**Computational Modeling of Threat Learning Reveals Links
with Anxiety and Neuroanatomy**

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Abstract

Influential theories implicate variations in the mechanisms supporting threat learning in variations in the severity of anxiety symptoms. We use computational models of associative learning in conjunction with structural imaging to explicate links among the computational mechanisms underlying threat learning, their neuroanatomical substrates, and anxiety severity. We recorded skin-conductance data during a threat-learning task from individuals with and without anxiety disorders (N=251; 8-50 years; 116 females). Reinforcement-learning model variants quantified processes hypothesized to relate to anxiety: threat conditioning, threat generalization, safety learning, and threat extinction. We then tested associations among latent learning parameters, whole-brain morphometry, and anxiety severity, as well as age moderation. Results indicate that greater anxiety severity related specifically to slower safety learning and threat extinction. Gray-matter volume in several subcortical structures moderated extinction-anxiety associations. Using a modeling approach, we identify computational mechanisms linking threat learning and anxiety severity and their neuroanatomical substrates.

Introduction

Threat learning encompasses processes that rapidly generate associations between neutral stimuli and aversive outcomes. Influential neurodevelopmental theories implicate age-related variations in the mechanisms underlying such conserved associative-learning processes in anxiety symptoms^{1,2}. Computational learning theory offers tools to quantify associative learning dynamics as they relate to variations in these mechanisms. Here, we study physiological data recorded during a threat learning paradigm in a large sample (N=251) featuring a wide range normative to pathological anxiety severity across childhood to adulthood. We use these data to uncover links among threat learning processes, their neuroanatomical substrates, and anxiety severity via latent learning parameters estimated by reinforcement learning models.

Neural circuits have evolved to allow rapid learning of threat associations following encounters with danger^{3,4}. Through threat conditioning, a neutral stimulus rapidly comes to elicit fear responding in anticipation of danger³. Through extinction, such conditioned anticipatory responding is attenuated if the stimulus no longer predicts the occurrence of threat⁵. Extensive research across species implicates conserved neural circuitry in these processes, highlighting their adaptive value⁶⁻¹³.

At the same time, aspects of these processes could prove maladaptive. Thus, influential theories link variations in threat learning to the emergence and persistence of excessive threat-anticipatory fear responses which are central in expression of anxiety symptoms^{1,2,14-16}. Moreover, maturational processes in the circuitry supporting such learning may underlie the emergence of anxiety symptoms in childhood and adolescence¹⁷⁻²³. However, studies in youth and adults attempting to link variations in threat learning and anxiety symptoms yield

inconsistent findings^{2,14,24}, hindering neuroscience research on normal and abnormal threat learning mechanisms.

Failure to detect robust and replicable associations between threat learning and anxiety symptoms could reflect limitations of standard analytic methods that are not designed to capture associative learning dynamics^{8,25}. Such limitations could potentially be overcome through applications of computational learning theory, which provides a mathematical framework for quantifying the temporal dynamics of associative learning processes, as indexed with latent variables^{11,13,26,27}. Based on the measurement of prediction errors between expected and experienced outcomes, associative learning models were initially applied to reward learning^{26,28,29}. Recent studies extend this approach to model associations between threat cues and aversive outcomes. These include studies in healthy subjects and in patients with post-traumatic stress disorder, identifying cumulative cue-associability over time as an important learning parameter that also relates to symptoms^{12,30-33}. This approach has yet to be applied to study the mechanisms that link individual differences in threat learning processes and anxiety symptoms^{1,2,14}.

Here, we address this gap by applying reinforcement learning models to skin conductance response (SCR) data recorded during a threat learning paradigm, in conjunction with structural brain imaging, to quantify age-dependent associations among threat learning processes, neuroanatomy, and anxiety severity. We complement and extend prior work in several ways. First, we study a sample that includes individuals with and without anxiety disorders falling along a wide age span, from age 8-50 years. This sample contains wide ranges of anxiety symptoms and age, which increase statistical power to detect associations among age, anxiety, and threat learning indices. Second, previous work modeled cue responding over many

reinforcement trials (e.g., >60 trials)^{12,30,31}, which may more closely model the *expression* of conditioned responses. Here, we focus instead on the rapid *learning* of threat associations that take place during a shorter schedule³. Third, we model four learning effects: threat conditioning, threat generalization, safety learning, and threat extinction. This provides tests of different theories that link mechanistic variations in these specific processes to the severity of anxiety^{1,8,23,34-36}. Finally, we use data from a relatively large sample (N=215) of medication-free subjects, enabling parameter estimation with greater accuracy and over a large model space. We hypothesize that anxiety severity is associated with latent learning parameters^{1,2}; that age moderates specifically the association between extinction learning and anxiety¹⁹; and that morphometry features in subcortical structures and prefrontal cortex moderate associations between learning parameters and anxiety^{37,38}.

Methods

Participants

Data from a sample of 351 individuals were initially considered. Due to our focus on model fitting with trial-by-trial data and the noisy nature of SCR data, we excluded individuals with excessive missing data, with similar exclusion proportion to prior work¹² (n=136; see Supplement). This led to a final sample of N=215, which included 104 healthy participants (53 females; ages 8-44 years) and 111 medication-free participants with anxiety disorders (63 females; ages 8-50 years). Healthy and anxiety groups did not differ in age, sex, or IQ, $ps > .05$. All participants were recruited from the community as paid volunteers for research at the National Institute of Mental Health (NIMH). Written informed consent was obtained from adult (≥ 18 years) participants as well as parents, and written assent was obtained from youth.

Procedures were approved by the NIMH Institutional Review Board. Analyses on raw psychophysiology data and neuroanatomy data from this sample have been previously reported^{34,39-41}. The current study reports novel analyses of these data.

Anxiety severity

All participants were interviewed by trained clinicians using semi-structured clinical interviews; see Supplement. Anxious patients were required to meet criteria for generalized, social, and/or separation anxiety disorder. Healthy participants did not meet criteria for any psychiatric diagnosis. See supplement for exclusionary criteria. To assess current anxiety symptom severity, youth and adult completed standard anxiety questionnaires. Youth completed the Screen for Child Anxiety Related Emotional Disorders (SCARED)⁴², and adults completed the trait subscale of the STAI⁴³, within 3 months of the task. The SCARED is a child- and parent-report measure comprising 41 items assessing recent anxiety symptoms and possessing strong psychometric properties^{42,44}; to reduce informant differences, child- and parent-report scores were averaged^{45,46}. The STAI⁴³ consists of 20 items relating to general anxious moods and possesses strong psychometric properties⁴⁷. To combine these anxiety measures, we Z-transformed each measure within its respective age sample; these Z-scores were then combined across samples and used in analyses⁴⁸. These anxiety severity scores manifested a unimodal, continuous distribution across the sample (see Fig. S1).

Threat conditioning and extinction task

The task involves rapid, uninstructed Pavlovian conditioning and extinction of threat associations³. The task has previously been found effective (i.e., produce conditioning while maintaining a low dropout rate) among individuals with anxiety and healthy participants from

both youth and adult populations^{21,35,39-41,49-51}. In the task (see Fig. 1), photographs of two women displaying neutral expressions⁵² served as the conditioned threat and safety stimuli (CS+ and CS-, respectively). The unconditioned stimulus (UCS) was a 1s presentation of the same actress displaying fear and co-occurring with a 95dB female scream delivered via headphones, co-terminating with the CS+. During pre-conditioning, each CS was presented 4 times. During conditioning, each CS was presented 10 times, and the CS+ was followed by the UCS with an 80% reinforcement schedule. During extinction, the CSs were each presented eight times and never reinforced. In all phases, the duration of the CS+ and CS- were presented for 8 seconds, but shortened to 7s when UCS occurred. See Supplement for additional details. Skin conductance, electromyography, and electrocardiography were recorded. Due to our focus on skin conductance responses as indexing conditioned anticipatory fear responses⁸, the other measures are not analyzed in the current report.

Skin conductance. Skin conductance was recorded at 1,000Hz using PsyLab from two Ag/AgCl electrodes from the medial phalanx of the middle and ring non-dominant-hand fingers. In line with prior research, skin conductance response (SCR) was determined by the square-root-transformed difference between base-to-peak amplitude within 1-5s after stimulus onset^{31-33,39,53,54}. To generate more accurate estimates from trial-by-trial data, we next cleaned trial-level data as reported in the Supplement.

Raw SCR data

Raw SCR data by trial and task phase are depicted in Figure 1. During the conditioning phase, rapid CS+ threat conditioning (acquisition of conditioned fear response) was noted; response to the CS- was characterized by generalization of conditioned fear response (increased response despite no reinforcement) and safety learning (diminishing response through continued

non-reinforcement). During the extinction phase, rapid extinction (diminishing response) was noted for both stimuli. Statistics on these data are reported in the Results section. As noted, perturbations in these processes have been suggested to contribute to the emergence and persistence of anxiety symptoms^{1,2,14,55-57}. Specifically, facilitated threat conditioning⁵⁸, greater threat generalization^{55,57,59}, and slower safety learning^{22,23} have each been theorized to lead to underlie anxiety symptoms. Further, threat extinction processes have been implicated in both anxiety symptoms and exposure-based treatment for anxiety^{5,19,22,57}. Due to the potential relevance of these learning processes to anxiety, and as they were evident in the data, we used reinforcement modeling to examine them.

Figure 1. Top: Schematic representation of the threat learning paradigm. During the pre-conditioning phase, the designated threat (CS+) and safety (CS-) stimuli were presented without reinforcement. During the conditioning phase, the CS+ was paired with a fearful face co-terminating with a scream (UCS); the CS- was never reinforced. During the extinction phase, both CS+ and CS- were not reinforced by the UCS.

Bottom: Mean raw skin conductance response for the CS+ and CS- by task phase and trial.

Note: Trial number indicates the nth trial for that stimulus. However, the CS+ and CS- trials were presented in counterbalanced order throughout the task. CS = conditioned stimulus; UCS = unconditioned stimulus. Error bars indicate one standard error of the mean.

Reinforcement learning models

In previous work on this data we used standard statistical models to assess the effects of anxiety on conditioning³⁴. In this manuscript, the goal was to explore dynamic learning processes that could account for the model-agnostic effects seen in the previous study. To model these dynamic processes during threat conditioning and extinction, we fit separately for each participant multiple reinforcement learning models to the trial-level SCR data. The models learn, trial by trial, the value of the CS based on the presence or absence of the aversive stimulus (UCS). See Fig. S2 for histograms depicting model estimates in the sample.

1. Conditioning phase: CS+ threat conditioning. First, we modeled threat conditioning whereby the CS+ comes to elicit a threat-anticipatory response via reinforcement by the UCS.

We fit nine reinforcement learning models to CS+ conditioning data that varied in the number of parameters used to model the psychophysiological responses, as detailed next. Parameters were estimated and optimized for each participant separately using the *fminsearch* function in MATLAB by minimizing the sum of squares error between the predicted and measured SCR to the CS³⁵. We then compared the model fits to the actual data per participant and across the sample to choose the best-fitting model.

All models were initially based on a Rescorla-Wagner (RW) model²⁷, whereby at trial $t + 1$, the value v_{CS+} of the CS+ is updated based on its value at the preceding trial $v_{CS+}(t)$ plus the prediction error obtained at trial t (corresponding to the difference between the value of the UCS at that trial and the expected value, multiplied by the learning rate parameter α):

$$v_{CS+}(t + 1) = v_{CS+}(t) + \alpha[r(t) - v_{CS+}(t)]. \quad (1)$$

where $r(t)$ is the SCR to the UCS on trial t . For each trial, the updated predicted SCR to the CS+ is defined as $v_{CS+}(t + 1)$.

The threat conditioning data displayed additional dynamics features that would not be captured by the base RW model (Fig. 1). Therefore, we explored additional learning mechanisms, which led to 8 models (see Table 1). First, we fit a learning inertia term⁶⁰, which assumed that the effect of the prediction error accumulated across m recent trials. Specifically, if we define the prediction error on trial t as $\delta(t) = r(t) - v_{CS+}(t)$, the learning inertia term updated the value using $v_{CS+}(t + 1) = v_{CS+}(t) + \alpha\delta^{in}$, where

$$\delta^{in}(t) = \sum_{k=0}^{k_m} \delta(t - k). \quad (2)$$

The value $k_m = 2$ maximized the fit across all participants. Qualitatively this model improved the fit, but we found only indeterminate statistical evidence to support it.

Second, we examined Bayesian learning rate decay. This assumes that the learning rate starts high and then diminishes over trials according to the information that has been accumulated⁶¹. In this model variant, α was a free parameter and the learning rate on each trial was given by:

$$\alpha(t) = \frac{\alpha}{\text{sqr}t(t)}. \quad (3)$$

This variant has no additional free parameters over the base RW model.

Third, we examined habituation of the conditioned response (diminished response over trials despite reinforcement). Accordingly, we fit a multiplicative exponential decay term, which resulted in an SCR estimate given by:

$$v_{CS+}^{hab}(t) = v_{CS+}(t)e^{-\varphi[t-t_0]^+}. \quad (4)$$

When we fit this model, we estimated $v_{CS+}(t)$ using equation 1, and then multiplied the estimated values by the habituation term given in equation 4. This model had an additional parameter for each participant, φ , which controlled the rate of habituation. The rectified linear operator, $[x]^+$, returns 0 for negative values and x for positive values. We also estimated a single value of t_0 across all participants, as it was clear that the habituation process did not start in the first conditioning trial. We found that $t_0 = 2$ was optimal and significantly improved the pooled model fit across participants.

Lastly, in addition to the 8 aforementioned models, we fit a RW-Pearce-Hall (PH) “hybrid” model to the data, given findings on its relevance to threat learning processes^{12,30-32}. This model utilizes equation 1 for the value update with absolute value of the prediction error. However, in the PH model the learning rate is adaptive, and updated on each trial as:

$$\alpha = \alpha(1 - \gamma) + \gamma|\delta(t)|. \quad (5)$$

The variable γ is a free parameter that controls the rate of update of the learning rate. The hybrid model, therefore, has 2 parameters (α, γ).

As these model structures were independent, we fit 9 models (see Table 1), where model 1 was the base RW model; model 2 included a prediction-error inertia term; model 3 assumed a Bayesian learning-rate decay; model 4 included a habituation term; model 5 included the inertia term and Bayesian learning-rate decay; model 6 included inertia and habituation terms; model 7 included Bayesian learning-rate decay and habituation; model 8 included inertia, Bayesian learning-rate decay, and habituation; and model 9 was the RW-PH hybrid model. See Table 1. We calculated the Bayesian Information Criterion (BIC)⁶², which offers a trade-off between model fit and model complexity, for each model, and then carried out t -tests on the BIC across the sample to identify the best-fitting model. Parameters from the best fitting model were then used in analyses of brain structure, anxiety symptoms, and age.

Model	Model specification	Free parameters
1. RW	$v_{CS+}(t + 1) = v_{CS+}(t) + \alpha\delta$	α
2. RW with inertia	$v_{CS+}(t + 1) = v_{CS+}(t) + \alpha\delta^{in}$, whereby $\delta^{in}(t) = \sum_{k=0}^{k_m} \delta(t - k)$, with m =number of recent trials	α
3. RW with Bayesian learning-rate decay	$v_{CS+}(t + 1) = v_{CS+}(t) + \alpha\delta$, whereby $\alpha(t) = \frac{\alpha}{\text{sqrt}(t)}$	α
4. RW with habituation	$v_{CS+}(t + 1) = v_{CS+}(t) + \alpha\delta$, with $v_{CS+}(t)$ multiplied by $e^{-\varphi[t-t_0]^+}$ after update	α, φ
5. RW with inertia and Bayesian learning-rate decay	$v_{CS+}(t + 1) = v_{CS+}(t) + \alpha\delta^{in}$, whereby $\alpha(t) = \frac{\alpha}{\text{sqrt}(t)}$, and $\delta^{in}(t) = \sum_{k=0}^{k_m} \delta(t - k)$, with m =number of recent trials	α

6. RW with inertia and habituation	$v_{CS+}(t+1) = v_{CS+}(t) + \alpha\delta^{in}$, whereby $\delta^{in}(t) = \sum_{k=0}^{k_m} \delta(t-k)$, with m =number of recent trials, and $v_{CS+}(t)$ multiplied by $e^{-\varphi[t-t_0]^+}$ after update	α, φ
7. RW with Bayesian learning-rate decay and habituation	$v_{CS+}(t+1) = v_{CS+}(t) + \alpha\delta$, whereby $\alpha(t) = \frac{\alpha}{\text{sqr}t(t)}$, and $v_{CS+}(t)$ multiplied by $e^{-\varphi[t-t_0]^+}$ after update	α, φ
8. RW with inertia and Bayesian learning-rate decay, and habituation	$v_{CS+}(t+1) = v_{CS+}(t) + \alpha\delta^{in}$, whereby $\alpha(t) = \frac{\alpha}{\text{sqr}t(t)}$, and $\delta^{in}(t) = \sum_{k=0}^{k_m} \delta(t-k)$, with m =number of recent trials, and $v_{CS+}(t)$ multiplied by $e^{-\varphi[t-t_0]^+}$ after update	α, φ
9. RW-PH hybrid	$v_{CS+}(t+1) = v_{CS+}(t) + \alpha\delta$, whereby $\alpha = \alpha(1-\gamma) + \gamma \delta(t) $	α, γ

Table 1. Specifications and estimated free parameters for each model fit to the threat conditioning data from the conditioning phase. In all models, prediction error is defined as: $\delta(t) = r(t) - v_{CS+}(t)$.

Note: RW = Rescorla-Wagner base model; t = current trial; $v_{CS+}(t+1)$ = predicted skin conductance response to CS+ at trial $t+1$; $r(t)$ = measured skin conductance response to UCS at trial t .

2. Conditioning phase: CS- threat generalization and safety learning. As can be seen in the conditioning phase data (Fig. 1), participants rapidly generalized a fear response to the CS- (i.e., showed an increase in response to CS- despite non-reinforcement), and learned its safety value as it was continually non-reinforced (i.e., safety learning). A standard RW model will not capture conditioning to the CS-, as this cue was never reinforced. Generalization of the conditioned response to the CS- and safety learning could be captured by a model that tracks the psychophysiological responses to the CS+ and “projects” them onto the CS-. This model

contains four parameters: a learning rate (equation 1) and a habituation term (equation 4) for each of the CS- and CS+. This uses the best-fitting model for the CS+ (see Results) with an additional value equation for the CS-. In this model, when a UCS was delivered, the value for the CS+ was updated according to equation 1 and, in addition, a value for the CS- was updated using

$$v_{CS-}(t + 1) = v_{CS-}(t) + \alpha_{CS-} \delta(t) \quad (6)$$

Note that $\delta(t)$ was only calculated in CS+ trials when a UCS was delivered. There was no update in CS- trials. Fourteen of the 215 participants had fewer than 3 CS- trials with non-zero data and were thus excluded from analyses.

3. Extinction phase: CS+ threat extinction learning. Next, we modeled CS+ threat extinction rates, whereby participants learn to omit anticipatory responses to the CS+ as this cue is no longer reinforced by the UCS. Data indicated that extinction learning follows exponential decay. Accordingly, this model considered one parameter for the decay rate, using equation 1 to model CS+ data during extinction.

Of note, the learning processes studied here manifest over few trials, which could make parameter estimates noisy. To accommodate for that, we use data from a large number of participants. Because our hypotheses were tested using hierarchical models, variance in parameter estimates at the first level can be compensated for with additional participants, when testing hypotheses at the second level.

Brain imaging

Analyses tested associations among threat learning parameters and imaging measures. MRI images (1 mm³), acquired on a 3-Tesla MR750 GE scanner with a 32-channel head coil (see Supplement for acquisition parameters), were collected from 148 of the 215 participants

(69%; 81 females, $Mage=18.38$ years). MRI data for a larger sample containing these participants appear in previous reports using different analyses^{34,63,64}. FreeSurfer (version 6.0, <http://surfer.nmr.mgh.harvard.edu>) was used for processing (see Supplement). Statistical tests were performed using PALM (Permutation Analysis of Linear Models)⁶⁵. Surface-based analyses considered whole-brain cortical thickness using the TFCE (threshold-free cluster enhancement) statistic⁶⁶, with a vertex-wise familywise-error (FWE)-corrected threshold of $p<0.05$. Analyses of subcortical volumes generated by FreeSurfer considered gray matter volume (GMV) with an FWE-corrected threshold of $p<0.05$. For each morphometry measure, analyses included global whole-brain estimates of the measure (global average thickness, total intracranial volume) as nuisance, as recommended in prior research⁶⁷. Sex was also used as a nuisance variable given reported sex differences in brain structure^{17,34,68}. See Supplement for additional details. To facilitate reproducibility, the full analysis pipeline has been previously published³⁴.

Data analysis

Analyses tested associations among threat learning parameters, morphometry measures, anxiety severity, and age. Specifically, for each of the three processes modeled (see above), we first identified the model best accounting for the process (e.g., α in threat conditioning). For each estimated parameter in this model, we next conducted two analyses. First, we examined whether the estimated learning parameter was associated with anxiety severity, as moderated by age, by testing the *Parameter* $\times$ *Age* interaction on anxiety scores. Second, we examined whether brain structure was associated with the learning parameter, by testing the *Structure* $\times$ *Anxiety* $\times$ *Age* main and interaction effects on parameter values.

All analyses used the general linear model and set significance at 0.05. In addition to the aforementioned corrections for multiple testing, within each of the three processes studied we further applied a Bonferroni correction to statistical tests to account for the number of parameters tested in the model; all reported p -values reflect these corrections.

Results

Raw SCR data

Raw SCR data by trial and phase are depicted in Figure 1. Repeated-measures ANOVA of SCR data with Phase (conditioning, extinction) and CS (CS-, CS+) as within-subject factors and anxiety severity (Z-scores) and age (years) as between-subject factors, indicated a significant Phase×CS interaction, $F(1,212)=10.97, p=0.001$. Follow-up analyses indicated greater response to CS+ than CS- during conditioning, $F(1,212)=24.24, p<0.001$, but not during extinction, $F(1,212)=0.24, p=0.63$, demonstrating successful conditioning and extinction in the task. Anxiety and age did not significantly moderate the Phase×CS interaction. Additional lower-order effects are reported in supplement.

Reinforcement models

1. Conditioning phase: CS+ threat conditioning

Model fit. Fig. 2A depicts empirical and modeled data for each of the 9 models fit to the CS+ conditioning data. Fig. 2B depicts for descriptive purposes, for each model, the mean correlation between empirical and modeled data across the sample. To determine which model provided the best fit, we ranked their BIC values using t -scores from dependent-samples t -tests. Models 7 (RW with Bayesian learning-rate decay and habituation term) and model 8 (RW with inertia

term, Bayesian learning-rate decay, and habituation term) provided better fit than the other models (all $ts \geq 3.89$, and $ts \geq 5.48$, respectively). While model 8 provided a slightly better fit than 7, $t=1.35$, the latter was simpler, and thus we used parameters from model 7 (threat learning rate, α ; and habituation rate, φ) in subsequent analyses.

A. Conditioning: Empirical Data vs. Modeled Data

B. Conditioning: Mean Correlations between Empirical and Modeled Data

Fig. 2. CS+ threat conditioning model fit. A) Graphs depict empirical skin conductance data (full line; bars indicate one standard error of the mean) and fitted data (dashed line) for each of the models fitted to CS+ conditioning data. B) For each model, the bar depicts the mean correlation coefficient between the empirical and modeled data (error bars reflect one standard error of the mean, all mean coefficients are significantly different than 0, $ps < 0.001$). Model numbers correspond to specification in (A) and to Table 1.

Anxiety and age. Threat learning rate and habituation rate during conditioning did not differ by anxiety severity or age, $\beta s < 0.06$, $ps > 0.41$.

Brain structure. No effects of brain structure on threat learning rate were noted. Habituation rate correlated positively with right thalamus GMV, $\beta = 0.28$, $p = 0.008$ (corrected); see Fig. 3. No other effects were observed, all $ps > 0.05$.

Conditioning: Thalamus Gray Matter Volume and CS+ Habituation Rate

Figure 3. Conditioning: CS+ habituation rate. Scatterplot depicts correlation between right thalamus gray matter volume and CS+ habituation rate during conditioning. Data shown are residuals after controlling for nuisance and other effects of interest.

2. Conditioning phase: CS- threat generalization and safety learning

Model fit. For the CS- data, we fit the best-fitting model as for the CS+. This model captured the generalization of fear response to the non-reinforced CS- and decay in response to CS- that reflects learning its safety value; see Fig. 3A. The average correlation across the sample between the modeled and empirical data was $r=0.54$, $p<0.001$.

Anxiety and age. Anxiety severity was associated with both CS- threat generalization rate, which captures initial transfer of CS+ threat learning to the CS- cue, and CS- safety learning rate, which captures the reduction in responding through non-reinforcement. CS- threat generalization rate interacted with age in predicting anxiety severity, $\beta=0.42$, $p=0.028$ (corrected). To interpret this developmental effect, we tested the generalization-anxiety simple correlation separately within each of three age-based groups broadly corresponding to pre-adolescence (age<13 years, $n=74$), adolescence ($13\leq\text{age}<18$ years, $n=57$), and adulthood (age>18 years, $n=69$); see Fig 3B. Threat generalization rate and anxiety showed a significant negative correlation in the pre-adolescence group, $r(73)=-0.29$, $p=0.011$; this correlation was not significant in the adolescence or adult age group, $r(56)=-0.21$, $p=0.11$, and $r(68)=0.18$, $p=0.15$, respectively. The correlation in the adult group was significantly different from the correlation in the adolescent group, $Z=2.15$, $p=0.032$, and in the pre-adolescent group, $Z=2.81$, $p=0.005$. Thus, generalization rate was associated with anxiety only in younger age.

In addition, CS- safety learning rate was correlated with anxiety severity, such that slower safety learning was associated with greater anxiety, regardless of age, $\beta=-0.22$, $p=0.004$ (corrected); see Fig. 3C. No other effects were observed.

Figure 3. A) Graph depicts empirical skin conductance data (full line; bars indicate one standard error of the mean) and fitted data (dashed line) for the model fit to the CS- conditioning data, which includes threat generalization rate and safety learning rate terms. B) Scatterplot depicts age moderation of association between CS- threat generalization rate during conditioning and anxiety severity, decomposed into three age groups. C) Scatterplot depicts correlation between anxiety severity and CS- safety learning rate during conditioning. Data shown are residuals after controlling for nuisance and other effects of interest.

Brain structure. No significant effects were observed, $ps>0.05$.

3. Extinction phase: CS+ threat extinction

Model fit. CS+ threat extinction featured exponential decay. Empirical data and modeled data are depicted in Fig. 4A. The average correlation across the sample between the modeled and empirical data was $r=0.52$, $p<0.001$.

Anxiety and age. Threat extinction rate correlated with anxiety severity, $\beta=-0.19$, $p=0.013$ (corrected), such that slower extinction was associated with greater anxiety, see Fig. 4B. No other effects were observed, $ps>0.05$.

Brain structure. GMV in several subcortical structures moderated the association between CS+ extinction learning rate and anxiety severity, including brain stem, bilateral ventral diencephalon (which includes hypothalamus and midbrain), bilateral caudate nucleus, and left putamen, all $\beta s \geq 1.06$, $ps \leq 0.013$ (corrected). Decomposition of this interaction revealed a consistent pattern, whereby as GMV was smaller, slower threat extinction was associated with greater anxiety severity; see Fig. 4C for a representative graphical depiction of this effect (brain stem GMV).

A. CS+ Extinction Model Fit

B. CS+ Extinction Rate and Anxiety Severity

C. Subcortical Volume Moderates Link between CS+ Extinction Rate and Anxiety Severity

Figure 4. A) Empirical data for skin conductance response to CS+ across extinction trials (full lines; bars reflect one standard error of the mean) and fitted data (dashed line) by the model. B) Scatterplot depicts correlation between anxiety severity and CS+ extinction rate. C) Left: Gray matter volume in several subcortical structures moderated the association between CS+ extinction learning rate and anxiety severity: brain stem (purple), bilateral ventral diencephalon (light blue), bilateral caudate nucleus (dark blue),

and left putamen (green). Right: in these structures, a similar pattern emerged for the interaction which is depicted in a plane; representative data from the brain stem are depicted. Warmer and cooler colors reflect more positive and negative values, respectively. All brain structure effects are significant at $p_{\text{FWER}} < 0.05$.

Discussion

This study modeled trial-by-trial psychophysiological data to quantify threat learning processes and their associations with anxiety symptoms, neuroanatomy, and age^{1-3,19}. Several key findings emerged. First, threat conditioning was optimally modeled with a RW model that featured Bayesian (diminishing) threat-learning rate and a habituation rate; habituation rate was associated with thalamus GMV. Second, using a similar model to characterize response to safety cues during conditioning, threat generalization rate was found to relate to anxiety severity only in younger age, whereas greater anxiety predicted slower safety learning across the sample. Finally, extinction learning featured exponential decay of response to threat cues, with slower decay being associated with greater anxiety. Further, GMV of multiple subcortical structures moderated the association between extinction learning rate and anxiety, such that as GMV was smaller, slower threat extinction was associated with greater anxiety severity. This study identifies specific latent threat-learning parameters that relate to anxiety symptom severity and neuroanatomical features.

The optimal fit for threat conditioning was a RW model that assumes Bayesian learning decay and habituation terms. A RW learning rule has long been proposed to underlie reinforcement learning, whereby point estimates of future outcomes are calculated by modifying current predictions according to prediction error, as weighted by a fixed learning rate²⁷. Models based on a RW rule have been shown to describe the acquisition of conditioned fear responses in animals and humans⁶⁹. Here, we show that a decrementally-diminishing threat-learning rate provides a better fit to physiology data in humans, suggesting that conditioning of threat-anticipatory physiological responses is governed by a set learning parameter that is weighted less in proportion to additional reinforcement trials. It therefore places greater emphasis on learning

from initial encounters with danger, supporting an adaptive role for this learning process in environments that contain threats³.

The inclusion of a CS+ habituation term could indicate that conditioned responding decreases as this cue becomes more predictable, beyond what is explained by the basic RW model itself²⁷. This could be a product of the 80% reinforcement schedule used here; a different reinforcement ratio could have affected this habituation term. Additionally, the habituation term could reflect our use of trial-level UCS value when modeling, rather than 0/1 as is often done, such that the magnitude of response to the UCS contributes to learning, rather than just its absence/presence. Indeed, response to UCS in conditioning paradigms is often shown to naturally diminish as learning is achieved, potentially reflecting effective and reliable anticipation of it^{40,70,71}. Further, in other work⁷² we show that increasing UCS potency results in increasing physiological response to the UCS. The response habituation term in the model may therefore account for individual differences in dynamic changes in the strength of response that both CS+ and UCS elicit. Our data suggest that this process involves thalamus GMV, such that greater GMV is associated with faster habituation. Indeed, thalamus has been shown to relay information on conditioned and unconditioned stimuli during threat conditioning⁷³. Our findings suggest that thalamus structure may play a more specific role relating to CS+ habituation. Threat conditioning parameters, however, were not associated with anxiety, suggesting that variations in symptom severity are not related to variations in the generation of threat associations^{1,58}.

Of note, prior work identified the RW-PH “hybrid” model as providing optimal fit to data for the expression of threat contingencies among healthy adults as well as adults with PTSD^{12,30,31}. In contrast, we found that this model did not provide the best fit for rapid threat conditioning among the models tested. This discrepancy could potentially be attributed to the

nature of threat learning processes studied. While we focused on rapid acquisition of threat contingencies which takes place over a short training schedule, prior studies examined threat contingencies over much longer durations (over 80 CS+ trials). The hybrid model includes a cumulative associability term which could be more sensitive to tracking contingency values or the expression of conditioned fear as it is optimized over longer durations. Thus, differences in rapid, crude acquisition vs optimized expression of threat contingencies processes could account for model differences. As such, the current and prior work could be seen as complementary in terms of threat learning processes studied, and both sets of findings could usefully inform study design for future work.

This study extends prior work by modeling additional learning effects that were evident in the data during threat conditioning. These additional effects showed associations with anxiety, age, and neuroanatomy. The introduction of an aversive UCS led to generalization of conditioned fear response to the CS- occurring most strongly early in conditioning, and followed by safety learning as this generalized response was inhibited as the CS- was not reinforced. Accordingly, this pattern of conditioned response to the CS- was modeled using two learning parameters. Learning theories of anxiety attribute each of these processes a role in the emergence and maintenance of pathological anxiety^{1,2,55,57,59}. Our modeling approach allowed us to test these theories, providing some support for them, as well as for neurodevelopmental theories of anxiety^{19,23}. First, threat generalization rate was significantly associated with anxiety severity, but only in participants under the age of 13 years. Given that anxiety symptoms typically emerge in late childhood and early adolescence^{17,74}, this could potentially relate to aberrant threat generalization. It should be noted, however, that generalization rate was found to negatively correlate with anxiety severity, in contrast to theory⁵⁹. This finding could potentially suggest that

generalization of conditioned responses may be normative and adaptive in children, whereas anxiety could involve limited generalization. Additional research in child samples could further clarify the role of this effect in anxiety. Second, our findings provide support for prior propositions^{1,75} that link greater anxiety with slower safety learning rates^{1,22}. This suggests that fear responses to aversive events may initially generalize to neutral stimuli, but that continued responding to these stimuli may contribute to the persistent and generalized fears associated with anxiety. Importantly, the use of computational modeling enabled us to extend prior work by directly examining associations between learning *rates* and anxiety.

Finally, our results show that threat extinction learning follows an exponential decay pattern. As in threat generalization and safety learning (see above), this is the first study to quantify the temporal dynamics of this learning process via modeling. Further, we show that slower extinction learning is associated with greater anxiety severity, providing support for major theories of anxiety and its treatment^{1,2,5,15,22,56,57,76}. Thus, individuals with higher anxiety symptoms continue to express conditioned fear responses although the CS+ no longer predicts danger. This effect involves a number of subcortical structures, including brainstem, diencephalon, and basal ganglia. Across these, a similar moderation pattern was noted, such that among individuals with smaller GMV, slower extinction was associated with greater anxiety severity. This finding converges with prior work in animals and humans that suggests the involvement of at least some of these structures in threat extinction, such as caudate, hypothalamus, and midbrain/brainstem^{37,77,78}. These regions are hypothesized to contribute to encoding of prediction errors and to physiological and behavioral aspects of response to threat^{7,76,78}. Our findings extend prior work by linking variation in GMV of these subcortical structures, extinction learning, and anxiety. It should be noted that functional imaging work in

humans identifies extensive cortical involvement during threat extinction paradigms. Our findings suggest that extinction learning rates, which are not assessed in prior work, may depend on more evolutionary-conserved subcortical structures, although studies that integrate functional imaging and modeling of threat extinction learning are required to further support this hypothesis. At the same time, it should be acknowledged that administering threat conditioning and extinction paradigms during scanning to anxious individuals, particularly youth, is challenging due to the aversive nature of such paradigms^{72,79}.

This study utilized reinforcement modeling to reveal novel links between specific threat-learning processes and anxiety symptom severity, and identify neuroanatomical moderators of these associations. The findings generated from this application of a computational approach to link biological, clinical, and imaging data could initiate continued research along several lines. In terms of clinical research, the identified associations between threat learning processes and anxiety severity could inform theories on the etiology of anxiety symptoms and guide studies that aim to further qualify the learning conditions and mechanisms that promote anxiety^{13,57}. Further, influential theories that place threat extinction processes at the center of exposure-based therapy^{5,22,56,76} could be evaluated more sensitively using modeling-derived indices. Translational research on mechanisms of threat learning could also benefit from these findings. Thus, neuroscience research in humans could focus on the specific processes identified here and extend our structural imaging findings to insight on function within this circuitry. Research in animals could complement such work by further delineating, via invasive manipulations⁸⁰, the roles in threat learning of the subcortical structures identified here.

Several important limitations should be acknowledged. First, modeling was based on relatively few task trials. While we focused on the specific processes of rapid learning of threat

associations that take place over very few pairings³, this could have led to noisier parameter estimates that could diminish accuracy and statistical power. Second, this was a cross-sectional study; a longitudinal design examining whether learning rates predict later emergence of symptoms would allow stronger inferences about developmental processes⁸¹. Third, only structural MRI data were examined; functional imaging during threat learning could reveal additional correlates of learning circuitry¹², although the delivery of aversive stimuli to participants with anxiety in the MRI scanner presents a challenge⁷⁹. Several strengths mitigate these limitations and address general shortcomings in threat learning research^{8,25}. First, the large sample size increases precision of estimated parameters⁸², offsetting, to some extent, the small number of trials used for modelling. Second, participants were carefully assessed and free of medications known to impact threat learning and psychophysiology⁸. Third, wide anxiety-symptom and age ranges generate inferences with reasonable statistical power. Fourth, task and setting were identical for all participants, reducing measurement confounds and noise.

In conclusion, in this study we used computational modeling to index dynamic learning processes associated with threat learning. Through this modeling approach, we quantified these learning processes, revealed specific associations with anxiety symptoms and age, and identified neuroanatomical substrates. These findings extend our knowledge of how these learning processes manifest in humans and how variations in these could potentially contribute to anxiety symptomatology.

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