

# 1 **Affective biases and their interaction with other reward-related deficits in** 2 **rodent models of psychiatric disorders**

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## 14 **Abstract**

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

## 32 **Keywords**

33 Depression; Animal models; Affective bias; Reward processing

## 34 **1. Introduction**

35 Depression is currently the leading global cause of disability [1]. According to the DSM-5,  
36 clinical depression or major depressive disorder (MDD) is a serious mood disorder

37 characterised by the presence of several symptoms including low mood, diminished interest  
38 or pleasure in almost all activities, slowness of thought processes/physical movements, and a  
39 diminished ability to think or concentrate [2].

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

51 Although descriptive accounts and more formal diagnoses of depression have been made for  
52 some centuries [6], it is only more recently that the idea of heterogeneity in depressed  
53 populations has been addressed. An individual patient can have a number of symptoms but  
54 not share a single one with another patient, even though they are diagnosed with the same  
55 disorder [7]. Despite this, treatments are not personalised to match the symptoms present in  
56 each patient, partly because we do not yet have a full understanding of the neurobiology  
57 underlying symptoms individually. Differences in the neurobiology of components in reward  
58 processing are becoming increasingly recognised [8], some of which can match to symptoms  
59 seen in MDD patients, and MDD can be seen as a disorder of reward processing [9]. Thus, in  
60 order to understand the neurobiological mechanisms of this complex disorder, we need to  
61 analyse the individual reward-related symptoms of MDD, for which reliable animal models  
62 and translational behavioural assays are essential. Recent developments to back translate the  
63 ideas of affective biases in MDD to rodent studies has revealed biases in rodents related to  
64 reward-related learning, memory and decision-making [10]. This work suggests that biases in  
65 reward-related behaviour may be relevant to the wider symptoms of anhedonia in MDD.

66 Current animal models of depression appear to demonstrate face validity in relation to  
67 behaviours comparable to distinct symptomology defined by the DSM criteria of MDD,  
68 including impairments following exposure to chronic stress, a major risk factor for depression  
69 [11, 12]. Whilst these behavioural assays (discussed in section 3) show good validity in terms  
70 of stress-induced behavioural deficits and are sensitive to some antidepressant treatments,  
71 how well they recapitulate the human condition, and hence can demonstrate translational  
72 validity, has been questioned [10, 13]. Recently, the idea that affective biases can be modelled  
73 in animals and provide a more translational approach to studying MDD in non-human species  
74 has emerged. The nature of the animal experiments has meant that such behaviours are often  
75 seen as biases in processing of reward-related stimuli, which has led us to consider the wider  
76 deficits in MDD, particularly anhedonia and the loss of motivation for previously rewarding  
77 activities [9, 14, 15].

78 Reliable behavioural assays in animal models can help to parse the underlying neurobiological  
79 mechanisms of these deficits, as well as how they interact, and provide clear targets for  
80 treating individual symptoms [8]. Traditional behavioural assays have focused on symptoms  
81 of behavioural despair/learned helplessness, in which MDD patients are conditioned to  
82 experience negative events such that they give up trying to escape such situations [16]. In  
83 rodents, this is often measured with the forced swim test (FST) for both mice and rats, or the  
84 tail suspension test (TST) for mice. Inescapable shock is also described as a method to induce  
85 learned helplessness [17] and has been used to induce a depression-like phenotype in animals  
86 with evidence for both vulnerable and resilient populations [18, 19]. In the FST, rodents are  
87 placed into an open container of water for a short period of time and their behaviour is  
88 recorded [20]. The animal swims around the container and attempts to escape, but eventually  
89 they stop moving and stay immobile. The time taken for the animal to become immobile can  
90 be used to measure this theory of learned helplessness. Pharmacological studies with pro-  
91 and anti-depressants have helped to validate this assay, with immobility time reducing with  
92 pro-depressants such as stressors, and increasing with typical antidepressants (see [21, 22]  
93 for a full review). The TST works on a similar principle, where mice are suspended by their tail  
94 so cannot escape. Immobility time is again used as a marker of learned helplessness [23].

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

109 This review will focus on direct assays of reward-related deficits which can be translated to  
110 symptoms often seen across patients with MDD. As anhedonia, the reduced ability to  
111 experience pleasure, is a core symptom of MDD, the most commonly used assay of reward-  
112 related deficits in rodents aims to model this symptom in the sucrose preference test (SPT),  
113 in which overall consumption of a rewarding solution containing sucrose in comparison to  
114 plain water is measured as a choice test [35]. This method has been used for decades as one  
115 of the go-to measurement of depressive-like behaviours and reduced sucrose preference has  
116 commonly been assumed to indicate consummatory anhedonia [12, 36]. However, it is  
117 important to note, there are many limitations in the current assays of reward deficits in  
118 animal models. For example, the direct link between sucrose preference and anhedonia has  
119 been questioned over the years [13, 14, 37-40]. While a reduced hedonic reaction to sucrose  
120 would be expected to lower sucrose preference, it should also be noted that general

121 consumption of reward relies highly on being motivated to attain it, and choice tests require  
122 intact cognitive processes to learn where the rewarding solution is. Thus, it cannot be  
123 concluded that differences in overall consumption of sucrose or sucrose preference  
124 specifically reflect hedonic deficits alone. This highlights the importance of improving current  
125 assays of depressive-like phenotypes such that they specifically measure the symptoms they  
126 are claimed to, and can therefore be used to parse differences in the underlying  
127 neurobiological mechanisms of this complex psychiatric disorder.

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

134 In this review, we aim to highlight the importance of modelling symptoms of MDD with more  
135 sensitive behavioural assays in rodent. We will summarise findings in conventional models as  
136 well as discussing new developments in relation to affective biases and reward processing  
137 including potential neurobiological underpinnings of reward processing deficits relevant to  
138 symptoms of MDD. As affective biases are a key symptom of MDD and novel, translatable  
139 methods have recently begun to be described, this review will focus on these recent  
140 developments, as well as how these biases may be dissociable from, but also interact with,  
141 other reward-related deficits.

## 142 **2. Affective biases in MDD**

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

153 Early theories of cognitive dysfunction in MDD note that negative stimuli and events are more  
154 salient to patients compared to healthy individuals, attributed to a negative self-schema  
155 caused by past experiences, which can lead to biases in processing their environment [45].  
156 These ‘cognitive’ biases can influence learning and memory, for example, patients often  
157 demonstrate increased recall of negative stimuli compared to positive stimuli [46], and learn  
158 to assign negative connotations to ambiguous stimuli, whilst healthy individuals would show  
159 more positive associations [47, 48]. This processing bias induces negative expectations of  
160 future events, and can alter other cognitive domains such as decision making and judgement  
161 [49, 50]. In addition to enhanced negative processing biases, patients with MDD show

162 reduced biases toward positively valenced stimuli including reduced recognition or  
163 interpretation of positive emotions, decreased memory for positively associated words and  
164 blunted responses to rewards [51, 52]. Studies have also shown that acute antidepressant  
165 treatment can enhance positive biases in healthy volunteers and patients with MDD [53-55].  
166 For a more detailed discussion of the proposed relationship between affective biases and  
167 mood disorders, and the neuropsychological hypothesis of antidepressant action see Harmer,  
168 Duman and Cowen 2017 [56].

169 A task frequently used to specifically measure reward processing biases in humans is the  
170 'Response Bias Probabilistic Reward Task' [57]. Here, subjects are presented with two  
171 ambiguous stimuli to which they must discriminatively respond to gain a reward. The correct  
172 identification of one stimulus is more frequently rewarded, so the expected response of  
173 healthy subjects would be to develop a bias for responding to the more frequently rewarded  
174 stimulus, thus demonstrating intact learning and decision-making about reward-related  
175 stimuli. Patients with MDD consistently show an impaired response bias to the more  
176 frequently rewarded cue when the reward is not present, compared to healthy controls [58-  
177 61]. This suggests depressed patients have impaired learning and decision-making biases for  
178 "hot" stimuli, i.e. stimuli with emotional value.

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

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

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

## 200 **2.1. Relationship between affective biases and other reward-related deficits**

201 For the purposes of this review, reward-related deficits are categorised in to three  
202 mechanisms of processing involving hedonic responses ('liking'), motivation ('wanting'), and

203 learning (including anticipation of reward and decision-making capability) [76]. A lack of  
204 consistent evidence for the traditional view of consummatory anhedonia in MDD patients has  
205 led to a re-conceptualization of the term ‘anhedonia’ to refer to an “impaired ability to  
206 pursue, experience and/or learn about pleasure” [77], suggesting anhedonia is not a deficit  
207 only in ‘liking’ but additionally encompasses ‘wanting’ and learning. Although the recognition  
208 of heterogeneity in patients indicates anhedonia might seem to include these three aspects,  
209 but they may not be seen all at the same time, nor all within the same individual.

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

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

### 231 **3. Reward-related deficits in rodents**

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

243 In the following sections, we discuss three major types of reward-related deficit and the  
244 behavioural assays used to measure these deficits in both patients and rodent models of  
245 MDD. Given the relationship observed between affective biases and reward-related learning,  
246 memory and decision-making, these are discussed within section 3.1. We describe our current  
247 understanding of the neurobiological substrates that might be underpinning these behaviours  
248 from using pharmacological and psychological manipulations, with the aim of elucidating  
249 where distinct or interacting, neurobiological mechanisms contributing to these reward-  
250 related deficits.

### 251 **3.1. Reward learning**

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

#### 258 *3.1.1. Associative learning*

259 Pavlovian associations between a neutral stimulus and an unconditioned stimulus (i.e.  
260 reward) are well known to be formed with repeated pairings [89], and can be strengthened  
261 with greater reward value or altering expectation of reward through prediction error [78].  
262 Instrumental associations are formed between a neutral stimulus requiring a response to  
263 produce a reward [90]. Dysfunctional associative learning has been linked to the development  
264 of depression, with patients often demonstrating impairments in positive reward associations  
265 [91].

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

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

278 In similar, contextual Pavlovian association tasks, Papp *et al* [12] demonstrated that healthy  
279 rodents show a greater preference for the environment in which several types of rewards  
280 were presented to them, indicating a learned conditioned place preference (CPP). However,  
281 models of chronic unpredictable stress showed reduced CPP, indicating they had reduced  
282 Pavlovian associative learning of reward-related contextual environments.

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

### 289 *3.1.2. Rodent behavioural assays of affective bias*

290 The influence of emotional cues on cognitive function is a major area of depression research  
291 [95] and the reward neuro-circuitry has been heavily linked to disrupted cognition in MDD  
292 [96]. Thus, changes in processing of rewarding stimuli is an important aspect to investigate  
293 when assessing rodent models.

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

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

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

318 Decision making and interpretation biases induced by affective biases in rodents can be  
319 measured by the judgement bias task (JBT) [103]. Rodents are trained to produce one  
320 response to the presentation of a positive stimulus, and a different response to the  
321 presentation of a negative or less positive stimulus. Rodents hypothesised to have a positive  
322 affective state display a bias whereby ambiguous stimuli are more likely to elicit the response  
323 trained to the positive stimulus. In contrast, rodents in a negative affective state exposed to

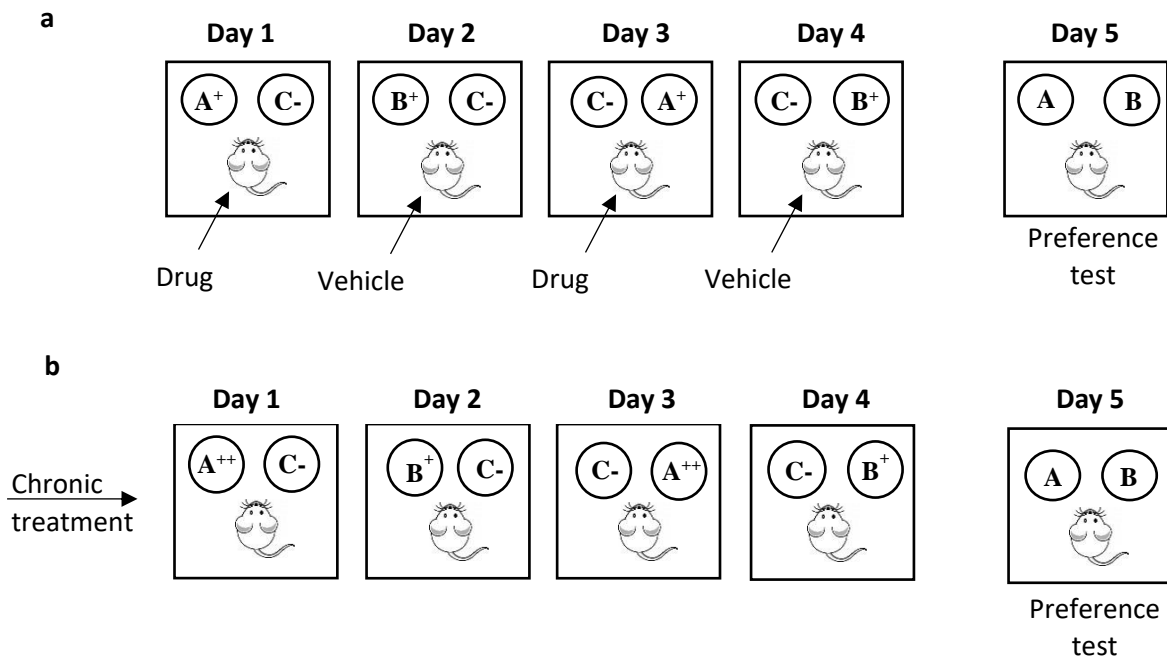


324 the same ambiguous stimuli display a bias to responses trained to the negative stimulus [104-  
325 107]. Thus, their judgements and/or interpretations of stimuli can be altered by changes to  
326 their affective states. A novel version of this task has also been developed which utilizes  
327 rodent natural investigative behaviours rather than lever pressing, which recapitulate similar  
328 effects of affective state manipulations on judgement bias [108]. Further, recent studies have  
329 evaluated translational human versions of this task, which link negative biases with  
330 pathological anxiety [95, 109, 110].

331 More recently, the affective bias test (ABT) has been developed to address the gap in  
332 assessing learning and memory impairments driven by affective biases (for full reviews of the  
333 ABT see [4, 10, 74]). In this task, rodents associate a particular digging substrate with a reward  
334 and a different substrate with no reward (figure 1a). Rodents hypothesised to have a  
335 pharmacologically induced positive affective state during the presentation of one reward-  
336 paired substrate will demonstrate a bias toward that substrate in a choice test with a different  
337 reward-paired substrate in which their affective state was not manipulated (neutral). In  
338 contrast, rodents in a negative affective state will show bias toward the neutral reward-paired  
339 substrate. [80, 111]. Thus, biases in reward-related learning and memory can be influenced  
340 by affective states and such biases can be modelled in rodents.

341 This task has also been modified to investigate the effects of long-term affective state  
342 manipulations, for example chronic drug treatments or environmental stressors on reward  
343 learning and the ability of an animal to develop a bias towards a cue previously associated  
344 with a higher value reward. In the modified ABT (mABT, figure 1b), rodents are given pairing  
345 sessions to learn the association between one digging substrate and a high value reward (i.e.  
346 two reward pellets), and another digging substrate with a low value reward (i.e. one reward  
347 pellet). A healthy animal develops a bias toward the substrate associated with the higher  
348 valued reward when presented with a choice between the two previously paired substrates,  
349 i.e. a reward-induced positive bias. In contrast, rodents in a putative negative affective state  
350 display no or reduced bias for the higher valued reward [80]. Thus indicating that a negative  
351 affective state can alter reward-related learning and memory. Important for this discussion,  
352 these same animals did not show consistent impairments in SPT or PR tasks suggesting this  
353 reward-learning deficit is not mediated by the same underlying neurobiology as reward  
354 consumption and motivation, and does not result from a change in either of these aspects of  
355 reward processing [80].

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



**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<sup>+</sup> and B<sup>+</sup> 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<sup>++</sup>) or another substrate containing one reward pellet (B<sup>+</sup>), 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.

363 **3.1.3. Neurobiological substrates of affective bias**

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

371 In rodents, pharmacological manipulations have been used to identify potential  
372 neurochemical factors and neurobiological pathways in affective processing biases (see table  
373 2 for a list of example evidence, for a detailed review see [74]). Taking the main affective bias  
374 assays in turn, administration of D2/D3 agonists expected to decrease dopamine signalling  
375 are shown to impair reward bias in rats using the PRT described in 3.2.2 [97], which matches  
376 findings in humans using the original task [123]. Psychosocial stress also impairs reward bias  
377 in both species with the PRT [124, 125].

378 Using the JBT, the number of studies investigating neurobiological mechanisms are still  
379 limited but do suggest involvement of monoamines (dopamine and 5-HT, although data for  
380 5-HT is mixed and may depend on acute versus chronic treatment) and the endocannabinoid  
381 system in inducing positive interpretation biases [126, 127]. The benzodiazepine inverse  
382 agonist and, interestingly, noradrenaline re-uptake inhibitors induce a negative bias following  
383 acute treatment [127]. Further, psychosocial stress induces negative interpretation biases  
384 [107] whilst environmental enrichment enhances positive biases [128].

385 Negative learning and memory biases have been found in the ABT with acute antagonism of  
386 the endocannabinoid system, along with psychosocial stress, whilst drugs of abuse do not  
387 influence biases [111], indicating the affective state manipulation drives altered learning and  
388 memory bias, not simply activation of the dopamine reward system. Monoamine depletors,  
389 such as tetrabenazine, and several immunomodulators are also shown to induce negative  
390 biases in the ABT [80]. Furthermore, chronic treatment with interferon-alpha (IFN- $\alpha$ ) or  
391 retinoic acid reduced reward-induced positive biases in the mABT compared to vehicle  
392 treated controls, whereas consummatory behaviour in the SPT was unaffected by these  
393 treatments [80]. IFN- $\alpha$  is used to treated viral diseases, such as hepatitis C, and has been  
394 associated with the development of depressive symptoms in patients receiving this treatment  
395 [129]. Similarly to findings in the ABT, hepatitis C patients receiving this treatment present  
396 negative biases in processing of emotional facial expressions, though these biases did not  
397 correlate with depression ratings [130].

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

### 410 **3.2. Hedonic experience**

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

#### 414 *3.2.1. Rodent behavioural assays of consummatory anhedonia*

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

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

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

444 Although these methods of assessing consummatory anhedonia in rodents has been refined  
445 and optimised, and orofacial reactivity has been compared to similar facial expressions  
446 produced by new born infants, it is still open to question how translatable these are to patient  
447 symptomology. As discussed previously, there is little evidence showing blunted or altered  
448 taste reactivity to sweet tastes in depression [135, 143]. Instead, impaired consummatory  
449 anhedonia has been found following self-reported pleasure ratings [144, 145], alongside  
450 deficits in anticipatory anhedonia. This apparent difference could reflect a number of factors,  
451 including difficulties in objectively measuring consummatory behaviour in humans whose

452 patterns of eating/drinking are presumably more complex than that of rodents, or that the  
453 majority of human studies use more monetary rewards than the natural rewards of food and  
454 water [41]. Nevertheless, reduced LCS and reduced orofacial reactions to sucrose solutions in  
455 rodents represent a functional analogue of anhedonia (i.e. a reduced response to normatively  
456 rewarding events), regardless of the subjective experience itself [13]. That said, it is important  
457 to acknowledge that these simple measures of consummatory behaviour may not reflect the  
458 complexity of hedonic experience in humans.

### 459 3.2.2. Neurobiological substrates of anhedonia

460 Traditional views of the neuropharmacology of anhedonia in MDD suggested that dopamine  
461 was a core mediator of this reward process, given evidence that dopaminergic receptor  
462 antagonists appeared to inhibit ICSS and CPP learning [146, 147], as well as reducing sucrose  
463 preference in the SPT [148]. More recently, the application of more sensitive analyses of  
464 hedonic experience suggest that consummatory anhedonia is not influenced by dopaminergic  
465 neurotransmission. Instead, these earlier assessments of ‘anhedonia’ did not appropriately  
466 dissociate motivational processes from ‘liking’, and dopamine plays a greater role in incentive  
467 salience than hedonic experience of reward [149-151]. While dopaminergic manipulations  
468 can influence selective consumption-based assays of hedonic responses - for example, Peciña  
469 *et al* [152] report taste reactivity responses to be influenced by the administration of  
470 dopamine antagonists – the effects are seen either after multiple sessions or late in extended  
471 test sessions. This implies the effects of dopamine on hedonic reactions is indirect and may  
472 rely on interactions with other reward processing aspects, such as learning [13].

473 Furthermore, some studies investigating alteration of serotonergic neurotransmission have  
474 also found no effect on lick cluster size (LCS), though inhibition does appear to reduce overall  
475 consumption whilst activation enhances consumption [153, 154]. However, Galistu *et al* [155]  
476 demonstrate that the atypical antipsychotic Clozapine does increase LCS without influencing  
477 overall consumption. Since Clozapine is believed to work through multiple neurotransmitter  
478 pathways including serotonin and dopamine it could be suggested that some monoaminergic  
479 transmission is involved in hedonic experience, however, their discussion of findings  
480 compared to previous research has ruled out the possibility of 5-HT<sub>2</sub> receptors and dopamine  
481 involvement in this process from clozapine’s multiple potential mechanistic actions.

482 Opioid receptor stimulation in the nucleus accumbens (NAc) and ventral pallidum (VP)  
483 increase positive hedonic orofacial reactions to reward [156, 157]. Lick microstructural  
484 analysis has been less consistent in reporting opioid contribution to hedonic experience, with  
485 many studies showing direct stimulation with opioid agonists/antagonists does not affect LCS  
486 [158, 159]. Based on the evidence in orofacial reactivity studies, it is suggested there are  
487 different ‘hotspots’ in the brains reward system that mediate different aspects of reward  
488 processing. As such, opioid stimulation in specific regions such as the rostradorsal NAc shell  
489 enhance hedonic reactions to reward [160], whilst in different regions opioid stimulation  
490 enhances motivation/incentive salience [161, 162], which could explain contradictory findings  
491 with less specific opioid stimulation.

492 Benzodiazepines, GABA<sub>A</sub> receptor agonists, have additionally shown to increase orofacial  
493 reactions to rewarding solutions, without affecting aversive reactions to a bitter solution  
494 [163]. Increased LCS following benzodiazepine administration has also been shown using lick  
495 microstructure analysis [164]. Evidence that blocking opioid receptors can attenuate the  
496 effects of benzodiazepines on hedonic reactions suggests the mechanisms by which  
497 benzodiazepines work in hedonic experience may involve opioid neurotransmission [165]

498 Recent studies in our group have shown distinct effects on hedonic responses following  
499 treatment with IFN- $\alpha$  and corticosterone, both known to induce negative affective biases in  
500 the ABT (Unpublished work; [142]). We found that chronic IFN- $\alpha$  treatment did not affect LCS  
501 in rats using microstructural analysis of licking, supporting findings from previous SPT data  
502 [80, 166]. IFN- $\alpha$  also does not alter the rate of sucrose pellet self-administration [167] or brain  
503 stimulation reward thresholds [168], suggesting its effects on depressive symptoms are not  
504 related to hedonic experience or sucrose preference.

505 We did find that chronic corticosterone treatment significantly reduced LCS in rats, supporting  
506 previous SPT data [169-171]. Further, psychosocial stress has consistently resulted in reduced  
507 reward sensitivity as indicated by the SPT [12, 35, 172], but there has been very limited  
508 investigation of psychosocial stress with more selective measures of hedonic experience  
509 (although see [13]).

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

### 517 **3.3. Motivation**

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

#### 525 *3.3.1. Rodent behavioural assays of motivational deficits*

526 One rodent assay that has been used for several decades to investigate the neurobiological  
527 basis of anhedonia is intracranial self-stimulation (ICSS) [174]. Electrodes are surgically  
528 implanted in specific regions of the limbic system, such as the ventral tegmental area (VTA),  
529 such that activation of the area was achieved by the rodent self-stimulating the electrodes  
530 through responding on a manipulandum. Levels of anhedonia would be scored through  
531 altering the reward stimulation frequency and assessing how much rodents would respond

532 to higher or lower frequencies. Models of anhedonia were suggested to show reduced  
533 responding to lower frequencies compared to healthy rodents, and the major neurobiological  
534 pathway thought to be involved in mediating ICSS were dopaminergic [175-177]. However,  
535 this task is now more associated with motivational processing, rather than hedonic  
536 experience [14, 178, 179], through measuring willingness to work for a reward. It could also  
537 be argued that changes in responding to reward frequencies may reflect alterations in motor  
538 activity, especially given dopamine's role in motor function [180], however, the discrete-trial  
539 current threshold version of the ICSS task has been developed to reduce the sensitivity of this  
540 task to motor impairments [176, 181].

541 Another commonly used method for examining motivation for reward in rodents is the  
542 progressive ratio (PR) task, in which the number of lever presses required to obtain a fixed  
543 reward progressively increases, and motivation is assessed as their 'breakpoint', i.e. at what  
544 level of effort required will they stop responding [182]. Humans with motivational deficits  
545 show dysfunctional dopaminergic transmission [183, 184] and similarly, disrupted  
546 dopaminergic systems in rodent models impairs motivation in the progressive ratio task [182,  
547 185, 186] suggesting translational neurobiological mechanisms underpinning behaviours in  
548 the PR task. However, in animal models of depression or schizophrenia there has been a lack  
549 of consistent deficits observed in PR tasks [187-189]. There are several limitations of using PR  
550 tasks to represent motivational deficits (see [190]) including difficulty in dissociating between  
551 motivational or motor impairments, whilst some might also argue PR tasks could be  
552 influenced by habitual responding or impulse control deficits [185]. See Salamone [184, 191]  
553 for detailed discussions of a behavioural economics approach suggested to overcome some  
554 of these limitations with PR tasks, which is beyond the scope of this review.

555 Reward motivation deficits are common in patients with MDD [178, 192] and translational  
556 behavioural assays for these impairments have been developed for humans and animal  
557 models. In patients, methods such as the computer game-based 'Effort Expenditure for  
558 Rewards Task' (EEfRT) [193] have been employed to measure such motivational impairments.  
559 Here, subjects have a choice between participating in a low difficulty task (requiring 30 button  
560 presses in 7 seconds) for a smaller monetary reward or a higher difficulty task (requiring 100  
561 button presses in 21 seconds) for a greater monetary reward, thus subjects are required to  
562 use a greater amount of effort to gain a higher value reward. Some studies using this task  
563 have shown a decreased amount of effort expenditure to gain the higher valued reward in  
564 both healthy people with higher ratings of anhedonia [42, 193] and with clinical MDD [194,  
565 195], and some evidence suggests these impairments in the EEfRT are predicted by greater  
566 levels of anticipatory anhedonia [42, 196].

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

573 *3.3.2. Neurobiological substrates of motivational deficits*

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

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

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

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

608 Alternately, serotonergic pathways do not appear to play a role in effort-choice/motivational  
609 processes. Denk *et al* demonstrated that treatment with a tryptophan hydroxylase inhibitor  
610 did not affect performance of rats in a T-maze task given a choice between climbing a barrier  
611 to gain a high valued reward or entering an obstacle-free arm to gain a low reward, whereas  
612 those treated with a dopamine receptor antagonist showed reduced effort [210]. Similarly,  
613 Izquierdo *et al* reproduced this lack of effect of the tryptophan hydroxylase inhibitor on the  
614 same task, but found that instead rats showed an impaired reversal learning, suggesting the  
615 serotonergic system may be more involved in cognitive reward processing [211]. However, it



616 has been shown that an antagonist for serotonin 2C receptors can enhance instrumental  
617 responding in a progressive ratio task and increase effort for greater reward in the effort-  
618 related choice paradigm [212]. Given that antagonism of these receptors increase  
619 dopaminergic firing from the ventral tegmental area and NAc, it is thought that this underlying  
620 mechanism involves dopamine signalling more than serotonin itself.

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

### 624 **3.4. Summary**

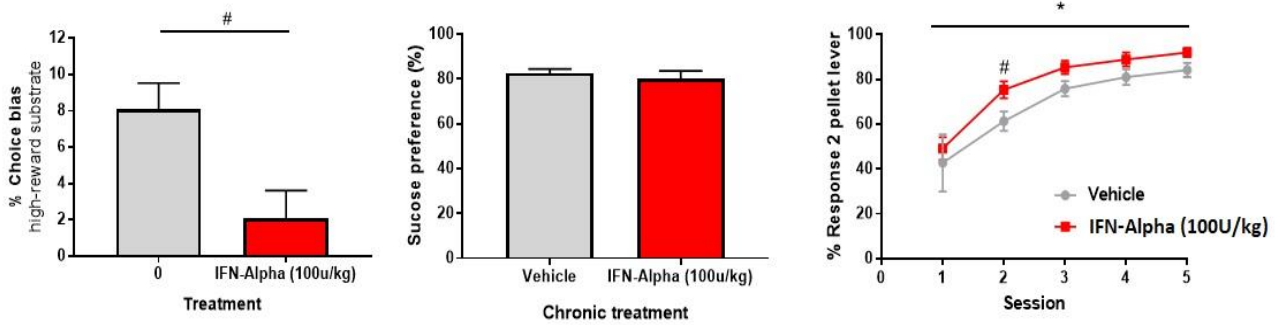
625 The challenge of reliably measuring and dissociating reward processing deficits has been  
626 highlighted through inconsistencies in reporting and treating patient symptoms. Assays often  
627 used in patients do not effectively differentiate between multiple reward-related  
628 components that may be disrupted, and as a result, treatments have had poor efficacy.  
629 Developments in rodent assays of reward-related deficits are beginning to reveal dissociable  
630 behaviours specifically linked to separate domains of reward processing. Important to this  
631 discussion is data for the same manipulations inducing dissociable effects on different  
632 measures of reward, as illustrated in figure 2. Here, and in Stuart *et al* [80], chronic  
633 pharmacological treatments were shown to induce a deficit in reward-induced positive biases  
634 with no effect in the SPT. We have also undertaken a pilot study to investigate reward learning  
635 using a lever press task where chronic IFN- $\alpha$  treatment had no effect, further supporting our  
636 conclusions that the effects seen in the modified ABT are specific.

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

649 From the evidence to date, we can support the hypothesis that distinct neurobiological  
650 mechanisms may underpin reward-related learning and memory deficits in models of MDD,  
651 as well as mechanisms involved in incentive motivation arising from the re-activation of  
652 reward-associated memories, compared to hedonic experience [74]. However, there are still  
653 some overlaps and interactions between these processes which indicate they are not entirely  
654 separate, thus, heterogeneity seen in patients may arise from differences in aberrant  
655 neurobiological changes, along with different environmental and genetic factors. Further,  
656 issues with clinical assessments remain, in particular relating to hedonic experience.  
657 Development of human tasks that can similarly dissociate between these different aspects of

658 reward processing would be valuable both in terms of understanding the relationship  
659 between these deficits and disease symptoms, but also to enhance the translational validity  
660 of rodent models [178].

661



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

662 Chronic interferon-alpha (IFN- $\alpha$ ) treatment induces a deficit in reward-induced positive bias (panel  
663 A) but has no effect on sucrose preference (panel B). The data shown in panel A and B are from  
664 the same animals which received a 14-day treatment with IFN- $\alpha$  (100u/kg, i.p. once daily) or control  
665 and then tested in the modified affective bias test and a 1% sucrose preference test (data taken  
666 from Stuart et al., 2017). In a separate cohort of rats (n=6 per group) a preliminary study using a  
667 lever press task failed to show any deficit in learning to associated one lever with a higher value  
668 reward (panel C, data unpublished, Benn et al). In this pilot studies, animals were first trained using  
669 a continuous reinforcement schedule where each lever was presented on alternate days until they  
670 were consistently responding with >50 lever presses/session. Animals were then switched to a  
671 protocol where both levers were presented and responses paired with either a one or 2 pellet  
672 reward (left or right lever press was paired with the higher value reward, counter-balanced across  
673 animals). IFN- $\alpha$  treatment (14 days, once daily, dosing before testing) failed to induce any learning  
674 deficit with the animals treated with IFN- $\alpha$  showing a higher rate of acquisition (main effect of  
675 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  
676 (2.4, 24.1) = 0.56, p = 0.607). Although only a small scale pilot experiment, these data do support  
677 our hypothesis that the deficits seen in the m-ABT are related to the ability to use reward  
678 information to guide behaviour when the current information available is ambiguous. During the  
679 choice test, rats must rely on their prior knowledge to make a decision about which substrate to  
680 choose as the reinforcement schedule is randomised for this phase of the task. In the sucrose  
681 preference test and lever press task, the information about reward value is available throughout  
682 the task and animals do not show the same impairment.

674

675

<b>Reward-related deficit</b>	<b>Rodent Behavioural Assay</b>	<b>Key References</b>	<b>Human Behaviours</b>
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> [10] 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]

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<sub>A</sub> agonists in the VP <i>reduces</i> incentive motivation/effort for reward.</p>	<p>Salamone <i>et al</i> [184, 197, 201]; DiFeliceantonio &amp; 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<sub>A</sub> 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 &amp; Berridge [156, 157]; Berridge &amp; Krangelbach [137]; Castro &amp; Berridge [160].</p> <p>Berridge &amp; 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> [12]</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<sub>A</sub> receptor agonist (FG7142), retinoic acid, monoamine depletors (tetrabenazine), corticosterone immunomodulators (lipopolysaccharide, IFN-<math>\alpha</math>). Positive biases induced by social enrichment.</p> <p>In the mABT, negative biases are induced by chronic treatment with IFN-<math>\alpha</math> and retinoic acid.</p>	<p>Pizzagalli <i>et al</i> [123]; Der-Avakian <i>et al</i> [97]</p> <p>Bogdan &amp; 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) [10]</p> <p>Robinson (review) [74]</p>

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

#### 676 **4. Antidepressant actions and implications for treatments**

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

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

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

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

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

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

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

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

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

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

## 769 **5. Conclusion**

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

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