Cognitive, Affective, & Behavioral Neuroscience (2019) 19:715–725
https://doi.org/10.3758/s13415-018-00657-0

The influence of the noradrenergic/stress system on perceptual biases for reward

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Published online: 24 October 2018

Abstract

Previous research has established a role for the norepinephrine (NE)/stress system in individual differences in biases to attend to reward or punishment. Outstanding questions concern its role in the flexibility with which such biases can be changed. The goal of this preregistered study was to examine the role of the NE/stress system in the degree to which biases can be trained along the axis of valence in the direction of reward. Participants genotyped for a common deletion variant of *ADRA2b* (linked to altered NE availability) experienced either an acute stress induction or a control procedure. Following stress induction, a "bias probe" task was presented before and after training. In the bias probe task, participants made forced choice judgments (happy or angry) on emotional faces with varying degrees of ambiguity. For bias training, participants viewed unambiguously angry faces in a task exploiting visual adaptation effects. The results revealed an overall shift from a slightly positive bias in categorizing faces pretraining to a more positive bias after training. Carriers of the deletion variant overall showed a more positive bias than did the noncarriers. Follow-up analyses showed that pretraining bias was a significant predictor of bias change, with those who showed a more negative bias preadaptation changing more in a positive direction. Critically, this effect was observed under control but not under stress conditions. These results suggest that the NE/stress system plays an important role in influencing trait-like biases as well as short-term changes in the tendency to perceive ambiguous stimuli as being more rewarding than threatening.

Keywords Emotion · Motivation · Norephinephrine · Reward

Decades of research have supported the common observation that some people see the world through rose-colored glasses, and others through lenses tinted gray (e.g., Eysenck & Eysenck, 1985). In general, we are all more likely to attend to and remember emotionally and motivationally salient environmental cues (Markovic, Anderson, & Todd, 2014; Pourtois, Schettino, & Vuilleumier, 2013). Yet, when a cue is ambiguous in signaling reward or punishment, individuals differ in their habitual tendency to interpret information as negative or positive (Derryberry & Reed, 1994). Moreover, more extreme biases can be symptomatic of psychopathology. For example, anxiety is characterized by biases toward threat, and depression and addiction are characterized by reduced versus enhanced sensitivity to rewarding information (Anderson, 2016; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Dalgleish et al., 2003; Peckham, McHugh, & Otto, 2010; Surguladze et al., 2004).

The norepinephrine (NE)/stress system is a key factor in sensitivity to emotionally or motivationally salient information, as well as in the emotional/motivational learning processes that give rise to such biases (for a review, see Ehlers & Todd, 2017b). Our previous research has implicated common neurogenetic variations in the NE system in affective biases in attention and subjective perception (Todd et al., 2015; Todd, Muller, et al., 2013b). Yet, whether such biases result from greater flexibility in emotional attributions, potentially in interaction with the slower-acting stress response induced by the hypothalamic–pituitary–adrenal (HPA) axis, is not known. Our previous research has also indicated that acute stress can

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impair reward learning (Ehlers & Todd, 2017a); however, outstanding questions concern whether stress influences the flexibility of biases to subjectively perceive rewarding information. The overall goal of this preregistered study was to examine the role of the NE/stress system in the degree to which emotional biases can be flexibly trained in the direction of reward. Specifically, we wished to examine the effects of naturally occurring differences in NE function and the effects of acute stress—both alone and in interaction—on the flexibility of emotional judgments.

Genetic differences influencing the NE system

One factor that has been associated with individual differences in affective bias is a genetic variation influencing the NE system. A common (~ 50% of the population; Li, Weerda, Guenzel, Wolf, & Thiel, 2013; Todd et al., 2014; Todd, Schmitz, Susskind, & Anderson, 2013a) deletion variant of the *ADRA2b* gene (Small, Brown, Forbes, & Liggett, 2001), which codes for the alpha2b adrenoceptor, has been associated with effects that are similar to those of an alpha2b receptor antagonist (de Quervain et al., 2007), suggesting increased NE availability. Previous research has demonstrated more pronounced affective biases in deletion carriers than in noncarriers in both memory and attention: In a seminal article, de Quervain et al. (2007) showed greater emotional memory enhancement for deletion carriers. We subsequently found the deletion variant to be associated with enhanced attentional biases toward (Todd, Muller, et al., 2013b) and more vivid perception of (Todd et al., 2015) emotionally salient stimuli, indicating that it plays a role in prioritized the encoding of emotional information. An outstanding question concerns whether the more pronounced affective biases in deletion carriers result from the influence of NE on learning—specifically, whether putative differences in NE availability influence flexibility in shifting biases based on experience. Thus, a further goal of the present study was to examine the role of *ADRA2b* in bias flexibility.

A hypothesized role for alpha2b noradrenergic receptors in emotional learning has been supported by rodent studies showing reduced emotional learning upon full development of inhibitory alpha2b receptors (Moriceau & Sullivan, 2004). Moreover, human studies investigating *ADRA2b* have suggested that deletion carriers show greater cognitive–affective flexibility than do noncarriers (Mammarella et al., 2016). Combining an emotional working memory task with a task requiring action to switch from negative to positive affective intonation, the authors found that deletion carriers remembered more positive words. In addition, despite the fact that deletion carriers were less willing to switch the intonation from negative to positive, they remembered more positive information, suggesting higher flexibility than noncarriers. We thus expected human deletion variant carriers, who are thought to have reduced alpha2b function, to show facilitated emotional learning, indicated by greater flexibility in shifting preexisting patterns of emotional biases.

Stress

Acute stress may also play a role in bias flexibility—either alone or in interaction with differences in *ADRA2b* variant. Acute stress leads to the activation of two sequentially linked stress systems: Immediate activation of a fast-acting stress system leads to a release of mostly catecholamines such as NE and dopamine (Schwabe, Wolf, & Oitzl, 2010). This early phase is followed by subsequent downstream activation of a glucocorticoid (cortisol, in humans) pathway, typically leading to an elevated processing threshold for incoming information (Herman, McKlveen, Solomon, Carvalho-Netto, & Myers, 2012; Roozendaal, McEwen, & Chattarji, 2009). Elevated cortisol levels can usually be detected 15–60 min after stress induction, with peak cortisol levels being reached after 30 min (Schwabe, Haddad, & Schachinger, 2008). Our own work has demonstrated that delayed acute stress can impair reward learning in healthy young adults (Ehlers & Todd, 2017a), which should reduce the initial formation of an attentional bias. As a result, the same general procedure and timing of stressors was chosen in the present study. However, there is also evidence that stress leads to enhanced processing of reward, when contingencies are overlearned and habitual (Mather & Lighthall, 2012; Schwabe & Wolf, 2009, 2011). Moreover, previous research has shown that acute stress can impair cognitive flexibility (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007; Plessow, Fischer, Kirschbaum, & Goschke, 2011). Whether acute stress influences the flexibility of preexisting affective biases, particularly in relation to preexisting individual differences in NE availability, remains to be investigated.

Judgments of morphed emotional faces as indices of biases to perceive reward

Biases for rewarding versus threatening stimuli are often tested using facial expressions as stimuli whose intensity or ambiguity can be parametrically modulated through morphing. Angry and happy facial expressions are ubiquitous and ecologically valid cues signaling threat and reward, which are overlearned through years of socialization (Denham, Zoller, & Couchoud, 1994). Whereas smiles signal social reward and elicit approach, angry faces signal punishment and elicit avoidance (Roelofs, Minelli, Mars, van Peer, & Toni, 2009; Todd, Evans, Morris, Lewis, & Taylor, 2011; Volman, Roelofs, Koch, Verhagen, & Toni, 2011). Moreover, smiling and angry faces elicit reliable visual adaptation effects: After repeated exposure to one of the expressions (e.g., angry),

ambiguous expressions are perceived as the opposite (e.g., happy) (Webster, Kaping, Mizokami, & Duhamel, 2004). In the present study, we wished to examine individual differences in judgment of threat/reward value as a measure of bias from intensely happy to intensely angry, as well as to examine the flexibility of bias by exploiting facial expression adaptation effects.

The present study

To examine the role of the NE/stress system in affective bias flexibility, we genotyped healthy young adults for the *ADRA2b* polymorphism and paired a stress induction procedure with a task that assessed bias flexibility by probing affective bias before and after a training procedure (Penton-Voak et al., 2013). Initial biases were assessed using a "bias probe" task in which faces morphed on a continuum from unambiguously angry to happy were presented in random order, and participants made forced choice valence judgments (happy or angry). In the training procedure, we capitalized on facial emotion adaptation effects by repeatedly exposing participants to unambiguously angry faces in a working memory task, leading to the perception of ambiguous faces as more positive. Bias flexibility was then assessed by the change in bias from the initial to the postadaptation bias probe. Stress was induced before the initial bias probe using the commonly employed socially evaluated cold pressor test (SECPT) (Schwabe et al., 2008).

Several central hypotheses were included in our preregistered protocol on the Open Science Framework (see https://osf.io/stqy4/). (1) We predicted that the adaptation effect pushing face judgments in a positive direction would be more pronounced in *ADRA2b* deletion carriers than in noncarriers following training, indexing greater flexibility linked to putatively greater NE availability. (2) We further predicted that the greater initial NE activity in deletion carriers would be potentiated by stress induction, leading to an enhanced adaptation effect in those participants. (3) On the basis of pilot data, we predicted that we would not observe differences in the degree of initial bias based on either genotype or stress condition.

Materials and methods

Participants

A total of 266 participants (192 females, 74 males; mean age: 21.0 ± 3.9 years) took part in the experiment. All participants indicated that they were of either European or East-Asian descent, and all were compensated for their participation with course credit. The sample size was based on power analyses included in the preregistration protocol. Power analysis for the effects of *ADRA2b* was based on the effect sizes found in previous studies (η_p of .05; Rasch et al., 2009; Todd, Muller, et al., 2013b). To produce sufficient power for a repeated measures ANOVA with *ADRA2b* and stress as between-subjects factors, we required a minimum sample size of 252. Data collection was continued until the end of the academic term, at which point the minimum was reached.

Participants were asked not to eat, to consume alcohol or caffeine, or to exercise for 2 h before the experiment, due to known effects on the stress response (Kudielka, Hellhammer, & Kirschbaum, 2007). Participants were randomly assigned to the stress and control conditions (129 and 137 participants, respectively). The study was approved by the Human Research Ethics Board of the University of British Columbia.

Materials

Stimulus presentation The MATLAB (The MathWorks, Natick, MA, USA) toolbox Cogent 2000 was used for all stimulus presentation.

Facial stimuli The stimuli subtended a visual angle of approximately 15° × 19°. All stimuli were emotional faces taken from the NimStim Face Stimulus Set (Tottenham et al., 2009). Using morphing software (Abrosoft Fantamorph, Version 5.4.5), the faces of two females (Caucasian and East Asian) with happy and angry expressions were morphed into two 15-image continua for the bias probe. Ten individual faces (five females) from all ethnic face categories (Asian, Caucasian, and African) in the NimStim set, all displaying angry expressions, were used in the adaptation phase.

Questionnaires Participants were asked to complete a battery of questionnaires in order to control for possible interactions between psychopathology, life experience, and personality with task performance and stress response. In addition to a demographic questionnaire, we administered the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994), the State–Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), the Liebowitz Social Anxiety Scale (LSAS), the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988).

Procedure

Overview After obtaining written informed consent, we acquired initial saliva samples for baseline measures of stress indicators (see Fig. 1). This was followed by the SECPT (described in more detail below) in either a stress or a control condition. The 3-min stress induction/control procedure was

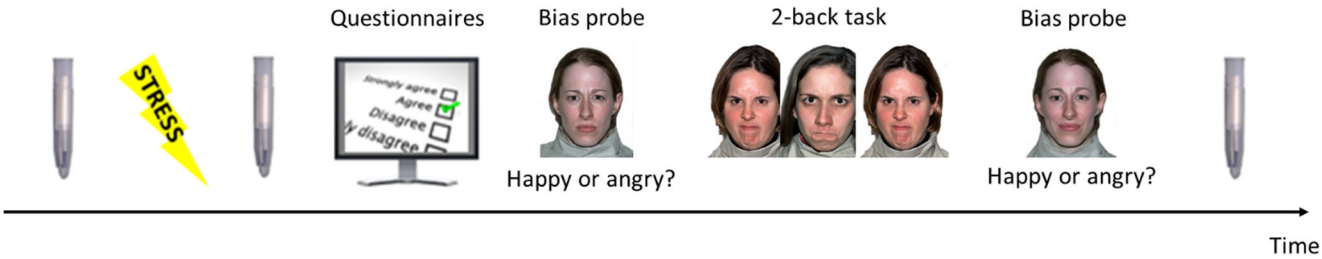

Fig. 1 Overview of the experimental procedure. Salivary cortisol samples were taken before and after stress induction by means of the socially evaluated cold pressor test. Participants were given 20 min to complete several online questionnaires before starting the experimental tasks. The initial bias probe was followed by a two-back memory task. The second bias probe task was completed before final stress measurements

followed by a second saliva sample. Successful stress induction was further assessed by administration of the SECPT questionnaire—a three-item questionnaire measuring subjective stress response (Schwabe et al., 2008). Participants were further asked to fill out a battery of questionnaires in order to control for individual differences that could potentially influence stress responses or operant conditioning performance. To capitalize on the effects of cortisol (delayed stress response) on behavior, the operant task started 20 min after the end of the SECPT (Schwabe et al., 2008). After participants had finished the task (about 60 min after the SECPT), the third and last saliva sample was taken. If participants did not complete all questionnaires in the 20-min period before the learning phase, they finished them before the debriefing.

Stress procedure In the stress condition, elevated stress levels were induced with the SECPT (Schwabe et al., 2008). First, the participants were informed that their faces would be videotaped during the upcoming test for future evaluation of their facial expressions by researchers. Participants were then asked to put their nondominant hand in ice water (0–4 °C). They were told to keep the hand in the water for as long as possible while looking straight into the camera. The experimenter observed the participant at all times and recorded the time period during which each participant's hand remained in the water. After 3 min, participants were instructed to remove their hands from the water, if they had not done so already. In the control condition, the ice water was replaced with warm water (35–37 °C), and participants were neither videotaped nor watched by the experimenter. They were also instructed to keep their hand in the water while the experimenter was present in the room.

SECPT questionnaire To obtain a measure of subjective, psychological stress responses, we asked participants to rate how stressful, painful, and unpleasant the SECPT had been, using a 10-point scale ranging from 1 (*not at all*) to 10 (*extremely*). The questionnaire was administered immediately after stress induction.

Salivary cortisol analysis Saliva was collected pre-SECPT, immediately post-SECPT, and posttask (~ 60 min after stress induction) with a Salivette collection kit (Sarstedt AG & Co., Nümbrecht, Germany) and stored at – 20 °C until the biochemical analysis of salivary levels of free cortisol. The analysis employed a luminescence immunoassay (IBL GmbH, Hamburg, Germany) performed at the lab of C. Kirschbaum, Dresden, Germany. The inter- and intra-assay variations were below 10%.

Bias probe

The bias probe task was adapted from that of Penton-Voak et al. (2013). This task was performed before and after the adaptation task, as an assessment of individual baseline biases in rating ambiguous faces as angry versus happy, and the degree to which they changed with facial adaptation (Fig. 1). Each trial began with the randomly jittered (1,500–2,000 ms) presentation of a fixation cross, followed by the display of a face (one of 15 frames taken from the continuum of emotional faces, ranging from unambiguously happy to unambiguously angry). A mask of visual noise was presented for 150 ms before participants were asked to judge whether the face just seen was happy or angry. Each participant completed a total of 90 trials (Fig. 2). The two sets of emotional continua, consisting of 15 frames, were presented three times each in randomized order. The bias probe presented pre- and postadaptation was the same task, but the stimuli were presented in different random orders. By randomizing face presentation and including many subtly varying morph frames, we ensured that participants would be unlikely to remember their previous ratings of each morph frame the second time they performed the task. The participants were reminded of the instructions before completing the posttest.

Adaptation task

The adaptation task served as a training task to shift biases toward more positive judgments of emotional expressions, by

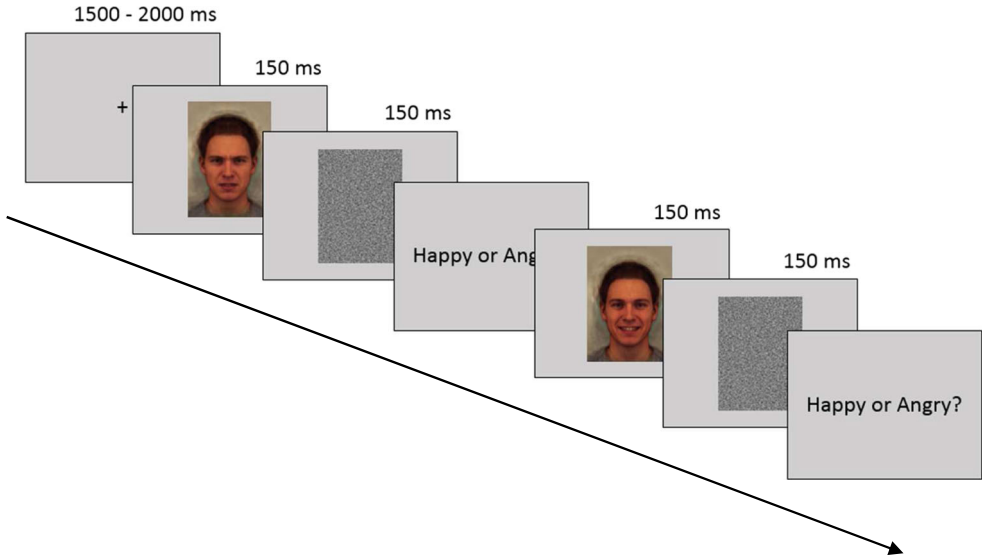

Fig. 2 Schematic of the bias probe task performed both before and after adaptation, adapted from that of Penton-Voak et al. (2013). Participants are presented with faces at different stages of parametric morphing between unambiguously happy and angry faces, and they were asked to make a forced choice assessment of whether a face was happy or angry

capitalizing on known visual adaptation effects for facial emotion. Participants were asked to perform a 21-min two-back working memory task, in which all of the faces showed angry expressions (Fig. 1). Whereas adaptation effects would result from repeated viewing of the faces, the working memory task ensured that participants paid attention to each individual face (Rhodes et al., 2011). The task exploited the well-documented phenomenon of visual aftereffects, in which, after repeated exposure to one category of visual stimulus, an ambiguous stimulus looks more like the opposite category. In the case of facial emotions, repeated exposure to an angry face shifts perception of a neutral or ambiguous facial expression to make it appear more happy (Webster et al., 2004). The two-back task was employed in order to ensure attention to the facial expressions: The faces were presented in random order, and participants indicated via button press whether a face was the same as that two faces back. Each face was displayed for 2,000 ms, with 20-ms intertrial intervals. Each participant completed 13 adaptation blocks, each block consisting of 48 trials containing eight targets each.

Genotyping

A saliva sample (~ 1 mL) was collected from each participant in an Oragene OG-500 DNA kit (DNA Genotek, Ottawa, ON). *ADRA2b* 9bp deletion was assayed using a PCR followed by Sanger sequencing. A total of 50 ng genomic DNA was combined with 1xAmpliTaq Gold 360 buffer, 2.0-mM magnesium chloride, 360GC Enhancer 4 μl, 200 μM dNTPs, 0.5 μM forward primer ACGAAGGTGAAGCGCTTCT and 0.5 μM reverse primer GGCCAGAAGGAGGGTGTTT, and AmpliTaq Gold 360 DNA Polymerase 0.625 U/reaction, for a total volume of 25 μL in a 96 well plate. Initial denaturation was performed at 95 °C for 8 min, followed by 38 cycles at 95 °C for 50 s, 60 °C for 30 s, and 72 °C for 50 s, as well as a final extension step of 7 min at 72 °C. The PCR products were cleaned up by ExoSAP-IT Express and analyzed by sequencing (ABI 3130, Applied Biosystems).

Results

Genotype frequencies fell within the Hardy–Weinberg equilibrium ($\chi^2 = 4.49$, $p > .05$). For all analyses, based on previous research (de Quervain et al., 2007; Todd et al., 2015; Todd, Muller, et al., 2013b; Todd et al., 2014), homozygote and heterozygote *ADRA2b* deletion carriers were treated as a single group, because of the low number of homozygotes. In all, 139 participants were deletion carriers, and 109 were non-carriers. Genotyping did not yield conclusive results for 18 of the participants. For all statistical analyses, Greenhouse–Geisser corrections were applied if sphericity was violated. All analyses were performed with IBM SPSS Statistics 21.

Stress manipulation

The effect of stress induction was assessed by both subjective ratings and salivary cortisol. On average, the participants in the stress group kept their hands in ice water for 151.8 ± 49.8 s, whereas all participants in the control group kept their hands

in the water for the full 180 s. The analysis of subjective stress ratings confirmed that, as compared to the control group, the participants in the stress group perceived the SECPT as being more stressful, $t(204.02) = -11.26$, $p < .001$, painful, $t(169.16) = -20.68$, $p < .001$, and unpleasant, $t(243.41) = -17.36$, $p < .001$. The individual stress ratings indicated successful stress induction in all participants. As a result, all participants were included in the following analyses (Fig. 3).

Salivary cortisol was analyzed in a mixed ANOVA with time point (pre-SECPT, post-SECPT, posttask) as a within-subjects factor and stress condition (stress vs. control) as a between-subjects factor. The analysis of cortisol showed a main effect of time, $F(1.47, 372.51) = 73.83$, $p < .001$. No main effect of stress condition or interaction with time was found, presumably because of the fact that the last sample was taken too long after stress induction (approximately 60 min). Whereas in some previous publications researchers had chosen to exclude participants on the basis of their cortisol response (Miller, Plessow, Kirschbaum, & Stalder, 2013), others, including ourselves, have chosen to maximize sample size by including as many participants as possible (Ehlers & Todd, 2017a; Schwabe & Wolf, 2009). Importantly, the pattern of results was the same if some participants were excluded on the basis of a more conservative subjective stress response criterion (Fig. 3).

Behavioral results

Exploratory analyses were performed to confirm that sex ($p = .432$) and racial identity (Caucasian vs. Asian, $p = .291$) had no significant effects on the behavioral measures. In addition, exploratory correlations were performed between the questionnaire measures and bias scores. Only state anxiety showed robust correlations with bias, and all subsequent analyses were performed both with and without state anxiety scores as a covariate.

Moreover, the exploratory analyses showed no difference between genotype or stress groups, nor any interactions with regard to working memory performance in the adaptation task. It should be noted that, whereas previous studies had shown interactions between *ADRA2b* and emotional effects on working memory (Mammarella et al., 2016), here there was no emotion manipulation, since all of the stimuli were negatively valenced.

Main analysis As stipulated at preregistration, we performed an analysis in which we assessed the probability of faces being rated as angry, frame by frame (i.e., for each degree of morphing from 100% angry to 100% happy), both pre- and posttraining, by *ADRA2b* genotype and stress condition. This was a mixed analysis of variance (ANOVA), with bias probe (pre- and postadaptation) and frame (15 frame per continuum) as within-subjects factors, and *ADRA2b* genotype (deletion and no deletion) and stress condition (stress and control) as between-subjects factors.

A main effect of frame, $F(5.57, 1357.88) = 3{,}097.33$, $p < .001$, indicated that, unsurprisingly, participants were sensitive to the amount of emotion signal in the faces. Unambiguously angry faces were most likely to be rated as angry, with decreasing probabilities as the continuum approached unambiguously happy faces. A main effect of test (pre- vs. posttraining), $F(1, 244) = 11.48$, $p = .001$, further revealed that the adaptation procedure led to an overall shift of affective bias toward judging faces as being more positive. These main effects were qualified by a Test × Frame interaction, $F(8.81, 2149.94) = 17.20$, $p = .001$ (Fig. 4a). Pairwise contrasts revealed shifts in judgment for Frame 1 (the most angry face), Frames 4–8, and Frames 11–15 (the most happy faces) ($ps < .05$). Taken

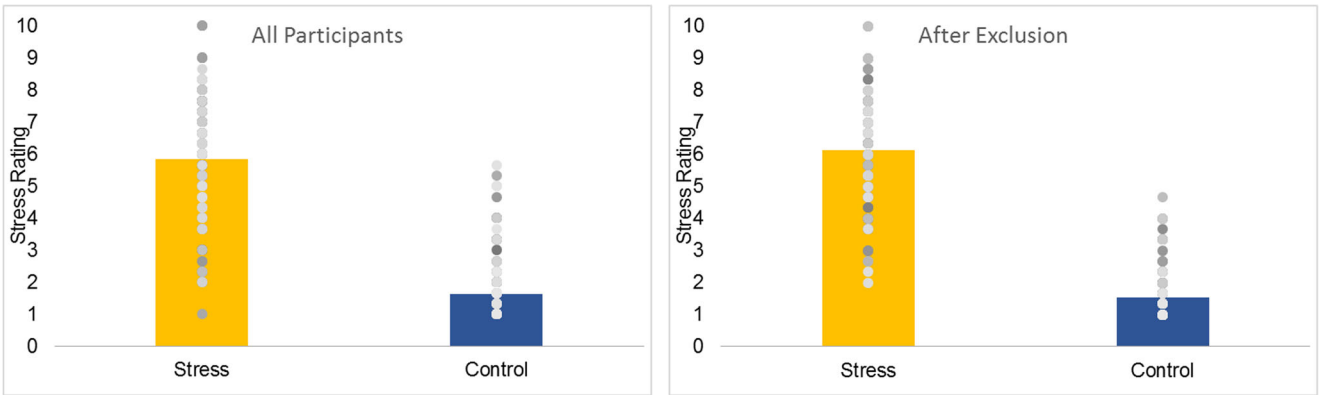

Fig. 3 Individual subjective stress ratings for stress and control groups, indicating successful stress induction in all individuals. Displayed are the individual averages derived from three different ratings: unpleasantness, stressfulness, and painfulness. On the left, ratings from all participants are presented. On the right, a total of 14 participants were excluded due to the fact that their ratings fell within one standard deviation of the mean of the other group. The main analyses were rerun with the reduced sample in order to ensure that the results were not due to individual differences in stress responses. The patterns of results are the same in both samples

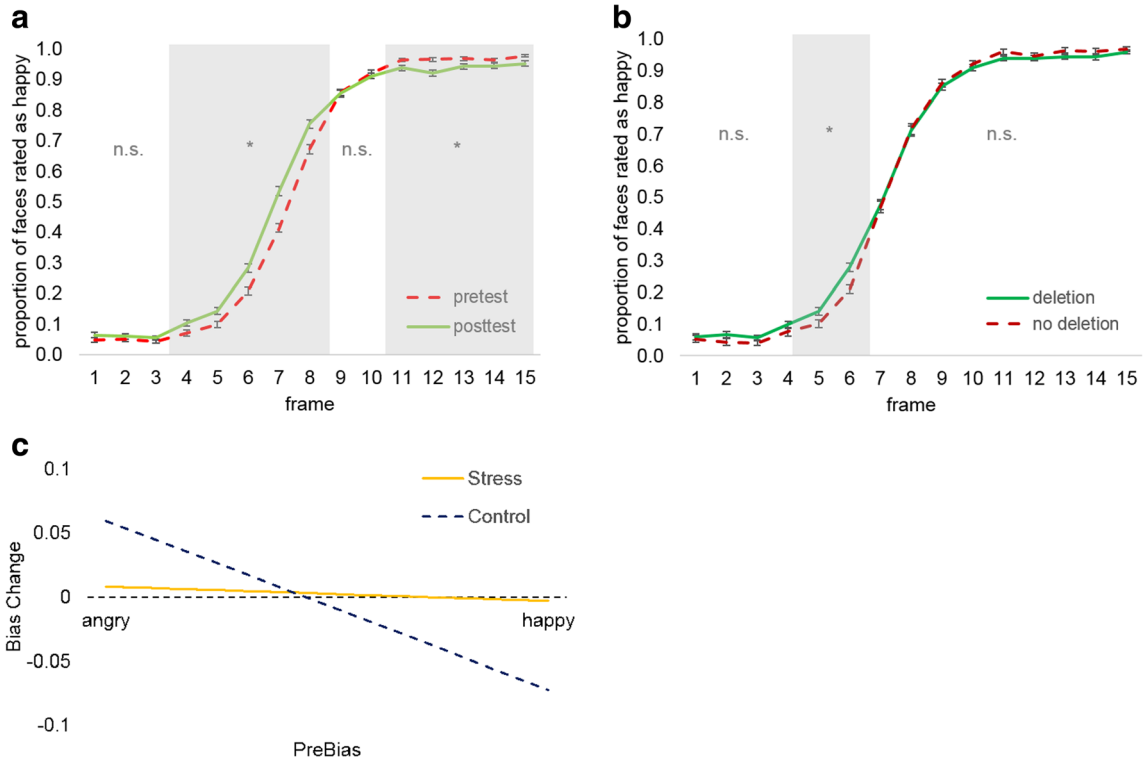

Fig. 4 Ambiguous faces (middle frames of the continuum) were rated as happy by a higher proportion (a) postadaptation and (b) of deletion carriers, relative to noncarriers. Asterisks and shading indicate significant differences. (c) Participants with a more negative bias preadaptation showed a stronger positive bias change, but only under control, not under stress conditions

together, the adaptation procedure resulted in a robust shift of affective bias in a positive direction.

Importantly, there was an *ADRA2b* × Frame interaction, $F(14, 3416) = 3.00$, $p < .001$, such that deletion carriers rated a greater proportion of faces as happy for frames toward the middle of the morph continuum (Frames 5 and 6, ps < .05) (Fig. 4b). However, we did not observe the hypothesized *ADRA2b* × Frame × Test interaction that would have indicated that carriers of the deletion variant shifted their bias more flexibly than did noncarriers. Rather, they simply showed a stronger version of the pattern observed in all participants: a slightly positive bias pretraining that became more positive after adaptation. We found no effect of stress, $F(1, 244) = 2.55$, $p = .112$, no two-way interaction between stress and test, $F(1, 244) = 0.001$, $p = .972$, and no three-way interaction between stress, test, and frame, $F(14, 3416) = 0.716$, $p = .761$.

When controlling for state anxiety, the same pattern of results reported above was found: The analysis revealed main effects of test, $F(1, 238) = 11.44$, $p = .001$, and frame, $F(5.56, 1324.01) = 3{,}024.71$, $p < .001$, as well as an interaction, $F(8.82, 2099.33) = 17.45$, $p < .001$. Similarly, the Frame × *ADRA2b* interaction, $F(14, 3332) = 3.08$, $p < .001$, showed a stronger bias toward the positive for Frames 5 and 6 for deletion carriers than for noncarriers (ps < .05).

Follow-up analysis We reasoned that, as had previously been observed in rodents (Enkel et al., 2010), the hypothesized effects of the stress manipulation might have been obscured because the effects of stress on bias change depended on the degree of initial bias. That is, stress might have moderated the effects on bias change of an initial predisposition to rate ambiguous faces as happy or angry. To test the hypothesis that the change in affective bias through adaptation depends on the baseline bias, and that this effect is moderated by stress, we performed a moderation analysis (Preacher & Hayes, 2004). In a regression model, preadaptation bias was defined as the predictor variable. This was operationalized as the proportion of trials rated as happy at Frame 7, the ambiguous frame at which participants were split evenly around the median into those who were positively and negatively biased. Stress condition was included as a moderator variable. The analysis revealed that preadaptation bias predicted the degree of bias change, $b = -0.05$, $t(244) = -2.73$, $p = .007$, such that those with an initial bias toward judging faces as angry showed greater change in the positive direction. Importantly, this was qualified by a Preadaptation Bias × Stress interaction, $b = 0.04$, $t(244) = 2.07$, $p = .04$, indicating a moderation effect: Pretraining bias was a significant predictor of bias change for those who showed a more negative bias preadaptation that changed in a positive direction in the control group, $b = -$

0.09, $t(244) = -3.17$, $p = .002$, but not in the stress group, $b = -0.01$, $t(246) = -0.51$, $p = .613$ (Fig. 4c). Thus, stress diminished the effect of preadaptation bias on bias flexibility that allowed the more negatively biased participants to show greater change (Fig. 4c).

Discussion

The aim of the present study was to examine the role of the NE/stress system in affective bias flexibility along a continuum ranging from stimuli signaling social punishment to those signaling social reward. The results revealed an overall robust adaptation effect in healthy young adults, such that judgments of facial emotion became more positive following repeated exposure to angry faces. Although it did not predict bias flexibility, carrying the deletion variant of the *ADRA2b* genotype was associated with a tendency to rate faces as more positive overall.

Acute stress administered by means of the SECPT moderated the relation between preadaptation bias and bias flexibility, such that preadaptation bias was a significant predictor of bias change in the control group only. Specifically, participants with a more negative pretraining bias showed the strongest change in a positive direction—an effect that was abolished under stress.

Our finding that an implicit training process involving repeated exposure to angry faces effectively shifted judgments in a more positive direction replicates and extends previous research. It has been demonstrated that humans show adaptation to various features of faces, such as gender or ethnicity (Webster & MacLeod, 2011). For example, an ambiguous face containing both female and male features is perceived as being more female after a participant has been exposed to male faces (Webster et al., 2004). This adaptation effect has also been shown for emotional expressions such as disgust and surprise (Webster et al., 2004). In the present study, we used a morphing paradigm in which ambiguous facial expressions were perceived as being happier (and less angry) after participants were exposed to a working memory task using angry facial expressions. To date, this training effect has been observed in a relatively small sample of aggressive adolescents (Penton-Voak et al., 2013) and in younger children (Picardo, Baron, Anderson, & Todd, 2016). In the present study, we were able to replicate this finding in a much larger population of healthy university students, validating and generalizing the previous findings. In the adolescent sample, the change in bias remained one week after training (Penton-Voak et al., 2013). Although we did not examine the long-term effects of training in our study, future research might determine how long such effects endure.

Our main focus, however, was on the effects of the NE/stress system on modulation of affective judgments by this short-term implicit-learning process. On the basis of previous research demonstrating a role of alpha2b noradrenergic receptors in emotional learning (Moriceau & Sullivan, 2004), as well as direct evidence that carriers of the deletion variant of the *ADRA2b* polymorphism show greater flexibility in working-memory-related affective biases (Mammarella et al., 2016), we hypothesized that *ADRA2b* deletion carriers would show more pronounced adaptation effects than noncarriers. However, the present study indicated no difference in bias shift between deletion carriers and noncarriers. Nonetheless, deletion carriers demonstrated a stronger overall tendency to rate ambiguous faces as positive than did noncarriers. An enhanced positivity bias is consistent with previous research showing a working memory advantage for positive items in deletion carriers (Mammarella et al., 2016), and it suggests that in this context deletion carriers perceived ambiguous faces as being more rewarding. Thus, the present results confirm *ADRA2b*-dependent exaggeration of typically observed affective biases, as has been demonstrated by multiple studies (e.g., de Quervain et al., 2007; Todd et al., 2015; Todd, Muller, et al., 2013) and confirmed in a recent meta-analytic review (Xie, Cappiello, Meng, Rosenthal, & Zhang, 2018); however, they suggest that putative differences in NE availability do not influence the degree of flexibility or change in subjective perceptions of rewarding information induced by implicit-learning processes. This divergence from previous studies investigating classical conditioning (Moriceau & Sullivan, 2004) and working/recognition memory (Mammarella et al., 2016) suggests that the effects of alpha2b receptor activity on learning likely differ across learning processes (Xie et al., 2018).

A large body of literature has focused on the effects of acute stress on *explicit* learning. It is well established that, when there is a delay between stress induction and a cognitive task, as in the present study, performance is typically impaired (Joels, Pu, Wiegert, Oitzl, & Krugers, 2006). In a recent study, we demonstrated that acute stress induction followed by a delay not only impairs explicit learning and memory, but also affects *implicit* operant and classical conditioning (Ehlers & Todd, 2017a). Here we found no overall influence of acute stress on preexisting biases or bias change. It should be noted that we cannot rule out that individual differences in cortisol response might add to the variability explained in the present findings. Yet, as has been suggested by studies of nonhuman animals, the effects of stress manipulation on adaptation can be masked by differences in initial bias (Enkel et al., 2010). Indeed, follow-up analyses showed that participants with more negative initial biases showed stronger positive bias changes. Importantly, this effect was visible only in the control, and not in the stress group. Thus, the results are consistent with previous research on stress and (emotional) learning in which acute stress induced with a delay impaired learning. Taken together, the present study adds to the field by

demonstrating that acute stress can also affect short-lasting perceptual effects.

Reduced sensitivity to rewarding information is a characteristic of depressive symptoms (Anderson, Leal, Hall, Yassa, & Yantis, 2014; Bogdan & Pizzagalli, 2006; Peckham et al., 2010), and stressful events have been found to play a causal role in depression (Hammen, 2005). Our past work has demonstrated that acute delayed stress can lead to reduced reward responsiveness in healthy young adults, in a manner reminiscent of anhedonia symptoms in depression (Ehlers & Todd, 2017a). The present study further demonstrates that acute stress can directly impair the training of negative biases in a more positive direction. An equivalent phenomenon has been observed in rodents, where a pharmacological manipulation mimicking the stress response shifted responses to ambiguous cues away from the positive, such that ambiguous cues were more likely to be judged as negative (Enkel et al., 2010). Taken together, the findings of the present study have implications for predicting responsiveness to depression treatment, in that we have shown that implicit training yielding more positive cognitive biases is hindered under acute stress.

Previous research has also demonstrated interactions between *ADRA2b* genotype and acute stress, such that amygdala activity was enhanced for deletion carriers only under acute stress (Cousijn et al., 2010). In contrast, we did not find any interactions between genotype and stress in the present study. In particular, we hypothesized that acute stress induction would amplify the putative difference in NE availability, and hence in behavior, between *ADRA2b* deletion carriers and noncarriers. There are several possible explanations for why we did not see the hypothesized effect. First and foremost, there may have been no differences to be amplified, since we observed no behavioral differences between deletion carriers and noncarriers with respect to bias flexibility. Moreover, acute stress is likely to affect the whole NE system, and hence all receptor subtypes, in the same way. Thus, it could be that an overall increase in NE availability that affects both inhibitory and excitatory receptors might cancel out and not result in any specific enhancements in deletion carriers. Finally, due to the timing of the stressor relative to the adaptation task, the present experiment capitalized more on the effects of the slow stress response, involving the release of cortisol, and less on immediate NE-driven effects (de Quervain, Roozendaal, & McGaugh, 1998; Joels et al., 2006). Thus, interactions with stress might be observed if training were to occur immediately after stress induction.

It should be noted that the dopaminergic system is also likely to play a role in stress-related alterations in reward processing (Di Chiara, Loddo, & Tanda, 1999). A review article has shed light on the effects of stress on dopaminergic transmission in the prefrontal cortex and the association with mood disorders (Moghaddam & Jackson, 2004). Moreover, a range of dopaminergic polymorphisms has been related to depressive symptoms (Pearson-Fuhrhop et al., 2014) and vulnerability to cognitive malfunctioning after traumatic stress (Klaus et al., 2017). Future research could further probe the role of the dopaminergic system in the effects of stress on bias flexibility.

Although subjective stress ratings indicated successful stress induction, it should be noted that there were no significant differences in cortisol levels between the stress and control groups. The initial measurements were taken right before and after stress induction, when no group differences were expected (Schwabe et al., 2008). The third measurement was taken at the end of the experiment, which was about 60 min after the stress induction. In our previous studies, the posttask measurement had been taken approximately 40 min after stress induction, and elevated cortisol levels were reliably observed (Ehlers & Todd, 2017a). Hence, we speculate that the reason for our present result was that we missed capturing the peak activation in cortisol about 25–30 min after stress induction (Schwabe et al., 2008). Nevertheless, we are confident that the tasks were performed under the influence of acute stress, due to the subjective ratings, the reliability of the induction procedure (Schwabe & Schachinger, 2018), and our own experience with it (Ehlers & Todd, 2017a).

In conclusion, the present study has shown that a common genetic variation putatively influencing NE availability was associated with subjective perceptions of ambiguous stimuli as being more rewarding. Moreover, delayed effects of acute stress diminished the positive change in affective bias predicted by initial biases, consistent with previous studies showing detrimental effects of delayed stress on appetitive learning. These findings add to our understanding of the influence of stress and the locus coeruleus/NE system on the perception of reward and the flexibility of underlying subjective biases.

Author note The authors declare no competing financial interests. This research was supported by Canadian Institutes for Health Research (CIHR) Operating Grant #491746 and by a grant from the Leaders Opportunity Fund from the Canadian Foundation for Innovation (FAS#: F13-03917), as well as by a CIHR New Investigator Salary Award and a Michael Smith Foundation for Health Research Scholar award to C.J.D.R. and R.M.T.

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