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Effects of pro-depressant and immunomodulatory drugs on biases in decision-making in the rat judgement bias task

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Abstract

Studies in human and non-human species suggest that decision-making behaviour can be biased by an affective state, also termed an affective bias. To study these behaviours in non-human species, judgement bias tasks (JBT) have been developed. Animals are trained to associate specific cues (tones) with a positive or negative/less positive outcome. Animals are then presented with intermediate ambiguous cues and affective biases quantified by observing whether animals make more optimistic or more pessimistic choices. Here we use a high versus low reward JBT and test whether pharmacologically distinct compounds, which induce negative biases in learning and memory, have similar effects on decision-making: tetrabenazine (0.0–1.0 mg/kg), retinoic acid (0.0–10.0 mg/kg), and rimonabant (0.0–10.0 mg/kg). We also tested immunomodulatory compounds: interferon- α (0–100 units/kg), lipopolysaccharide (0.0–10.0 μ g/kg), and corticosterone (0.0–10.0 mg/kg). We observed no specific effects in the JBT with any acute treatment except corticosterone which induced a negative bias. We have previously observed a similar lack of effect with acute but not chronic psychosocial stress and so next tested decision-making behaviour following chronic interferon-alpha. Animals developed a negative bias which was sustained even after treatment was ended. These data suggest that decision-making behaviour in the task is sensitive to chronic but not acute effects of most pro-depressant drugs or immunomodulators, but the exogenous administration of acute corticosterone induces pessimistic behaviour. This work supports our hypothesis that biases in decision-making develop over a different temporal scale to those seen with learning and memory which may be relevant in the development and perpetuation of mood disorders.

KEYWORDS

animal model, cognition, emotion, major depressive disorder, neuropsychological

Abbreviations: ABT, affective bias test; ANOVA, analysis of variance; CBI, cognitive bias index; DMSO, dimethyl sulfoxide; FST, forced swim test; IFN- α , interferon- α ; ITI, intertrial interval; JBT, judgement bias task; LPS, lipopolysaccharide; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; PCP, phencyclidine; RAAD, rapid-acting antidepressants; rmANOVA, repeated-measures analysis of variance; SPT, sucrose preference test.

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1 | INTRODUCTION

Affective biases, when emotions alter cognitive processing, occur across many different cognitive domains. Studies have demonstrated that negative affective biases in processes such as emotional interpretation, learning, memory, and decision-making contribute to the development and maintenance of mood disorders such as depression and anxiety (Mathews & MacLeod, 2005; Leppänen, 2006; Elliott et al., 2011; Roiser et al., 2012; Robinson & Roiser, 2016). In healthy participants and in major depressive disorder (MDD), it has been shown that positive biases in emotional processing can be induced following acute treatments with antidepressants, despite a lack of subjectively reported change in mood (Harmer et al., 2017). These findings support earlier hypotheses relating to the role of neuropsychological processes in MDD (Beck, 1967, 1976), and adds to the proposal that negative affective biases have a causal role in the development, maintenance, and treatment of MDD (Clark et al., 2009; Harmer et al., 2009; Robinson & Sahakian, 2008). This theory also posits that pharmacological treatments may work by remediating the negative processing of information that, over time, leads to symptomatic improvements. Therefore, investigating the time courses and mechanisms that underlie changes in affective biases may provide further insight into the underlying psychology of mood disorders.

Affective biases can be measured in animal models (Hales et al., 2014; Robinson, 2018; Slaney et al., 2018). The judgement bias task (JBT) is a rodent decision-making task that measures biases in the interpretation of ambiguous cues (Hales et al., 2014; Papciak & Rygula, 2017). In the JBT an animal learns to respond to two distinct stimuli (tones) to receive two different outcomes: positive versus avoidance of negative or high reward versus low reward (Hales et al., 2014; Papciak & Rygula, 2017). Once learnt, judgement bias is tested by presenting an ambiguous stimulus (tone with frequency midway between the two reference tones), with more responses associated with the positive/more rewarding outcome indicative of a positive decision-making bias, and more responses for the negative avoidance/less rewarding outcome indicative of a negative bias. The task has been reverse-translated for use in humans and has shown translational validity (Anderson et al., 2012; Aylward et al., 2020; Daniel-Watanabe et al., 2020). In humans, self-reported state anxiety correlated with a degree of negative bias (Anderson et al., 2012), and people with pathological anxiety symptoms exhibited the same negative biases in the task (Aylward et al., 2020) as those observed in rats that have experienced anxiogenic manipulations (Hales et al., 2016). Furthermore, individual differences in decision-making bias have been shown to be reliably linked to individual differences in depression symptoms (Daniel-Watanabe et al., 2020). Studies in putative models of depression suggest that rats in negative

affective states make more pessimistic choices during ambiguous cue presentation (Chaby et al., 2013; Hales et al., 2016; Harding et al., 2004; Papciak et al., 2013; Rygula et al., 2013). Studies with pharmacological treatments, including antidepressant drugs have resulted in a more mixed picture (Neville et al., 2020). Our work in rats has revealed differences between the time course of biases seen following treatment with conventional antidepressants compared to rapid-acting antidepressants (RAAD) that have shown efficacy in clinical settings, including ketamine (Hales et al., 2017, 2020), an N-methyl-D-aspartate (NMDA) receptor antagonist; CP-101,606, a GluN2B receptor subunit antagonist; and scopolamine, a muscarinic receptor antagonist (Hales et al., 2020). When given acutely fluoxetine, reboxetine, and venlafaxine (conventional antidepressants) had no effect on bias, but chronic treatment with fluoxetine resulted in a positive judgement bias that was seen in the second and third weeks of treatment (Hales et al., 2017). This contrasts with acute ketamine, CP-101,606 or scopolamine treatment, which all induce an immediate positive judgement bias (Hales et al., 2017, 2020). Other NMDA receptor antagonists that have not shown clinical antidepressant efficacy (phencyclidine [PCP], lanicemine, and memantine) also fail to induce a change in bias when given acutely (Hales et al., 2017, 2020). These data suggest that this reward-based JBT is sensitive to pharmacological treatments that induce biases across time courses that correspond to subjectively reported changes in mood in humans following these drug treatments.

In contrast, another rodent task that measures affective biases in learning and memory, the affective bias test (ABT; Stuart et al., 2013), is sensitive to acute changes induced by conventional antidepressants, as in humans (Harmer et al., 2017). In the ABT, dissociation between conventional antidepressants and RAADs is also observed (Stuart et al., 2015). Acute treatments with conventional antidepressants positively biased new learning but failed to attenuate previously acquired negative biases when administered immediately before testing memory recall (Stuart et al., 2013, 2015), whereas ketamine had the opposite effect (Stuart et al., 2015). It has also been shown that acute treatment with putative pro-depressant treatments, including drugs with distinct pharmacological mechanisms that have been linked to increased risk of depression in the clinic, and immunomodulators that alter immune system function, are able to induce negative biases in this task (Stuart et al., 2013, 2017).

In this study, we investigate whether the putative pro-depressant drugs that induce negative biases in learning and memory when given acutely in the ABT have the same effect on decision-making biases in the JBT. Specifically, we tested rimonabant, the anti-obesity drug that was withdrawn from the market following evidence that it causes an increased risk of suicidal tendencies and depression (Rumsfeld & Nallamotheu, 2008); retinoic acid, the active ingredient

of the acne drug Roaccutane that has been associated with an increased incidence of depression in patients (Bremner et al., 2012); and tetrabenazine, a vesicular monoamine transport inhibitor used as an off-label treatment for chorea in Huntington's disease and has also been associated with adverse psychiatric symptoms (Jankovic & Beach, 1997; Kenney et al., 2006). We also tested the immunomodulators interferon- α (IFN- α), an immunotherapy drug shown to increase the risk of depression and suicidality in patients (Raison et al., 2005, 2006); lipopolysaccharide (LPS), the proinflammatory mediator used chronically as a depression model in rodents (Remus & Dantzer, 2016); and corticosterone, the rodent stress hormone that has also been shown to induce depression-like behaviour in rodents following chronic treatment (Gregus et al., 2005). In previous studies using psychosocial stress, we observed negative decision-making biases in the JBT following chronic but not acute exposure (Hales et al., 2016), hence here we also tested IFN- α effects following chronic treatment.

2 | METHODS

2.1 | Animals and apparatus

Three cohorts of male Lister Hooded rats (cohort 1: $n = 16$; cohort 2: $n = 16$; cohort 3: $n = 16$) were used (Harlan). Rats weighed 260–305 g (cohort 1)/270–305 g (cohort 2)/275–295 g (cohort 3) at the start of training, and 305–445 g (cohort 1)/400–465 g (cohort 2)/390–460 g (cohort 3) by the start of experimental manipulations. Studies used only male rats, which is a limitation and there may be sex differences in sensitivity to these manipulations. We have used only male rats previously in our JBT studies (Hales et al., 2016, 2017, 2020) and make comparisons based on these data. Further studies undertaking specific comparisons of drug effects in both sexes are needed. Rats were housed in a conventional (non-specified pathogen-free) facility in pairs in RC2R NKP-Isotec cages (56 × 38 × 22 cm; North Kent Plastic Cages) with IPS Lignocel IRR Select bedding and environmental enrichment consisting of a red Perspex house (30 × 10 × 17 cm), cardboard tube, wood chew block and rope tied across the cage lid. Cage bases with fresh sawdust and bedding were changed once per week, and rats were kept under temperature (19–23°C) and humidity (45%–65%) controlled conditions on a 12 hr reverse lighting cycle (lights off at 08:00 hr). Water was available ad libitum in the home cage (with water bottles emptied and refilled with fresh tap water once per week), but rats were maintained at no less than 90% of their free-feeding body weight, matched to a standard growth curve, by restricting access to laboratory chow (LabDiet, PMI Nutrition International) to ~18 g per rat per day. All procedures were carried out under local institutional

guidelines (University of Bristol Animal Welfare and Ethical Review Board) and in accordance with the UK Animals (Scientific Procedures) Act 1986. During experiments, all efforts were made to minimise suffering, and at the end of experiments, rats were killed by giving an overdose of sodium pentobarbital (200 mg/kg) administered by intraperitoneal injection using a low-stress, non-restrained technique (Stuart & Robinson, 2015). Behavioural testing was carried out between 08:00 and 18:00 hr, using standard rat operant chambers (Med Associates, Sandown Scientific) as previously described (Hales et al., 2016, 2017, 2020). Operant chambers (30.5 × 24.1 × 21.0 cm) used for behavioural testing were housed inside a light-resistant and sound-attenuating box. They were equipped with two retractable response levers positioned on each side of the centrally located food magazine. The magazine had a house light (28V, 100 mA) located above it. An audio generator (ANL-926, Med Associates, Sandown Scientific) produced tones that were delivered to each chamber via a speaker positioned above the left lever. Operant chambers and audio generators were controlled using K-Limbic software (Conclusive Solutions Ltd.).

2.2 | Behavioural task

Animals were tested using a high versus low reward version of the JBT as previously reported (Hales et al., 2016, 2017, 2020; Figure 1). Rats were first trained to associate one tone (2 kHz at 83 dB rats, designated high reward) with a high-value reward (four 45 mg reward pellets; TestDiet, Sandown Scientific) and the other tone (8 kHz at 66 dB, designated low reward) with a low-value reward (one 45 mg reward pellet) if they pressed the associated lever (either left or right, counterbalanced across rats) during the 20 s tone (see Figure 1; Figure S1 for detailed depictions of the task). Response levers were extended at the beginning of every session and remained extended for the duration of the session (maximum 1 hr for all session types). All trials were self-initiated via a head entry into the magazine, followed by an intertrial interval (ITI), and then the presentation of the tone. Pressing the incorrect lever during a tone was punished by a 10 s timeout, as was an omission if the rat failed to press any lever during the 20 s tone. Lever presses during the ITI (premature responses) were punished by a 10 s timeout. During a timeout, the house light was illuminated, and responses made on levers were recorded but had no programmed consequences.

2.3 | Training

Training was the same for all cohorts. Table S1 contains a detailed summary of training stages used, but briefly were as follows (and see Figure 1):

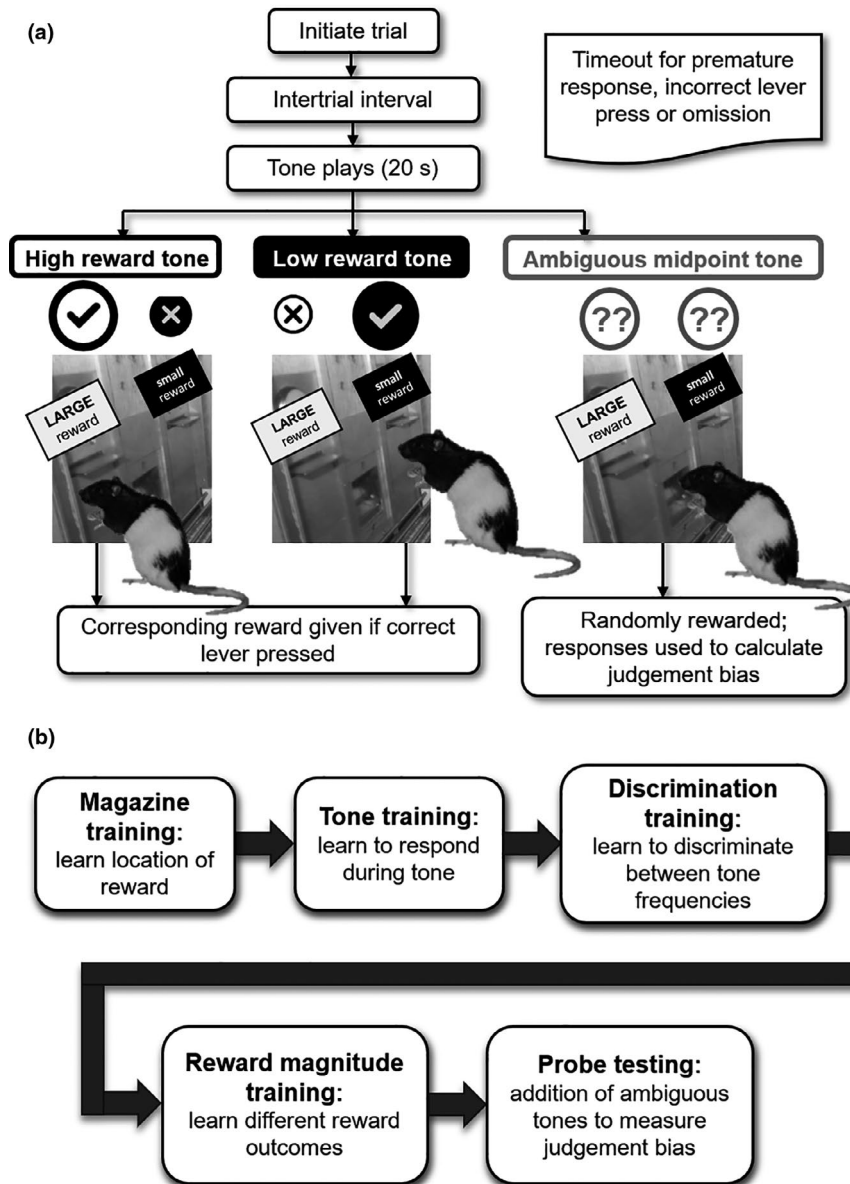


FIGURE 1 Schematic depicting the format of the judgement bias task (JBT) and training schedule. In the reward-based JBT rats learn to associate one frequency of tone with receiving a large value reward following a correct lever press (designated the high reward tone) and a low value reward following a correct lever press when a second, distinct frequency of tone plays (designated the low reward tone). Once this is learnt, judgement bias can be measured by presenting an ambiguous, midpoint frequency tone, and rats' responses to this tone can be used as a measure of whether they more often expect the high reward (a positive bias) or the low reward (a negative bias). (a) The task begins when the rat self-initiates a trial. Following a short intertrial interval (ITI), the tone plays. Correct responses to high and low reward tones are rewarded with the corresponding sized reward. Responses to the ambiguous midpoint tone are randomly reinforced. Premature responses (made during the ITI), incorrect responses or omissions (no response during the tone) are punished with a short timeout, during which time another trial cannot be initiated. (b) Rats are trained on the JBT following a graduated training process, where only reference (high and low reward) tones are played. Each stage has criteria that must be met before progression to the following stage. Once trained, animals can be tested by using probe test sessions that have the addition of the ambiguous midpoint tone

1. Magazine training: tone played for 20 s followed by the release of one pellet into a magazine. Criteria: 20 pellets eaten for each tone frequency.
2. Tone training: response on lever during the tone rewarded with one pellet. Only one tone frequency, and one lever available per session. Criteria: >50 trials completed.
3. Discrimination training: response on the correct corresponding lever only during the tone rewarded with one pellet. Both tones played (pseudorandomly) and both levers available. Criteria: >70% accuracy for both tones, <1:1 ratio of correct:premature responses, and no significant difference on any behavioural measure analysed over three sessions.

4. Reward magnitude training: As for discrimination training but the 2 kHz tone is now rewarded with four pellets and the 8 kHz tone rewarded with one pellet. Criteria: as for discrimination training but with >60% accuracy for both tones.

Rats were required to meet criteria for at least two consecutive sessions before progressing to the next training stage. Once trained (29 total sessions, see Table S1 for the number of sessions required for each training stage), animals were used in judgement bias experiments.

2.4 | Judgement bias testing

Baseline sessions (100 trials: 50 high reward (2 kHz) and 50 low reward (8 kHz) tones; pseudorandomly, for details see Table S1) were conducted on Monday and Thursday. Probe test sessions (120 trials: 40 high reward, 40 low reward, and 40 ambiguous midpoint tones (frequency between the high and low reward tones: either 5 or 4.75 kHz, see below and Table 1) presented pseudorandomly (for details see Table S1) were conducted on Tuesday and Friday. The ambiguous midpoint tone, responses to which are used as a measure of judgement bias, was randomly reinforced whereby 50% of trials had outcomes as for the high reward tone, and 50% as for the low reward tone. This was to ensure a specific outcome could not be learnt (i.e., that this midpoint frequency remained ambiguous), and to maintain responding throughout the experiments (see Figure S1; Table S1 for a detailed description of how this was implemented). Visual inspection of behavioural measures for the midpoint tone on vehicle test sessions across different drug dose-response studies, as well as the data from the chronic INF- α manipulation, indicates that this reinforcement schedule prevents the extinction of

responding to the midpoint tone across repeated test sessions. All rats were initially tested using a 5 kHz (75 dB) midpoint tone. Cohort 1 ($n = 16$) were then used to test the acute effect of treatment with corticosterone (Table 1). Following this, half of these rats (cohort 1a, $n = 8$; Table 1) were used for another experiment, while the other half (cohort 1b, $n = 8$) were then used for the remaining acute treatments conducted in this study (listed in Table 1). After being split, it was found that cohort 1b displayed more negative baseline interpretation of the midpoint ambiguous tone (see Figure S2). As drugs hypothesised to induce a negative affective state were to be tested in these rats, these animals were subsequently switched to a 4.75 kHz ambiguous midpoint tone to prevent a “floor effect” for the remaining manipulations (i.e., to allow room for drugs to cause more negative responding; Figure S2). Rats in cohort 2 were initially used to test the effect of acute treatments with NMDA receptor antagonists on judgement bias of the 5 kHz midpoint tone (experiments not reported here; see Hales et al., 2020). These rats then went on to be used to test the effects of acute treatments listed in Table 1 along with cohort 1b, and so cohort 2 was also moved to a 4.75 kHz ambiguous midpoint tone to match (Figure S2). Although it might be possible that the use of a different frequency of midpoint tone could impact on the results, both cohorts responded to the 4.75 kHz frequency with cognitive bias index (CBI) scores (see data analysis section for a description) that indicated this frequency was perceived with a similar level of ambiguity as to the 5 kHz frequency (Figure S2). Furthermore, we ensured that bias could still be detected using this different midpoint frequency (4.75 kHz) by testing a drug we had previously shown to induce a positive bias using the 5 kHz tone: amphetamine (see Hales et al., 2017 for this data). We found that amphetamine also induces a positive bias when tested with a 4.75 kHz midpoint tone (Figure S3). Cohort 3 was used to test the effect of chronic treatment with INF- α .

TABLE 1 Drug treatments given to each cohort of rats

Cohort	# rats	Midpoint tone frequency	Treatment	Doses (mg/kg unless otherwise stated)
1	16	5 kHz	Corticosterone	0, 1, 10
1a	8	5 kHz	Used in a chronic study (not reported here)	
1b	8	4.75 kHz	Lipopolysaccharide	0, 1, 3, 10 μ g/kg
			Retinoic acid	0, 3, 10
			Rimonabant	0, 3, 10
			Tetrabenazine	0.0, 0.3, 1.0
2	16	4.75 kHz	Interferon- α (acute)	0, 10, 100 units/kg
			Lipopolysaccharide	0, 1, 3, 10 μ g/kg
			Retinoic acid	0, 3, 10
			Rimonabant	0, 3, 10
			Tetrabenazine	0.0, 0.3, 1.0
3	16	5 kHz	Chronic interferon- α	0, 100 units/kg (daily)

2.5 | Experimental design and drugs

All acute dose-response studies used a within-subject fully counterbalanced drug treatment schedule (see Table 1 for details of individual treatments). All drugs (except corticosterone) were given by intraperitoneal injection using a low-stress, non-restrained technique (Stuart & Robinson, 2015). Corticosterone (Sigma Aldrich) was dissolved in 5% dimethyl sulfoxide (DMSO) and 95% sesame oil and administered by subcutaneous injection 30 min prior to testing. Rimonabant (kindly provided by Pfizer) and 13-cis retinoic acid (Sigma Aldrich) were dissolved in 5% DMSO, 10% cremophor, and 85% sterile saline and given 30 and 60 min (respectively) prior to testing. Tetrabenazine was dissolved in 20% DMSO and 80% saline at pH 2.0 which was then adjusted to pH 5.5 for dosing, and given 30 min prior to testing. IFN- α and LPS were resuspended in saline and stocks stored at -20°C until use. These were also given 30 min prior to testing. Drug doses were selected based on previous rodent behavioural studies, particularly the ABT at doses that had shown efficacy (Stuart et al., 2013, 2017). For all studies, the experimenter (female) was blind to dose within each drug study. Each dose-response study was separated by at least 1 week (five sessions) of baseline testing.

For the chronic INF- α experiment, a between-subjects study design was used. This was split into three parts: (a) a pre-drug week, (b) 4 weeks of drug treatment, and (c) 1-week post-drug testing. Rats were split into control (0.9% sterile saline vehicle) or INF- α (100 units/kg) groups based on task performance (matched for all analysed behavioural variables) during the pre-drug week. The experimenter (female) was blind to the treatment group. Rats were dosed daily 30 min prior to behavioural testing (or at an equivalent time on days when behavioural testing did not occur) by intraperitoneal injection using a low-stress, non-restrained technique (Stuart & Robinson, 2015). Treatment commenced on the Monday of the first drug week and ended on the Friday of the final drug week.

2.6 | Data and statistical analysis

Sample size was estimated using power calculations (G*Power 3.1.9.7) carried out on data from our previous studies using the JBT (Hales et al., 2016, 2017, 2020). Details of sample sizes used can be found in Table 2. Changes in bias should occur without effects on other variables; therefore, strict inclusion criteria were established to reduce any potential confound in the data analysis. Only animals that maintained more than 60% accuracy for each reference tone, less than 50% omissions, and also completed more than 50% of the total trials were used for analysis. Details of animals excluded from each study are given in Table 2. CBI was used as a measure of judgement bias in response to the midpoint tone. CBI was calculated by subtracting the proportion of

responses made on the low reward lever from the proportion made on the high reward lever. This created a score between -1 and 1 , where negative values represent a negative bias and positive values a positive bias. Change from baseline in CBI was then calculated for all experimental manipulations as follows: vehicle (0.0 mg/kg) probe test CBI – drug dose probe test CBI, for acute experiments; and pre-drug week probe test CBI – drug week probe test CBI for the chronic study. This was calculated to take into account individual differences in baseline bias, and to make directional changes caused by drug treatments clearer. Although individuals within a cohort were variable regarding their CBI scores at baseline (see Figure S4 for raw CBI data for all acute drug studies), performance was consistent across repeated sessions. To provide individual values for vehicle probe test sessions for this measure, the population average for this session was taken away from each individual rats' CBI score for the same session. This allowed analysis with repeated-measures analysis of variance (rmANOVA) with session as the within-subjects factor for acute studies, and a mixed ANOVA with the addition of group as the between-subjects factor for the chronic study.

Response latency and percentages of positive responses, omissions, and premature responses were also analysed (see Table S2 for details). For acute drug studies, these were analysed with rmANOVAs with session and tone as the within-subjects factors. The chronic study was analysed similarly, but with the addition of group as a between-subjects factor. Paired t tests (acute studies) and/or independent samples t tests (chronic study) were performed as post hoc tests if significant effects were established. Huynh-Feldt corrections were used to adjust for violations of the sphericity assumption, and Sidak correction was applied for multiple comparisons. All statistical tests were conducted using SPSS 24.0.0.2 for Windows (IBM SPSS Statistics) with $\alpha = 0.05$. Results are reported with the ANOVA F -value (degrees of freedom, error) and p -value as well as any post hoc p -values. All graphs were made using GraphPad Prism 7.04 for Windows (GraphPad Software).

3 | RESULTS

3.1 | Effects of acute treatment with putative pro-depressant drugs on the interpretation of the ambiguous cue in the JBT

For tetrabenazine, seven rats were excluded from the final analysis as they failed to complete sufficient trials on the 1.0 mg/kg dose. For rimonabant, the highest dose (10.0 mg/kg) had to be excluded from the final analysis as only four rats completed sufficient trials. Three rats were excluded from the rest of the data analysis because they failed to

TABLE 2 Details of rats excluded for each drug treatment

Drug	Cohort(s)	Total number rats	Rats excluded from analysis	N number for final analysis
Tetrabenazine	1b and 2	24	7: failure to complete sufficient trials on the 1 mg/kg dose	17
Rimonabant	1b and 2	24	3: failure to complete sufficient trials on the 3 mg/kg dose (10 mg/kg dose completely excluded as the majority of animals failed to complete sufficient trials)	21
Retinoic acid	1b and 2	24	0	24
Interferon- α	2	16	0	16
Lipopolysaccharide	1b and 2	24	1: did not meet accuracy criteria on vehicle session	23
Corticosterone	1	16	0	16
Chronic interferon- α	3	16 (15)	15 rats began the drug study as one animal died from an unrelated health issue during training. 1 rat was excluded from the INF- α group for failing to meet accuracy criteria and 1 animal was euthanised during the study as it developed seizures	13 ($n = 8$ control, $n = 5$ INF- α)

complete sufficient trials on a 3.0 mg/kg dose. No rats were excluded from the analysis for retinoic acid. The full data sets for behavioural measures without these exclusions can be found in Figures S5 and S6. Inspection of these full data sets indicates that the higher dose of tetrabenazine and rimonabant did not impair decision-making ability, as the percentage of positive responses was not impacted (Figures S5d and S6d). This indicates that accuracy to respond to the reference tones on trials that were initiated and completed was equivalent to normal performance. Instead, these higher doses reduced the number of trials that were self-initiated (or total trials; Figures S5a and S6a) and increased the number of initiated trials where no response was then made during the tone (omissions; Figures S5e and S6e), suggesting that these higher doses caused motivational impairments or reduced engagement with the task.

Tetrabenazine, rimonabant, and retinoic acid did not change CBI at any of the doses tested (Figures 2–4, panel a). For tetrabenazine, there was a main effect of session for response latency ($F_{2,32} = 3.593$, $p = 0.039$). Post hoc analyses revealed a main effect of session for the high tone only ($F_{2,32} = 3.508$, $p = 0.042$), with a trend towards a difference between the 0.0 and 1.0 mg/kg doses ($p = 0.072$; Figure 2b). There were no effects on other behavioural measures (Figure 2c–e). Rimonabant (3.0 mg/kg) caused changes in responding to the reference tones (session \times tone interaction: $F_{2,40} = 4.240$, $p = 0.021$), whereby rats became less accurate for the high tone ($p = 0.045$; Figure 3c), with a tendency for responding with greater accuracy for the low tone ($p = 0.062$; Figure 3c). Rimonabant (3.0 mg/kg) also increased omissions (main effect of session: $F_{1,20} = 10.671$, $p = 0.004$ and session \times tone interaction: $F_{1,1515,30,297} = 4.316$, $p = 0.032$) for the

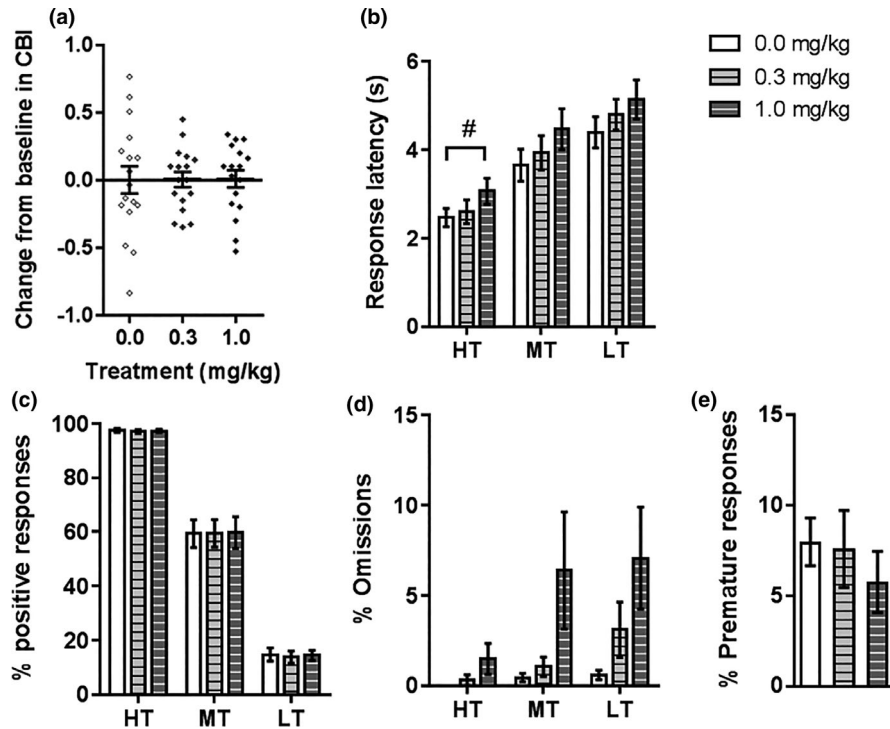


FIGURE 2 The effect of acute treatment with the putative pro-depressant drug tetrabenazine on judgement bias. Acute doses of tetrabenazine (0.0, 0.3, 1.0 mg/kg; $n = 17$) were administered by intraperitoneal injection prior to testing on the judgement bias task. (a) None of the doses tested induced a change in cognitive bias index (CBI) for the midpoint tone. (b) The higher dose of tetrabenazine (1.0 mg/kg) tended towards increasing response latency for the high reward tone (main effect of drug: $F_{2,32} = 3.593$, $p = 0.039$ and posthoc test: $p = 0.072$). (c–e) There was no other effect of the doses tested on any other behavioural measures. Data shown and represent mean \pm SEM (bars and error bars) overlaid with individual data points for each rat on panel a. # $p < 0.08$. 30 min pre-treatment. HT, high reward tone; LT, low reward tone; MT, midpoint tone

midpoint ($p = 0.002$) and low ($p = 0.021$) tones (Figure 3d). There was no effect on response latencies (Figure 3b) or premature responses (Figure 3e). Retinoic acid had no effect on any behavioural measures (Figure 4b–e).

3.2 | Effects of acute treatment with immunomodulators on the interpretation of the ambiguous cue in the JBT

One rat had to be excluded from the LPS drug study as it did not meet accuracy criteria for the reference tones on the 0.0 mg/kg session. All rats were included in the analysis for the INF- α and corticosterone drug studies.

None of the doses of INF- α or LPS tested caused a change in CBI (Figures 5a and 6a). These drugs also did not alter any other behavioural measures (Figures 5b–e and 6b–e). Corticosterone (10.0 mg/kg) caused a negative change in CBI for the midpoint tone (main effect of session: $F_{2,30} = 4.493$, $p = 0.020$; post hoc: $p = 0.030$; Figure 7a). Corticosterone had no effect on other behavioural measures (Figure 7b,d,e), apart from the 10 mg/kg dose reducing percentage positive responses for the midpoint tone (session \times tone interaction: $F_{4,60} = 2.612$, $p = 0.044$; post hoc main effect of session for

midpoint tone: $F_{2,30} = 4.009$, $p = 0.029$; post hoc comparison: $p = 0.026$; Figure 7c), which reflects the effect seen on CBI (Figure 7a).

3.3 | Effect of chronic treatment with an immunomodulator on the interpretation of the ambiguous cue in the JBT

Fifteen rats were initially split into control ($n = 8$) and INF- α ($n = 7$ groups). Data from one rat in the INF- α group could not be included as the animal died before the end of the study. Data from one other rat in the INF- α were excluded from the analyses as it did not meet accuracy criteria. This meant eight control animals and five INF- α animals were included in the final analysis.

There were no significant differences in any behavioural measures between groups in the pre-drug week (see Pre-drug sections of Figure 8; Figure S7). There was a main effect of group ($F_{1,11} = 5.297$, $p = 0.042$) and a trend towards a session \times group interaction ($F_{5,55} = 2.077$, $p = 0.082$) across the entire study period (pre-drug, drug, and post-drug) for change from baseline in CBI (Figure 8a). Analysing these data split by the group revealed no effect of session for the

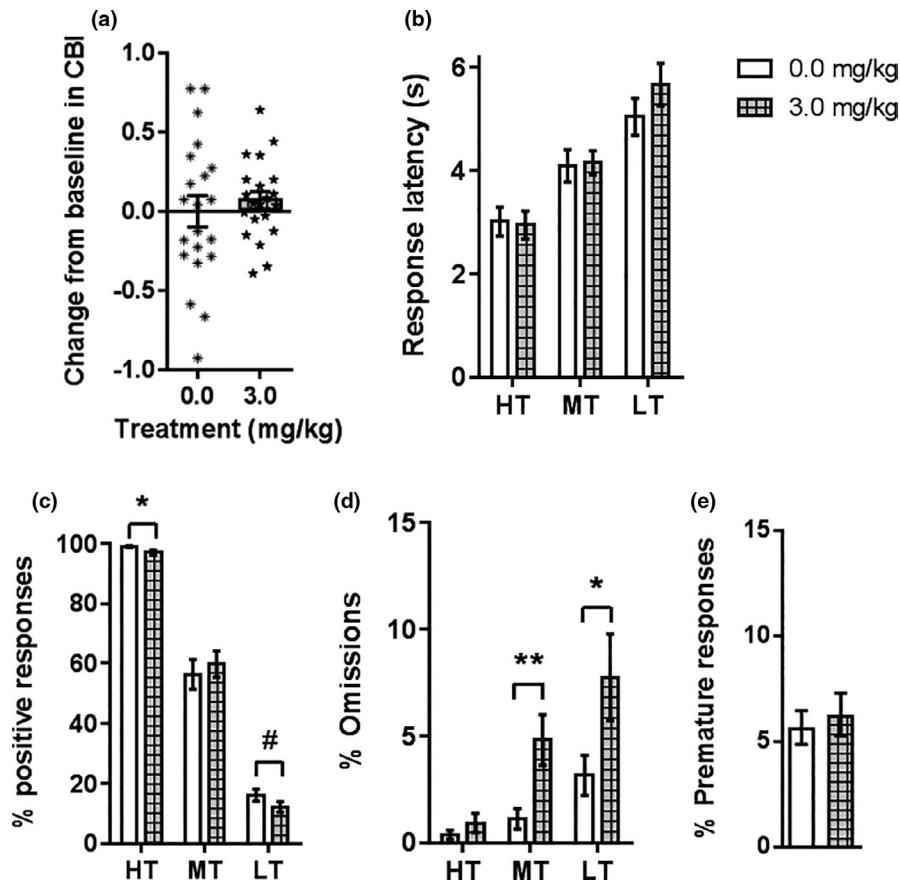


FIGURE 3 The effect of acute treatment with the putative pro-depressant drug rimonabant on judgement bias. Acute doses of rimonabant (0.0, 3.0 mg/kg; $n = 21$) were administered by intraperitoneal injection prior to testing on the judgement bias task. (a) Rimonabant did not induce a change in cognitive bias index (CBI) for the midpoint tone. (b,e) Rimonabant (3.0 mg/kg) had no effect on response latency or premature responding, but did cause (c) changes in positive responding (significant drug \times tone interaction: $F_{2,40} = 4.240$, $p = 0.021$). Accuracy was reduced for the high reward tone ($p = 0.045$) whilst there was a tendency for accuracy to be increased for the low reward tone ($p = 0.062$). (d) Rimonabant also increased omissions (significant drug \times tone interaction: $F_{1,515,30,297} = 4.316$, $p = 0.032$ for the midpoint ($p = 0.002$) and low reward tones ($p = 0.021$). Data shown and represent mean \pm SEM (bars and error bars) overlaid with individual data points for each rat in panel a. $**p < 0.01$; $*p < 0.05$, $\#p < 0.08$. 30 min pre-treatment. HT, high reward tone; LT, low reward tone; MT, midpoint tone

control group ($F_{1,860,13,022} = 0.324$, $p = 0.714$), but a main effect for the INF- α group ($F_{5,35} = 3.579$, $p = 0.018$), indicating that CBI was changed across the experimental period in the INF- α -treated rats. Post hoc analysis showed that the INF- α group had a more negative change in CBI compared to control animals in the 3rd and 4th drug weeks, and in the post-drug week (independent samples t tests: $p = 0.027$, $p = 0.042$ and $p = 0.029$, respectively). The INF- α -treated animals were also more negative compared to their own baseline from drug week 2 onwards (one-sample t tests: $ps \leq 0.033$). Chronic INF- α treatment did not cause changes in other behavioural measures, except for percentage positive responses for the midpoint tone (main effect of session: $F_{5,55} = 5.379$, $p < 0.001$; and trend towards session \times group interaction: $F_{5,55} = 2.317$, $p = 0.056$; Figure 8c), which reflects the change in CBI. There were some changes in behavioural measures irrespective of the treatment group. For all three tones, there was a main effect of session for response latency ($F_s \geq 2.799$, $ps \leq 0.025$; Figure 8b; Figure S7a), indicating

that both groups became quicker to respond over the entire study period. There was also a main effect of session for low tone omissions ($F_{5,55} = 4.668$, $p = 0.001$), driven by both groups making fewer omissions in the drug and post-drug periods compared to the pre-drug week (Figure S7c).

4 | DISCUSSION

Acute administration of pro-depressant drugs and immunomodulators that have previously been shown to induce negative learning and memory biases in the ABT (Stuart et al., 2013, 2017) failed to alter decision-making bias in the reward-based JBT, with the exception of acute treatment with corticosterone. Acute corticosterone treatment induced a negative judgement bias without altering other behavioural measures. Furthermore, chronic treatment with INF- α induced a negative decision-making bias in weeks 3 and 4 of treatment, and this negative bias lasted after treatment ended,

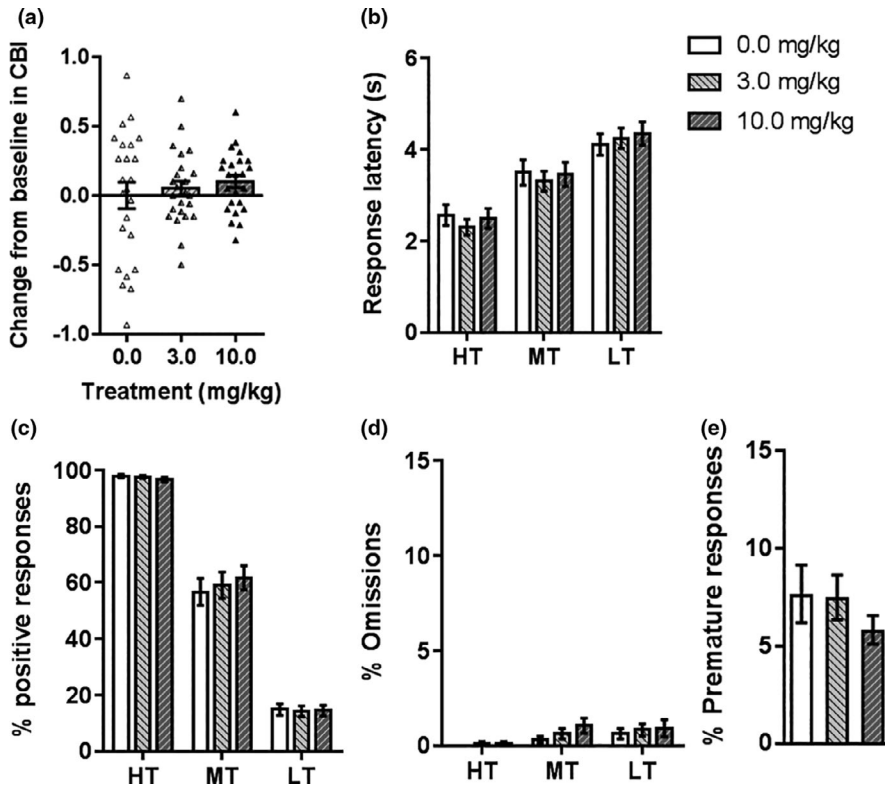


FIGURE 4 The effect of acute treatment with the putative pro-depressant drug retinoic acid on judgement bias. Acute doses of retinoic acid (0.0, 3.0, 10.0 mg/kg; $n = 24$) were administered by intraperitoneal injection prior to testing on the judgement bias task. (a–e) There were no effects of retinoic acid on any behavioural measures analysed. Data shown and represent mean \pm SEM (bars and error bars) overlaid with individual data points for each rat on panel a. 60 min pre-treatment. CBI, cognitive bias index; HT, high reward tone; LT, low reward tone; MT, midpoint tone

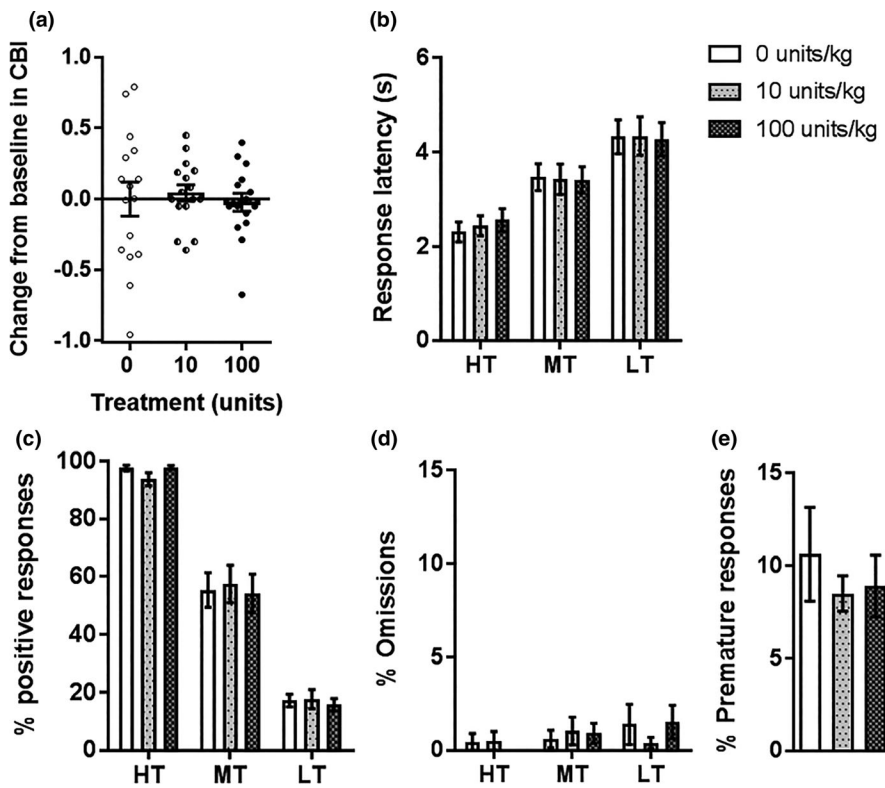


FIGURE 5 The effect of acute treatment with the immunomodulator interferon- α on judgement bias. Acute doses of interferon- α (IFN- α ; 0, 10, 100 units/kg; $n = 16$) were administered by intraperitoneal injection prior to testing on the judgement bias task. (a) IFN- α did not induce a change in cognitive bias index (CBI) for the midpoint tone at the doses tested. (b–e) There was also no effect on other behavioural measures. Data shown and represent mean \pm SEM (bars and error bars) overlaid with individual data points for each rat in panel a. 30 min pre-treatment. HT, high reward tone; LT, low reward tone; MT, midpoint tone

despite acute treatment having no effect. This mirrors what has been seen previously in this JBT with psychosocial stress (Hales et al., 2016) and conventional antidepressants (Hales et al., 2017), where chronic but not acute manipulations altered judgement bias.

Acute treatments with pro-depressant drugs (rimonabant, retinoic acid, and tetrabenazine) or immunomodulators (INF- α and LPS) did not induce a change in decision-making bias in this JBT. This mirrors findings with acute restraint stress (Hales et al., 2016), acute

FIGURE 6 The effect of acute treatment with the immunomodulator lipopolysaccharide on judgement bias. Acute doses of lipopolysaccharide (0.0, 1.0, 3.0, 10.0 $\mu\text{g}/\text{kg}$; $n = 23$) were administered by intraperitoneal injection prior to testing on the judgement bias task. (a–e) There were no effects on behavioural measures at any of the doses tested. Data shown and represent mean \pm SEM (bars and error bars) overlaid with individual data points for each rat in panel a. 30 min pre-treatment. HT, high reward tone; LT, low reward tone; MT, midpoint tone

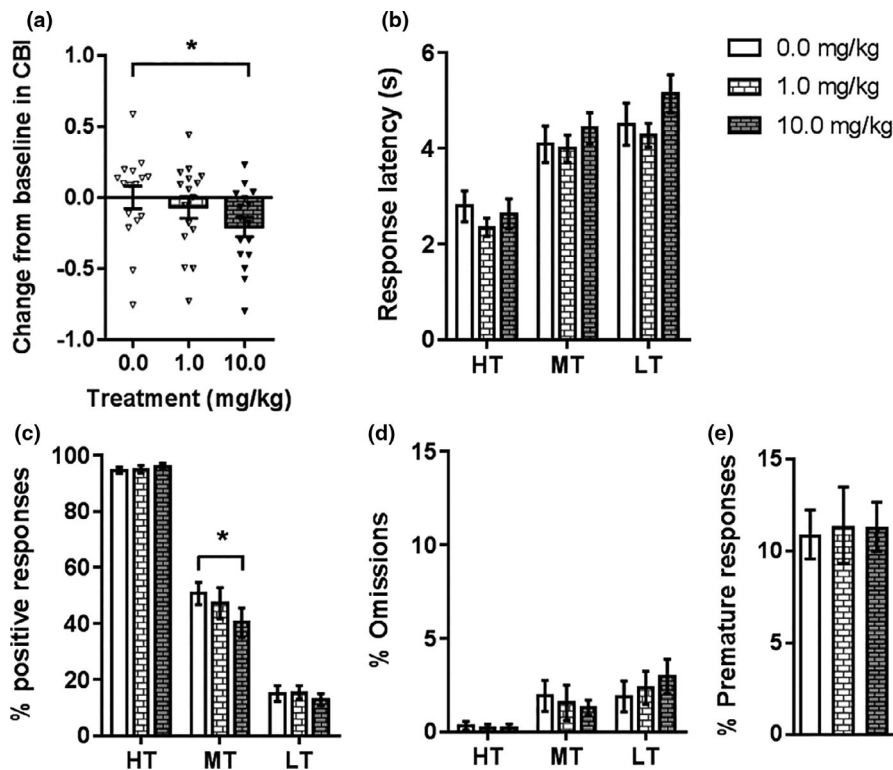
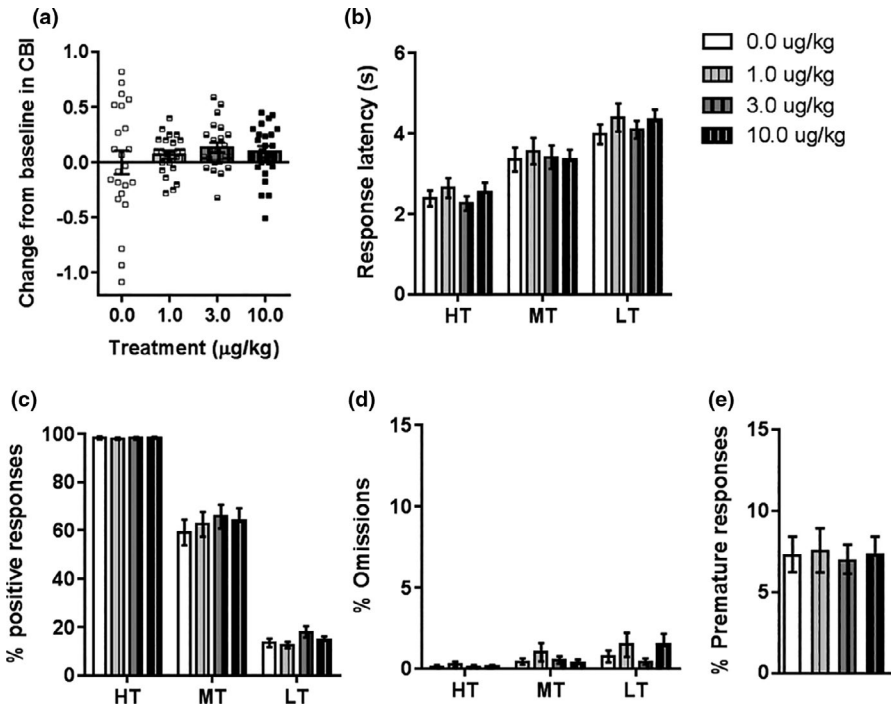


FIGURE 7 The effect of acute treatment with the immunomodulator corticosterone on judgement bias. Acute doses of corticosterone (CORT; 0.0, 1.0, 10.0 mg/kg ; $n = 16$) were administered by subcutaneous injection prior to testing on the judgement bias task. (a) The 10.0 mg/kg dose of CORT caused a negative change in cognitive bias index (CBI) for the midpoint tone. (b) CORT did not alter response latencies. (c) CORT (10.0 mg/kg) reduced the percentage of positive responses for the midpoint tone (significant drug \times tone interaction: $F_{4,60} = 2.612$, $p = 0.044$ and posthoc: $p = 0.026$), which was also seen as in change in CBI (panel a). (d,e) CORT did not alter omissions or premature responses. Data shown and represent mean \pm SEM (bars and error bars) overlaid with individual data points for each rat in panel a. 30 min pretreatment. * $p < 0.05$. HT, high reward tone; LT, low reward tone; MT, midpoint tone

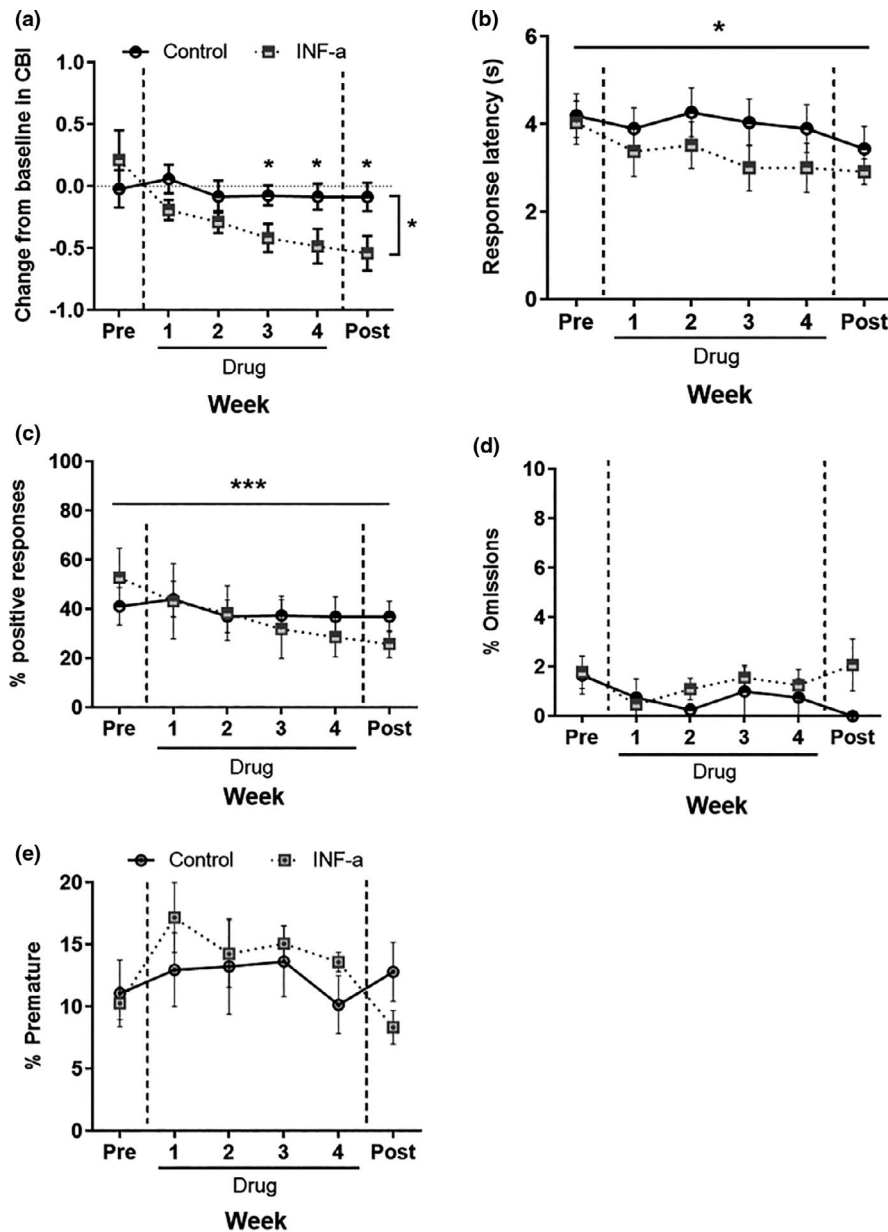


FIGURE 8 The effect of chronic treatment with the immunomodulator interferon- α on judgement bias. Rats assigned to the chronic interferon- α (INF- α) group experienced intraperitoneal injections of INF- α (100 units/kg) daily for 4 weeks, whilst control rats experienced daily intraperitoneal injections of saline vehicle (0.0 mg/kg). Twice weekly test sessions (averaged) were conducted 1 week prior to treatment (Pre), for the 4 weeks during treatment (Drug 1–4) and for 1 week following the end of treatment (Post). There were no significant differences between groups during the pre-drug period for any measure. (a) Rats in the INF- α group became more negative as treatment progressed (main effect of group: $F_{1,11} = 5.297$, $p = 0.042$, trend towards session \times group interaction: $F_{5,55} = 2.077$, $p = 0.082$), with a more negative change in cognitive bias index (CBI) compared to controls during the 3rd and 4th drug week, and as well as during the post drug period (post Thoc comparisons: $p = 0.027$, $p = 0.042$, $p = 0.029$ respectively). (b–e) Behavioural data for other measures are shown here for the midpoint tone only (see Figure S2 for data for reference tones). (b) Irrespective of treatment, rats became quicker to respond to the midpoint tone across weeks. (c) There was a main effect of session ($F_{5,55} = 5.379$, $p < 0.001$), and trend towards session \times group interaction ($F_{5,55} = 2.317$, $p = 0.056$) for percentage of positive responses, reflecting the change in CBI shown in (a). (d) There were no differences in omissions between the control and INF- α groups. (e) There were also no changes in premature responding. Data shown are for the midpoint tone only, and represent mean \pm SEM. Control group: $n = 8$, INF- α group: $n = 5$. *** $p < 0.001$, * $p < 0.05$

treatment with conventional antidepressants (fluoxetine, reboxetine, and venlafaxine; Hales et al., 2017), and acute treatments with NMDA receptor antagonists (PCP, lanicemine, memantine; Hales et al., 2020) which all failed to

change decision-making biases in this task. Drug doses were chosen based on ranges that were shown to be efficacious in altering learning and memory biases in the ABT, and that are predicted to achieve selective targeting of the

relevant receptors (see Stuart et al., 2013, 2017 and references within). It is possible that higher doses may induce changes in decision-making behaviour in the JBT, but these are also likely to generate non-specific effects. A common factor linking these results is the time course over which these drugs cause subjective reporting in a change in mood or depression symptoms in humans. Patients only report improvements in depression rating weeks to months after the onset of treatment with conventional antidepressants (Anderson et al., 2000). Rimonabant was withdrawn as an anti-obesity drug after evidence that long-term treatment increased the risk of depressed mood disorders and anxiety (Christensen et al., 2007), and a later study showed that acute rimonabant treatment did not alter subjective reports of mood in humans (Horder et al., 2009). Retinoic acid has been linked to an increased risk for depression, with most cases developing after 1–2 months of treatment (Bremner et al., 2012). For tetrabenazine, it has been reported that depression occurs in up to 15% of patients receiving long-term treatment for Huntington's disease (Jankovic & Beach, 1997; Kenney et al., 2006). IFN- α has been shown to induce depressive symptoms after weeks to months of treatment in 20%–50% of patients (Raison et al., 2006). LPS is not generally given to humans, instead of being an endotoxin found on the cell wall of gram-negative bacteria, but acute treatment in rodents (at higher doses than used in this study) induces sickness-like behaviour (Yirmiya, 1996) that is thought to be comparable to bacterial infection in humans (Yirmiya et al., 2000). Chronic treatment with LPS has been used as a rodent model to induce depression-like behaviours (Remus & Dantzer, 2016), and has been shown to cause reduced sucrose preference, a rodent test for anhedonia, following chronic, but not acute treatment (Kubera et al., 2013). The lack of effect on decision-making biases across all these drugs when given acutely, but the development of more negatively biased decision-making over a longer time period with chronic IFN- α treatment suggests that this reward-based JBT is sensitive to measuring affective biases that manifest on timescales that are more aligned with subjectively reported mood change in humans. This corroborates previous studies using this JBT, where chronic psychosocial stress (Hales et al., 2016) and chronic treatment with a conventional antidepressant (Hales et al., 2017) both induce changes in bias, whilst an acute stress manipulation (Hales et al., 2016), or acute treatments with antidepressants (fluoxetine, reboxetine, and venlafaxine; Hales et al., 2017) do not.

These findings contrast effects on learning and memory biases seen in the ABT, where acute treatment with conventional antidepressants (including fluoxetine, reboxetine, and venlafaxine) did induce positive affective biases (Stuart et al., 2013), whilst the same pro-depressant drugs and immunomodulators (tested at the same doses) induced negative

affective biases (Stuart et al., 2013, 2017), suggesting that these two tasks are measuring distinct types of affective bias. Evidence from these two tasks suggests that learning can be modified acutely whilst alterations in decision-making take longer. This could be due to the nature of the two tasks: in the JBT, decision-making about the ambiguous cue requires the animal to have learnt, over a long training period, outcomes about two other related cues, and recall this information to make a judgement about their choice on an ambiguous trial. However, in the ABT, specific memories (one following treatment, one following control) that have been learnt over only four sessions (two per manipulation) are being tested (Stuart et al., 2013). These are likely to be modifiable on a much shorter time scale. In humans, it has been shown that acute treatments with conventional antidepressants can positively bias learning about emotional words and subsequent memory, despite a lack of subjectively reported change in mood (Harmer et al., 2017), similar to findings with the ABT (Stuart et al., 2013). In human versions of the JBT, it has been shown that negative bias was correlated with questionnaire measures of state anxiety (Anderson et al., 2012), which could be thought of as a readout of “long term” affective state, and that an acute anxiety manipulation (threat of electric shock) had no effect on bias, whilst participants with pathological anxiety symptoms displayed more negative interpretation of the ambiguous cue (Aylward et al., 2020). Together, these findings suggest that the same dichotomy might exist in the time courses of effects on different types of biases in humans. The implications relating to the treatment of MDD are important, as both types of bias are likely to play a role in the pathology of the disorder, but decision-making biases may be slower to change, whilst potentially also being more likely to impact on people's behaviour. For example, if a person subjectively feels more negative, and hence pessimistic, they will be less likely to make good decisions.

The clear-cut but contrasting effects of these drug treatments on two tasks measuring affective biases in rats are not reflected in other rodent tasks traditionally used to measure depression-like behaviour, such as the forced swim test (FST), a measure of behavioural despair, and the sucrose preference test (SPT), a measure of anhedonia. For example, in preclinical studies acute rimonabant has been shown to either have no effect on depression-like behaviours, or even to show antidepressant-like effects (e.g., Griebel et al., 2005 and references within). However, chronic rimonabant treatment reduced sucrose consumption and increased immobility time in the FST (Beyer et al., 2010). For IFN- α treatment, there are reports showing that acute and chronic treatment regimes in rodents increase immobility in the FST (Fischer et al., 2015; Makino et al., 1998, 2000; Ping et al., 2012) and reduce sucrose preference (Ping et al., 2012), as well as reports that show no effect (De La Garza et al., 2005). This adds to

growing evidence that traditionally used preclinical tests such as the FST and SPT may not be the most reliable and lack aspects of validity for detecting pro-depressant or antidepressant efficacy across drugs with a range of pharmacological actions (Planchez et al., 2019). Instead, tasks measuring affective biases, which are translatable across species, may be more useful measures in preclinical research.

The exception to the lack of effects on decision-making biases with pro-depressant drugs and immunomodulators was acute treatment with corticosterone, which did induce a negative bias. Acute, negative decision-making biases have also been seen in this reward-based JBT with FG7142 (Hales et al., 2016), an anxiogenic drug that acts as a partial inverse agonist at the GABA_A receptor, as well as acute treatments with noradrenergic drugs in the reward-punishment JBT, including reboxetine (Anderson et al., 2013), desipramine (Rygula et al., 2014), and co-treatment with reboxetine and corticosterone (Enkel et al., 2010). This finding, therefore, partially replicates previous findings by Enkel et al. (2010), but also suggests that negative decision-making biases can be induced by the direct activation of the stress system.

5 | CONCLUSIONS

Overall, these findings back up previous studies using the reward-based JBT that have shown differential effects of acute and chronic pharmacological manipulations on decision-making biases. Growing evidence suggests that acute treatments, which do not cause subjectively reported changes in mood in humans, fail to change decision making biases measured by JBTs, but do alter learning and memory biases in both humans and rodents in the ABT, whilst decision making biases take longer to be modified, across timescales that mirror the length of time it takes treatments to affect mood in humans. Therefore, the ABT could be useful as a screening tool for novel compounds to detect either antidepressant, or pro-depressant effects, but may not necessarily be able to detect the timescale over which these might occur. Moreover, the time-course specific effects of the JBT suggest this task could be useful for detecting novel treatments that may cause rapid changes in subjective mood in humans, as we have previously shown for already-known rapidly acting antidepressants (Hales et al., 2017, 2020).

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

CAH ran the experiments, analysed data, and wrote and edited the manuscript. JMB ran the experiments and analysed data. RA and BH formulated the overall concept and read the paper. ESJR formulated the overall concept and wrote and edited the paper.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/ejn.15127>.

DATA AVAILABILITY STATEMENT

Supporting data available on request.

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REFERENCES

- Anderson, I. M., Nutt, D. J., & Deakin, J. F. W. (2000). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 1993 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology*, *14*(1), 3–20. <https://doi.org/10.1177/026988110001400101>
- Anderson, M., Hardcastle, C., Munafò, M., & Robinson, E. J. (2012). Evaluation of a novel translational task for assessing emotional biases in different species. *Cognitive, Affective, & Behavioral Neuroscience*, *12*(2), 373–381. <https://doi.org/10.3758/s13415-011-0076-4>
- Anderson, M., Munafò, M., & Robinson, E. J. (2013). Investigating the psychopharmacology of cognitive affective bias in rats using an affective tone discrimination task. *Psychopharmacology (Berl)*, *226*(3), 601–613. <https://doi.org/10.1007/s00213-012-2932-5>
- Aylward, J., Hales, C., Robinson, E., & Robinson, O. J. (2020). Translating a rodent measure of negative bias into humans: The impact of induced anxiety and unmedicated mood and anxiety disorders. *Psychological Medicine*, *50*(2), 237–246. <https://doi.org/10.1017/S0033291718004117>
- Beck, A. T. (1967). *Depression: Clinical, experimental, and theoretical aspects*. Harper and Row.
- Beck, A. T. (1976). *Cognitive therapy and the emotional disorders*. Meridian.
- Beyer, C. E., Dwyer, J. M., Piesla, M. J., Platt, B. J., Shen, R. U., Rahman, Z., Chan, K., Manners, M. T., Samad, T. A., Kennedy, J. D., Bingham, B., & Whiteside, G. T. (2010). Depression-like phenotype following chronic CB1 receptor antagonism. *Neurobiological Disorders*, *39*(2), 148–155. <https://doi.org/10.1016/j.nbd.2010.03.020>
- Bremner, J. D., Shearer, K. D., & McCaffery, P. J. (2012). Retinoic acid and affective disorders: The evidence for an association. *The Journal of Clinical Psychiatry*, *73*(1), 37–50. <https://doi.org/10.4088/JCP.10r05993>

- Chaby, L. E., Cavigelli, S. A., White, A., Wang, K., & Braithwaite, V. A. (2013). Long-term changes in cognitive bias and coping response as a result of chronic unpredictable stress during adolescence. *Frontiers in Human Neuroscience*, *7*, 328. <https://doi.org/10.3389/fnhum.2013.00328>
- Christensen, R., Kristensen, P. K., Bartels, E. M., Bliddal, H., & Astrup, A. (2007). Efficacy and safety of the weight-loss drug rimonabant: A meta-analysis of randomised trials. *Lancet*, *370*(9600), 1706–1713. [https://doi.org/10.1016/S0140-6736\(07\)61721-8](https://doi.org/10.1016/S0140-6736(07)61721-8)
- Clark, L., Chamberlain, S. R., & Sahakian, B. J. (2009). Neurocognitive mechanisms in depression: Implications for treatment. *Annual Review of Neuroscience*, *32*(1), 57–74. <https://doi.org/10.1146/annurev.neuro.31.060407.125618>
- Daniel-Watanabe, L., McLaughlin, M., Gormley, S., & Robinson, O. J. (2020). Association between a directly translated cognitive measure of negative bias and self-reported psychiatric symptoms. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. <https://doi.org/10.1016/j.bpsc.2020.02.010>
- De La Garza II, R., Asnis, G. M., Pedrosa, E., Stearns, C., Migdal, A. L., Reinus, J. F., Paladugu, R., & Vemulapalli, S. (2005). Recombinant human interferon-alpha does not alter reward behavior, or neuro-immune and neuroendocrine activation in rats. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *29*(5), 781–792.
- Elliott, R., Zahn, R., Deakin, J. F., & Anderson, I. M. (2011). Affective cognition and its disruption in mood disorders. *Neuropsychopharmacology*, *36*(1), 153–182. <https://doi.org/10.1038/npp.2010.77>
- Enkel, T., Gholizadeh, D., von Bohlen und Halbach, O., Sanchis-Segura, C., Hurlmann, R., Spanagel, R., Gass, P., & Vollmayr, B. (2010). Ambiguous-cue interpretation is biased under stress- and depression-like states in rats. *Neuropsychopharmacology*, *35*(4), 1008–1015. <https://doi.org/10.1038/npp.2009.204>
- Fischer, C. W., Eskelund, A., Budac, D. P., Tillmann, S., Liebenberg, N., Elfving, B., & Wegener, G. (2015). Interferon-alpha treatment induces depression-like behaviour accompanied by elevated hippocampal quinolinic acid levels in rats. *Behavioural Brain Research*, *293*, 166–172. <https://doi.org/10.1016/j.bbr.2015.07.015>
- Gregus, A., Wintink, A. J., Davis, A. C., & Kalynchuk, L. E. (2005). Effect of repeated corticosterone injections and restraint stress on anxiety and depression-like behavior in male rats. *Behavioural Brain Research*, *156*(1), 105–114. <https://doi.org/10.1016/j.bbr.2004.05.013>
- Griebel, G., Stemmelin, J., & Scatton, B. (2005). Effects of the cannabinoid CB1 receptor antagonist rimonabant in models of emotional reactivity in rodents. *Biological Psychiatry*, *57*(3), 261–267. <https://doi.org/10.1016/j.biopsych.2004.10.032>
- Hales, C. A., Bartlett, J. M., Arban, R., Hengerer, B., & Robinson, E. S. J. (2020). Role of the medial prefrontal cortex in the effects of rapid acting antidepressants on decision-making biases in rodents. *Neuropsychopharmacology*, *45*(13), 2278–2288. <https://doi.org/10.1038/s41386-020-00797-3>
- Hales, C. A., Houghton, C. J., & Robinson, E. S. J. (2017). Behavioural and computational methods reveal differential effects for how delayed and rapid onset antidepressants effect decision making in rats. *European Neuropsychopharmacology*, *27*(12), 1268–1280. <https://doi.org/10.1016/j.euroneuro.2017.09.008>
- Hales, C. A., Robinson, E. S., & Houghton, C. J. (2016). Diffusion modelling reveals the decision making processes underlying negative judgement bias in rats. *PLoS One*, *11*(3), e0152592. <https://doi.org/10.1371/journal.pone.0152592>
- Hales, C. A., Stuart, S. A., Anderson, M. H., & Robinson, E. S. J. (2014). Modelling cognitive affective biases in major depressive disorder using rodents. *British Journal of Pharmacology*, *171*(20), 4524–4538. <https://doi.org/10.1111/bph.12603>
- Harding, E. J., Paul, E. S., & Mendl, M. (2004). Animal behaviour: Cognitive bias and affective state. *Nature*, *427*(6972), 312. <https://doi.org/10.1038/427312a>
- Harmer, C. J., Duman, R. S., & Cowen, P. J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. *Lancet Psychiatry*, *4*(5), 409–418. [https://doi.org/10.1016/S2215-0366\(17\)30015-9](https://doi.org/10.1016/S2215-0366(17)30015-9)
- Harmer, C. J., Goodwin, G. M., & Cowen, P. J. (2009). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *The British Journal of Psychiatry*, *195*(2), 102–108.
- Horder, J., Cowen, P. J., Di Simplicio, M., Browning, M., & Harmer, C. J. (2009). Acute administration of the cannabinoid CB1 antagonist rimonabant impairs positive affective memory in healthy volunteers. *Psychopharmacology (Berl)*, *205*(1), 85–91. <https://doi.org/10.1007/s00213-009-1517-4>
- Jankovic, J., & Beach, J. (1997). Long-term effects of tetrabenazine in hyperkinetic movement disorders. *Neurology*, *48*(2), 358–362. <https://doi.org/10.1212/WNL.48.2.358>
- Kenney, C., Hunter, C., Mejia, N., & Jankovic, J. (2006). Is history of depression a contraindication to treatment with tetrabenazine? *Clinical Neuropharmacology*, *29*(5), 259–264. <https://doi.org/10.1097/01.WNF.0000228369.25593.35>
- Kubera, M., Curzytek, K., Duda, W., Leskiewicz, M., Basta-Kaim, A., Budziszewska, B., Roman, A., Zajicova, A., Holan, V., Szczesny, E., Lason, W., & Maes, M. (2013). A new animal model of (chronic) depression induced by repeated and intermittent lipopolysaccharide administration for 4 months. *Brain, Behavior, and Immunity*, *31*, 96–104. <https://doi.org/10.1016/j.bbi.2013.01.001>
- Leppänen, J. M. (2006). Emotional information processing in mood disorders: A review of behavioral and neuroimaging findings. *Current Opinion in Psychiatry*, *19*(1), 34–39. <https://doi.org/10.1097/01.yco.0000191500.46411.00>
- Makino, M., Kitano, Y., Hirohashi, M., & Takasuna, K. (1998). Enhancement of immobility in mouse forced swimming test by treatment with human interferon. *European Journal of Pharmacology*, *356*(1), 1–7. [https://doi.org/10.1016/S0014-2999\(98\)00474-9](https://doi.org/10.1016/S0014-2999(98)00474-9)
- Makino, M., Kitano, Y., Komiyama, C., & Takasuna, K. (2000). Human interferon-alpha increases immobility in the forced swimming test in rats. *Psychopharmacology (Berl)*, *148*(1), 106–110.
- Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology*, *1*(1), 167–195. <https://doi.org/10.1146/annurev.clinpsy.1.102803.143916>
- Neville, V., Nakagawa, S., Zidar, J., Paul, E. S., Lagisz, M., Bateson, M., Løvlie, H., & Mendl, M. (2020). Pharmacological manipulations of judgement bias: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, *108*, 269–286. <https://doi.org/10.1016/j.neubiorev.2019.11.008>
- Papciak, J., Popik, P., Fuchs, E., & Rygula, R. (2013). Chronic psychosocial stress makes rats more ‘pessimistic’ in the ambiguous-cue interpretation paradigm. *Behavioural Brain Research*, *256*, 305–310. <https://doi.org/10.1016/j.bbr.2013.08.036>
- Papciak, J., & Rygula, R. (2017). Measuring cognitive judgement bias in rats using the ambiguous-cue interpretation test. *Current Protocols in Neuroscience*, *78*(9), 57.1–57.22.

- Ping, F., Shang, J., Zhou, J., Zhang, H., & Zhang, L. (2012). 5-HT(1A) receptor and apoptosis contribute to interferon- α -induced "depressive-like" behavior in mice. *Neuroscience Letters*, *514*(2), 173–178. <https://doi.org/10.1016/j.neulet.2012.02.087>
- Planchez, B., Surget, A., & Belzung, C. (2019). Animal models of major depression: Drawbacks and challenges. *Journal of Neural Transmission*, *126*(11), 1383–1408. <https://doi.org/10.1007/s00702-019-02084-y>
- Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology*, *27*(1), 24–31. <https://doi.org/10.1016/j.it.2005.11.006>
- Raison, C. L., Demetrashvili, M., Capuron, L., & Miller, A. H. (2005). Neuropsychiatric adverse effects of interferon-alpha: Recognition and management. *CNS Drugs*, *19*(2), 105–123. <https://doi.org/10.2165/00023210-200519020-00002>
- Remus, J. L., & Dantzer, R. (2016). Inflammation models of depression in rodents: Relevance to psychotropic drug discovery. *The International Journal of Neuropsychopharmacology*, *19*(9). <https://doi.org/10.1093/ijnp/pyw028>
- Robinson, E. S. J. (2018). Translational new approaches for investigating mood disorders in rodents and what they may reveal about the underlying neurobiology of major depressive disorder. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *373*(1742). <https://doi.org/10.1098/rstb.2017.0036>
- Robinson, E. S., & Roiser, J. P. (2016). Affective biases in humans and animals. *Current Topics in Behavioral Neurosciences*, *28*, 263–286.
- Robinson, O. J., & Sahakian, B. J. (2008). Recurrence in major depressive disorder: A neurocognitive perspective. *Psychological Medicine*, *38*(3), 315–318. <https://doi.org/10.1017/S0033291707001249>
- Roiser, J. P., Elliott, R., & Sahakian, B. J. (2012). Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology*, *37*(1), 117–136. <https://doi.org/10.1038/npp.2011.183>
- Rumsfeld, J. S., & Nallamothu, B. K. (2008). The hope and fear of rimonabant. *The Journal of the American Medical Association*, *299*(13), 1601–1602. <https://doi.org/10.1001/jama.299.13.1601>
- Rygula, R., Papciak, J., & Popik, P. (2013). Trait pessimism predicts vulnerability to stress-induced anhedonia in rats. *Neuropsychopharmacology*, *38*(11), 2188–2196. <https://doi.org/10.1038/npp.2013.116>
- Rygula, R., Papciak, J., & Popik, P. (2014). The effects of acute pharmacological stimulation of the 5-HT, NA and DA systems on the cognitive judgement bias of rats in the ambiguous-cue interpretation paradigm. *European Neuropsychopharmacology*, *24*(7), 1103–1111. <https://doi.org/10.1016/j.euroneuro.2014.01.012>
- Slaney, C. L., Hales, C. A., & Robinson, E. S. J. (2018). Rat models of reward deficits in psychiatric disorders. *Current Opinion in Behavioral Sciences*, *22*, 136–142. <https://doi.org/10.1016/j.cobeha.2018.05.001>
- Stuart, S. A., Butler, P., Munafò, M. R., Nutt, D. J., & Robinson, E. S. (2013). A translational rodent assay of affective biases in depression and antidepressant therapy. *Neuropsychopharmacology*, *38*(9), 1625–1635. <https://doi.org/10.1038/npp.2013.69>
- Stuart, S. A., Butler, P., Munafò, M. R., Nutt, D. J., & Robinson, E. S. (2015). Distinct neuropsychological mechanisms may explain delayed- versus rapid-onset antidepressant efficacy. *Neuropsychopharmacology*, *40*(9), 2165–2174. <https://doi.org/10.1038/npp.2015.59>
- Stuart, S. A., & Robinson, E. S. J. (2015). Reducing the stress of drug administration: Implications for the 3Rs. *Scientific Reports*, *5*, 14288. <https://doi.org/10.1038/srep14288>
- Stuart, S. A., Wood, C. M., & Robinson, E. S. J. (2017). Using the affective bias test to predict drug-induced negative affect: Implications for drug safety. *British Journal of Pharmacology*, *174*(19), 3200–3210. <https://doi.org/10.1111/bph.13972>
- Yirmiya, R. (1996). Endotoxin produces a depressive-like episode in rats. *Brain Research*, *711*(1–2), 163–174. [https://doi.org/10.1016/0006-8993\(95\)01415-2](https://doi.org/10.1016/0006-8993(95)01415-2)
- Yirmiya, R., Pollak, Y., Morag, M., Reichenberg, A., Barak, O., Avitsur, R., Shavit, Y., Ovadia, H., Weidenfeld, J., Morag, A., Newman, M. E., & Pollmächer, T. (2000). Illness, cytokines, and depression. *Annals of the New York Academy of Sciences*, *917*, 478–487. <https://doi.org/10.1111/j.1749-6632.2000.tb05412.x>

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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