



Pavlovian influences on learning differ between rats and mice in a counter-balanced Go/NoGo judgement bias task



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ABSTRACT

Judgement bias tests of animal affect and hence welfare assume that the animal's responses to ambiguous stimuli, which may herald positive or negative outcomes, are under instrumental control and reflect 'optimism' or 'pessimism' about what will happen. However, Pavlovian control favours responses (e.g. approach or withdrawal) according to the valence associated with a stimulus, rather than the anticipated response outcomes. Typically, positive contexts promote action and approach whilst negative contexts promote inhibition or withdrawal. The prevalence of Go-for-reward (*Go-pos*) and NoGo-to-avoid-punishment (*NoGo-neg*) judgement bias tasks reflects this Pavlovian influence. A Pavlovian increase or decrease in activity or vigour has also been argued to accompany positive or negative affective states, and this may interfere with instrumental Go or NoGo decisions under ambiguity based on anticipated decision outcomes. One approach to these issues is to develop counter-balanced *Go-pos/NoGo-neg* and *Go-neg/NoGo-pos* tasks. Here we implement such tasks in Sprague Dawley rats and C57BL/6J mice using food and air-puff as decision outcomes. We find striking species/strain differences with rats achieving criterion performance on the *Go-pos/NoGo-neg* task but failing to learn the *Go-neg/NoGo-pos* task, in line with predictions, whilst mice do exactly the opposite. Pavlovian predispositions may thus differ between species, for example reflecting foraging and predation ecology and/or baseline activity rates. Learning failures are restricted to cues predicting a negative outcome; use of a more powerful air-puff stimulus may thus allow implementation of a fully counter-balanced task. Rats and mice achieve criterion faster than in comparable automated tasks and also show the expected generalisation of responses across ambiguous tones. A fully counter-balanced task thus offers a potentially rapidly implemented and automated method for assessing animal welfare, identifying welfare problems and areas for welfare improvement and 3Rs *Refinement*, and assessing the effectiveness of refinements.

1. Introduction

Valid translational models of affective disorders, better measures of animal welfare that allow more effective detection of welfare problems and implementation of 3Rs *Refinements*, and a deeper understanding of the evolutionary history and mechanistic underpinnings of affective states, all require accurate measurement of affect in animals. Over the last decade, an assay to measure decision-making under ambiguity (the so-called 'cognitive' or 'judgement' bias test) has been used in a wide range of species as a new indicator of affective valence (positivity or negativity) [1–8]. This approach is based on empirical findings that people in negative affective states (as judged by their reports of the subjective experience of negative emotions) make more negative and pessimistic judgements about ambiguous or future events than happier

people [9,10], and on theoretical arguments that such affect-related changes in decisions about ambiguity have adaptive value and hence are likely to be observed across species [11–13]. For example, a negative state resulting from recent experience of negative or punishing events should increase prior expectations of the future likelihood of punishment, thus favouring cautious decisions, especially under ambiguity where there is a lack of information about the true current situation, including choice outcomes [12].

Originally developed for rats [1], the generic judgement bias assay involves training animals to make one type of response (*P*: e.g. lever-press) to a cue predicting a positive event or reward (*p*: e.g. a tone of a particular frequency) in order to receive that reward (e.g. food delivery), and another type of response (*N*: e.g. no lever-press) to a cue predicting a negative event or punisher (*n*: e.g. a tone of a different

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frequency) in order to avoid that event (e.g. white noise). Once this discrimination is learnt, subjects receive occasional ‘ambiguous’ cues (e.g. tones in between p and n). Their tendency to make P (‘optimistic’) or N (‘pessimistic’) responses to these ambiguous cues is used to infer whether they anticipate that a positive or negative outcome is more likely, and hence whether their underlying affective state is, respectively, relatively positive or negative. The task has been adapted for use in a range of mammals (e.g. rats [14–20]; mice [21,22]; hamsters [23]; dogs [24,25]; sheep [26,27]; pigs [28,29]; cattle [30,31]; monkeys [32,33]; peccary [34]), birds (e.g. starling [35,36]; chicken [37,38]), and insects [39–41], and it has also been back-translated to humans [42–45]. A variety of affect manipulations has been employed. Many of the published findings (but not all [37,46–52]) are consistent with the hypothesis that, like humans, non-human animals in assumed negative affective states show negatively biased judgements of ambiguity. Thus, judgement biases may be useful indicators of the valence of an animal’s affective state even though, like all measures of animal affect, they cannot tell us whether the inferred affective state is consciously experienced in other species [53].

Judgement bias tests assume that the animal’s response to an ambiguous stimulus is under instrumental control; it reflects the learnt contingency between response and outcome (e.g. response P indicates anticipation of a positive outcome). However, decisions are also influenced by Pavlovian control which elicits responses, primarily approach or withdrawal, according to the valence associated with a cue rather than the consequences of the responses. There is evidence for a natural predisposition for active approach and engagement in a rewarding context (e.g. in response to a p cue that may be intrinsically rewarding, or acquire positive valence through a rewarding outcome), and inhibition or withdrawal in the face of punishment (e.g. in response to an n cue) [54–57]. The resulting ‘hard-wired’ stimulus-response decision policies may be implemented in the functional architecture of the basal ganglia where excitation of the ‘direct pathway’ generates active responses for reward whereas excitation of the ‘indirect pathway’ inhibits motor responses in the context of punishment. Likewise, the dopaminergic system plays a role in active reward-seeking behaviour whilst the serotonergic system may be more involved in aversion-related behavioural inhibition [54,58,59].

One effect of this Pavlovian influence is that active P responses are learnt faster than active N responses. For example, in balanced active two-choice judgement bias tasks (e.g. P = left lever press; N = right lever press), active lever-pressing to avoid a predicted punisher (N) is much more difficult to learn than the same response to acquire a predicted reward (P) (e.g. 6 vs 13–17 days; 14–17 vs 25–26 days; see Ref. [19]), making these tasks very time consuming to implement. A pragmatic, and likely implicit, consequence is the popularity of making the P response active (Go) and the N response inactive (NoGo) in the majority of judgement bias tasks.

However, in these commonly-used Go-for-reward and NoGo-to-avoid-punishment tasks, Pavlovian influences can further complicate interpretation of P or N responses to ambiguity during an affective manipulation. This is because the relative ease of performing P and N may be directly influenced by affective state, hence obscuring the ability of affect to modulate judgement of ambiguity. In particular, an increase or decrease in vigour has been argued to accompany positive or negative affective states respectively [59], hence influencing the type of decision response shown (Go or NoGo) irrespective of the associated outcome of that decision. Experimental treatments may also cause non-affect related changes in general activity that favour Go or NoGo responses, and any extinction of response to ambiguous cues [60], or failure to attend when a cue is presented, will lead to a NoGo response that may be erroneously interpreted as ‘pessimistic’.

One hitherto unexplored solution to these problems is to counter-balance the relationship between vigour and valence, using both a Go-for-reward vs NoGo-to-avoid-punishment contingency as well as its opposite (NoGo-for-reward vs Go-to-avoid-punishment). This design

has been employed to examine Pavlovian biases in human studies [55,58,61,62], but has not been used in the context of animal tests of judgement bias. Such a counter-balanced task would allow direct investigation of the interplay between affective valence, outcome prediction (‘pessimism’ vs ‘optimism’), and Pavlovian response selection (active (Go) vs inactive (NoGo)). For example, if positive valence generates both ‘optimism’ and enhanced vigour, positive (‘optimistic’) choices under ambiguity would be clearly evident in the Go-for-reward contingency but less so under NoGo-for-reward where the two effects are in opposition. If ‘optimistic’ responses are clearly seen in both contingencies, this would indicate that Pavlovian control of response selection is subservient to instrumental control [54]. Thus, a counter-balanced task has the potential to shed new light on processes mediating decision-making under ambiguity in the judgement bias task.

The aim of this study was, therefore, to investigate how easy it is for laboratory rodents to learn counter-balanced Go/NoGo tasks and, in particular, to investigate the hypothesis that Pavlovian predispositions favour more rapid learning of the Go-for-reward/NoGo-to-avoid-punishment contingency. We also sought to develop automated methods which can be readily implemented using widely available equipment, and to develop tests for both rats and mice. The latter are relatively understudied in cognitive bias research, and automated testing is notably absent. The development of an easily implementable test would allow more widespread use of this measure of laboratory animal affect and welfare, hence facilitating better detection of animal welfare problems and areas where 3Rs *Refinement* of housing or experimental procedures would improve welfare, and more accurate assessment of the effectiveness of refinements. To these ends, we studied commonly used rat (Sprague Dawley) and mouse (C57BL/6J) strains in a shuttle-box task in which subjects were trained on one of the two Go/NoGo contingencies. For example, in the Go-for-reward/NoGo-to-avoid-punishment contingency, subjects needed to respond to cues predicting reward by shuttling (Go) from the half of the box in which they were currently located to the other half in order to receive reward. In contrast, they had to respond to negative cues by staying (NoGo) in their current half of the box in order to avoid a negative event.

2. Materials and methods

2.1. Experiment 1: rat study

2.1.1. Animals and husbandry

The experimental subjects were 12 male Sprague Dawley rats (*Rattus norvegicus*; Harlan UK Ltd, UK). They were 3 months-old on arrival, and housed in pairs in standard cages (56 cm L × 33.5 cm W × 20 cm H, containing sawdust, shredded bedding, red shelter, wooden chew block and cardboard tube), under a 12hr reversed light-dark cycle (lights on 1900–0700). Food (LabDiet, St Louis, MO, USA) and water were available *ad-libitum*. All the rats were checked regularly for any health issues throughout the experiment, which was conducted under UK Home Office licence 30/2954.

2.1.2. Apparatus

Two shuttle boxes (50.8 cm L × 25.4 cm W × 30.5 cm H) and associated hardware were used. Each box was divided in half by a metal panel to form two chambers between which the rats could move (shuttle) through a central opening (8 cm W × 9 cm H) in the panel (Fig. 1). This apparatus allowed us to train the Go-(shuttle)-for-reward/NoGo-(stay)-to-avoid-punishment and reverse contingencies. Sensors monitored rat movement between the chambers. A loudspeaker was positioned centrally above the panel separating the two compartments, and a feeding trough supplied by an automated food dispenser was positioned at each end of the shuttle box accessible through an opening (3.2 cm W × 4 cm H) in the rear wall of each chamber. The two food dispensers delivered Bioserv (Flemington, NJ, USA) Dustless Precision Pellets (45 mg sucrose pellets). Air-puffs could also be delivered into

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