Back-translating a rodent measure of negative bias into humans: the impact of induced anxiety and unmedicated mood and anxiety disorders

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Abstract

Negative affective biases are a core feature in the development and maintenance of mood and anxiety disorders and a key target for treatment development. However, recent years have seen a number of promising pre-clinical interventions fail to translate into clinical efficacy in humans. One reason for this is that, in some cases, the animal models inadequately scale-up to human symptoms. To address this, here we directly adapt– i.e. back-translate - a rodent measure of negative affective bias into humans, and explore its relationship with a) pathological mood and anxiety disorders (study 1: N=77; 30 symptomatic) and b) transient induced anxiety (study 2: within-subject threat of shock; N=47 asymptomatic). As in prior rodent work, an adapted drift diffusion model was also fitted to reaction time data. In study 1, pathological anxiety was associated with a negative bias in choice behaviour alongside a reduced drift rate towards the positive choice in drift diffusion analysis. In study 2 there was no significant effect of induced anxiety on any measure. The pathological anxiety findings directly mimic rodents undergoing anxiogenic manipulations, whilst the lack of sensitivity to transient anxiety suggests the paradigm may be more sensitive to clinically relevant

symptoms. Our results therefore establish a direct translational pipeline from negative affective bias in rodents to pathological mood and anxiety symptoms in humans.

Introduction

Mood and anxiety disorders are extremely prevalent worldwide, with costs across psychological, economical and social levels(1). One prominent group of symptoms are processing biases, called "affective biases" which span many domains of cognition(2). For example, anxious and depressed individuals demonstrate increased sensitivity to aversive stimuli(3), an attentional bias towards threatening information(2), and biased interpretation of ambiguous information(4) (for a review see(5)). Cognitive neuropsychiatry models of mood and anxiety disorders propose that these biases both precipitate the onset of disorders and contribute to their maintenance(5–7). As such, targeting these biases is a key goal of treatment development.

Unfortunately, for a sizeable number of individuals, none of our current treatments lead to clinical improvement(8,9) so the search for effective interventions continues. Recent years have moreover seen a number of high-profile failures in drug development(10,11). There are a number of reasons for this(8,9), but one issue is that some pre-clinical animal tests do not adequately translate the human behaviour they are designed to model(10–12). Indeed some paradigms - the forced swim test(13), or tail suspension test(14) to give prominent examples – do not have clear human analogues. We argue, therefore, that development of *identical* paradigms across humans and animal models will help reduce pre-clinical to clinical translation failure. Given that the range of behaviours that can be probed in humans is far greater than animal models, instead of *scaling-back* paradigms developed in humans into animals, the present paper aims to take a paradigm developed within the constraints of an animal model, and directly *'back translate'* it for human use.

Specifically, we aimed to back translate a rodent model of affective bias into humans. In the original task(15), rats learn to make correct responses to high or low tones, which are associated (100%) with high or low rewards (food pellets). In the test-phase they are then required to respond to an ambiguous mid-tone reinforced randomly with both outcomes. The proportion of low reward responses made to the ambiguous tone represents the degree of negative affective bias. In one study, rats were administrated an anxiogenic drug, subjected to acute restraint stress for 15 minutes, or subjected to chronic stress (repeated restraint stress and social isolation)(15). Following both acute pharmacological manipulation and chronic stress, rats showed increased negative affective bias in choice behaviour. No significant behavioural effect was observed for the acute restraint stress manipulation.

In this study, we explored the impact of two types of anxiety on a human version of this task: a) pathological anxiety in mood and anxiety disorders, and b) acute anxiety/stress induced using threat of unpredictable shock. The threat of shock stress induction is a well-validated and reliable technique which is also back-translated from animal models(17,18). Critically, it can be used to explore the interaction between cognition and anxiety within-subjects and has been shown to elicit 'adaptive anxiety' responses such as response inhibition and harm avoidance(18–20) as well as 'negative bias'(17,21,22) in healthy individuals. During a previous related, albeit more complex, human task, healthy participants were more likely to make avoidance responses to an ambiguous tone which fell directly in the middle of a tone paired with a reward and a tone paired with punishment(16). Notably, the degree to which healthy participants made avoidance responses was correlated with their self-reported state anxiety level. As such, we predicted that a direct back-translation of the rodent task would be sensitive to both pathological and induced anxiety.

In order to get a more fine-grained understanding of decision-making, a drift diffusion model was previously applied to the rodent data(15). This is an established model(23) which

parameterises decision-making as a process of noisy accumulation of evidence and enables a more principled and nuanced view of reaction time data. The negative bias in choice behaviour following acute pharmacological manipulation and chronic stress was accompanied by increased 'boundary separation' (more information required in order to reach a decision) in this model, whereas a slower 'drift rate' (rate of information accumulation) was seen following the pharmacological manipulation only. In this paper we applied the E-Z drift model(24) - a pared down version of the drift diffusion model which has been shown to recover parameter differences better than more complex models(25) – to our human data.

In sum, we aimed to back translate a rodent measure of affective bias into humans. We had two predictions. Firstly, considering the well-documented biases in pathological anxiety(26) as well as prior work with related tasks(16), we predicted that individuals with mood and anxiety disorders, relative to the asymptomatic group, would demonstrate increased negative affective bias in this task as evidenced by a smaller proportion of positive responses to the ambiguous tone. Secondly, as induced anxiety instantiates biases across cognition(27), we predicted that in asymptomatic individuals, threat of shock would also instantiate a negative affective bias. In both cases, we predicted that negative bias in choice behaviour would be associated with alterations to drift diffusion parameters comparable to those seen in the rodent model.

Method

Participants

Participants were recruited by the posting of internet advertisements and via subject databases held at the university. The only difference between groups in recruitment was the wording of the adverts; asymptomatic healthy participants replied to adverts asking for participants with no psychiatric symptoms; whilst participants with low mood and / or anxiety symptoms replied to adverts asking for participants who self-defined as experiencing persistent low mood / anxiety symptoms.

A total of 77 participants were included in study 1: 47 asymptomatic participants (Mean age=28.83, SD=10.52; 25 female) and 30 (N= 31 originally, but one excluded as they failed to follow task instructions), unmedicated participants with low mood and or anxiety symptoms (mean age=28.93, SD=10.92; 21 Female). A total of 47 asymptomatic participants were included in study 2 (Mean age=28.96, SD=10.45; 25 female; 46 overlap with study 1). The neutral version of the task (study 1) was always completed first to ensure consistency with the symptomatic group (who did not complete the stress version).

Symptomatic group details

As depressive and anxiety symptoms are highly comorbid and may not have distinct underlying causes, we include a mixed sample in our symptomatic group (see Supplement). Following an initial screening process involving a secure online screening questionnaire and subsequent phone contact, participants were invited in to take part in a comprehensive screening carried out by a trained researcher. Participants who met criteria for mood or anxiety disorder symptomatology according to a face-to-face Mini International Neuropsychiatric Interview (M.I.N.I.(28)) were included in the study symptomatic group,

those who did not meet any criteria according to the M.I.N.I. (both past and present) were included in the asymptomatic group. A measure of trait anxiety was collected for all participants using the State-Trait Anxiety Inventory (STAI(29)). Exclusion criteria included any psychiatric medication in the last 6 months, meeting M.I.N.I criteria for mania, hypomania, or psychotic disorder, having a first degree relative with bipolar disorder or schizophrenia, current or past neurological disorder, current or past learning disability, recreational drug use in the last month or past drug dependence ('mild' accepted if within an episode), and current or past alcohol dependence ('mild' accepted if within a depressive episode).

Procedure

Participants provided written informed consent to take part in the study (UCL ethics reference: 6198/001 or 1764/001). They completed a task coded using the Cogent (Wellcome Trust Centre for Neuroimaging and Institute of Cognitive Neuroscience, UCL, London, UK) toolbox for Matlab (2014b, The MathWorks, Inc., Natick, MA, United States). Scripts available here: 10.6084/m9.figshare.4868303.

Acquisition task

During the acquisition block, participants heard high (1000Hz) and low tones (500Hz). The tones are a lower frequency than the rat task to take account of cross-species differences in hearing. These two tones were associated with different reward values (tone / reward pairings were counterbalanced across participants). They were instructed to learn to make correct key presses following each tone ("z" or "m" key on a laptop keyboard) and informed that correct responses would be rewarded. They were told that they should try and maximise earnings. 10 low and 10 high tones, randomly presented, were played during the practice block. A tone was played for 1000ms followed by an interstimulus interval of 750ms. A white fixation cross appeared in the middle of the screen for the duration of the tone. Participants could

make their response from the onset of the tone presentation. Following the key press participants were given feedback on their performance. Making a correct key press to the low reward tone (low or high frequency counterbalanced) resulted in "*Correct, Win £1*" presented for 750ms. Making a correct key press to the high reward tone (the other frequency, counterbalanced) resulted in "*Correct, Win £4*" presented on the screen for 750ms. If participants made an incorrect response, or were too slow to respond, "*Timeout for incorrect response*" appeared on the screen for 3250ms. As the tone / reward pairings were randomised across subjects, the practice block enabled the participant to work out the associations between the key and tone. The practice block could last between 50 - 100 seconds depending on performance.

Testing phase

The tone / reward pairings remained the same as in acquisition but the participants were also presented with a mid-tone, ambiguous tone (750Hz) which fell directly in between the low and high tones. Participants were informed that they might hear other tones and that if the tone was unclear, that they should make a key press that corresponded to the closest tone. For half of the trials this mid-tone was associated with a high reward outcome, and for the other half of the trials it was associated with a low reward outcome. As in the practice block, a tone was played for 1000ms, followed by an interstimulus interval of 750ms. Participants made their response as quickly as possible following the tone presentation. Following correct responses the feedback was presented on the screen for 750ms, whilst following incorrect or slow responses *"Timeout for incorrect response"* was presented on the screen for 3250ms.

Study 1 Symptomatic group vs asymptomatic controls.

Details

The main task consisted of 120 trials (40 low/ mid-tone/high tones, randomly presented). The main task could therefore last between 300 – 600 seconds (See Fig 1).

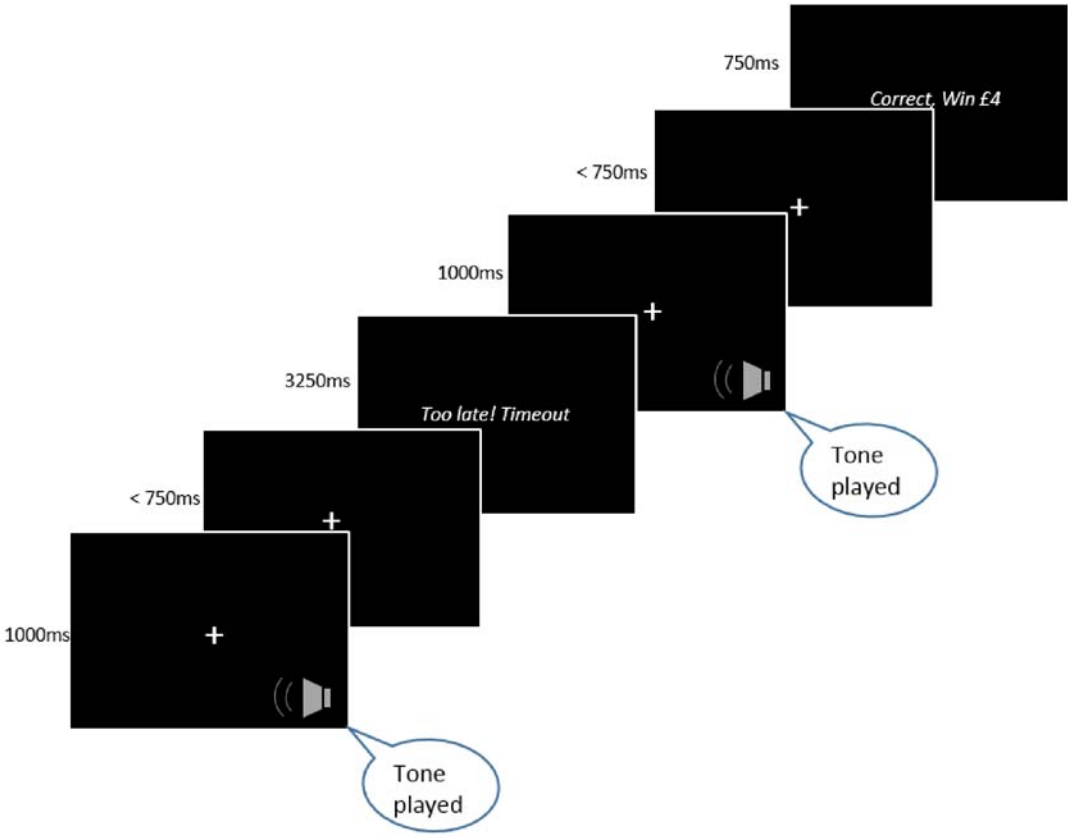

Figure 1. Participants were required to make a key press ("z" or "m" key) following a tone played for 1000ms. After making their response, participants received feedback on their performance. Correct responses saw feedback appear on the screen for 750ms, whilst incorrect responses, or responses made outside the 750ms window, saw feedback appear on the screen for 3250ms. The task consisted of 120 trials, during which 40 low, mid-tone and high tones were presented.

Study 2: Induced anxiety version

Shock work-up

A Digitimer DS5 Constant Current Stimulator (Digitimer Ltd., Welwyn Garden City, UK) delivered the shocks, via two electrodes attached to the back of the participant's non-dominant wrist. The shock intensity was increased until it was rated by the participant as "unpleasant, but not painful"(30).

Stimuli details

They performed the task under instructed threat and safe conditions in manner the same as(18). Each block (total=4) consisted of 60 randomly presented trials (20 low/mid-tone/high tones; total=240). The main task could therefore last between 600 – 1200 seconds. Participants either received a shock in the first threat block (post-threat-trial=45), in the second threat block (post-threat-trial=96) or at both of these times (this was randomised across participants). As a manipulation check, participants were asked to retrospectively rate their anxiety (/10) under threat and safe.

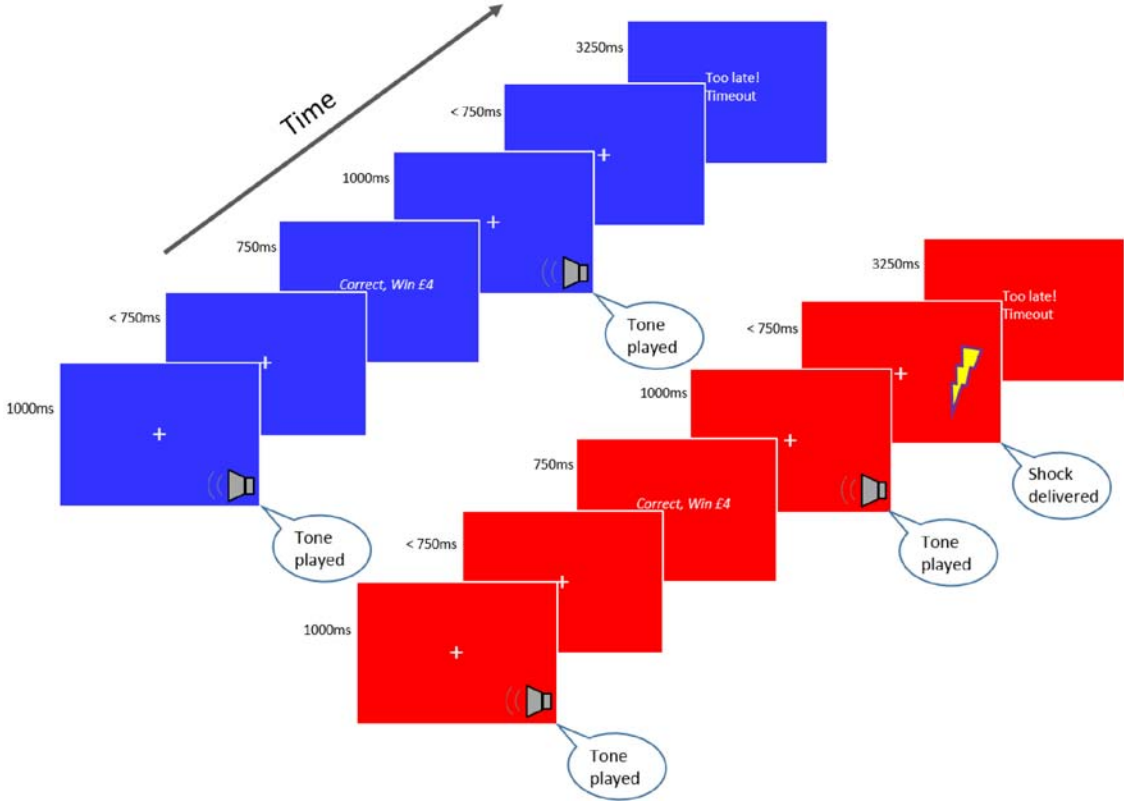

Figure 2. Participants were required to make a key press ("z"/"m") following a tone played for 1000ms. After making their response, participants received feedback on their performance. Feedback for correct responses lasted 750ms, whilst feedback for incorrect (or slower than 750ms) responses lasted 3250ms. During the safe condition, in which the

background was blue, participants were not at risk of shock. During the threat condition, in which the background was red, participants were at risk of unpredictable electric shock.

Statistical analyses

Reaction time and negative bias measures (data available here: 10.6084/m9.figshare.4868303) were analysed using SPSS Version 22 (IBM Crop, Armonk, NY). For all analyses, p=0.05, was considered significant. Affective bias (percentage of ambiguous tones classified as high reward) was calculated by dividing the number of 'high reward' responses made to the ambiguous mid-tone by the total number of key presses made to the mid-tone. The time taken to respond to the mid-tone was normally distributed and was analysed using independent and paired sample t-tests for study 1 and 2 respectively.

Bayesian statistics were also run (JASP, version 0.7(31)), employing the default prior. The Bayesian approach considers the likelihood of the data if the alternative hypothesis is true versus if the null hypothesis is true, allowing for inferences to be made about which model best explains the data. Bayesian ANOVAs and t-tests were used to generate BF_{10} factors which provided evidence for a model of interest relative to a null model. A model of interest with a BF_{10} of greater than one signifies that model is better at explaining the data relative to the null model, whilst a model of interest with a BF_{10} of less than 1 signifies that the data is better explained by the null model. To interpret the magnitude differences between models the following labels were assigned to BF_{10}: anecdotal (1-3), substantial (3-10), strong (10-30) decisive (>100)(32).

Mean reaction time, variance and proportion of positive responses to the mid-tone were fed into the E-Z drift diffusion model (script available here: 10.6084/m9.figshare.4868303). The parameters of interest were: boundary separation (a), drift rate (v) and non-decision time (Ter). Briefly these refer to the amount of information

required before a response can be made (a), the rate at which this information is accumulated (v) and the proportion of the RT that is not accounted for by evidence accumulation (Ter).

Correlation analyses were also run to investigate correlations between STAI trait anxiety scores, affective bias and drift rate.

Results

Study 1

Choice behaviour

Accuracy for the high and low tones were high (Table 1) and comparable across groups (*t(75)*=0.96, *p*=0.338, and *t(75)*=0.28, *p*=0.78, respectively). However, there was a significant effect of group on mid-tone choice ($t_{(75)}$=3.08, *p*=0.003, See Fig.3). The symptomatic group were less likely to associate the mid-tone with high reward compared to the asymptomatic group, Bayesian analysis provided strong evidence for a significant difference in affective bias between groups ($BF_{10=}$12.51).

Reaction time

See Table 1 for average reaction time to all tone types across group. Time to respond to the mid-tone did not differ across groups ($t_{(75)}$=1.08, *p*=0.29). Bayesian analysis favoured the null model (BF_{10}=0.40).

DDM

Despite comparable overall reaction times there was a significant difference in drift rate between the symptomatic and asymptomatic groups ($t_{(75)=}$2.70, *p*=0.008; but not boundary separation $t_{(75)=}$-0.79, *p*=0.43 or non decision time $t_{(75)=}$1.3, *p*=0.96). The symptomatic group had a slower drift rate towards making a positive choice to the mid-tone (asymptomatic mean=0.013, SD=0.075, symptomatic mean=-0.032, SD=0.066; see Fig.3). Bayesian analysis provided substantial evidence for a significant difference between groups in drift rate ($BF_{10=}$5.22; all other BF_{10}<0.31).

Correlations

There was a strong positive correlation between affective bias and drift rate (r=0.93, p<0.001), in other words, those who had a bias away from choosing high rewards had a slower drift rate towards high rewards. Bayesian analysis provided decisive evidence in favour of this model versus a null model with no correlation (BF_{10}=1.12 e^{10}).

There was weak evidence for a correlation between affective bias and STAI trait scores (r=-0.207, *p(two-tailed)*=0.07, *p(one-tailed)*=0.035) and between drift rate and STAI trait scores (r=-0.21, *p(two-tailed)*=0.066 *p(one-tailed)*=0.033).

Table 1: *Average choice, accuracy and reaction time (ms) to all tones in study 1*

Asymptomatic	**Accuracy (Standard Deviation)**
Low Tone	0.98 (0.05)
High Tone	0.93 (0.083)
Symptomatic	**Accuracy**
Low Tone	0.97 (0.039)
High Tone	0.95 (0.069)
Group	**Proportion high reward responses to mid-tone**
Asymptomatic	0.53 (0.17)
Symptomatic	0.42 (0.14)
Asymptomatic	**Reaction Time**
Low Tone	819.51 (212.00)
Mid-tone	942.41 (181.78)
High Tone	757.33 (228.47)
Symptomatic	**Reaction Time**
Low Tone	763.17 (197.78)
Mid-tone	894.54 (203.57)
High Tone	694.56 (194.32)

Study 2

Threat of shock manipulation check

Participant ratings of anxiety were significantly higher during the threat condition relative to the safe condition $t_{(44)=}8.92$, $p<0.001$, safe mean=1.64, SD=1.05; threat mean=4.93, SD=2.21). Bayesian analysis provided decisive evidence that a model with a main effect of threat was the winning model ($BF_{10=}4.68\ e^{8}$).

Choice Behaviour

Accuracy for the high and low tones were high (Table 2) and the same across conditions (*t(46)*=0.975, *p*=0.335, and *t(46)*=1.597, *p*=0.117, respectively). During the threat condition the proportion of mid-tones associated with high reward was smaller relative to the safe condition but this did not achieve significance ($t_{(46)=}1.94$, $p=0.06$; see Fig.3) and Bayesian analysis anecdotally favoured the null model ($BF_{10}=0.863$).

Reaction time

See Table 2 for reaction time to different tone types across conditions. There was no difference between conditions in time taken to respond to the mid-tone ($t_{(46)=}1.24$, $p=0.221$). Bayesian analysis confirmed that the null model was the winning model ($BF_{10}=0.325$).

DDM

In addition to the lack of effect on reaction time as a whole, there was no significant difference between conditions in drift rate, non-decision time or boundary separation in decision making to the mid-tones (*p*s> 0.125). Bayesian analysis confirmed that the null model was the winning model in all cases ($BF_{10}<1$).

Table 2: *Average choice, accuracy, and reaction time (ms) to respond to tones in each condition in study 2.*

Tone / Condition	**Accuracy (standard deviation)**
Low tone (safe)	0.99 (0.030)
High tone (safe)	0.96 (0.047)
Low tone (threat)	0.98 (0.036)
High tone (threat)	0.95 (0.061)
Condition	**Proportion high reward responses to mid-tone**
Safe	0.53 (0.20)
Threat	0.49 (0.19)
Tone / Condition	**Reaction Time**
Low tone (safe)	815.29 (192.09)
Low tone (threat)	767.84 (206.84)
Mid-tone (safe)	954.36 (185.63)
Mid-tone (threat)	970.05 (168.97)
High tone (safe)	830.46 (185.60)
High tone (threat)	787.37 (205.78)

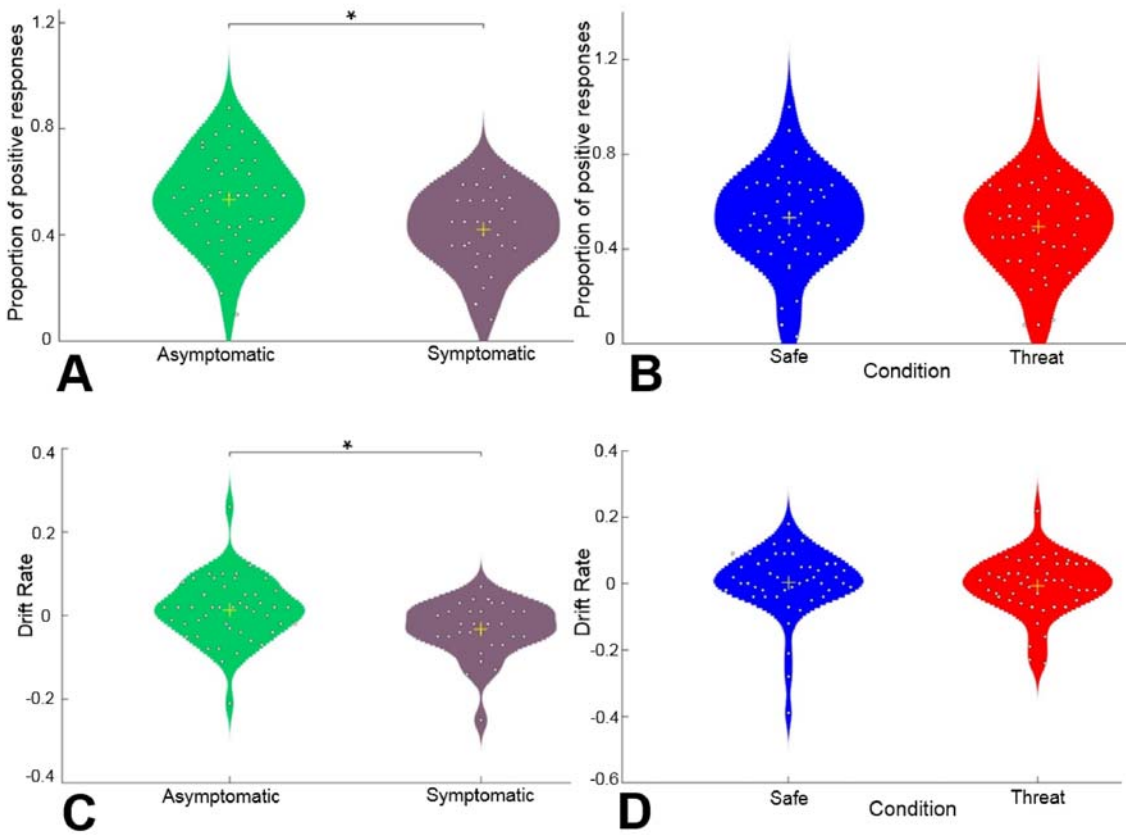

Figure 3. The impact of pathological and induced anxiety on task performance. Violin plots of the proportion of positive responses made to ambiguous tone and 'drift rate' - the rate of accumulation of evidence to classify a tone as high reward (shaded area represents a smoothed histogram; yellow cross represents the mean; each circle represents an individual). **A**) Symptomatic individuals had more negative bias (p=0.003, BF_{10}=12.51) but **B**) There was no significant difference in affective bias following induced anxiety (p=0.06 , BF_{10}=0.863). **C**) The symptomatic group had a more negative drift rate towards classifying the mid-tone as high reward (p=0.008, BF_{10}=5.22) but **D**) There was no significant difference in drift rate across conditions (p>0.125, BF_{10}<1).

Conclusion

In this study we directly back-translate a rodent measure of affective bias. We demonstrate that pathological mood and anxiety disorders, but not transient induced anxiety in asymptomatic individuals, is associated with increased negative affective bias in task performance.

The observation of negative bias in the symptomatic group is consistent with a large body of evidence documenting negative affective bias in mood and anxiety disorders. People with mood and anxiety symptoms display an attentional bias towards negative information(2), have an increased sensitivity to aversive stimuli(3), and, emulating the results we present here, display an interpretative bias in which they link ambiguous cues with negative associations(4,16,33). In the present study, the symptomatic group also demonstrated increased drift rate on a model of reaction times which is consistent with two prior studies(34)(35) linking mood disorder symptomatology to drift rates (although the tasks performed were conceptually different; note also that unlike the animal model, we saw similar reaction times across groups, and therefore no change in boundary parameter). Critically, however, the anxiety-negative bias interaction translates the impact of a) acute anxiogenic pharmacological manipulation (FG7142; a GABA-A receptor partial inverse agonist) and b) chronic stress in the rodent model on task performance(15)(Figure 4), suggesting that they may be suitable screens for candidate therapeutics.

Counter to predictions, however, induced anxiety in asymptomatic individuals did not reliably shift task performance. This was originally predicted because prior work suggests that threat of shock can induce negative biases across cognition(27). One explanation is that the absence of punishment rendered our task insensitive to transient anxiety. In participants with high trait anxiety scores, fearful, negative cues have an attentional bias over neutral or positive cues(36) and an operant judgement bias task with reward-reward outcomes gave rise

to a different profile of responding compared to a task with reward-punishment outcomes(16). Another explanation is that the non-significant effect in the asymptomatic group is a consequence of an insufficiently anxiogenic manipulation. However we believe this is unlikely as self-reported anxiety measures show a significant increase in threat conditions, and this manipulation has a clear impact across other areas of cognition(27).

Perhaps more importantly, the present pattern where decision making is more sensitive to pathological anxiety than transient anxiety is actually in keeping with findings following chronic vs acute restraint stress in rats(15). In both cases this may be because acute environmental anxiety promotes *adaptive* harm-avoidance(21) which promotes attentional and perceptual biases towards threats, but does not influence higher-order decision making processes. This theory is supported by a human study which showed that whilst a behavioural change in higher order decision making did not occur under threat of shock, encoding of values in 'lower-level' brain valuation structures did change as a function of threat-induced anxiety(38). Indeed, a number of our own studies have shown higher order decision-making processes to be unperturbed by transient threat of shock(39,40) despite clear evidence of negative bias on some tasks(27). As such it may be that whilst lower-level learning and memory are *immediately* influenced by transient states, the impact upon higher order processes builds up over time(37). Critically, however, this suggests that, at least on the present measure, there is something quantifiably different between transient anxiety in healthy humans and pathological anxiety. From a clinical perspective this is unsurprising, but it is notable because some effects do overlap across induced and pathological anxiety(27,41).

A further caveat is that there is a numerical trend towards negative bias under threat and, as such, we might simply be underpowered to detect an effect. If this is the case it nevertheless remains that any within-subject effect of transient anxiety is likely considerably smaller than the between-subject effect we were able to detect in the group study. As such,

the dissociation across studies suggests that this task is more sensitive to the pathological state than transient changes in anxiety in asymptomatic individuals. On reflection, this extends the translational potential of this paradigm. Given the failure of many preclinical to phase 1 clinical trials(10,11) translational paradigms which are *more* sensitive to the clinical state than transient mood changes are valuable.

Modifying affective biases in mood and anxiety disorders is crucial given their proposed role in the development and maintenance of symptoms(5–7). Both pharmacological and psychological treatments(42–44), are thought to exert their effects via altering affective biases(5). In addition to facilitating screening of novel anxiolytics, the present translational pipeline provides a potential means of understanding the mechanisms underpinning this negative bias(45). We can run causal studies in rodents that can help us delineate the neurobiological processes underpinning biased choices on this task(12). Indeed, linking task performance to a formal model of decision-making (DDM) provides a step in this direction. The parameters of this model are thought to be biophysically plausible; they can be computed by populations of neurons(46); which takes us a step towards bridging the gap between underlying neural activity and symptoms. Such bridges are necessary for a full mechanistic account of psychiatric symptoms and are the guiding principal of the burgeoning field of computational psychiatry(47). Ultimately, we argue that improved treatments are unlikely without a better understanding of the underlying biological mechanisms that any putative treatments should attempt to target. Given the individual, social and economic burden of mood and anxiety disorders; as well as the large number of individuals for whom none of our current treatments work; new and improved treatments are long overdue.

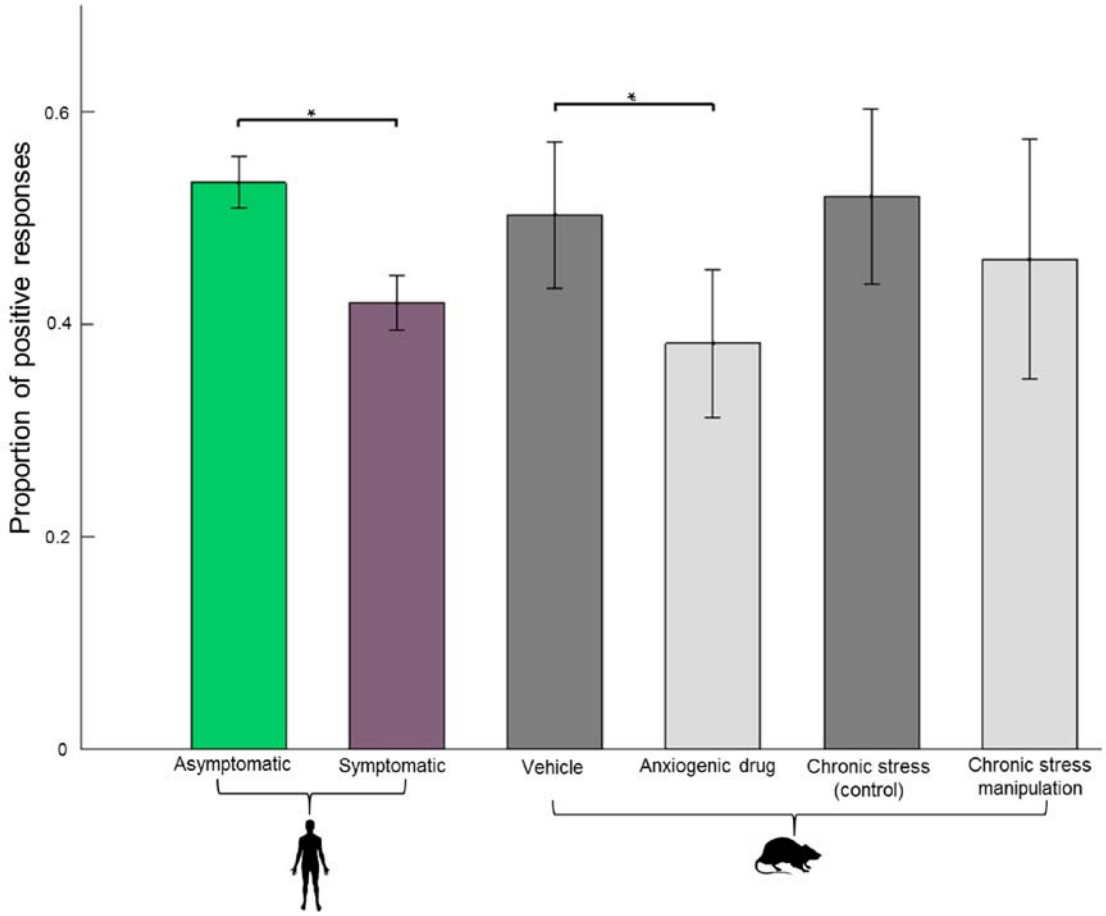

Figure 4: Cross-species performance comparison. Plots illustrating the overlap of human pathological anxiety and rodent anxiety models on choice performance. (*$p < 0.05$). After acute pharmacological manipulation with FG7142 (3mg or 5mg; average dose plotted), rats showed an increased negative affective bias in choice behaviour on the ambiguous tone, relative to vehicle. For the chronic stress manipulation between weeks 3 and 4 post-stress intervention average of 6 post-stress intervention weeks plotted), rats showed an increased negative affective bias in choice behaviour on the ambiguous tone, relative to control.

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Author Contributions

O.J.R. conceived of the experiment. E.R conceived of the original animal task and provided detailed comments on the interpretation. O.J.R. wrote the task scripts with guidance from C.H. J.A completed testing and data collection. J.A completed data analysis under the supervision of O.J.R. J.A. and O.J.R wrote first draft of the paper and C.H. and E.R. provided critical feedback. All authors approved the final version for submission.

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