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Rat models of reward deficits in psychiatric disorders

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Loss of interest in rewarding activities is a hallmark of many psychiatric disorders and may be relevant for neurodegenerative disorders and patients suffering from brain injury. There is increasing evidence that deficits in reward-related behaviour are more complex than previously described. The traditional view of anhedonia as 'the inability to experience pleasure' may be too limited to fully encompass the types of reward deficit observed in these patients. Developments in methods to measure different aspects of reward processing in humans and animals are starting to provide insights into the complexity of this behaviour. In this article we consider the rodent models which have traditionally been used to study reward deficits in psychiatric disorders and consider their limitations relative to clinical findings. We then discuss work where methods derived from human neuropsychological tests are providing insights into the complexity of reward-related behaviour. Specifically, we consider tasks which investigate different aspects of reward-related behaviour focusing on learning and memory as well as decision-making and consider what these may mean in terms of how we model reward deficits in rodents.

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Introduction

Deficits in reward processing are observed across a range of psychiatric disorders [1–6]. More broadly, impairments in reward processing may contribute to the observed motivational deficits, loss of interest in social interaction, and apathy. Whilst reward deficits are clearly an important feature of these clinical conditions, there are currently no treatments which specifically target these symptoms. Animal models are an important element of aetiological studies and drug development programmes. However, using animals to study complex human psychological symptoms is often challenging. In this article, we consider why traditional consummatory and motivational tests for anhedonia may be limited in terms of providing a valid translational approach to studying the reward deficits that are most prevalent in these different patient populations. We also consider whether new tasks, which look at more complex processing of reward information, may provide a better approach. Specifically, we discuss new data from models looking at reward learning and decision-making as well as studies where biases in reward-related behaviour have been linked to changes in affective state.

What is anhedonia?

Historically, anhedonia was defined as an 'inability to experience pleasure' [7]. However, in the last 20 years, knowledge relating to the neurobiology of reward and how we consider this in relation to anhedonia has developed. This has resulted in a growing interest in how we define anhedonia and consequently how we model this in rodents. Whilst the exact definitions are debated (see Table 1 and review articles [8–11,12•,13,14]), it is suggested that symptoms of anhedonia observed in patients may be due to deficits in one or several different components of reward processing: firstly, consummatory experience of reward, secondly motivation for reward, thirdly reward learning and finally decision making. In relation to major depressive disorder, impairments in reward-related behaviour are more broadly set out in the DSM-5 as a 'loss of interest or pleasure in previously rewarding activities'. Reward-related behavioural deficits are also considered within the recent concept of Research Domains Criteria (RDoC) framework for mental health research [15–17]. The positive valance system makes up one of the key domains which has been included in this framework. In this article, we will focus our discussion on methods to assess these different subcomponents of reward (see Figure 1, panel a for summary). We briefly discuss why traditional consummatory and motivational tests for anhedonia may be limited in terms of providing a valid translational approach to studying the reward deficits that are most prevalent in different patient populations. We also discuss whether recently developed methods looking at reward learning, memory and decision-making may provide a better approach. Specifically, we discuss new data from behavioural tasks which have been looking at reward learning and decision-making as well as studies where biases in reward-related cognition have been linked to changes in the emotional state of the animal, more commonly referred to as affective state in non-human species.

Table 1

Summary of some of the key papers relating to the discussions about how we define anhedonia and reward-related deficits in psychiatric disorders [7,8,9,12•,13,14]

Year	Definition of anhedonia	Reference
1896	'The inability to experience pleasure'	Ribot (1896)
2003	Liking Wanting	Robinson and Berridge (2003)
2008	Liking, wanting, learning (pleasure cycle = appetitive, consummatory and satiety	Berridge and Kringelbach (2008)
2011	Distinction between consummatory, motivational and decision-making	Treadway and Zald (2011)
2012	Distinction between anhedonia and cognitive aspects of reward	Der-Avakian and Markou (2012)
2015	'Impairments in the ability to pursue, experience and/or learn about pleasure'	Thomsen (2015)

Limitations associated with consummatory and motivational deficits in reward-related behaviour in rats

Most studies investigating reward processing in rodents have used tasks based on consummatory behaviour (hedonia) and motivation for reward (see [1,2,12•,13,14,18,19] for detailed review of relevant methodology). For example, reward sensitivity can be measured directly using intracerebral self-stimulation methods where deficits resulting from chronic stress are observed as an increase in the stimulation threshold [20]. A simpler and more commonly used method to study anhedonia, particularly for depression research, has been the sucrose preference test (SPT) where the ability of an animal to detect and show a preference for a weak sucrose or saccharin solution over water is measured [21]. Animals in putative negative affective states following exposure to chronic stress show a reduced sucrose preference [21–23]. However, not all depression models show impairments in the SPT and studies in Schizophrenia models also fail to observe deficits [1,24]. Additionally, in the human literature, depressed patients do not exhibit deficits in a similar sweet taste test [25,26] suggesting limited translational validity of the SPT.

Motivation for reward tasks, such as progressive ratio and effort-based tasks, provide an alternative method to study reward-related behaviours [15,27]. In the progressive ratio task, over several trials rats are required to perform incrementally higher operant responses (e.g. press a lever) in order to obtain the same amount of reward. Motivation in this task is determined as the point at which rats stop responding (i.e. their 'breakpoint'). Whilst this task displays reasonable translational validity, with both humans and rodents displaying motivational deficits related to dopamine depletion [28–30] models of depression (e.g. chronic mild stress and maternal separation) and other psychiatric disorders in rodents display less consistent changes in motivation [31,32•,33], although also see [34•]. In progressive ratio tasks, increased effort (number of responses) is also associated with an increase in time to obtain reward and therefore may be confounded by motor impairments. There is also the potential for animal's tolerance to delayed reward to contribute to behavioural outcomes which, whilst potentially of interest, may relate more to neural circuits modulating impulse control as opposed to reward. Because of the limitations of the standard progressive ratio task, effort-based choice tasks have been developed where animals are required to choose between an easy to obtain low-value reward versus a high-value/high-effort reward [5,35••,36,37•,38,39]. This task requires the animal to make a choice based on motivation for the different reward option and hence also models decision-making behaviour. Validation of the model is still limited but there is a clear translational advantage with similar human methods now being used [40]. More detailed discussion about these tasks and their associated psychopharmacology are reviewed in [1,18,38,40].

New developments in methods to study reward-related cognition and affective biases

Advances in measuring reward-related behaviour in humans, such as the move away from subjective, questionnaire-based methods and the development of computer-based neuropsychological tasks, have supported reverse translation into animal research. An excellent example of this is the probabilistic reward learning task [41–43] and probabilistic reversal learning task [44,45]. In both models, the animal is required to learn contingencies associated with different cues despite receiving false feedback resulting from the probabilistic nature of the reward delivery. Probability of reward can be altered to increase task difficulty, and response bias, discriminability, accuracy, reaction time and sensitivity to positive and negative feedback can all be collected. Tasks using operant chambers with spatial cues or tones, a touchscreen task and methods using odour cues have all been piloted [1,43]. However, it should be noted that there are marked differences between human and rat data in terms of the proportion of lose-shift responses after misleading negative feedback suggesting the underlying biology may be different.

In our own laboratory, we started looking at how affective states could modify reward learning as part of our research into affective biases [46,47]. Affective bias is a term used to describe how affective states influence cognitive