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Altered learning under uncertainty in unmedicated mood and anxiety disorders

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Anxiety is characterized by altered responses under uncertain conditions, but the precise mechanism by which uncertainty changes the behaviour of anxious individuals is unclear. Here we probe the computational basis of learning under uncertainty in healthy individuals and individuals suffering from a mix of mood and anxiety disorders. Participants were asked to choose between four competing slot machines with fluctuating reward and punishment outcomes during safety and stress. We predicted that anxious individuals under stress would learn faster about punishments and exhibit choices that were more affected by those punishments, thus formalizing our predictions as parameters in reinforcement learning accounts of behaviour. Overall, the data suggest that anxious individuals are quicker to update their behaviour in response to negative outcomes (increased punishment learning rates). When treating anxiety, it may therefore be more fruitful to encourage anxious individuals to integrate information over longer horizons when bad things happen, rather than try to blunt their responses to negative outcomes.

Mood and anxiety disorders are the most common mental health problems in the developed world, accounting for 4% of all years lived with disability[1]. In spite of this, we have very little understanding of the mechanisms driving pathological feelings of anxiety and the associated alterations to cognitive processes, such as decision-making, when people are anxious. This hinders our ability to improve treatments[2].

Altered psychological, behavioural and neural responses to uncertainty are thought to be key to the manifestation of anxiety[3]. First, anxious individuals report finding uncertain situations distressing[4]. Second, anxious individuals have been shown to be averse to uncertain decisions, preferring less profitable but more predictable options over more profitable but uncertain ones[5]. Finally, in translational research, a well-established dissociation is made between the processing of predictable and unpredictable threats[6], with unpredictable threats used as a preclinical model of anxiety in which uncertainty is a central component, whereas predictable shocks are a model for fear and phobias. In humans, the neural signatures of unpredictable-threat response[7] overlap with those of pathological anxiety[8], indicating that this model is relevant to understanding the pathological state.

Nevertheless, decision-making under uncertainty is ubiquitous in daily life[9]. Multi-armed bandit tasks can be used to probe decision-making under uncertainty by asking individuals to select one of multiple slot machines (bandits) with slowly fluctuating pay-offs. In any given trial, the best option might be one that you chose recently (and so have some knowledge about) or it might be one you haven't chosen (and so do not have up-to-date information about). It has been demonstrated computationally that the balance of decision-making regarding which bandit to choose can be captured through reinforcement learning algorithms that approximately optimize decisions based on the history of feedback from the bandits[9,10]. Specifically, decisions are made according to the relative weights afforded to rewards and punishments (sensitivity—how much one anticipates liking being rewarded or disliking being punished) and how quickly the information is integrated over time (learning rate—how quickly one might switch bandits following a punishment or how long one persists in choosing a previously rewarded bandit). If altered response to uncertainty were a core feature of anxiety symptoms, we would predict that the mechanisms parameterized by reinforcement learning models should differ in individuals with high levels of anxiety symptomatology[11]. Specifically, given that anxiety is associated with a bias towards aversive processing (negative affective bias[12–14]), we would predict that anxiety selectively increases the weights of aversive-specific parameters in reinforcement learning algorithms (punishment sensitivity and punishment learning rate).

In this study, we therefore sought to formalize the differences in decision-making under uncertainty between healthy individuals and those with high levels of anxiety in terms of differences in the parameters of reinforcement learning models. Moreover, given that the diathesis–stress hypothesis[15] predicts that some symptoms of mood and anxiety disorders are revealed only when an individual is under stress[13], we also transiently induced stress in participants using a threat of unpredictable shock (where shock probability was unrelated to the participant's behaviour). Thus, we predicted that anxiety symptoms would selectively increase punishment sensitivity and punishment learning rate in the reinforcement learning algorithm, and that this would be exaggerated under acute stress.

Results

Healthy controls ($N=88$) and individuals with unmedicated mood and anxiety symptoms ($N=44$; see Table 1 for the full demographics) completed a four-armed bandit task under conditions of threat of shock (stress) and safety as illustrated in Fig. 1. The data are available online[16] (see Data availability statement).

Self-report analysis. As expected, the mood and anxiety group demonstrated higher levels of trait anxiety (data missing from one participant in each group; Student's t-test: $t(128)=8.7$; $P<0.001$; Cohen's $d=1.6$; 95% confidence interval (CI): 1.2, 2.0) and recent

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Table 1 | Demographics and mood measures

	Asymptomatic				Symptomatic			
N	88				44			
Female	50				28			
Higher education	[a]				37			
	Mean	s.d.	Minimum	Maximum	Mean	s.d.	Minimum	Maximum
Age (years)	23	5.1	18	41	29	8.7	20	64
Raven's IQ	–	–	–	–	8	2.6	3	12
STAI state	38	9.8	18	53	47	10.7	21	68
STAI trait	41	10.6	20	69	57	8.2	41	74
BDI	7	7.1	0	36	20	9.4	6	54

The higher education count represents those who were in undergraduate education or higher. Raven's IQ refers to the IQ estimate obtained from Raven's progressive matrices. STAI, State–Trait Anxiety Inventory; BDI, Beck Depression Inventory. [a]This group was recruited from the institutional subject database and ~90% are estimated to be in the higher education group, but detailed information is unfortunately not available.

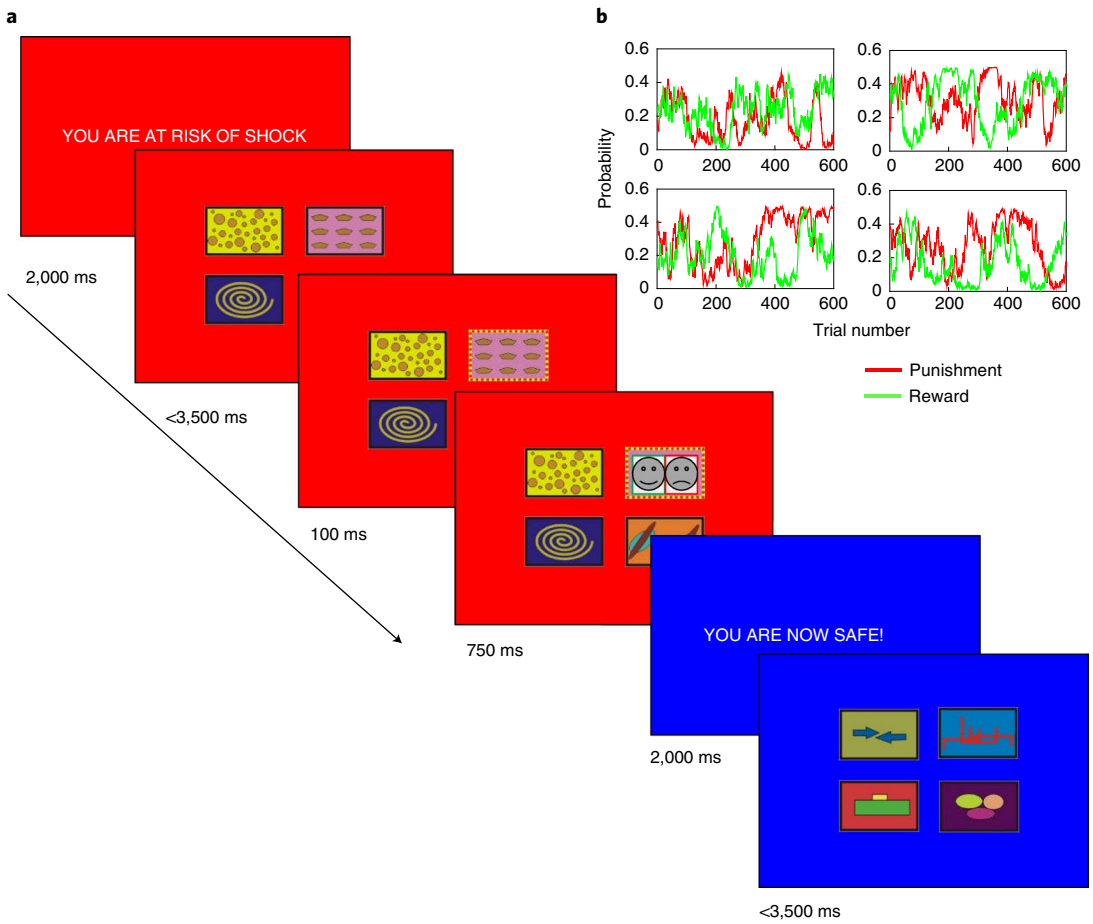

Fig. 1 | Task schematic. a, Participants were asked to select one of four bandits in each trial. Following the selection of, for example, the top right bandit (under the threat condition, indicated by the red border) the outcome (here illustrated as a combined reward and punishment; these were black and white photos of real human happy or fearful faces in the original experiment) was overlaid on the selected bandit and the bandit border changed colour (to blue, indicating the safe condition). The task proceeded in the same manner under the safe condition, but with a different set of bandits. **b**, An example of the independent fluctuations of reward and punishment probabilities across four bandits. At the start of a new condition, the bandits had the same probabilities as at the end of the previous condition; that is, the bandits at the end of one safe block paused during the subsequent threat block and vice versa.

depression symptoms (data missing from three patients and four controls; $t(124)=9.0$; $P<0.001$; $d=1.7$; 95% CI: 1.2, 2.01), relative to healthy controls (Table 1). Moreover, participants reported feeling more anxious under the threat condition relative to the safe condition (data missing for the second block for one patient; variance ratio $F(1, 129)=319$; $P<0.001$; $\eta^2=0.7$; 95% CI: 0.62, 0.77), but this did not differ according to group (group × condition interaction: $F(1, 129)=0.04$; $P=0.8$; $\eta^2<0.001$; 95% CI: 0, 0.03).

Table 2 | Model specification

Model	NP	Parameters					
bandit4arm_4par	4	Reward sensitivity	Punishment sensitivity	Reward learning rate	Punishment learning rate		
bandit4arm_lapse	5	Reward sensitivity	Punishment sensitivity	Reward learning rate	Punishment learning rate	Lapse	
igt_pvl_decay	4	Decay rate	Shape	Consistency	Loss aversion		
igt_pvl_delta	4	Learning rate	Shape	Consistency	Loss aversion		
bandit4arm_2par_lapse	3			Reward learning rate	Punishment learning rate	Lapse	
bandit4arm_singleA_lapse	4	Reward sensitivity	Punishment sensitivity	Learning rate	Lapse		
bandit4arm_lapse_decay	6	Reward sensitivity	Punishment sensitivity	Reward learning rate	Punishment learning rate	Lapse	Decay

We fitted seven different models using the hBayesDM package (v. 0.7.2). The model names are those implemented in the hBayesDM package. NP, number of parameters.

Model-agnostic task analysis. As expected, participants were more likely to repeat a choice following a win than a loss ($F(1, 130) = 78$; $P < 0.001$; $\eta^2 = 0.4$; 95% CI: 0.25, 0.48). However, this was not modulated by group (group × outcome interaction: $F(1, 130) = 0.18$; $P = 0.68$; $\eta^2 = 0.001$; 95% CI: 0, 0.04) or stress condition (stress condition × outcome interaction: $F(1, 130) = 2.6$; $P = 0.11$; $\eta^2 = 0.019$; 95% CI: 0, 0.09) and the three-way interaction was not significant ($F(1, 130) = 3.6$; $P = 0.061$; $\eta^2 = 0.026$; 95% CI: 0, 0.1).

A Bayesian version of the same analysis confirmed that the winning model included only outcome ($\log BF_{10} = 91$), which scored eight-times better than the next best model (main effects of outcome and stress condition; $\log BF_{10} = 89.3$). The full set of Bayes Factors from this analysis is presented in Supplementary Table 1.

Modelling results. We fitted seven models to the data (Table 2). The winning model fitted with a full prior specification was the six-parameter model that included a lapse and a decay parameter (Table 3, top). We then fitted the top two models with the different combinations of group/condition hierarchical priors and demonstrated that both models were actually best fitted using only two priors: one for each group (Table 3, bottom). However, our model-fitting procedure did not converge for the decay model with a single prior; probably because the single prior failed to capture the nature of the underlying distribution (which may be better represented by two distributions as seen in Table 3). Specifically, there are multiple Gelman–Rubin statistics[17] ($R\hat{}$) greater than 1.1 (even if we increase the number of samples in the chains from 2,000 to 10,000). Therefore, fit indices such as the Leave-One-Out Information Criterion (LOOIC) are not meaningful and are not reported.

Extracting the parameters from the models fitted using two priors (one for each group) demonstrated elevated punishment learning rates and lapse parameters in symptomatic relative to control individuals (the highest density interval (HDI) for the comparison across groups does not overlap zero). In the model including a decay parameter, decay rate was also elevated in the symptomatic group (Table 4; Fig. 2). Note that this same pattern (main effect of group on punishment learning rates and lapse parameters only) was seen when parameters were extracted from the four-prior model and there was no effect of condition on any parameter (see Supplementary Results 1).

Model check. Finally, we simulated data for this model for each participant based on their parameter estimates. For both the simulated and real data we calculated the proportion of all trials in which

Table 3 | Model and prior fits

Model	LOOIC	
bandit4arm	128,456	
bandit4arm_lapse	**128,198**	
igt_pvl_decay	132,008	
igt_pvl_delta	131,774	
bandit4arm_2par_lapse	140,144	
bandit4arm_singleA_lapse	129,120	
bandit4arm_lapse_decay	**126,289**	
Prior	**LOOIC**	
	bandit4arm_lapse	**bandit4arm_lapse_decay**
Diagnosis and condition priors (4)	128,198	126,289
Diagnosis priors (2)	**128,166**	**126,094**
Condition priors (2)	128,225	126,233
Single prior (1)	128,174	[a]

The winning model in the top part of table is that with the lowest LOOIC. The lowest two values (for bandit4arm_lapse and bandit4arm_lapse_decay) are displayed in bold. In the bottom part of the table, the lowest LOOIC is then obtained when those two models are fitted with two priors: one for symptomatic and one for healthy individuals (diagnosis priors). [a]Fitting the decay model with a single prior did not converge, rendering the LOOIC value meaningless.

Table 4 | Parameter estimates and group comparison on the winning model and prior combination

	Symptomatic	Control	Between-group HDI	
bandit4arm_lapse				
Reward sensitivity	7.47 (2.91)	9.61 (4.87)	−4.55	0.65
Punishment sensitivity	7.41 (7.21)	6.67 (4.83)	−4.95	2.24
Reward learning rate	0.31 (0.30)	0.25 (0.22)	−0.11	0.17
Punishment learning rate	0.51 (0.18)	0.31 (0.15)	0.08	**0.38**
Lapse	0.21 (0.10)	0.13 (0.11)	0.02	**0.2**
bandit4arm_lapse_decay				
Reward sensitivity	11.41 (5.03)	10.94 (7.20)	−4.77	6.35
Punishment sensitivity	4.64 (5.02)	3.00 (3.10)	−0.87	1.93
Reward learning rate	0.21 (0.23)	0.23 (0.22)	−0.13	0.07
Punishment learning rate	0.95 (0.01)	0.75 (0.14)	0.04	**0.26**
Lapse	0.22 (0.10)	0.10 (0.03)	0.04	**0.18**
Decay	0.61 (0.25)	0.41 (0.31)	0.10	**0.40**

Values represent the mean (standard deviation) of the final estimated posterior mean estimates for each individual. The between-group HDI comprises the upper and lower bounds of the 95% HDI of the comparison between the symptomatic and control groups. If the HDI does not encompass zero, we consider there to be a meaningful difference between the groups. We found a main effect of group on only the punishment learning rate, lapse and decay (when included) parameters (in bold).

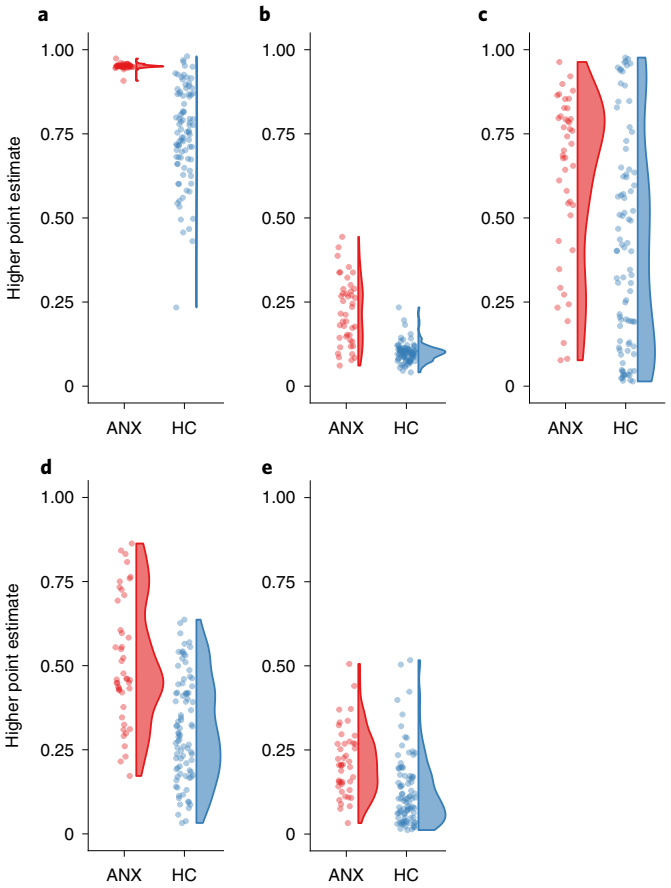

Fig. 2 | Group difference in parameters. a–c, Higher point estimates of punishment learning rates (**a**), lapse rates (**b**) and decay rates (**c**) in the symptomatic group (ANX; $N=44$) relative to the healthy controls (HC; $N=88$) in the bandit4arm_lapse_decay model. **d**,**e**, The same pattern is seen in punishment learning rates (**d**) and lapse rates (**e**) in the bandit4arm_lapse model (which does not include a decay parameter). The final estimated posterior mean of each parameter for each individual is plotted in each panel.

participants switched bandits. Real and simulated data showed close correspondence (coefficient of correlation $r(132)=0.84$; $P<0.001$; 95% CI: 0.78, 0.89; for both models; Fig. 3).

Moreover, simulated data recapitulated the model-agnostic analysis. There was a main effect of outcome ($F(1, 130)=434$; $P<0.001$; $\eta^2=0.8$; 95% CI: 0.70, 0.81) driven by greater stay probability following wins than losses, which did not interact with diagnosis ($F(1, 130)=0.003$; $P=0.95$; $\eta^2<0.001$; 95% CI: 0, 0.008).

Continuous symptom analyses. Extracting each individual's posterior mean estimated parameters supported the existence of positive correlations between trait anxiety and the lapse (lapse: $r(130)=0.32$, 95% CI: 0.16, 0.47, $\log BF_{10}=4.5$, $P<0.001$; lapse_decay: $r(130)=0.42$, 95% CI: 0.27, 0.56, $\log BF_{10}=10.44$, $P<0.001$) and punishment learning rate (lapse: $r(130)=0.28$, 95% CI: 0.11, 0.43, $\log BF_{10}=2.9$, $P=0.001$; lapse_decay: $r(130)=0.42$, 95% CI: 0.27, 0.56, $\log BF_{10}=10.4$, $P<0.001$), but no supported correlation for the decay parameter (lapse_decay: $r(130)=0.19$, 95% CI: 0.02, 0.35, $\log BF_{10}=0.074$, $P=0.032$) or any other parameter (all $\log BF_{10}<0.4$). Trait anxiety was, as expected, strongly correlated with recent depression symptoms (BDI; $r(126)=0.8$, 95% CI: 0.73, 0.85, $\log BF_{10}=60$, $P<0.001$) and therefore similar correlations were observed between BDI scores and model parameters (Fig. 4). Note that the interaction between trait anxiety and parameters of interest remained significant (all $t=3.1$–5.1, $P<0.002$) when age was also included as a predictor in the models, suggesting that the effects were not driven by age.

Discussion

We found that higher mood and anxiety symptoms were associated with altered decision-making in the aversive domain (specifically, greater punishment learning rates). This finding was partially consistent with our hypotheses. Contrary to our hypotheses, however, we found no evidence that this was influenced by stress and no evidence of a group difference in punishment sensitivity. Moreover, the higher learning rate for punishments occurred in combination with lower reliance on the modelled reinforcement learning parameters in general (as evidenced by an increased influence of the lapse parameter in the symptomatic group) and increased propensity to forget the previous values of unchosen options (increased reliance on a decay parameter).

A greater punishment learning rate means that individuals with mood and anxiety symptoms learn faster about punishments and will therefore more readily update their behaviour on the basis of more recent negative outcomes instead of integrating over longer time scales. This is also reflected in the lower stay probabilities immediately following punishment in the model-agnostic analysis (which was recapitulated in the model simulations). Importantly, this occurred in the absence of evidence for a group difference in punishment sensitivity, which suggests that anxious individuals do not overweigh punishments per se. This lack of evidence for an effect of anxiety on punishment sensitivity is consistent with our earlier work with reinforcement learning paradigms[13] and work indicating similar loss aversion between anxious and healthy individuals (albeit in the context of higher risk aversion)[5]. Taken together, these results indicate that it is not that anxious individuals weigh negative outcomes more heavily in themselves; they instead use that information differently. Specifically, a greater

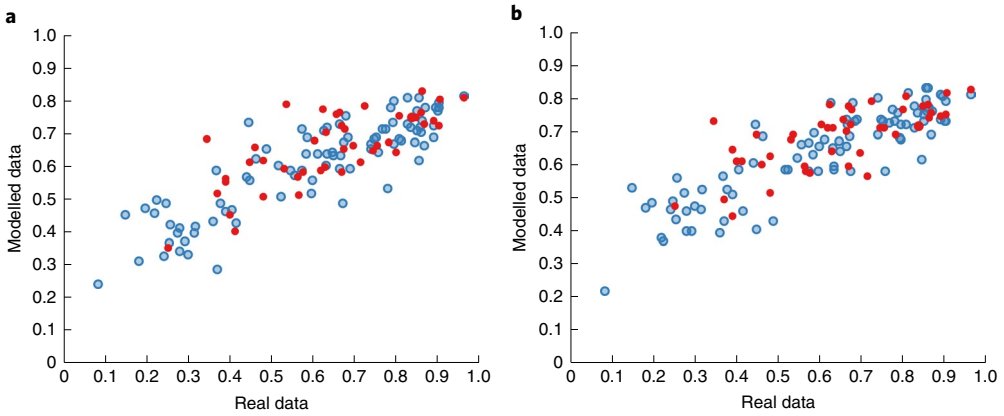

Fig. 3 | Sensitivity plots. a,**b**, Simulated data for each individual ($N = 132$) show close correspondence with real data on a simple metric p_{switch} (the proportion of trials in which the individual (or simulated agent) selected a different bandit from the previous trial) for the bandit4arm_lapse_decay (**a**) and bandit4arm_lapse (**b**) models. Healthy controls ($N = 88$) are plotted in blue and symptomatic individuals in red ($N = 44$).

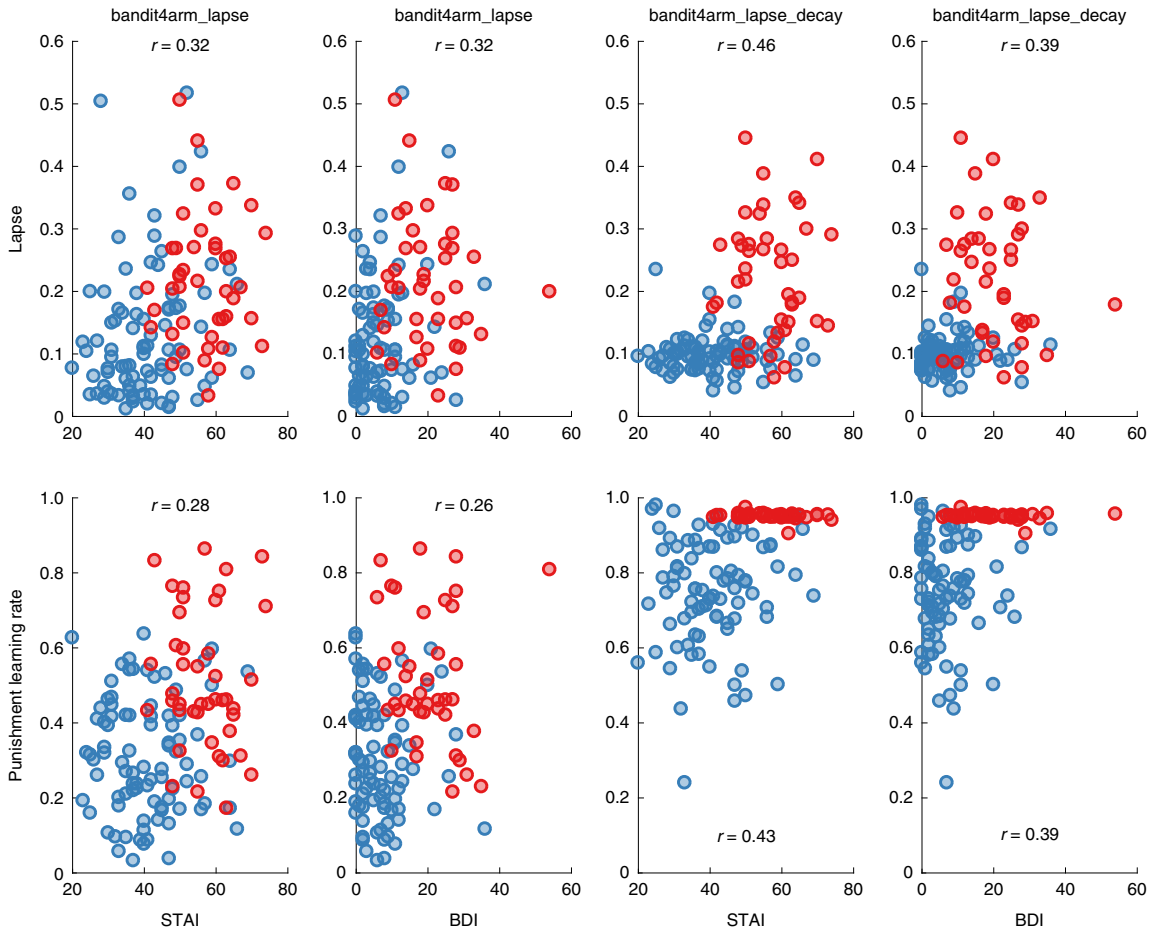

Fig. 4 | Continuous symptom analysis. Individual parameter posteriors for both models plotted against anxiety symptoms (STAI) and depression symptoms (BDI). Healthy controls ($N = 88$) are plotted in blue and symptomatic individuals ($N = 44$) in red. The punishment learning rate parameter is at the boundary for the symptomatic group in the decay model. The *r* values were calculated between the symptom and the parameter for the entire sample. The lowest score on the STAI is 20 (a score of 1 for 'almost never' on all 20 questions).

punishment learning rate implies that individuals with anxiety integrate information about threats over fewer trials, overestimate the probability of bad outcomes and hence engage in avoidance behaviours[18]. Clinically, this might result in overestimating negative events. For example, in the aftermath of a heavily reported plane crash an anxious individual might overestimate the risk of it reoccurring and therefore avoid flying[14]. In the long run, such avoidance behaviour will reduce an anxious individual's ability to update learning and hence overestimation persists and avoidance behaviour is upheld.

That it is the learning rate, rather than sensitivity to punishment, which is elevated in mood and anxiety disorders[12,19] may be important in relation to potential interventions that could mitigate such a negative bias. In particular, we may not need to blunt aversive responses through treatment—rather we should focus on treatments that seek to modify how negative information is used[20]. Indeed, changing the way individuals use the same information is one principle underpinning psychological interventions for mood and anxiety disorders, such as cognitive behavioural therapy[20]. One specific recommendation that follows from our findings is in line with what is already practised in exposure therapy[20]: therapists expose patients to sources of anxiety (for example, a spider) and encourage them to hold off on implementing decisions (running away) based on predicted negative outcomes (the spider causing them harm) until they learn how infrequent (or frequent) the negative outcomes are[20]. The present work takes us a step towards formalizing the behavioural effect as a defined parameter in a reinforcement learning model that we can directly measure and hence target to refine future treatments.

The altered punishment learning rates in the symptomatic group do, however, need to be considered in the context of an accompanying increased reliance on the lapse and decay parameters. In the model, the lapse parameter quantifies dependence on a form of unexpected responding. This could occur as a result of participants losing concentration during a trial and choosing at random, or possibly increasing their tendency towards undirected exploration in an attempt to avoid unpredictable punishments[21]. In other words, anxiety may shift the balance in explore–exploit trade-offs towards exploration, perhaps as a form of exploration-driven avoidance, in which individuals shift their behaviour to avoid bad outcomes. This should be considered alongside prior work demonstrating that high anxiety (in healthy individuals) is associated with an impoverished ability to detect shifts from stable to unpredictable punishments, perhaps because their default assumption is that the environment is unpredictable[22]. Increased exploration may therefore be due to an assumption of increased unpredictability. The effect on the decay parameter suggests that anxious individuals also forget the previous values of unchosen bandits more rapidly, which could also contribute to their propensity towards increased exploration. Future experiments should test the different predictions made by these explanations. However, the lapse parameter also captures aspects of decision-making that are not encompassed by the model. In other words, what we have consigned to categories of irreducible uncertainty might actually be reduced by more sophisticated and proficient models. Our data are available online[16] (see Data availability statement) for the future exploration of different models as the field and literature develop.

Finally, it is worth noting that we found no evidence that the modelled effects were affected by acute stress. We predicted that they would be, because the diathesis–stress hypothesis predicts that symptoms of anxiety will be exacerbated in stressful circumstances[15]. Indeed, our prior work indicated that reliance on Pavlovian avoidance biases in anxiety disorders is exacerbated by the same stress manipulation adopted here[13]. Nevertheless, it remains possible that such an effect exists, but that it is weak relative to the strong effects of diagnosis and outcome, and the current study was simply too underpowered to detect it. Alternatively, our threat of shock manipulation may not be sufficiently strong. Future work could consider measuring concurrent startle response during the task to confirm the efficacy of the manipulation beyond self-report. Another caveat is that the reinforcers we used (faces) may not have been as motivating as other outcomes, such as money. It is possible that stronger outcomes may have driven changes in sensitivities and/or revealed a significant influence of stress. Alternatively, it may be that stronger feedback would actually remove the group effects we observe[23]. In either case, future work should explicitly test the impact of modulating feedback strength on task performance. Relatedly, it is possible that the within-subject nature of the safe/threat conditions meant that the overall context was anxiogenic and there was no true baseline. Note though, that self-report measures did vary between conditions, and also that many prior studies have shown within-subject differences using this manipulation[12]. However, a between-subject design with separate groups, and critically a safe group with no electrode contact, would control for this. A final caveat is that we recruited a mixed sample of people who had anxiety and people who had depression. Our post hoc analyses (see Supplementary Results 2) provide some evidence that there is no difference in parameters across the different diagnostic groupings. However, the study was not designed to disambiguate depression from anxiety, which are, in any case, highly comorbid (and highly correlated at a symptom scale level) and may not represent true natural kinds. Although we have no a priori reason to suspect that IQ or socio-economic status differed between our groups (or that it drives group differences), we do not have complete data on this and so cannot entirely rule it out.

These findings extend our prior work attempting to formalize the behavioural alterations seen in anxiety disorders in terms of computational models[5,13]. Such models aim to bridge the gap between observable symptoms (which form the basis of current diagnostic categories) and the underlying cognitive computations in the brain. Ultimately, the experience of debilitating anxiety emerges from interactions between an individual and their environment; fully optimized treatments are unlikely to be developed without a clearer understanding of how these symptoms emerge mechanistically. Formally specifying some of the behavioural changes that occur in clinical anxiety takes us a step closer to this goal.

Methods

Participants. We recruited 132 participants, $N=88$ healthy controls (50 female; age $=23\pm5$ yr) and $N=44$ people with unmedicated mood and anxiety symptoms (28 female; age $=28\pm9$ yr), from the local community (that is not through clinical services, but rather through advertisements on noticeboards and internet sites; this was to increase the probability of recruiting unmedicated participants). The two groups were recruited through separate advertising campaigns. The symptomatic group responded to an advert asking for people for whom anxiety/depression was impacting their lives and then underwent a standardized clinical screen. The groups did not significantly differ in gender ($X^2=0.65$; $P=0.5$), but the patient group was slightly older (mean ages: 29 versus 23 yr; $t(130)=4.4$; $P<0.001$; $d=0.8$; 95% CI: 0.4, 1.2). We set an a priori minimum group size of $N=40$ in the original grant application (MR/K024280/1) based on a previously observed difference between groups of effect size $d=1.09$ (ref. [24]), which was decreased to 0.7 for the purpose of a conservative power analysis. The final $N=44$ in the clinical group and $N=88$ in the healthy group provides >95% power for a between-groups t-test with $\alpha=0.05$ (two-tailed). Ultimately we wanted to collect as much data as possible within our time and financial constraints, as parameter recovery in modelling is dependent on sample size[25]. Critically, model comparison and inference were completed only after we stopped recruitment.

Although our focus was on anxiety symptoms, we recruited a mixed sample because mood and anxiety disorder symptoms show considerable overlap, and the disorders are strongly comorbid indicating that they may not be mechanistically dissociable. The majority of the people in our pathological sample ($N=28$) had a mixed diagnosis of generalized anxiety disorder (GAD) and major depressive disorder (MDD); eight had a GAD diagnosis alone; three had panic disorder with MDD; and five had MDD alone. These diagnoses were assigned according to the Mini International Neuropsychiatric Interview and completed by a trained researcher under the guidance of a clinical psychologist or psychiatrist[26]. The average number of depressive episodes was 5 (s.d. ±7), with the average onset of the first episode at 20 ± 8 yr. All were unmedicated at the time, but $N=18$ had tried psychiatric medication more than 6 months before the experiment and $N=21$ had undergone some form of psychological treatment. Exclusion criteria were any form of psychiatric medication within the last 6 months, any current psychiatric diagnosis (other than MDD or GAD), a neurological disorder or a pacemaker. Continuous measures of anxiety symptomatology were obtained using the STAI and recent depression symptoms using the BDI. All participants provided written informed consent and were reimbursed £7.50 h^{-1} for their participation. The study was given ethical approval from the UCL Research Ethics Committee (project nos. 1764/001 and 6198/001). Note that all relevant data distributions are plotted. In some cases they are non-normal, but the inference (for example using Bayesian model comparison approaches) is not reliant on the same assumptions as classic

frequentist statistics. Due to the nature of the recruitment, data collection and analysis were not performed blind to the conditions of the experiments and the participants were not randomized into groups. However, the task stimuli and threat condition were randomized across participants.

Four-armed bandit task. The task was adapted from Seymour et al.[10] and presented using the Cogent toolbox for MATLAB on a laptop computer[27]. Positive feedback was a single happy face and negative feedback was a single fearful face (consistent with our prior work[13,19]). The task was completed under alternating conditions of safety and threat (see Stress manipulation section), with a different set of four bandits in each condition leading to a total of eight bandits (a set of four that was consistent throughout the safe condition; four throughout the threat condition).

In each trial, participants were asked to select one of the four bandits (within 3.5 s) and were then provided (for just the selected bandit; Fig. 1a) with one of: no feedback; positive feedback; negative feedback; or both positive and negative feedback. The probabilities of these outcomes fluctuated independently and slowly across bandits, such that the bandit that was most beneficial changed over time (Fig. 1b) and participants had to keep track of reward and punishment separately. Note, however, that the outcomes themselves were binary (present or not). The participants were instructed to 'Try to get happy faces! Avoid fearful!'. The bandits remained in the same spatial location on every trial. The face stimuli were chosen because our prior work using them showed that reinforcement learning (RL) mechanisms (striatal prediction error signals) are sensitive to the same stress manipulation[19] (and this study itself built on a line of studies[28] that explored the impact of stress on the same stimuli in other contexts). There was no additional outcome (for example monetary loss/gain).

Stress manipulation. State anxiety was induced via the threat of unpredictable electric shocks delivered with two electrodes attached to the non-dominant wrist using a Digitimer Constant Current Stimulator (Digitimer Ltd). The appropriate shock level was established using a shock workup procedure before testing. Specifically, up to five shocks of increasing intensity were administered and participants rated each one on a scale from 1 (barely felt) to 5 (unbearable), with the final shock level set to 4. The experimental task was programmed using the Cogent toolbox for MATLAB 2014, presented on a laptop and administered under alternating safe and threat blocks. At the start of the safe block, the background colour changed to blue and a 2,000 ms message stating 'YOU ARE NOW SAFE!' was displayed. At the start of the threat block, the background colour changed to red and the message 'YOU ARE AT RISK OF SHOCK' was presented for 2,000 ms. The electrodes remained on the participant's wrist throughout both types of condition. Participants were told that they might receive a shock during only the threat condition but that the shocks were not dependent on their performance. As a manipulation check, participants retrospectively rated how anxious they felt during the safe and threat conditions on a scale from 1 (not at all) to 10 (very much so). This well-established[12] manipulation has been shown to have high reliability[19] and replicability[29]. There were four threat and four safe conditions, each involving 50 trials and lasting ~5 min each. Thus, there were a total of 400 trials for a maximum duration of ~45 min, depending on participant response times. Participants received one shock per threat condition (four in total). They were given shocks on the 33rd trial of the 1st and 3rd threat conditions and the 15th trial of the 2nd and 4th threat conditions.

Manipulation check and model-agnostic task analysis. The retrospective manipulation check was taken once in the middle and once at the end of the task (first half and second half) and analysed in a 2 (half) × 2 (condition) × 2 (diagnosis) repeated measures analysis of variance (ANOVA). For model-agnostic task analysis, we calculated stay probability following win-only and loss-only trials (excluding trials in which both wins and losses were given) and included them in a 2 (outcome) × 2 (condition) × 2 (diagnosis) repeated measures ANOVA. We implemented frequentist and Bayesian (adopting a default Cauchy prior) repeated measures ANOVAs using JASP[30] (for data and associated JASP analyses see Data and Code availability statements). All *t*-tests are two-sided and effect sizes were calculated using the default settings in JASP. For frequentist tests we used an α-level of 0.05.

Computational modelling. We fitted seven different models[10] using the hBayesDM package for R (ref. [31]; see Code availability statement). This toolbox simplifies the implementation of hierarchical Bayesian parameter estimation using Stan v. 2.18.2[32]. We fitted three chains for each model with 1,000 burn-in samples and 2,000 samples. For more details please refer to ref. [31]. Previous studies showed that hierarchical parameter estimation outperforms individual parameter estimation in parameter recovery[33]. We fitted the models, shown in Table 2, to three pieces of information per trial: choice (1:4), gain (0, 1) and loss (0, −1).

The bandit4arm models (where *i* refers to a given bandit and *t* refers to trial) were calculated by inputting reward (rew) and punishment (pun) values separately into the following equations:

$$\mathrm{Value}^{\mathrm{rew}}_{t(i)} = \mathrm{Value}^{\mathrm{rew}}_{t(i)} + \mathrm{LearningRate}_{\mathrm{rew}} \times \mathrm{PredictionError}^{\mathrm{rew}}_{t(i)} \quad (1)$$

$$\mathrm{Value}^{\mathrm{pun}}_{t(i)} = \mathrm{Value}^{\mathrm{pun}}_{t(i)} + \mathrm{LearningRate}_{\mathrm{pun}} \times \mathrm{PredictionError}^{\mathrm{pun}}_{t(i)} \quad (2)$$

$$\mathrm{PredictionError}^{\mathrm{rew}}_{t(i)} = \begin{cases} \mathrm{Sensitivity}_{\mathrm{rew}} \times \mathrm{RewardOutcome}(t) - \mathrm{Value}^{\mathrm{rew}}_{t-1(i)} & \text{if } i = \text{chosen} \\ -\mathrm{Value}^{\mathrm{rew}}_{t-1(i)} & \text{if } i = \text{unchosen} \end{cases} \quad (3)$$

$$\mathrm{PredictionError}^{\mathrm{pun}}_{t(i)} = \begin{cases} \mathrm{Sensitivity}_{\mathrm{pun}} \times \mathrm{PunishmentOutcome}(t) - \mathrm{Value}^{\mathrm{pun}}_{t-1(i)} & \text{if } i = \text{chosen} \\ -\mathrm{Value}^{\mathrm{pun}}_{t-1(i)} & \text{if } i = \text{unchosen} \end{cases} \quad (4)$$

Choice probability was determined by passing the reward and punishment values through a softmax function in the _4par model, where *j* represents all the bandits:

$$\mathrm{ChoiceProbability}_{t(i)} = \frac{\exp\left(\mathrm{Value}^{\mathrm{rew}}_{t(i)} + \mathrm{Value}^{\mathrm{pun}}_{t(i)}\right)}{\sum_j \exp\left(\mathrm{Value}^{\mathrm{rew}}_{t(j)} + \mathrm{Value}^{\mathrm{pun}}_{t(j)}\right)} \quad (5)$$

For the _lapse model, the addition of an irreducible noise parameter (lapse) allowed for the possibility of decisions made at random, irrespective of the inferred values of the bandits (sometimes referred to as 'trembling hand' decisions)[34]. Note that this lapse parameter serves a similar purpose as an (inverse) temperature parameter in the softmax, but it is less liable to trade off against the other parameters[35]:

$$\mathrm{ChoiceProbability}_{t(i)} = \frac{\exp\left(\mathrm{Value}^{\mathrm{rew}}_{t(i)} + \mathrm{Value}^{\mathrm{pun}}_{t(i)}\right)}{\sum_j \exp\left(\mathrm{Value}^{\mathrm{rew}}_{t(j)} + \mathrm{Value}^{\mathrm{pun}}_{t(j)}\right)} \times (1 - \mathrm{Lapse}) + \frac{\mathrm{Lapse}}{4} \quad (6)$$

For the _2par_lapse model, there are no sensitivity parameters in equations (3) and (4). For the _singleA_lapse model, there is a single learning rate across equations (1) and (2); this parameter is not allowed to take on separate values depending on whether the outcome was rewarding or punishing. For the _lapse_decay model we added a decay rate based on ref. [36] such that the weights of features that were not chosen gradually decayed to 0, according to the decay rate:

$$\mathrm{Value}_{t(i)} = (1 - \mathrm{Decay}) \times \mathrm{Value}_{t-1(i)} \text{ if } i = \text{unchosen} \quad (7)$$

We implemented the two IGT_pvl models, exactly following refs. [31,37]. These models are substantially worse at describing the current data (Table 3, top) but are detailed in Supplementary Methods 1. Briefly, they are prospect valence learning models that integrate aspects of reinforcement learning and prospect theory learning models.

Model selection. Parameters for all of the models were initially fitted under four separate hierarchical priors: anxious/depressed individuals under threat; healthy controls under threat; anxious/depressed individuals under the safe condition; and healthy controls under the safe condition. The winning model was defined as the model with the lowest LOOIC summed across these four priors.

We then followed up initial model selection with a subsequent exploration of all four combinations of group and condition priors (all four; two representing each condition; two representing each group; and one pooling everyone together) on the top two models. We then compared parameter estimates from the top two models across the two groups using the 95% HDI. Specifically, for each comparison, we calculated the difference in the hyper parameters and reported the 95% HDI of the difference. If this HDI did not overlap zero, we consider there to be a meaningful difference between the groups[38,39]. Note that the 95% HDIs do not test whether we can reject the null hypothesis (that is, that two groups are the same on a given parameter), but instead whether the hyper parameters differ between the groups/conditions[38,39]. To illustrate group differences, we plotted the individual mean posterior parameter estimates using raincloud plots[40].

Finally, parameter estimates from the top two model/prior combinations were used to simulate choices for each individual and then compared to each individual's real choices to confirm that the models were not only the best of those tested, but also realistic models of the data (we required a correlation of greater than 0.7). Finally, we confirmed that the simulated data recapitulated patterns observed in the model-agnostic task analysis.

Continuous symptom analysis. Individual parameters (mean posterior estimates) for the overall winning model were extracted and correlated with individual trait anxiety and depression scores in Bayesian and frequentist correlation matrices using JASP[30].

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

All data used in this analysis are available on OSF at https://doi.org/10.17605/OSF.IO/UB6J7 (ref. [16]).

Code availability

Scripts for model fitting are available on OSF at https://doi.org/10.17605/OSF.IO/UB6J7 (ref. [16]) and in the Supplementary Software. For the hBayesDM package, please see https://github.com/CCS-Lab/hBayesDM.

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References

1. *GBD Compare Data Visualization* (IHME, accessed 17 November 2016).
2. LeDoux, J. E. & Pine, D. S. Using neuroscience to help understand fear and anxiety: a two-system framework. *Am. J. Psychiat.* **173**, 1083–1093 (2016).
3. Grupe, D. W. & Nitschke, J. B. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nat. Rev. Neurosci.* **14**, 488–501 (2013).
4. Birrell, J., Meares, K., Wilkinson, A. & Freeston, M. Toward a definition of intolerance of uncertainty: a review of factor analytical studies of the Intolerance of Uncertainty Scale. *Clin. Psychol. Rev.* **31**, 1198–1208 (2011).
5. Charpentier, C. J., Aylward, J., Roiser, J. P. & Robinson, O. J. Enhanced risk aversion, but not loss aversion, in unmedicated pathological anxiety. *Biol. Psychiat.* **81**, 1014–1022 (2017).
6. Grillon, C. Models and mechanisms of anxiety: evidence from startle studies. *Psychopharmacology* **199**, 421–437 (2008).
7. Robinson, O. J., Overstreet, C., Allen, P. S., Pine, D. S. & Grillon, C. Acute tryptophan depletion increases translational indices of anxiety but not fear: serotonergic modulation of the bed nucleus of the stria terminalis? *Neuropsychopharmacology* **37**, 1963–1971 (2012).
8. Robinson, O. J. et al. The dorsal medial prefrontal (anterior cingulate) cortex–amygdala aversive amplification circuit in unmedicated generalised and social anxiety disorders: an observational study. *Lancet Psychiat.* **1**, 294–302 (2014).
9. Daw, N. D., O'Doherty, J. P., Dayan, P., Seymour, B. & Dolan, R. J. Cortical substrates for exploratory decisions in humans. *Nature* **441**, 876–879 (2006).
10. Seymour, B., Daw, N. D., Roiser, J. P., Dayan, P. & Dolan, R. Serotonin selectively modulates reward value in human decision-making. *J. Neurosci.* **32**, 5833–5842 (2012).
11. Sharp, P. B. & Eldar, E. Computational models of anxiety: nascent efforts and future directions. *Curr. Dir. Psychol. Sci.* **28**, 170–176 (2019).
12. Robinson, O. J., Vytal, K., Cornwell, B. R. & Grillon, C. The impact of anxiety upon cognition: perspectives from human threat of shock studies. *Front. Human Neurosci.* **7**, 203 (2013).
13. Mkrtchian, A., Aylward, J., Dayan, P., Roiser, J. P. & Robinson, O. J. Modeling avoidance in mood and anxiety disorders using reinforcement learning. *Biol. Psychiat.* **82**, 532–539 (2017).
14. Gagne, C., Dayan, P. & Bishop, S. J. When planning to survive goes wrong: predicting the future and replaying the past in anxiety and PTSD. *Curr. Opin. Behav. Sci.* **24**, 89–95 (2018).
15. Monroe, S. M. & Simons, A. D. Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. *Psychol. Bull.* **110**, 406–425 (1991).
16. Robinson, O. J. Altered learning under uncertainty in unmedicated mood and anxiety disorders—EU storage. Preprint at *OSF* https://doi.org/10.17605/OSF.IO/UB6J7 (2018).
17. Gelman, A. & Rubin, D. B. Inference from iterative simulation using multiple sequences. *Stat. Sci.* **7**, 457–472 (1992).
18. Bach, D. R. Anxiety-like behavioural inhibition is normative under environmental threat-reward correlations. *PLoS Comput. Biol.* **11**, e1004646 (2015).
19. Robinson, O. J., Overstreet, C., Charney, D. S., Vytal, K. & Grillon, C. Stress increases aversive prediction-error signal in the ventral striatum. *Proc. Natl Acad. Sci. USA* **110**, 4129–4133 (2013).
20. Deacon, B. J. & Abramowitz, J. S. Cognitive and behavioral treatments for anxiety disorders: a review of meta-analytic findings. *J. Clin. Psychol.* **60**, 429–441 (2004).
21. Wilson, A., Fern, A., Ray, S. & Tadepalli, P. Multi-task reinforcement learning: a hierarchical Bayesian approach. In *Proc. 24th International Conference on Machine Learning* 1015–1022 (ACM, 2007).
22. Browning, M., Behrens, T. E., Jocham, G., O'Reilly, J. X. & Bishop, S. J. Anxious individuals have difficulty learning the causal statistics of aversive environments. *Nat. Neurosci.* **18**, 590–596 (2015).
23. Lissek, S., Pine, D. S. & Grillon, C. The strong situation: a potential impediment to studying the psychobiology and pharmacology of anxiety disorders. *Biol. Psychol.* **72**, 265–270 (2006).
24. Robinson, O. J., Cools, R., Carlisi, C. O., Sahakian, B. J. & Drevets, W. C. Ventral striatum response during reward and punishment reversal learning in unmedicated major depressive disorder. *Am. J. Psychiat.* **169**, 152–159 (2012).
25. Maxwell, S. E., Kelley, K. & Rausch, J. R. Sample size planning for statistical power and accuracy in parameter estimation. *Annu. Rev. Psychol.* **59**, 537–563 (2008).
26. Sheehan, D. et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *Eur. Psychiat.* **12**, 232–241 (1997).
27. Cogent 2000 Team at the FIL and the ICN. Cogent http://www.vislab.ucl.ac.uk/cogent.php (2013).
28. Carlisi, C. O. & Robinson, O. J.. The role of prefrontal–subcortical circuitry in negative bias in anxiety: translational, developmental and treatment perspectives. *Brain Neurosci. Adv.* https://doi.org/10.1177/2398212818774223 (2018).
29. Mkrtchian, A., Roiser, J. P. & Robinson, O. J. Threat of shock and aversive inhibition: induced anxiety modulates Pavlovian-instrumental interactions. *J. Exp. Psychol. Gen.* **146**, 1694–1704 (2017).
30. JASP Team. JASP (Version 0.7. 5.5) *Google Sch.* **765**, 766 (2016).
31. Ahn, W.-Y., Haines, N. & Zhang, L. Revealing neurocomputational mechanisms of reinforcement learning and decision-making with the hBayesDM package. *Comp. Psychiat.* **1**, 24–57 (2017).
32. Stan Development Team. RStan: the R interface to Stan. R package version 2.17.3, http://mc-stan.org/ (2018).
33. Ahn, W.-Y., Krawitz, A., Kim, W., Busemeyer, J. R. & Brown, J. W. A model-based fMRI analysis with hierarchical Bayesian parameter estimation. *J. Neurosci. Psychol. Econ.* **4**, 95–110 (2011).
34. Guitart-Masip, M. et al. Go and no-go learning in reward and punishment: interactions between affect and effect. *Neuroimage* **62**, 154–166 (2012).
35. Huys, Q. J., Pizzagalli, D. A., Bogdan, R. & Dayan, P. Mapping anhedonia onto reinforcement learning: a behavioural meta-analysis. *Biol. Mood Anxiety Disord.* **3**, 12 (2013).
36. Niv, Y. et al. Reinforcement learning in multidimensional environments relies on attention mechanisms. *J. Neurosci.* **35**, 8145–8157 (2015).
37. Ahn, W. Y., Busemeyer, J. R., Wagenmakers, E. J. & Stout, J. C. Comparison of decision learning models using the generalization criterion method. *Cogn. Sci.* **32**, 1376–1402 (2008).
38. Ahn, W.-Y. et al. Decision-making in stimulant and opiate addicts in protracted abstinence: evidence from computational modeling with pure users. *Front. Psychol.* **5**, 849 (2014).
39. Kruschke, J. *Doing Bayesian Data Analysis: A Tutorial with R, JAGS, and Stan* (Academic, 2014).
40. Allen, M., et al. Raincloud plots: a multi-platform tool for robust data visualization [version 1; peer review: 2 approved]. *Wellcome Open Res.* **4**, 63 (2019).

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Author contributions

O.J.R., J.A. and R.L.B. conceived and designed the study and acquired the data. O.J.R., J.A., V.V., J.P.R., P.D. and W.-Y.A. analysed and interpreted the data. W.-Y.A. and O.J.R. contributed to the creation of new software used in this work. All authors drafted the Article or substantively revised it and all authors approved the Article and are individually accountable for their own contributions.

Competing interests

The authors declare no competing interests.

Additional information

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Software and code

Policy information about availability of computer code

Data collection	We used the Cogent toolbox (version 2000) and MATLAB (versions from 2010-2014) to collect data
Data analysis	Data analysis was performed using MATLAB, JASP, R and the hBayesDM toolbox for R (Data, analyses and scripts available here osf.io/2jx87). Multiple versions of software used but will replicate on Matlab 2014, R 3.5 and JASP 0.9

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☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

Behavioural & social sciences study design

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Study description	Quantitative experimental
Research sample	We recruited 132 participants, N=88 healthy controls (50 female; age=23±5) and N=44 with unmedicated mood and anxiety symptoms (28 female; age=28±9) from the local community (i.e. not through clinical services, but rather through advertisements on noticeboards and internet sites; this was to increase the probability of recruiting unmedicated participants). The two groups were recruited through separate advertising campaigns. The symptomatic group responded to an advert asking for people for whom anxiety/depression was impacting their lives, and then underwent a standardized clinical screen. The groups did not significantly differ in gender (X2=0.65, p=0.5) but the patient group was slightly older (mean ages: 29 vs 23; t(130)=4.4, p<0.001,d=0.8 [95% CI 0.4, 1.2]). Although our focus was on anxiety symptoms, we recruited a mixed sample because mood and anxiety disorder symptoms show considerable overlap, and the disorders are strongly comorbid indicating that they may not be mechanistically dissociable. The majority of our pathological sample (N=28) had a mixed diagnosis of Generalised Anxiety Disorder (GAD) and Major Depressive Disorder (MDD); eight had GAD diagnosis alone; three had panic disorder with MDD; and five had MDD alone (These diagnoses were assigned according to the Mini International Neuropsychiatric Interview (MINI) and completed by a trained researcher under the guidance of a clinical psychologist or psychiatrist)26. The average number of depressive episodes was 5 (SD±7), with the average onset of first episode 20±8 years. All were currently unmedicated, but N=18 had tried psychiatric medication more than 6 months prior to the experiment, and N=21 had undergone some form of psychological treatment. Exclusion criteria were any form of psychiatric medication within the last 6 months, any current psychiatric diagnosis (other than major depression or anxiety disorder), neurological disorder, or pacemaker. Continuous measures of anxiety symptomatology were obtained using the State-Trait Anxiety Inventory (STAI) and recent depression symptoms using the Beck depression inventory (BDI). All participants provided written informed consent and were reimbursed £7.50/ hour for participation. Demographics: Control Symptomatic Total N 88 44 % female 57 64 Age 23±5 28±9 Anxiety 41±11 57±8 Depression 7±7 20±9
Sampling strategy	We set an a priori minimum group size of N=40 in the original grant application (MR/K024280/1) based on a previously observed difference between groups of effect size d=1.0924, which was decreased to 0.7 for the purpose of a conservative power analysis. The final N=44 in the clinical group and N=88 in the healthy group, provides >95% power for a between-groups t-test with α = 0.05 (two-tailed). Ultimately we wanted to collect as much data as possible within our time and financial constraints, as parameter recovery in modelling is dependent upon sample size. Critically, model comparison and inference was only completed after we stopped recruitment.
Data collection	Data was collected using a laptop computer. The participant and researcher were present. The researcher collecting data was not blind to group allocation or condition but was blind to hypothesis.
Timing	Healthy control sample data collected 04/02/2014 - 29/05/2015 Clinical sample 23/03/2015 -03/02/2016
Data exclusions	No data were excluded
Non-participation	No participants dropped out.
Randomization	Patients and controls were assigned to groups on the basis of clinical screening.

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☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
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Human research participants

Policy information about studies involving human research participants

Population characteristics	see above
Recruitment	Community healthy and clinical samples recruited from central London. All clinical samples screened for mood and anxiety disorders. It is representative of the local community who are willing to participate in experimental research (thus may not be representative of a sample who is not willing to participate in research).
Ethics oversight	The study obtained ethical approval from the UCL Research Ethics Committee (Project ID Numbers: 1764/001 and 6198/001).

Note that full information on the approval of the study protocol must also be provided in the manuscript.