negative depression-like phenotypes induced by known risk factors. Thus, more studies are needed to determine whether, and how, these antidepressants can alleviate negative processing biases induced by negative affective states, as well as further examinations of how different antidepressants might influence hedonic and motivational processing.

Despite this evidence that enhancing monoaminergic transmission may improve affective bias and dopamine replenishment could improve motivational deficits, the therapeutic effects of monoaminergic antidepressants take several weeks to become effective, even though increases in monoamine release can be detected immediately [228]. This observation has led to potential implications of more prolonged downstream changes in neuroplasticity leading from these monoamine changes in the efficacy of antidepressants [229].

This theory of the delayed onset action of typical antidepressants has brought about an abundance of literature in support of neuro-adaptive changes involvement in the development and treatment of MDD symptoms [230-233]. However, a more recent theory has been proposed, describing a cognitive neuropsychological mechanism of action for antidepressants that combines the clinical and preclinical evidence of affective biases in MDD with this neuroplasticity hypothesis [64]. In this model, antidepressants rapidly induce a positive shift in the negative processing biases experienced by patients, which is then gradually expected to improve the impairments in behaviour and mood. Thus, suggesting positive affective biases may not directly enhance mood and other deficits in MDD but could provide a cognitive neuropsychological mechanism for this to occur. It also suggests that the delayed improvement in mood may result from the need for re-learning positive associations between affective and social stimuli [56]. This would also fit with the evidential link between neuroplasticity and learning [234], indicating potentially antidepressants improve plasticity which improves positive affective learning, or it may be that the improved learning through positive affective biases enhances plasticity as suggested in an alternative hypothesis outlined by Robinson 2018 [74].

Some antidepressants, such as the NMDA receptor antagonist ketamine, are shown to have rapid-onset improvements in MDD patients [235], including in patients shown to be unresponsive to several courses of typical antidepressant treatments. This is thought to occur through a more rapid activation of neuroplasticity changes [236, 237]. However, a new proposal suggests differences in delayed vs rapid onset antidepressants might lie in the way they influence affective biases [74]. In the ABT, FG7142- and psychosocial stress-induced negative affective biases in rodent models can be reduced following ketamine treatment, but not treatment with the delayed onset antidepressant, venlafaxine, whereas ketamine failed to induce any bias alone [131]. This effect of ketamine was specific to the medial prefrontal cortex (mPFC), whilst venlafaxine was specific to the amygdala. These findings could suggest that rapid onset antidepressants act upon previously learned negative biases through changes in the mPFC to stabilise these biases rapidly, which is separate from delayed onset actions of initiating new learning of positive biases in other limbic areas [74].

Recent studies using the JBT have also investigated the effects of ketamine on decision-making biases, demonstrating similar temporal differences between rapid-onset and conventional antidepressants in inducing positive biases as seen in clinical populations, as well as indicating the involvement of distinct neurobiological substrates underlying these differences (for a more detailed discussion see Hales *et al* [106]). However, there are still patients for which these antidepressants do not work at all and are possibly resistant to the neuropsychological changes mentioned here. A potential hypothesis for treatment-resistant

patients is that these patients may have poorer social support and continuous negative environmental interactions that dampen the improvements in affective biases through pharmacological treatment alone [56]. This could lead to failure to re-engage with social and/or rewarding activities that is essential for re-learning positive experiences.

Thus, the cognitive neuropsychological model for MDD suggests taking more integrated approaches in investigating the underlying causes, as well as treatment, of MDD, and potential differences in the neurobiological and behavioural mechanisms of distinct symptoms suggest that understanding this complex disorder should involve combining assessments of different aspects that are impaired.

5. Conclusion

Although hedonic value, motivation and reward-related cognition all contribute to reward processing and associated reward-related deficits, important differences underlie these behaviours. Biases in the processing of reward-related information, including biases in learning and memory and decision-making, have been observed in humans and, more recently, in rodents. These behaviours are not directly related to the more typical measures of reward, and add another dimension to the discussions relating to how reward-related behaviours may be altered in diseases such as MDD. In this review, we show that commonly impaired aspects of reward processing could have some distinct neurobiological underpinnings. We emphasise the importance of investigating different reward-related deficits separately, and potentially combining various sensitive behavioural methods in clinical and preclinical research, to thoroughly identify neurobiological targets of individual symptoms of MDD, in order to improve the development and evaluation of novel therapies.

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References

- [1] WHO. Depression: World Health Organization [Fact Sheet]. 2018, <http://www.who.int/en/news-room/fact-sheets/detail/depression>.
- [2] Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th ed: American Psychiatric Association; 2013.
- [3] Murrough JW, Iacoviello B, Neumeister A, Charney DS, Iosifescu DV. Cognitive dysfunction in depression: Neurocircuitry and new therapeutic strategies. *Neurobiology of Learning and Memory*. 2011;96:553-63. <https://doi.org/10.1016/j.nlm.2011.06.006>.
- [4] Robinson ESJ, Roiser JP. Affective Biases in Humans and Animals. In: Robbins TW, Sahakian BJ, editors. *Translational Neuropsychopharmacology*, Cham: Springer International Publishing; 2016. p. 263-86. https://doi.org/10.1007/7854_2015_5011.
- [5] Chamberlain SR, Sahakian BJ. The Neuropsychology of Mood Disorders. *Current Psychiatry Reports*. 2006;8:458-63. <https://doi.org/10.1007/s11920-006-0051-x>.
- [6] Horwitz A, Wakefield JC, Lorenzo-Luaces L. History of Depression. In: DeRubeis RJ, Strunk DR, editors. *The Oxford Handbook of Mood Disorders*, New York, USA: Oxford University Press; 2017. <https://doi.org/10.1093/oxfordhb/9780199973965.001.0001>.

- [7] Monroe SM, Anderson SF. Depression: The Shroud of Heterogeneity. *Current Directions in Psychological Science*. 2015;24:227-31. <https://doi.org/10.1177/0963721414568342>.
- [8] Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: 'liking', 'wanting', and learning. *Current Opinion in Pharmacology*. 2009;9:65-73. <https://dx.doi.org/10.1016/j.coph.2008.12.014>.
- [9] Whitton AE, Treadway MT, Pizzagalli DA. Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Current Opinion in Psychiatry*. 2015;28:7-12. <https://doi.org/10.1097/YCO.0000000000000122>.
- [10] Li N, Liu R-J, Dwyer JM, Banasr M, Lee B, Son H, et al. Glutamate N-methyl-D-aspartate Receptor Antagonists Rapidly Reverse Behavioral and Synaptic Deficits Caused by Chronic Stress Exposure. *Biological Psychiatry*. 2011;69:754-61. <https://doi.org/10.1016/j.biopsych.2010.12.015>.
- [11] Papp M, Willner P, Muscat R. An animal model of anhedonia: attenuation of sucrose consumption and place preference conditioning by chronic unpredictable mild stress. *Psychopharmacology*. 1991;104:255-9. <https://doi.org/10.1007/BF02244188>.
- [12] Hales CA, Stuart SA, Anderson MH, Robinson ES. Modelling cognitive affective biases in major depressive disorder using rodents. *British Journal of Pharmacology*. 2014;171:4524-38. <https://dx.doi.org/10.1111/bph.12603>.
- [13] Dwyer DM. Licking and liking: The assessment of hedonic responses in rodents. *Quarterly Journal of Experimental Psychology*. 2012;65:371-94. <https://doi.org/10.1080/17470218.2011.652969>.
- [14] Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. *Trends in Neurosciences*. 2012;35:68-77. <https://doi.org/10.1016/j.tins.2011.11.005>.
- [15] Admon R, Pizzagalli DA. Dysfunctional Reward Processing in Depression. *Current Opinion in Psychology*. 2015;1:114-8. <https://doi.org/10.1016/j.copsyc.2014.12.011>.
- [16] Abramson LY, Seligman ME, Teasdale JD. Learned helplessness in humans: Critique and reformulation. *Journal of Abnormal Psychology*. 1978;87:49-74. <https://psycnet.apa.org/doi/10.1037/0021-843X.87.1.49>.
- [17] Seligman ME, Gwyneth B. Learned helplessness in the rat. *Journal of Comparative and Physiological Psychology*. 1975;88:534-41. <http://dx.doi.org/10.1037/h0076430>.
- [18] Maier SF. Learned helplessness and animal models of depression. *Progress in Neuropsychopharmacology & Biological Psychiatry*. 1984;8:435-46. [https://doi.org/10.1016/S0278-5846\(84\)80032-9](https://doi.org/10.1016/S0278-5846(84)80032-9).
- [19] Sherman AD, Sacquitne JL, Petty F. Specificity of the learned helplessness model of depression. *Pharmacology Biochemistry and Behavior*. 1982;16:449-54. [https://doi.org/10.1016/0091-3057\(82\)90451-8](https://doi.org/10.1016/0091-3057(82)90451-8).
- [20] Porsolt RD, Anton G, Blavet N, Jalfre M. Behavioural despair in rats: a new model sensitive to antidepressant treatments. *European Journal of Pharmacology*. 1978;47:379-91. [https://doi.org/10.1016/0014-2999\(78\)90118-8](https://doi.org/10.1016/0014-2999(78)90118-8).
- [21] Cryan JF, Valentino RJ, Lucki I. Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. *Neuroscience and biobehavioural reviews*. 2005;29:547-69. <https://doi.org/10.1016/j.neubiorev.2005.03.008>.
- [22] Slattery DA, Cryan JF. Using the rat forced swim test to assess antidepressant-like activity in rodents. *Nature Protocols*. 2012;7:1009-14. <https://doi.org/10.1038/nprot.2012.044>.
- [23] Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology*. 1985;85:367-70. <https://doi.org/10.1007/BF00428203>.
- [24] Borsini F, Meli A. Is the forced swimming test a suitable model for revealing antidepressant activity? *Psychopharmacology*. 1988;94:147-60. <https://doi.org/10.1007/BF00176837>.
- [25] Vollmayr B, Henn FA. Learned helplessness in the rat: improvements in validity and reliability. *Brain Research Protocols*. 2001;8:1-7. [https://doi.org/10.1016/S1385-299X\(01\)00067-8](https://doi.org/10.1016/S1385-299X(01)00067-8).

- [26] Wesolowska A, Partyka A, Jastrzębska-Więsek M, Kolarz A, Mierzejewski P, Bienkowski P, et al. Tail suspension test does not detect antidepressant-like properties of atypical antipsychotics. *Behavioural Pharmacology*. 2011;22:7-13. <https://doi.org/10.1097/FBP.0b013e3283423d6b>.
- [27] Nestler EJ, Hyman SE. Animal models of neuropsychiatric disorders. *Nature Neuroscience*. 2010;13:1161-9. <https://doi.org/10.1038/nn.2647>.
- [28] Genty J, Nomigni MT, Anton F, Hanesch U. The combination of postnatal maternal separation and social stress in young adulthood does not lead to enhanced inflammatory pain sensitivity and depression-related behavior in rats. *PLOS One*. 2018;13:e0202599. <https://doi.org/10.1371/journal.pone.0202599>.
- [29] Molendijk ML, De Kloet R. Immobility in the forced swim test is adaptive and does not reflect depression. *Psychoneuroendocrinology*. 2015;62:389-91. <https://doi.org/10.1016/j.psyneuen.2015.08.028>.
- [30] Savignac HM, Dinan TG, Cryan JF. Resistance to Early-Life Stress in Mice: Effects of Genetic Background and Stress Duration. *Frontiers in Behavioral Neuroscience*. 2011;5. <https://doi.org/10.3389/fnbeh.2011.00013>.
- [31] Stuart SA, Butler P, Robinson ESJ. Animal Models of Risk Factors for Suicidal Ideation and Behaviour. In: Cannon K, Hudzik T, editors. *Suicide: Phenomenology and Neurobiology*, Cham, Switzerland: Springer International Publishing; 2014. p. 295-314. https://doi.org/10.1007/978-3-319-09964-4_18.
- [32] Costa AP, Vieira C, Bohner LO, Silva CF, Santos EC, De Lima TC, et al. A proposal for refining the forced swim test in Swiss mice. *Progress in Neuropsychopharmacology & Biological Psychiatry*. 2013;45:150-5. <https://doi.org/10.1016/j.pnpbp.2013.05.002>.
- [33] Stanford SC. Confusing preclinical (predictive) drug screens with animal 'models' of psychiatric disorders, or 'disorder-like' behaviour, is undermining confidence in behavioural neuroscience. *Journal of Psychopharmacology*. 2017;31:1-3. <https://doi.org/10.1177/0269881116689260>.
- [34] Commons KG, Cholansians AB, Babb JA, Ehlinger DG. The Rodent Forced Swim Test Measures Stress-Coping Strategy, Not Depression-like Behavior. *ACA Chemical Neuroscience*. 2017;8:955-60. <https://doi.org/10.1021/acscchemneuro.7b00042>.
- [35] Willner P, Towell A, Sampson D, Sophokleous S, Muscat R. Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. *Psychopharmacology*. 1987;93:358-64. <https://doi.org/10.1007/BF00187257>.
- [36] Eagle AL, Mazei-Robison M, Robison AJ. Sucrose Preference Test to Measure Stress-induced Anhedonia. *Bio-protocol*. 2016;6:e1822. <https://doi.org/10.1038/s41596-018-0011-z>.
- [37] Anisman H, Matheson K. Stress, depression, and anhedonia: Caveats concerning animal models. *Neuroscience and biobehavioural reviews*. 2005;29:525-46. <https://doi.org/10.1016/j.neubiorev.2005.03.007>.
- [38] Konkle ATM, Baker SL, Kentner AC, Barbagallo LS-M, Merali Z, Bielajew C. Evaluation of the effects of chronic mild stressors on hedonic and physiological responses: sex and strain compared. *Brain Research*. 2003;992:227-38. <https://doi.org/10.1016/j.brainres.2003.08.047>.
- [39] Mateus-Pinheiro A, Patricio P, Alves N, Machado-Santos A, Morais M, Bessa J, et al. The Sweet Drive Test: refining phenotypic characterization of anhedonic behavior in rodents. *Frontiers in Behavioral Neuroscience*. 2014;8. <https://doi.org/10.3389/fnbeh.2014.00074>.
- [40] Matthews K, Forbes N, Reid IC. Sucrose consumption as an hedonic measure following chronic unpredictable mild stress. *Physiology & Behavior*. 1995;57:241-8. [https://doi.org/10.1016/0031-9384\(94\)00286-E](https://doi.org/10.1016/0031-9384(94)00286-E).
- [41] Rizvi SJ, Pizzagalli DA, Sproule BA, Kennedy SH. Assessing anhedonia in depression: potentials and pitfalls. *Neuroscience and biobehavioural reviews*. 2016;65:21-35. <https://doi.org/10.1016/j.neubiorev.2016.03.004>.
- [42] Geaney JT, Treadway MT, Smillie LD. Trait anticipatory pleasure predicts effort expenditure for reward. *PLOS One*. 2015;10:e0131357. <https://doi.org/10.1371/journal.pone.0131357>.

- [43] Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine*. 2014;44:2029-40. <https://doi.org/10.1017/S0033291713002535>.
- [44] Roiser JP, Sahakian BJ. Hot and cold cognition in depression. *CNS Spectrums*. 2013;18:139-49. <https://doi.org/10.1017/S1092852913000072>.
- [45] Beck AT. *Depression: Clinical, experimental, and theoretical aspects*. New York: Harper & Row; 1967.
- [46] Matt GE, Vazquez C, Campbell WK. Mood-congruent recall of affectively toned stimuli: a meta-analytic review. *Clinical Psychology Review*. 1992;12:227-55. [https://doi.org/10.1016/0272-7358\(92\)90116-P](https://doi.org/10.1016/0272-7358(92)90116-P).
- [47] Mathews A, Macleod C. Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology*. 2005;1:167-95. <https://doi.org/10.1146/annurev.clinpsy.1.102803.143916>.
- [48] Everaert J, Podina IR, Koster EHW. A comprehensive meta-analysis of interpretation biases in depression. *Clinical Psychology Review*. 2017;58:33-48. <https://doi.org/10.1016/j.cpr.2017.09.005>.
- [49] Beck AT. The Evolution of the Cognitive Model of Depression and its Neurobiological Correlates. *American Journal of Psychiatry*. 2008;165:969-77. <https://doi.org/10.1176/appi.ajp.2008.08050721>.
- [50] Blanchette I, Richards A. The influence of affect on higher level cognition: A review of research on interpretation, judgement, decision making and reasoning. *Cognition & Emotion*. 2010;24:561-95. <https://doi.org/10.1080/02699930903132496>.
- [51] Rzepa E, Fisk J, McCabe C. Blunted neural response to anticipation, effort and consummation of reward and aversion in adolescents with depression symptomatology. *Journal of Psychopharmacology*. 2017;31:303-11. <https://doi.org/10.1177/0269881116681416>.
- [52] Dean Z, Horndasch S, Giannopoulos P, McCabe C. Enhanced neural response to anticipation, effort and consummation of reward and aversion during bupropion treatment. *Psychological Medicine*. 2016;46:2263-74. <https://doi.org/10.1017/S003329171600088X>.
- [53] Harmer CJ, de Bodinat C, Dawson GR, Dourish CT, Waldenmaier L, Adams S, et al. Agomelatine facilitates positive versus negative affective processing in healthy volunteer models *Journal of Psychopharmacology*. 2010;25:1159-67. <https://doi.org/10.1177/0269881110376689>.
- [54] Scholl J, Kolling N, Nelissen N, Browning M, Rushworth MF, Harmer CJ. Beyond negative valence: 2-week administration of a serotonergic antidepressant enhances both reward and effort learning signals. *PLoS Biology*. 2017;15:e2000756. <https://doi.org/10.1371/journal.pbio.2000756>.
- [55] Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM. Increased Positive Versus Negative Affective Perception and Memory in Healthy Volunteers Following Selective Serotonin and Norepinephrine Reuptake Inhibition. *American Journal of Psychiatry*. 2004;161:1256-63. <https://doi.org/10.1176/appi.ajp.161.7.1256>.
- [56] Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New perspectives for refining future treatment approaches. *Lancet Psychiatry*. 2017;4:409-18. [https://doi.org/10.1016/S2215-0366\(17\)30015-9](https://doi.org/10.1016/S2215-0366(17)30015-9).
- [57] Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: A signal detection approach. *Biological Psychiatry*. 2005;57:319-27. <https://doi.org/10.1016/j.biopsych.2004.11.026>.
- [58] Pizzagalli DA, Iosifescu DV, Hallet LA, Ratner KG, Fava M. Reduced Hedonic Capacity in Major Depressive Disorder: Evidence from a Probabilistic Reward Task. *Journal of Psychiatric Research*. 2008;43:76-87. <https://doi.org/10.1016/j.jpsychires.2008.03.001>.
- [59] Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienaert P, de Boer P, et al. Reduced Reward Learning Predicts Outcome in Major Depressive Disorder. *Biological Psychiatry*. 2013;73:639-45. <https://doi.org/10.1016/j.biopsych.2012.10.014>.
- [60] Liu W-h, Chan RCK, Wang L-z, Huang J, Cheung EFC, Gong Q-y, et al. Deficits in sustaining reward response in subsyndromal and syndromal major depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2011;35:1045-52. <https://doi.org/10.1016/j.pnpbp.2011.02.018>.

- [61] Whitton AE, Kakani P, Foti D, Veer AV, Haile A, Crowley DJ, et al. Blunted Neural Responses to Reward in Remitted Major Depression: A High-Density Event-Related Potential Study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. 2016;1:87-95. <https://doi.org/10.1016/j.bpsc.2015.09.007>.
- [62] Elhwuegi AS. Central monoamines and their role in major depression. *Progress in Neuropsychopharmacology & Biological Psychiatry*. 2004;28:435-51. <https://doi.org/10.1016/j.pnpbp.2003.11.018>.
- [63] Roiser JP, Elliott R, Sahakian BJ. Cognitive Mechanisms of Treatment in Depression. *Neuropsychopharmacology Reviews*. 2012;37:117-36. <https://doi.org/10.1038/npp.2011.183>.
- [64] Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *British Journal of Psychiatry*. 2009;195:102-8. <https://doi.org/10.1192/bjp.bp.108.051193>.
- [65] Joormann J, Talbot L, Gotlib IH. Biased processing of emotional information in girls at risk for depression. *Journal of Abnormal Psychology*. 2007;116:135-43. <https://doi.org/10.1037/0021-843X.116.1.135>.
- [66] Chan SW, Goodwin GM, Harmer CJ. Highly neurotic never-depressed students have negative biases in information processing. *Psychological Medicine*. 2007;37:1281-91. <https://doi.org/10.1017/S0033291707000669>.
- [67] Rawal A, Collishaw S, Thapar A, Rice F. 'The risks of playing it safe': a prospective longitudinal study of response to reward in the adolescent offspring of depressed parents. *Psychological Medicine*. 2013;43:27-38. <https://doi.org/10.1017/S0033291712001158>.
- [68] Romero N, Sanchez A, Vazquez C. Memory biases in remitted depression: The role of negative cognitions at explicit and automatic processing levels. *Journal of Behavior Therapy and Experimental Psychiatry*. 2014;45:128-35. <https://doi.org/10.1016/j.jbtep.2013.09.008>.
- [69] Rude SS, Valdez CR, Odom S, Ebrahimi A. Negative Cognitive Biases Predict Subsequent Depression. *Cognitive Therapy and Research*. 2003;27:415-29. <https://doi.org/10.1023/A:1025472413805>.
- [70] Pizzagalli DA, Goetz E, Ostacher M, Iosifescu DV, Perlis RH. Euthymic patients with bipolar disorder show decreased reward learning in a probabilistic reward task. *Biological Psychiatry*. 2008;64:162-8. <https://doi.org/10.1016/j.biopsych.2007.12.001>.
- [71] Kilford EJ, Foulkes L, Potter R, Collishaw S, Thapar A, Rice F. Affective bias and current, past and future adolescent depression: a familial high risk study. *Journal of Affective Disorders*. 2015;174:265-71. <https://doi.org/10.1016/j.jad.2014.11.046>.
- [72] Timmer MHM, Sescousse G, van der Schaaf ME, Esselink RAJ, Cools R. Reward learning deficits in Parkinson's disease depend on depression. *Psychological Medicine*. 2017;47:2302-11. <https://doi.org/10.1017/S0033291717000769>.
- [73] Warren MB, Pringle A, Harmer CJ. A neurocognitive model for understanding treatment action in depression. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences*. 2015;370:20140213. <https://doi.org/10.1098/rstb.2014.0213>.
- [74] Robinson ESJ. Translational new approaches for investigating mood disorders in rodents and what they may reveal about the underlying neurobiology of major depressive disorder. *Philosophical Transactions of the Royal Society B*. 2018;373. <https://doi.org/10.1098/rstb.2017.0036>.
- [75] Teasdale JD, Barnard PJ. *Affect, Cognition and Change: Re-modelling depressive thought*. New York, NY: Psychology Press; 1993. [https://doi.org/10.1016/0005-7967\(94\)90171-6](https://doi.org/10.1016/0005-7967(94)90171-6).
- [76] Berridge KC, Robinson TE. Parsing reward. *Trends in Neurosciences*. 2003;26:507-13. [https://doi.org/10.1016/S0166-2236\(03\)00233-9](https://doi.org/10.1016/S0166-2236(03)00233-9).
- [77] Thomsen KR. Measuring anhedonia: impaired ability to pursue, experience, and learn about reward. *Frontiers in Psychology*. 2015;6. <https://doi.org/10.3389/fpsyg.2015.01409>.
- [78] Rescorla RA, Wagner AR. A theory of Pavlovian conditioning and the effectiveness of reinforcement and non-reinforcement. In: Black AH, Prokasy WF, editors. *Classical conditioning 2 Current research and theory*, New York, NY: Appleton-Century-Crofts; 1972. p. 64-9.

- [79] Ward RD, Winiger V, Higa KK, Kahn JB, Kandel ER, Balsam PD, et al. The Impact of Motivation on Cognitive Performance in an Animal Model of the Negative and Cognitive Symptoms of Schizophrenia. *Behavioural Neuroscience*. 2015;129:292-9. <https://doi.org/10.1037/bne0000051>.
- [80] Stuart SA, Wood CM, Robinson ES. Using the affective bias test to predict drug-induced negative affect: implications for drug safety. *British Journal of Pharmacology*. 2017;174:3200-10. <https://doi.org/10.1111/bph.13972>.
- [81] Sahin C, Doostdar N, Neill JC. Towards the development of improved tests for negative symptoms of schizophrenia in a validated animal model. *Behavioural Brain Research*. 2016;312:93-101. <https://doi.org/10.1016/j.bbr.2016.06.021>.
- [82] Lydall ES, Gilmour G, Dwyer DM. Analysis of licking microstructure provides no evidence for a reduction in reward value following acute or sub-chronic pencyclidine administration. *Psychopharmacology*. 2010;209:153-62. <https://doi.org/10.1007/s00213-010-1779-x>.
- [83] Olney JJ, Warlow SM, Naffziger EE, Berridge KC. Current perspectives on incentive salience and applications to clinical disorders. *Current Opinion in Behavioral Sciences*. 2018;22:59-69. <https://doi.org/10.1016/j.cobeha.2018.01.007>.
- [84] Delgado PL. Depression: The Case for a Monoamine Deficiency. *Journal of Clinical Psychiatry*. 2000;61:7-11.
- [85] Groves JO. Is it time to reassess the BDNF hypothesis of depression? *Molecular Psychiatry*. 2007;12:1079-88. <https://doi.org/10.1038/sj.mp.4002075>.
- [86] Duman RS, Heninger GR, Nestler EJ. A Molecular and Cellular Theory of Depression *Archives of General Psychiatry*. 1997;54:597-606. <https://doi.org/10.1001/archpsyc.1997.01830190015002>.
- [87] Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: An emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology*. 2012;62:63-77. <https://doi.org/10.1016/j.neuropharm.2011.07.036>.
- [88] Darcet F, Gardier AM, Gaillard R, David DJ, Guilloux J-P. Cognitive Dysfunction in Major Depressive Disorder. A Translational Review in Animal Models of the Disease. *Pharmaceuticals*. 2016;9. <https://doi.org/10.3390/ph9010009>.
- [89] Pavlov IP. *Conditioned Reflexes*. Mineola, New York, USA.: Dover Publications, Inc.; 2003.
- [90] Thorndike EL. *Animal intelligence: An experimental study of the associative processes in animals*. Psychological Monographs: General and Applied. 1898;2:i-109. <http://dx.doi.org/10.1037/h0092987>.
- [91] Rescorla RA. Pavlovian conditioning. It's not what you think it is. *American Journal of Psychology*. 1988;43:151-60. <http://dx.doi.org/10.1037/0003-066X.43.3.151>.
- [92] Olausson P, Kiraly DD, Gourley SL, Taylor JR. Persistent effects of prior chronic exposure to corticosterone on reward-related learning and motivation in rodents. *Psychopharmacology*. 2013;225:569-77. <https://doi.org/10.1007/s00213-012-2844-4>.
- [93] Darcet F, Mendez-David I, Tritschler L, Gardier AM, Guilloux J-P, David DJ. Learning and memory impairments in a neuroendocrine mouse model of anxiety/depression. *Frontiers in Behavioral Neuroscience*. 2014;8. <https://doi.org/10.3389/fnbeh.2014.00136>.
- [94] Xu P, Wang K, Lu C, Dong L, Chen Y, Wang Q, et al. Effects of the chronic restraint stress induced depression on reward-related learning in rats. *Behavioural Brain Research*. 2017;321:185-92. <https://doi.org/10.1016/j.bbr.2016.12.045>.
- [95] Elliott R, Zahn R, Deakin JFW, Anderson IM. Affective Cognition and its Disruption in Mood Disorders. *Neuropsychopharmacology Reviews*. 2011;36:153-82. <https://doi.org/10.1038/npp.2010.77>.
- [96] Gong L, Yin Y, He C, Ye Q, Bai F, Yuan Y, et al. Disrupted reward circuits is associated with cognitive deficits and depression severity in major depressive disorder. *Journal of Psychiatric Research*. 2017;84:9-17. <https://doi.org/10.1016/j.jpsychires.2016.09.016>.
- [97] Der-Avakian A, D'Souza MS, Pizzagalli DA, Markou A. Assessment of reward responsiveness in the response bias probabilistic reward task in rats: implications for cross-species translational research. *Translational Psychiatry*. 2013;3:e297. <https://doi.org/10.1038/tp.2013.74>.

- [98] Bari A, Theobald DE, Caprioli D, Mar AC, Aidoo-Micah A, Dalley JW, et al. Serotonin modulates sensitivity to reward and negative feedback in a probabilistic reversal learning task in rats. *Neuropsychopharmacology* : official publication of the American College of Neuropsychopharmacology. 2010;35:1290-301. <https://doi.org/10.1038/npp.2009.233>.
- [99] Chamberlain SR, Müller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science (New York, NY)*. 2006;311:861-3. <https://doi.org/10.1126/science.1121218>.
- [100] Murphy FC, Michael A, Robbins TW, Sahakian BJ. Neuropsychological impairment in patients with major depressive disorder: the effects of feedback on task performance. *Psychological Medicine*. 2003;33:455-67. <https://doi.org/10.1017/S0033291702007018>.
- [101] Murphy FC, Sahakian BJ, Rubinsztein JS, Michael A, Rogers RD, Robbins TW, et al. Emotional bias and inhibitory control processes in mania and depression. *Psychological Medicine*. 1999;29:1307-21. <http://dx.doi.org/10.1017/S0033291799001233>.
- [102] Mkrtchian A, Aylward J, Dayan P, Roiser JP, Robinson OJ. Modeling Avoidance in Mood and Anxiety Disorders Using Reinforcement Learning. *Biological Psychiatry*. 2017;82:532-9. <https://doi.org/10.1016/j.biopsych.2017.01.017>.
- [103] Harding EJ, Paul ES, Mendl M. Animal behaviour: Cognitive bias and affective state. *Nature*. 2004;427:312. <https://doi.org/10.1038/427312a>.
- [104] Mendl M, Parker RMA, Burman OHP. Cognitive bias as an indicator of animal emotion and welfare: Emerging evidence and underlying mechanisms. *Applied Animal Behaviour Science*. 2009;118:161-81. <https://doi.org/10.1016/j.applanim.2009.02.023>.
- [105] Anderson MH, Munafo MR, Robinson ESJ. Investigating the psychopharmacology of cognitive affective bias in rats using an affective tone discrimination task. *Psychopharmacology*. 2013;226:601-13. <https://doi.org/10.1007/s00213-012-2932-5>.
- [106] Hales CA, Houghton CJ, Robinson ESJ. Behavioural and computational methods reveal differential effects for how delayed and rapid onset antidepressants affect decision making in rats. *European Neuropsychopharmacology*. 2017;27:1268-80. <https://doi.org/10.1016/j.euroneuro.2017.09.008>.
- [107] Hales CA, Robinson ESJ, Houghton CJ. Diffusion Modelling Reveals the Decision Making Processes Underlying Negative Judgement Bias in Rats. *PLOS One*. 2016;11:e0152592. <https://doi.org/10.1371/journal.pone.0152592>.
- [108] Jones S, Neville V, Higgs L, Paul ES, Dayan P, Robinson ESJ, et al. Assessing animal affect: an automated and self-initiated judgement bias task based on natural investigative behaviour. *Scientific reports*. 2018;8:12400-. <https://doi.org/10.1038/s41598-018-30571-x>.
- [109] Aylward J, Hales C, Robinson E, Robinson OJ. Back-Translating A Rodent Measure Of Negative Bias Into Humans: The Impact Of Induced Anxiety And Unmedicated Mood And Anxiety Disorders. *bioRxiv*. 2017:143453. <https://doi.org/10.1101/143453>.
- [110] Anderson MH, Hardcastle C, Munafo MR, Robinson ESJ. Evaluation of a novel translational task for assessing emotional biases in different species. *Cognitive, Affective, & Behavioral Neuroscience*. 2012;12:373-81. <https://doi.org/10.3758/s13415-011-0076-4>.
- [111] Stuart SA, Butler P, Munafo MR, Nutt DJ, Robinson ES. A translational rodent assay of affective biases in depression and antidepressant therapy. *Neuropsychopharmacology*. 2013;38:1625-35. <https://doi.org/10.1038/npp.2013.69>.
- [112] Kirsch I, Lynn SJ, Vigorito M, Miller RR. The Role of Cognition in Classical and Operant Conditioning. *Journal of Clinical Psychology*. 2004;60:369-92. <https://doi.org/10.1002/jclp.10251>.
- [113] Rogers RD, Blackshaw AJ, Middleton HC, Matthews K, Hawtin K, Crowley C, et al. Tryptophan depletion impairs stimulus-reward learning while methylphenidate disrupts attentional control in healthy young adults: implications for the monoaminergic basis of impulsive behaviour. *Psychopharmacology*. 1999;146:482-91. <https://doi.org/10.1007/PL00005494>.

- [114] Roiser JP, Levy J, Fromm SJ, Wang H, Hasler G, Sahakian BJ, et al. The effect of acute tryptophan depletion on the neural correlates of emotional processing in healthy volunteers. *Neuropsychopharmacology*. 2008;33:1992-2006. <https://doi.org/10.1038/sj.npp.1301581>.
- [115] Murphy FC, Smith KA, Cowen PJ, Robbins TW, Sahakian BJ. The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. *Psychopharmacology*. 2002;163:42-53. <https://doi.org/10.1007/s00213-002-1128-9>.
- [116] McLean A, Rubinsztein JS, Robbins TW, Sahakian BJ. The effects of tyrosine depletion in normal healthy volunteers: implications for unipolar depression. *Psychopharmacology*. 2004;171:286-97. <https://doi.org/10.1007/s00213-003-1586-8>.
- [117] Rogers RD, Tunbridge EM, Bhagwagar Z, Drevets WC, Sahakian BJ, Carter CS. Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues. *Neuropsychopharmacology*. 2003;28:153-62. <https://doi.org/10.1038/sj.npp.1300001>.
- [118] Robinson OJ, Cools R, Carlisi CO, Sahakian BJ, Drevets WC. Ventral Striatum Response During Reward and Punishment Reversal Learning in Unmedicated Major Depressive Disorder. *American Journal of Psychiatry*. 2012;169:152-9. <https://doi.org/10.1176/appi.ajp.2011.11010137>.
- [119] Komater M, Schmidt A, Bachmann R, Studerus E, Seifritz E, Vollenweider FX. Psilocybin Biases Facial Recognition, Goal-Directed Behavior, and Mood State Toward Positive Relative to Negative Emotions Through Different Serotonergic Subreceptors. *Biological Psychiatry*. 2012;72:898-906. <https://doi.org/10.1016/j.biopsych.2012.04.005>.
- [120] Delgado PL, Price LH, Miller HL, Salomon RM, Aghajanian GK, Heninger GR, et al. Serotonin and the neurobiology of depression. Effects of tryptophan depletion in drug-free depressed patients. *Archives of General Psychiatry*. 1994;51:865-74. <https://psycnet.apa.org/doi/10.1001/archpsyc.1994.03950110025005>.
- [121] Hayward G, Goodwin GM, Cowen PJ, Harmer CJ. Low-dose tryptophan depletion in recovered depressed patients induces changes in cognitive processing without depressive symptoms. *Biological Psychiatry*. 2005;57:517-24. <https://doi.org/10.1016/j.biopsych.2004.11.016>.
- [122] Ruhe HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Molecular Psychiatry*. 2007;12:331-59. <https://doi.org/10.1038/sj.mp.4001949>.
- [123] Pizzagalli DA, Evins AE, Schetter EC, Frank MJ, Pajtas PE, Santesso DL, et al. Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. *Psychopharmacology*. 2008;196:221-32. [10.1007/s00213-007-0957-y](https://doi.org/10.1007/s00213-007-0957-y).
- [124] Bogdan R, Pizzagalli DA. Acute stress reduces reward responsiveness: implications for depression. *Biological Psychiatry*. 2006;60:1147-54. <https://doi.org/10.1016/j.biopsych.2006.03.037>.
- [125] Der-Avakian A, D'Souza MS, Potter DN, Chartoff EH, Carlezon Jr WA, Pizzagalli DA, et al. Social defeat disrupts reward learning and potentiates striatal nociceptin/orphanin FQ mRNA in rats. *Psychopharmacology*. 2017;234:1603-14. <https://doi.org/10.1007/s00213-017-4584-y>.
- [126] Kregiel J, Malek N, Popik P, Starowicz K, Rygula R. Anandamide mediates cognitive judgement bias in rats. *Neuropharmacology*. 2016;101:146-53. <https://doi.org/10.1016/j.neuropharm.2015.09.009>.
- [127] Rygula R, Papciak J, Popik P. The effects of acute pharmacological stimulation of the 5-HT, NA and DA systems on the cognitive judgement bias of rats in the ambiguous-cue interpretation paradigm. *European Neuropsychopharmacology*. 2014;24:1103-11. <https://doi.org/10.1016/j.euroneuro.2014.01.012>.
- [128] Brydges NM, Leach M, Nicol K, Wright R, Bateson M. Environmental enrichment induces optimistic cognitive bias in rats. *Animal Behaviour*. 2011;81:169-75. <https://doi.org/10.1016/j.anbehav.2010.09.030>.
- [129] Bonaccorso S, Marino V, Biondi M, Grimaldi F, Ippoliti F, Maes M. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. *Journal of Affective Disorders*. 2002;72:237-41. [https://doi.org/10.1016/S0165-0327\(02\)00264-1](https://doi.org/10.1016/S0165-0327(02)00264-1).

- [130] Cooper CM, Godlewska B, Sharpley AL, Barnes E, Cowen PJ, Harmer CJ. Interferon- α induces negative biases in emotional processing in patients with hepatitis C virus infection: a preliminary study. *Psychological Medicine*. 2018;48:998-1007. <https://doi.org/10.1017/S0033291717002379>.
- [131] Stuart SA, Butler P, Munafo MR, Nutt DJ, Robinson ESJ. Distinct Neuropsychological Mechanisms May Explain Delayed- Versus Rapid-Onset Antidepressant Efficacy. *Neuropsychopharmacology*. 2015;40:2165-74. <https://doi.org/10.1038/npp.2015.59>.
- [132] DiFeliceantonio AG, Berridge KC. Dorsolateral neostriatum contribution to incentive salience: Opioid or dopamine stimulation makes one reward cue more motivationally attractive than another. *European Journal of Neuroscience*. 2016;43:1203-18. <https://doi.org/10.1111/ejn.13220>.
- [133] Berridge KC, Kringelbach ML. Neuroscience of affect: brain mechanisms of pleasure and displeasure. *Current Opinion in Neurobiology*. 2013;23:294-303. <https://doi.org/10.1016/j.conb.2013.01.017>.
- [134] Kampov-Polevoy AB, Garbutt JC, Janowsky D. Evidence of preference for a high-concentration sucrose solution in alcoholic men. *American Journal of Psychiatry*. 1997;154:269-70. <https://doi.org/10.1176/ajp.154.2.269>.
- [135] Dichter GS, Smoski MJ, Kampov-Polevoy AB, Gallop R, Garbutt JC. Unipolar depression does not moderate responses to the sweet taste test. *Depression and Anxiety*. 2010;27:859-63. <https://doi.org/10.1002/da.20690>.
- [136] Berlin I, Givry-Steiner L, Lecrubier Y, Puech AJ. Measures of anhedonia and hedonic responses to sucrose in depressive and schizophrenic patients in comparison with healthy subjects. *European Psychiatry*. 1998;13:303-9. [https://doi.org/10.1016/S0924-9338\(98\)80048-5](https://doi.org/10.1016/S0924-9338(98)80048-5).
- [137] Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. *Psychopharmacology*. 2008;199:457-80. <https://dx.doi.org/10.1007/s00213-008-1099-6>.
- [138] Berridge KC, Kringelbach ML. Pleasure Systems in the Brain. *Neuron*. 2015;86:646-64. <https://doi.org/10.1016/j.neuron.2015.02.018>.
- [139] Davis JD. The Microstructure of Ingestive Behaviour. *Annals of the New York Academy of Sciences*. 1989;575:106-19. <https://doi.org/10.1111/j.1749-6632.1989.tb53236.x>.
- [140] Dwyer DM, Gasalla Canto P, Bura S, Lopez M. Flavors paired with internal pain or nausea elicit divergent types of hedonic responses. *Behavioural Neuroscience*. 2017;131:235-48. <https://doi.org/10.1037/bne0000197>.
- [141] Pelchat ML, Grill HJ, Rozin P, Jacobs J. Quality of acquired responses to tastes by *Rattus norvegicus* depends on type of associated discomfort. *Journal of Computational Psychology*. 1983;97:140-53. <http://dx.doi.org/10.1037/0735-7036.97.2.140>.
- [142] Lewis LR, Robinson ESJ, Dwyer DM. Differential effects of chronic corticosterone and interferon-alpha treatment on inducing anhedonia-like reward processing deficits in rats. *BNA Festival of Neuroscience*. Dublin, Ireland 2019.
- [143] Scinska A, Sienkiewicz-Jarosz H, Kuran W, Ryglewicz D, Rogowski A, Wrobel E, et al. Depressive symptoms and taste reactivity in humans. *Physiology and Behaviour*. 2004;82:899-904. <https://doi.org/10.1016/j.physbeh.2004.07.012>.
- [144] Wu H, Mata J, Furman DJ, Whitmer AJ, Gotlib IH, Thompson RJ. Anticipatory and consummatory pleasure and displeasure in major depressive disorder: An experience sampling study. *Journal of Abnormal Psychology*. 2017;126:149-59. <https://doi.org/10.1037/abn0000244>.
- [145] Rizvi SJ, Quilty LC, Sproule BA, Cyriac A, Bagby RM, Kennedy SH. Development and validation of the Dimensional Anhedonia Rating Scale (DARS) in a community sample and individuals with major depression. *Psychiatry Research*. 2015;229:109-19. <https://doi.org/10.1016/j.psychres.2015.07.062>.
- [146] Wise MG. Neurobiology of addiction. *Current Opinion in Neurobiology*. 1996;6:243-51. [https://doi.org/10.1016/S0959-4388\(96\)80079-1](https://doi.org/10.1016/S0959-4388(96)80079-1).
- [147] Bardo MT. Neuropharmacological mechanisms of drug reward: beyond dopamine in the nucleus accumbens. *Critical Reviews in Neurobiology*. 1998;12:37-67. <https://doi.org/10.1615/CritRevNeurobiol.v12.i1-2.30>.

- [148] Muscat R, Willner P. Effects of dopamine receptor antagonists on sucrose consumption and preference. *Psychopharmacology*. 1989;99:98-102. <https://doi.org/10.1007/BF00634461>.
- [149] Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology*. 2007;191:391-431. <https://doi.org/10.1007/s00213-006-0578-x>.
- [150] Peciña S, Cagniard B, Berridge KC, Aldridge JW, Zhuang X. Hyperdopaminergic Mutant Mice Have Higher "Wanting" But Not "Liking" for Sweet Rewards. *Journal of Neuroscience*. 2003;23:9395-402. <https://doi.org/10.1523/JNEUROSCI.23-28-09395.2003>.
- [151] Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Review*. 1998;28:309-69. [https://doi.org/10.1016/S0165-0173\(98\)00019-8](https://doi.org/10.1016/S0165-0173(98)00019-8).
- [152] Peciña S, Berridge KC, Parker LA. Pimozide does not shift palatability: separation of anhedonia from sensorimotor suppression by taste reactivity. *Pharmacology, Biochemistry and Behavior*. 1997;58:801-11. [https://doi.org/10.1016/S0091-3057\(97\)00044-0](https://doi.org/10.1016/S0091-3057(97)00044-0).
- [153] Lee MD, Simansky KJ. CP-94, 253: a selective serotonin1B (5-HT1B) agonist that promotes satiety. *Psychopharmacology*. 1997;131:264-70. <http://doi.org/10.1007/s002130050292>.
- [154] Clifton PG, Lee MD, Dourish CT. Similarities in the action of Ro 60-0175, a 5-HT2C receptor agonist, and d-fenfluramine on feeding patterns in the rat. *Psychopharmacology*. 2000;152:256-67. <https://doi.org/10.1007/s002130000504>.
- [155] Galistu A, Modde C, Pireddu MC, Franconi F, Serra G, D'Aquila PS. Clozapine increases reward evaluation but not overall ingestive behaviour in rats licking for sucrose. *Psychopharmacology*. 2011;216:411-20. <https://doi.org/10.1007/s00213-011-2237-0>.
- [156] Peciña S, Berridge KC. Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness? *Journal of Neuroscience*. 2005;25:11777-86. <https://doi.org/10.1523/JNEUROSCI.2329-05.2005>.
- [157] Peciña S, Berridge KC. Opioid eating site in accumbens shell mediates food intake and hedonic 'liking': map based on microinjection Fos plumes. *Brain Research*. 2000;863:71-86. [https://doi.org/10.1016/S0006-8993\(00\)02102-8](https://doi.org/10.1016/S0006-8993(00)02102-8).
- [158] Frisina PG, Sclafani A. Naltrexone suppresses the late but not early licking response to a palatable sweet solution: opioid hedonic hypothesis reconsidered. *Pharmacology, Biochemistry and Behavior*. 2002;74:163-72. [https://doi.org/10.1016/S0091-3057\(02\)00995-4](https://doi.org/10.1016/S0091-3057(02)00995-4).
- [159] Higgs S, Cooper SJ. Evidence for early opioid modulation of licking responses to sucrose and intralipid: a microstructural analysis in the rat. *Psychopharmacology*. 1998;139:342-55. <https://doi.org/10.1007/s002130050725>.
- [160] Castro DC, Berridge KC. Opioid hedonic hotspot in nucleus accumbens shell: mu, delta and kappa maps for enhancement of sweetness "liking" and "wanting". *Journal of Neuroscience*. 2014;34. <https://doi.org/10.1523/JNEUROSCI.4458-13.2014>.
- [161] Wassum KM, Ostlund SB, Maidment NT, Balleine BW. Distinct opioid circuits determine the palatability and the desirability of rewarding events. *Proceedings of the National Academy of Science*. 2009;106:12512-7. <https://doi.org/10.1073/pnas.0905874106>.
- [162] Richard JM, Fields HL. Mu-opioid receptor activation in the medial shell of nucleus accumbens promotes alcohol consumption, self-administration and cue-induced reinstatement. *Neuropharmacology*. 2016;108:14-23. <https://doi.org/10.1016/j.neuropharm.2016.04.010>.
- [163] Berridge KC, Treit D. A Comparison of Benzodiazepine, Serotonin, and Dopamine Agents in the Taste-Reactivity Paradigm. *Pharmacology Biochemistry and Behavior*. 1990;37:451-6. [https://doi.org/10.1016/0091-3057\(90\)90011-6](https://doi.org/10.1016/0091-3057(90)90011-6).
- [164] Pittman DW, McGinnis MR, Richardson LM, Miller EJ, Alimohamed ML, Baird JP. Multiple Processes Underlie Benzodiazepine-Mediated Increases in the Consumption of Accepted and Avoided Stimuli. *Chemical Senses*. 2012;37:431-44. <https://doi.org/10.1093/chemse/bjr125>.
- [165] Richardson DK, Reynolds SM, Cooper SJ, Berridge KC. Endogenous opioids are necessary for benzodiazepine palatability enhancement: Naltrexone blocks diazepam-induced increase of sucrose-

- 'liking'. *Pharmacology Biochemistry and Behavior*. 2005;81:657-63.
<https://doi.org/10.1016/j.pbb.2005.05.006>.
- [166] Kosel M, Bilkei-Gorzo A, Zawatzky R, Zimmer A, Schlaepfer TE. Pegylated human interferon alpha 2a does not induce depression-associated changes in mice. *Psychiatry Research*. 2011;185:243-7. <https://doi.org/10.1016/j.psychres.2009.10.012>.
- [167] De La Garza R, Asnis GM, Pedrosa E, Stearns C, Migdal AL, Reinus JF, et al. Recombinant human interferon-alpha does not alter reward behaviour, or neuroimmune and neuroendocrine activation in rats. *Progress in Neuropsychopharmacological & Biological Psychiatry*. 2005;29:781-92.
<https://doi.org/10.1016/j.pnpbp.2005.03.008>.
- [168] Kentner AC, James JS, Miguez M, Bielajew C. Investigating the hedonic effects of interferon-alpha on female rats using brain-stimulation reward. *Behavioural Brain Research*. 2007;177:90-9.
<https://doi.org/10.1016/j.bbr.2006.10.033>.
- [169] Sturm M, Becker A, Schroeder A, Bilkei-Gorzo A, Zimmer A. Effect of chronic corticosterone application on depression-like behaviour in C57BL/6N and C57BL/6J mice. *Genes, brain and behaviour*. 2015;14:292-300. <https://doi.org/10.1111/gbb.12208>.
- [170] Zhao Y, Ma R, Shen J, Su H, Xing D, Du L. A mouse model of depression induced by repeated corticosterone injections. *European Journal of Pharmacology*. 2008;581:113-20.
<https://doi.org/10.1016/j.ejphar.2007.12.005>.
- [171] Li Y-C, Liu Y-M, Shen J-D, Chen J-J, Pei Y-Y, Fang X-Y. Resveratrol Ameliorates the Depressive-Like Behaviours and Metabolic Abnormalities Induced by Chronic Corticosterone Injection. *Molecules*. 2016;21:E1341. <https://doi.org/10.3390/molecules21101341>.
- [172] Forbes NF, Stewart CA, Matthews K, Reid IC. Chronic Mild Stress and Sucrose Consumption: Validity as a Model of Depression. *Physiology and Behaviour*. 1996;60:1481-4.
[https://psycnet.apa.org/doi/10.1016/S0031-9384\(96\)00305-8](https://psycnet.apa.org/doi/10.1016/S0031-9384(96)00305-8).
- [173] Berridge KC. From prediction error to incentive salience: mesolimbic computation of reward motivation. *European Journal of Neuroscience*. 2012;35:1124-43. <https://doi.org/10.1111/j.1460-9568.2012.07990.x>.
- [174] Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology*. 1954;47:419-27.
<https://doi.org/10.1037/h0058775>.
- [175] Moreau JL, Jenck F, Martin JR, Mortas P, Haefely WE. Antidepressant treatment prevents chronic unpredictable mild stress-induced anhedonia as assessed by ventral tegmentum self-stimulation behavior in rats. *European Neuropsychopharmacology*. 1992;2:43-9.
[https://doi.org/10.1016/0924-977X\(92\)90035-7](https://doi.org/10.1016/0924-977X(92)90035-7).
- [176] Markou A, Koob GF. Construct validity of a self-stimulation threshold paradigm: Effects of reward and performance manipulations. *Physiology & Behavior*. 1992;51:111-9.
[https://doi.org/10.1016/0031-9384\(92\)90211-J](https://doi.org/10.1016/0031-9384(92)90211-J).
- [177] Paterson NE, Myers C, Markou A. Effects of repeated withdrawal from continuous amphetamine administration on brain reward function in rats. *Psychopharmacology*. 2000;152:440-6. <http://dx.doi.org/10.1007/s002130000559>.
- [178] Der-Avakian A, Barnes SA, Markou A, Pizzagalli DA. Translational Assessment of Reward and Motivational Deficits in Psychiatric Disorders. In: Robbins TW, Sahakian BJ, editors. *Translational Neuropsychopharmacology*, Cham: Springer International Publishing; 2015. p. 231-62.
https://doi.org/10.1007/7854_2015_5004.
- [179] Carlezon Jr WA, Chartoff EH. Intracranial self-stimulation (ICSS) in rodents to study the neurobiology of motivation. *Nature Protocols*. 2007;2:2987.
<https://doi.org/10.1038/nprot.2007.441>.
- [180] Barnes SA, Der-Avakian A, Markou A. Anhedonia, avolition, and anticipatory deficits: Assessments in animals with relevance to the negative symptoms of schizophrenia. *European Neuropsychopharmacology*. 2014;24:744-58. <https://dx.doi.org/10.1016/j.euroneuro.2013.10.001>.

- [181] Esposito R, Kornetsky C. Morphine lowering of self-stimulation thresholds: Lack of tolerance with long-term administration. *Science*. 1977;195:189-91. <https://doi.org/10.1126/science.831268>.
- [182] Randall PA, Pardo M, Nunes EJ, López Cruz L, Vemuri VK, Makriyannis A, et al. Dopaminergic modulation of effort-related choice behavior as assessed by a progressive ratio chow task: pharmacological studies and role of individual differences. *PLOS One*. 2012;7:e47934. <https://doi.org/10.1371/journal.pone.0047934>.
- [183] Belujon P, Grace AA. Dopamine System Dysregulation in Major Depressive Disorder. *International Journal of Neuropsychopharmacology*. 2017;20:1036-46. <https://dx.doi.org/10.1093/ijnp/pyx056>.
- [184] Salamone JD, Correa M, Yang J-H, Rotolo R, Presby R. Dopamine, Effort-Based Choice, and Behavioral Economics: Basic and Translational Research. *Frontiers in Behavioral Neuroscience*. 2018;12. <https://doi.org/10.3389/fnbeh.2018.00052>.
- [185] Salamone JD, Koychev I, Correa M, McGuire P. Neurobiological basis of motivational deficits in psychopathology. *European Neuropsychopharmacology*. 2015;25:1225-38. <https://doi.org/10.1016/j.euroneuro.2014.08.014>.
- [186] Aberman JE, Ward SJ, Salamone JD. Effects of dopamine antagonists and accumbens dopamine depletions on time-constrained progressive-ratio performance. *Pharmacology, Biochemistry and Behaviour*. 1998;61:341-8. [https://doi.org/10.1016/S0091-3057\(98\)00112-9](https://doi.org/10.1016/S0091-3057(98)00112-9).
- [187] Barr AM, Phillips AG. Chronic mild stress has no effect on responding by rats for sucrose under a progressive ratio schedule. *Physiology & Behavior*. 1998;64:591-7. [https://doi.org/10.1016/S0031-9384\(98\)00060-2](https://doi.org/10.1016/S0031-9384(98)00060-2).
- [188] Leventopoulos M, Russig H, Feldon J, Pryce CR, Opacka-Juffry J. Early deprivation leads to long-term reductions in motivation for reward and 5-HT1A binding and both effects are reversed by fluoxetine. *Neuropharmacology*. 2009;56:692-701. <https://doi.org/10.1016/j.neuropharm.2008.12.005>.
- [189] Amitai N, Powell SB, Young JW. Phencyclidine increased while isolation rearing did not affect progressive ratio responding in rats: Investigating potential models of amotivation in schizophrenia. *Behavioural Brain Research*. 2017. <https://doi.org/10.1016/j.bbr.2017.11.026>.
- [190] Slaney CL, Hales CA, Robinson ESJ. Rat models of reward deficits in psychiatric disorders. *Current Opinion in Behavioral Sciences*. 2018;22:136-42. <https://doi.org/10.1016/j.cobeha.2018.05.001>.
- [191] Salamone JD, Correa M, Farrar AM, Nunes EJ, Pardo M. Dopamine, behavioral economics, and effort. *Frontiers in Behavioral Neuroscience*. 2009;3. <https://doi.org/10.3389/neuro.08.013.2009>.
- [192] Groeneweg-Koolhoven I, Ploeg M, Comijs HC, Penninx BWJH, van der Mast RC, Schoevers R, et al. Apathy in early and late-life depression. *Journal of Affective Disorders*. 2017;223:76-81. <https://doi.org/10.1016/j.jad.2017.07.022>.
- [193] Treadway MT, Buckholz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the 'EEfRT'? The Effort Expenditure for Rewards Task as an Objective Measure of Motivation and Anhedonia. *PLOS One*. 2009;4:e6598. <https://doi.org/10.1371/journal.pone.0006598>.
- [194] Treadway MT, Bossaller N, Shelton RC, Zald DH. Effort-based decision-making in Major Depressive Disorder: A translational model of motivational anhedonia. *Journal of Abnormal Psychology*. 2012;121:553-8. <https://doi.org/10.1037/a0028813>.
- [195] Yang X-h, Huang J, Zhu C-y, Wang Y-f, Cheung EFC, Chan RCK, et al. Motivational deficits in effort-based decision making in individuals with subsyndromal depression, first-episode and remitted depression patients. *Psychiatry Research*. 2014;220:874-82. <https://doi.org/10.1016/j.psychres.2014.08.056>.
- [196] Bryant J, Winer ES, Salem T, Nadorff MR. Struggling toward reward: Recent experience of anhedonia interacts with motivation to predict reward pursuit in the face of a stressful manipulation. *PLOS One*. 2017;12:e0173439. <https://doi.org/10.1371/journal.pone.0173439>.
- [197] Salamone JD, Steinpreis RE, McCullough LD, Smith P, Grebel D, Mahan K. Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food

- consumption in a novel food choice procedure. *Psychopharmacology*. 1991;104:515-21. <https://doi.org/10.1007/BF02245659>.
- [198] Salamone JD, Correa M, Yohn S, Cruz LL, San Miguel N, Alatorre L. The pharmacology of effort-related choice behavior: Dopamine, depression, and individual differences. *Behavioural Processes*. 2016;127:3-17. <https://doi.org/10.1016/j.beproc.2016.02.008>.
- [199] Salamone JD, Correa M, Ferrigno S, Yang J-H, Rotolo R, Presby RE. The Psychopharmacology of Effort-Related Decision Making: Dopamine, Adenosine, and Insights into the Neurochemistry of Motivation. *Pharmacological Reviews*. 2018;70:747-62. <https://doi.org/10.1124/pr.117.015107>.
- [200] Walton ME, Bouret S. What is the Relationship between Dopamine and Effort? *Trends in Neurosciences*. 2018;S0166-2236:30272-8. <https://doi.org/10.1016/j.tins.2018.10.001>.
- [201] Salamone JD, Kurth PA, McCullough LD, Sokolowski JD, Cousins MS. The role of brain dopamine in response initiation: effects of haloperidol and regionally specific dopamine depletions on the local rate of instrumental responding. *Brain Research*. 1993;628:218-26. [https://doi.org/10.1016/0006-8993\(93\)90958-P](https://doi.org/10.1016/0006-8993(93)90958-P).
- [202] Wassum KM, Ostlund SB, Balleine BW, Maidment NT. Differential dependence of Pavlovian incentive motivation and instrumental incentive learning processes on dopamine signalling. *Learning & Memory*. 2011;18:475-83. <https://doi.org/10.1101/lm.2229311>.
- [203] Zhang M, Balmadrid C, Kelley AE. Nucleus Accumbens Opioid, GABAergic, and Dopaminergic Modulation of Palatable Food Motivation: Contrasting Effects Revealed by a Progressive Ratio Study in the Rat. *Behavioural Neuroscience*. 2003;117:202-11. <https://doi.org/10.1037/0735-7044.117.2.202>.
- [204] Salamone JD, Correa M. Motivational views of reinforcement: implications for understanding the behavioral functions of nucleus accumbens dopamine. *Behavioural Brain Research*. 2002;137:3-25. [https://doi.org/10.1016/S0166-4328\(02\)00282-6](https://doi.org/10.1016/S0166-4328(02)00282-6).
- [205] Park IH, Lee BC, Kim JJ, Kim JI, Koo MS. Effort-Based Reinforcement Processing and Functional Connectivity Underlying Amotivation in Medicated Patients with Depression and Schizophrenia. *Journal of Neuroscience*. 2017;37:4370-80. <https://doi.org/10.1523/JNEUROSCI.2524-16.2017>.
- [206] Font L, Mingote S, Farrar AM, Pereira M, Worden LT, Stopper CM, et al. Intra-accumbens injections of the adenosine A2A agonist CGS 21680 affect effort-related choice behavior in rats. *Psychopharmacology*. 2008;199:515-26. <https://doi.org/10.1007/s00213-008-1174-z>.
- [207] Mingote S, Font L, Farrar AM, Vontell R, Worden LT, Stopper CM, et al. Nucleus Accumbens Adenosine A2A Receptors Regulate Exertion of Effort by Acting on the Ventral Striatopallidal Pathway. *Journal of Neuroscience*. 2008;28:9037-46. <https://dx.doi.org/10.1523/JNEUROSCI.1525-08.2008>.
- [208] Nunes EJ, Randall PA, Podurciel S, Correa M, Salamone JD. Nucleus accumbens neurotransmission and effort-related choice behavior in food motivation: Effects of drugs acting on dopamine, adenosine and muscarinic acetylcholine receptors. *Neuroscience and biobehavioural reviews*. 2013;37:2015-25. <https://doi.org/10.1016/j.neubiorev.2013.04.002>.
- [209] Farrar AM, Font L, Pereira M, Mingote S, Bunce JG, Chrobak JJ, et al. Forebrain circuitry involved in effort-related choice: injections of the GABAA agonist muscimol into ventral pallidum alter response allocation in food-seeking behavior. *Neuroscience*. 2008;152:321-30. <https://dx.doi.org/10.1016/j.neuroscience.2007.12.034>.
- [210] Denk F, Walton ME, Jennings KA, Sharp T, Rushworth MF, Bannerman DM. Differential involvement of serotonin and dopamine systems in cost-benefit decisions about delay or effort. *Psychopharmacology*. 2005;179:587-96. <https://doi.org/10.1007/s00213-004-2059-4>.
- [211] Izquierdo A, Carlos K, Ostrander S, Rodriguez D, McCall-Craddolph A, Yagnik G, et al. Impaired reward learning and intact motivation after serotonin depletion in rats. *Behavioural Brain Research*. 2012;233:494-9. <https://doi.org/10.1016/j.bbr.2012.05.032>.
- [212] Bailey MR, Williamson C, Mezas C, Winiger V, Silver R, Balsam PD, et al. The effects of pharmacological modulation of the serotonin 2C receptor on goal-directed behavior in mice. *Psychopharmacology*. 2016;233:615-24. <https://doi.org/10.1007/s00213-015-4135-3>.

- [213] Steiner JE. The gustofacial response: observation on normal and anencephalic newborn infants. Symposium on oral sensation and perception 1973.
- [214] Lawrence AD, Sahakian BJ, Rogers RD, Hodges JR, Robbins TW. Discrimination, reversal, and shift learning in Huntington's disease: mechanisms of impaired response selection. *Neuropsychologia*. 1999;37:1359-74. [https://doi.org/10.1016/S0028-3932\(99\)00035-4](https://doi.org/10.1016/S0028-3932(99)00035-4).
- [215] Swainson R, Rogers RD, Sahakian BJ, Summers BA, Polkey CE, Robbins TW. Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia*. 2000;38:596-612. [https://doi.org/10.1016/S0028-3932\(99\)00103-7](https://doi.org/10.1016/S0028-3932(99)00103-7).
- [216] Morales I, Font L, Currie PJ, Pastor R. Involvement of opioid signaling in food preference and motivation: Studies in laboratory animals. *Progress in Brain Research*. 2016;229:159-87. <https://doi.org/10.1016/bs.pbr.2016.06.002>.
- [217] Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *American Journal of Psychiatry*. 2006;163:28-40. <https://doi.org/10.1176/appi.ajp.163.1.28>.
- [218] Treadway MT, Zald DH. Reconsidering Anhedonia in Depression: Lessons from Translational Neuroscience. *Neuroscience and biobehavioural reviews*. 2011;35:537-55. <https://doi.org/10.1016/j.neubiorev.2010.06.006>.
- [219] Harmer CJ, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, et al. Effect of Acute Antidepressant Administration on Negative Affective Bias in Depressed Patients. *American Journal of Psychiatry*. 2009;166:1178-84. <https://doi.org/10.1176/appi.ajp.2009.09020149>.
- [220] Calabrese JR, Fava M, Garibaldi G, Grunze H, Krystal AD, Laughren T, et al. Methodological approaches and magnitude of the clinical unmet need associated with amotivation in mood disorders. *Journal of Affective Disorders*. 2014;168:439-51. <https://doi.org/10.1016/j.jad.2014.06.056>.
- [221] Argyropoulos SV, Nutt DJ. Anhedonia revisited: Is there a role for dopamine-targeting drugs for depression? *Journal of Psychopharmacology*. 2013;27:869-77. <https://doi.org/10.1177/0269881113494104>.
- [222] Gregus A, Wintink AJ, Davis AC, Kalynchuk LE. Effect of repeated corticosterone injections and restraint stress on anxiety and depression-like behavior in male rats. *Behavioural Brain Research*. 2005;156:105-14. <https://doi.org/10.1016/j.bbr.2004.05.013>.
- [223] Gourley SL, Taylor JR. Recapitulation and reversal of a persistent depression-like syndrome in rodents. *Current protocols in neuroscience*. 2009;Chapter 9:Unit-9.32. <https://doi.org/10.1002/0471142301.ns0932s49>.
- [224] Yohn SE, Lopez-Cruz L, Hutson PH, Correa M, Salamone JD. Effects of lisdexamfetamine and s-citalopram, alone and in combination, on effort-related choice behavior in the rat. *Psychopharmacology*. 2016;233:949-60. <https://doi.org/10.1007/s00213-015-4176-7>.
- [225] Yohn SE, Collins SL, Contreras-Mora HM, Errante EL, Rowland MA, Correa M, et al. Not All Antidepressants Are Created Equal: Differential Effects of Monoamine Uptake Inhibitors on Effort-Related Choice Behavior. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2016;41:686-94. <https://doi.org/10.1038/npp.2015.188>.
- [226] Refsgaard LK, Haubro K, Pickering DS, Stuart SA, Robinson ESJ, Andreasen JT. Effects of sertraline, duloxetine, vortioxetine, and idazoxan in the rat affective bias test. *Psychopharmacology*. 2016;233:3763-70. <https://doi.org/10.1007/s00213-016-4407-6>.
- [227] Hinchcliffe JK, Stuart SA, Mendl M, Robinson ESJ. Further validation of the affective bias test for predicting antidepressant and pro-depressant risk: effects of pharmacological and social manipulations in male and female rats. *Psychopharmacology*. 2017;234:3105-16. <https://doi.org/10.1007/s00213-017-4687-5>.
- [228] Frazer A, Benmansour S. Delayed pharmacological effects of antidepressants. *Molecular Psychiatry*. 2002;7:S23-8. <https://doi.org/10.1038/sj.mp.4001015>.

- [229] Manji HK, Quiroz JA, Sporn J, Payne JL, Denicoff K, Gray A, et al. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biological Psychiatry*. 2003;53:707-42. [https://doi.org/10.1016/S0006-3223\(03\)00117-3](https://doi.org/10.1016/S0006-3223(03)00117-3).
- [230] Duman RS, Li N. A neurotrophic hypothesis of depression: role of synaptogenesis in the actions of NMDA receptor antagonists. *Philosophical Transactions of the Royal Society B*. 2012;367:2475-84. <https://dx.doi.org/10.1098/rstb.2011.0357>.
- [231] Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biological Psychiatry*. 2006;59:1116-27. <https://doi.org/10.1016/j.biopsych.2006.02.013>.
- [232] Phillips C. Brain-derived neurotrophic factor, depression, and physical activity: making the neuroplastic connection. *Neural Plasticity*. 2017;2017:7260130. <https://doi.org/10.1155/2017/7260130>.
- [233] Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. *Nature Reviews Neuroscience*. 2006;7:137-51. <https://doi.org/10.1038/nrn1846>.
- [234] Titley HK, Brunel N, Hansel C. Toward a Neurocentric View of Learning. *Neuron*. 2017;95:19-32. <https://doi.org/10.1016/j.neuron.2017.05.021>.
- [235] Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry*. 2000;47:351-4. [https://doi.org/10.1016/S0006-3223\(99\)00230-9](https://doi.org/10.1016/S0006-3223(99)00230-9).
- [236] Duman R, Aghajanian A, Sanacora G, Krystal JH. A synaptic hypothesis of depression: new insights from studies of stress systems and rapid-acting antidepressant. *Nature Medicine*. 2016;22:238-49. <https://doi.org/10.1038/nm.4050>.
- [237] Miller OH, Moran JT, Hall BJ. Two cellular hypotheses explaining the initiation of ketamine's antidepressant actions: direct inhibition and disinhibition. *Neuropharmacology*. 2016;100:17-26. <https://doi.org/10.1016/j.neuropharm.2015.07.028>.