Starting Fear Is a Stronger Predictor of Long-Term Fear than Rate of Change in Fear in Human Fear Conditioning

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Abstract

In rodent studies, faster extinction rate has been shown to predict less long-term fear. However, this has scarcely been studied in humans. The present report investigated the association between extinction rate and long-term fear in humans. We secondarily evaluated specificity of extinction rate by including other fear conditioning values as predictors, including acquisition intercept, acquisition rate, and extinction intercept. Results show that slower extinction rate predicted less long-term fear when tested alone in the model. However, when including other fear conditioning variables, extinction rate no longer predicted long-term fear. Instead, greater fear at the beginning of acquisition was the most robust predictor of greater long-term fear (all three measures of fear), followed by greater fear at the beginning of extinction (US expectancy only). These effects occurred for both the danger signal (i.e., CS+) and safety signal (i.e., CS-). The results de-emphasize rate of change in fear during both acquisition and extinction as predictors of long-term fear and instead suggest that the magnitude of fear at the start of acquisition and, secondarily, extinction are more important predictors of long-term fear. This report has relevance for improving our understanding and treatment of anxiety disorders.

Keywords: fear conditioning, individual differences, acquisition, extinction, anxiety, extinction rate

Extinction of an acquired fear response is essential to adaptive emotional responding and resilience across species. According to inhibitory learning models of Pavlovian extinction, memory of the conditional stimulus (CS)/unconditional stimulus (US) association is not erased during extinction, but rather a new inhibitory CS/no US association is learned that competes with the original CS/US association (Bouton, 1993). Individuals with anxiety disorders demonstrate deficits in extinction learning (Duits et al., 2015; Lissek et al., 2005), possibly rendering them more susceptible to the persistence of anxiety and return of fear following extinction (Craske et al., 2018). Exposure therapy and is a major component of cognitive-behavioral therapy – the gold standard treatment for anxiety disorders – and is thought to be largely based on extinction learning (Craske et al., 2014). However, cognitive-behavioral therapy is effective in only approximately 50% of individuals (Loerinc et al., 2015). Because anxiety disorders affect approximately 31.6% of individuals in the United States during their lifetime (Kessler et al., 2012), this leaves millions of people underserved. Thus, identifying factors that contribute to impaired extinction learning and increased risk for anxiety may identify at-risk individuals and inform treatment.

The evidence pertaining to the effects of extinction rate on long-term fear is quite scarce. The majority of evidence from animal studies suggests that faster fear reduction during extinction is predictive of lower fear at follow-up test (Bush et al., 2007; King et al., 2017, 2018; Reznikov et al., 2015), though one human study found no effects (Brown et al., 2017).

First, Reznikov et al. (2015) compared “weak” extinguishers and “strong” extinguishers in rodents by measuring freezing during the CS+. Weak extinguishers demonstrated more than 70% freezing behaviors during the last four trials of extinction (12 trials total), whereas strong extinguishers demonstrated less than 30% freezing during the last four trials of extinction. Weak

extinguishers displayed significantly more freezing than strong extinguishers one day and 15 days after extinction. A second rodent study (Bush et al., 2007) bred “fast” extinguishers and “slow” extinguishers and measured freezing during the CS+. “Fast” extinguishers were rodents with the lowest 20% freezing rate on trials 5-7 of extinction (out of 20 trials total), and “slow” extinguishers had the top 20% freezing rate. Results showed that fast extinguishers had less fear than slow extinguishers at test one day later. Furthermore, King et al. (2017) measured freezing to the CS+ and separated groups of rodents based on the number of trials needed to reach < 35% freezing to the CS+ during extinction; “fast” extinguishers did so in ≤ 13 blocks of three trials, whereas “slow” extinguishers did so in ≥ 16 blocks. The results showed that fast extinguishers had less fear one day after extinction than slow extinguishers. In a subsequent series of three experiments, King et al. (2018) calculated extinction rate using the same CS+ freezing criteria above in a renewal study (ABA, ABB, ABC), reinstatement study (no US, 1 US, or 2 USs during reinstatement), and spontaneous recovery study (tested immediately, 8 days, or 29 days after extinction). Their results showed that, compared to slower extinction rate, faster extinction rate predicted less renewal, reinstatement, and spontaneous recovery fear for “mild” forms of each (i.e., ABC renewal, 1 reinstatement US, 8 days after extinction training). However, there were no effects of extinction rate with “strong” return of fear conditions (i.e., ABA renewal, 2 reinstatement USs, 29 days after extinction training). Thus, while there are only a few studies, the animal literature consistently suggests that faster extinction rate predicts less long-term fear (Bush et al., 2007; King et al., 2017, 2018; Reznikov et al., 2015), though this effect may be stronger with “milder” forms of return of fear (King et al., 2018).

In contrast to rodent studies, only one human study has reported rate of extinction in relation to long-term fear using self-report fear and startle reflex to the CS+ and CS- (Brown et

al., 2017). In this study, rate of extinction of the startle reflex did not predict startle reflex one week later; similarly, changes in self-report fear from before to after extinction did not predict self-report fear one week later. Unfortunately, we were unable to identify any experiments that examined individual differences in acquisition rate as a predictor of long-term fear.

The present study extends the existing literature (Brown et al., 2017; Bush et al., 2007; King et al., 2017, 2018; Reznikov et al., 2015) examining whether individual differences in extinction rate predict long-term fear. We do so by investigating whether extinction rate predicts long-term fear reduction from four human fear conditioning studies conducted with similar procedures in the same laboratory. We conducted a series of a priori and secondary/exploratory tests to evaluate extinction rate and other fear conditioning variables as predictors of long-term fear reduction (measured one week after extinction). First, with our a priori analyses, we hypothesized that faster extinction rate would predict less long-term fear. Second, with our secondary/exploratory analyses, we evaluated specificity of the effects of extinction rate by including other potentially relevant fear conditioning variables from acquisition and extinction (i.e., acquisition intercept, acquisition rate, and extinction intercept).

Methods

Participants

Participants (N = 264) were students from the University of California, Los Angeles, who participated for course credit or cash: Study 1 (n = 100) (Zbozinek et al., 2015), Study 2 (n = 62) (Zbozinek & Craske, 2017b), Study 3 (n = 58; Experiment 2) (Zbozinek, 2017), and Study 4 (n = 44) (Zbozinek & Craske, 2018). Twenty-two participants dropped out, leaving 242 completers. Participants were 61.1% female (38.9% male); mean age 21.83 years (SD = 3.93); and 3.6% Black or African-American, 0.4% American-Indian or Alaska Native, 41.1% Asian or Asian-American, 20.6% Hispanic/Latinx, 0.4% Native Hawaiian or Other Pacific Islander, 26.6% White, and 7.3% Multiracial or Other. These studies were approved by the University of California, Los Angeles Institutional Review Board, and all participants provided informed consent prior to commencing the study.

Study Selection and Design

We combined the data from four fear conditioning studies to maximize sample size and power. The four studies shared the following characteristics: experimental phases of habituation, acquisition, extinction, and test (i.e., CS+ and CS-); similar intertrial interval duration; electric shock US; no changes in context; number of CS trials (i.e., 7-8 for acquisition; 8-9 for extinction); time between acquisition and extinction (i.e., < 1 hour) and between extinction and test (i.e., one week); and measures of fear (i.e., US expectancy, skin conductance response (SCR), and startle reflex). Participants underwent habituation, acquisition, and extinction on Day

1. One week later (i.e., Day 8), participants conducted extinction test. All studies were conducted within the same laboratory. Throughout the manuscript, we use the term “fear” to refer to the broad latent construct of fear, which was measured during the CS+ and CS- using US expectancy, SCR, and startle reflex. In our model-free analyses, we used CS Type (CS+, CS-) as a factor, and we estimate latent intercepts and slopes separately to the CS+ and CS- (see Data Analysis). In each analysis/result, we specify which measure of fear and which CS we are referring to.

Materials and Apparatus

The Pavlovian conditioning procedures were programmed using E-Prime 2. CSs were 8 sec images on a computer screen, including a CS+ (paired with shock during acquisition) and CS- (never paired with shock). The US was 0.5sec electric shock to the bicep delivered 7.5sec after CS+ onset. Intertrial intervals (ITIs) varied between 25, 30, and 35 seconds. The CS+ and CS- were either a picture of a neutral human face (Study 1, (Zbozinek et al., 2015); Study 2, (Zbozinek & Craske, 2017b); Study 3, Experiment 2, (Zbozinek, 2017)) or a picture of a green triangle or a drawing of fork (Study 4) (Zbozinek & Craske, 2018). The CSs were pseudo-randomized with no more than two consecutive presentations of the CS+ or CS- in a given phase for every phase. Relatedly, the first trial of acquisition and extinction had a 50% chance of being the CS+ and a 50% chance of being the CS- (all studies). This same notion applied during extinction test for Studies 1-3; Study 4 tested the CS- and three generalization stimuli before the

CS+, in which the CS- had a 50% chance of being the first stimulus presented.¹ An electric shock US was delivered to the dominant arm bicep using the STMEPM, two LEAD110A (BIOPAC, Inc.), and two Telectrode T716 Ag/AgCl electrodes. The shock consisted of 10 consecutive pulses .05 seconds in duration, totaling to .5 seconds. The CS+/US reinforcement rate during acquisition was 100%.

US expectancy.

BIOPAC MP150 hardware unit and AcqKnowledge version 4.2 software (BIOPAC Systems, Inc.) were used to acquire US expectancy, skin conductance, and electromyography (i.e., startle reflex) data. For US expectancy, participants used a sliding scale (BIOPAC model TSD115) and were asked to “Please rate how certain you are that you will receive electric shock in the next few moments.” The values ranged from 0 = “Certain no electric shock”, 4.5 = “Uncertain,” and 9 = “Certain electric shock.” US expectancy was calculated as the mean rating 4.5-5 seconds (Studies 1-3) or 6.5-7 seconds (Study 4) after CS onset. Studies 1-3 used the term “muscle stimulation” instead of “electric shock.”

Skin conductance response (SCR).

SCR was recorded as a measure of arousal from two EL507 11mm diameter Ag/AgCl electrodes placed on the distal phalanx of the index and middle fingers of the non-dominant hand

¹ Because of this methodological difference in Study 4 vs Studies 1-3, we ran the main analyses with and without Study 4's data. The results were consistent with each other, suggesting this testing procedure had little-to-no impact on our results.

(Bradley et al., 1990). Using a GSR100C amplifier and two LEAD110A, SCR data were sampled at a rate of 31.25 Hz and filtered using an FIR low pass filter with a frequency cutoff fixed at 2Hz. SCR was calculated as a difference score between the maximum skin conductance value 1 to 6 seconds after CS or US onset minus the mean skin conductance value -2 to 0 seconds prior to CS or US onset. This difference score was then square-root-transformed to normalize the data, as well as range-corrected by dividing the difference score by the largest observed skin conductance response. SCRs less than zero were coded as zero.

Startle Reflex.

Startle reflex was measured with electromyography (EMG) orbicularis oculi activity under the left eye using two EL254S 4mm Ag/AgCl electrodes filled with SignaGel electrode gel and measured with the EMG100C amplifier. Electrode placement was 8-10mm beneath the outer corner of the eye. The second electrode was placed 1cm medial to the first electrode and 8-10mm beneath the bottom eyelid (Fridlund & Cacioppo, 1986). The startle probes consisted of 50 milliseconds, 65dB (Study 1) or 102 dB (Studies 2-4) bursts of white noise. Startle probes occurred 5 or 6.5 sec after CS onset (Study 1) or 7 seconds after CS onset (Studies 2-4) and at 10, 15, or 25 seconds after onset of the inter-trial interval (i.e., ITI), averaging at 16.25 seconds. Startle habituation was conducted for Studies 2-4 prior to acquisition (Day 1) and extinction test (Day 8), consisting of 10 startle probes across a 2.5-minute period. EMG data was sampled at a rate of 2kHz and filtered using an FIR band pass filter with a low frequency cutoff of 30Hz (Study 1) or 60Hz (Studies 2-4) and a high frequency cutoff of 1,000Hz (Study 1) or 500Hz (Studies 2-4). Data was then converted to an absolute value and smoothed using .005 samples

mean value smoothing. Startle reflex was calculated as the difference between the absolute maximum EMG level in volts during the 20ms-150ms immediately after the startle probe and the mean EMG level in volts during the 200ms immediately preceding the startle probe. EMG data was then transformed into a within-subjects t-score using responses to all CSs and ITIs across both days (startle habituation trials were excluded from t-score calculations).

Model-Based Calculations of Acquisition and Extinction Intercepts and Slopes.

We used structural equation modeling to calculate latent intercept, linear slope, and quadratic slope separately for CS+ acquisition, CS+ extinction, CS- acquisition, and CS- extinction for each measure of fear. The latent intercept, linear slope, and quadratic slope were calculated from acquisition trials 1-7 and extinction trials 1-8, where the intercept maintained its value across all trials, linear slope increased its value linearly by increments of 1 across trials, and quadratic slope increased its value exponentially to the power of 2 across trials. We first tried estimating the quadratic model in which intercept, linear slope, and quadratic slope were estimated separately. If this model did not converge, we dropped the quadratic slope and estimated the intercept and linear slope. The quadratic slope did not converge for CS+ acquisition (startle), CS- acquisition (US expectancy, SCR, startle), CS+ extinction (SCR, startle), and CS- extinction (US expectancy, SCR, startle). In all models, the intercept and linear slope converged. We saved to the dataset participants' estimated intercept, linear slope, and quadratic slope for the CS+ and CS- for acquisition and extinction and for each measure of fear. We then used these saved values in subsequent analyses to predict long-term fear (i.e., extinction test), in which CS+ variables predicted CS+ extinction test fear, and CS- variables predicted CS-

extinction test fear. While the startle reflex CS+ acquisition linear slope converged, the estimates were very restricted and highly invariant, and our subsequent structural equation modeling analyses predicting extinction test fear showed that their standard errors were generally over 100x that of the other standard errors; thus, we removed CS+ acquisition linear slope from analyses.

Procedure

On Day 1, participants provided informed consent, physiological equipment was attached, and a shock workup procedure was conducted. In the shock workup procedure, shocks started at a low intensity and increased to the level the participant considered “uncomfortable but not painful” using a 0-10 discomfort scale (0 = “Not at all,” 5 = “Moderately,” and 10 = “Very”; $M = 6.13$, $SD = 1.72$). Shock voltage ranged from 5 to 80 across all studies with a mean of 45.68 ($SD = 11.97$). There were similar means between studies ($F(3,266) = 2.56$, $p = .055$; Study 1 ($M = 43.57$, $SE = 1.166$); Study 2 ($M = 46.23$, $SE = 1.484$); Study 3 ($M = 48.89$, $SE = 1.534$); Study 4 ($M = 45.49$, $SE = 1.737$)). The primary experimental phases included: startle habituation (10 startle probes during an ITI; Studies 2-4), habituation (2 CS+, 2 CS-), acquisition (CS+/US and CS-; Studies 1-3: 8 trials each; Study 4: 7 trials each), extinction (CS+/US and CS-; Studies 1-3: 8 trials each; Study 4: 9 trials each), and extinction test (1 CS+, 1 CS-). Between acquisition and extinction, Studies 1-3 included mood inductions (Zbozinek et al., 2015; Zbozinek & Craske, 2017b; Zbozinek, 2017). Mood induction was not a significant predictor of Extinction Test fear in any of the individual studies, it was not of theoretical interest to this paper, and including it as a predictor reduced our sample size (since Study 4 had no mood induction). However, for completeness, we conducted secondary analyses including mood induction as a predictor.

On Day 8, after physiological equipment was attached, procedures included startle habituation (10 startle probes during an ITI; Studies 2-4) and extinction test (2 CS+, 2 CS-).

Data Analysis

We used Stata 15.1. For model-free acquisition and extinction (analyzed separately), level 1 predictors included CS Type (CS+, CS-), Linear Slope (Acquisition: Trials 1-7; Extinction: Trials 1-8), and Quadratic Slope (Acquisition: Trials 1-7; Extinction: Trials 1-8). If the Quadratic Slope was not significant, it was removed from the model. For Extinction Test, level 1 predictors included CS Type (CS+, CS-) and Linear Slope (Extinction Trial 8, Extinction Test).

For predictors of long-term fear, we used our measures of latent intercepts and linear slopes to predict extinction test fear for the CS+ and CS- separately. We excluded the quadratic slopes as predictors in these analyses since they were theoretically of little interest and offered low interpretability, though we kept them in the models (if they converged) in order to model the data more accurately. In our analyses, we focused on linear slope as our measure of acquisition or extinction rate. In our analyses, we first conceptually replicated the literature by conducting linear regressions using only extinction rate (i.e., extinction linear slope) to predict extinction test fear (Brown et al., 2017; Bush et al., 2007; King et al., 2017; Reznikov et al., 2015). Then, we built upon the previous literature by examining the specificity of effects of extinction rate vs other variables that could plausibly predict long-term fear. Specifically, we added extinction intercept to the regression model (with extinction rate) to see which of the two would be a stronger predictor of extinction test fear. Lastly, we added acquisition intercept and acquisition slope to the model to determine the specific effects of acquisition/extinction intercept/slope in

predicting long-term fear. This was conducted using structural equation modeling (SEM) in which each predictor was entered in the model chronologically to predict all subsequent variables in the model, ultimately ending with extinction test (i.e., acquisition intercept → acquisition linear slope → extinction intercept → extinction linear slope → extinction test). We standardized all variables in the regression and SEM analyses to produce β values. Additionally, our SEM models were just-identified, which did not allow us to quantitatively assess model fit. However, model comparison was not the goal of our analyses, and our models qualitatively showed very good fit with the observed data (see Figure 1). Rather, we chose a SEM approach because it allowed us to estimate direct, indirect, and total effects (a regression model would only assess direct effects in predicting extinction test fear). Also, our model-based estimates showed moderate-to-strong correlations with the model-free data (see Results).

Results

Model-Free Acquisition

See Figures 1a-c for fear across experimental phases. Overall, there was significant differential acquisition for all three measures of fear.

For US expectancy and SCR, there was a significant CS Type x Linear Slope x Quadratic Slope interaction ($\chi^2(1) = 97.77$, $f = .174$ (US expectancy) and $\chi^2(1) = 30.02$, $f = .096$ (SCR); $ps < .001$) with greater deceleration for the CS+ than the CS-. There was also a significant CS Type x Linear Slope interaction ($\chi^2(1) = 219.19$, $f = .260$ (US expectancy) and $\chi^2(1) = 65.12$, $f = .142$ (SCR); $ps < .001$) with a steeper incline for the CS+ than the CS-.

For startle reflex, the CS Type x Linear Slope x Quadratic Slope interaction was not significant ($\chi^2(1) = 2.11$, $f = .026$, $p = .146$). However, there was a significant CS Type x Linear Slope interaction ($\chi^2(1) = 40.83$, $f = .113$, $p < .001$) with a steeper decline for the CS- than the CS+.

Model-Free Extinction

Overall, there was significant differential extinction for US expectancy and SCR in which the CS+ extinguished to a greater extent than the CS-; startle reflex also showed differential extinction, though the CS- extinguished more quickly than the CS+.

For US expectancy, there was a significant CS Type x Linear Slope x Quadratic Slope interaction ($\chi^2(1) = 25.44$, $f = .083$, $p < .001$) with greater acceleration for the CS+ than the CS-.

There was also a significant CS Type x Linear Slope interaction ($\chi^2(1) = 52.23$, $f = .119$, $p < .001$) with a steeper decline for the CS+ than the CS-.

For SCR, the CS Type x Linear Slope x Quadratic Slope interaction was not significant ($\chi^2(1) = 1.62$, $f = .021$, $p = .203$). However, there was a significant CS Type x Linear Slope interaction ($\chi^2(1) = 12.92$, $f = .059$, $p < .001$) with a steeper decline for the CS+ than the CS-.

For startle reflex, there was a significant CS Type x Linear Slope x Quadratic Slope interaction ($\chi^2(1) = 4.98$, $f = .037$, $p = .026$) with greater acceleration for the CS- than the CS+ (i.e., the CS- approached a minimum asymptote more quickly). There was also a significant CS Type x Linear Slope interaction ($\chi^2(1) = 4.18$, $f = .034$, $p = .041$) with a steeper decline for the CS- than the CS+.

Model-Free Extinction Test

Overall, there was a significantly greater increase in US expectancy and startle reflex for the CS+ than the CS- from the end of extinction to extinction test. For SCR, there was a non-differential increase with the CS+ and CS-.

For US expectancy and startle reflex, there was a significant CS Type (CS+, CS-) x Linear Slope (Extinction Trial 8, Extinction Test) interaction ($\chi^2(1) = 40.50$, $f = .227$, $p < .001$ (US expectancy) and $\chi^2(1) = 4.99$, $f = .081$, $p = .026$ (startle reflex)) with a steeper incline for the CS+ than the CS-.

For SCR, the CS Type (CS+, CS-) x Linear Slope (Extinction Trial 8, Extinction Test) interaction was not significant ($\chi^2(1) = 0.28$, $f = .019$, $p = .594$), nor was the main effect of CS

Type ($\chi^2(1) = 1.08, f = .013, p = .299$). However, there was a significant main effect increase in Linear Slope for both CSs ($\chi^2(1) = 79.40, f = .498, p < .001$).

Figure 1. Fear Conditioning Results. **Panels a-c** present model-free (real) fear conditioning data across habituation, acquisition, extinction, and extinction test. Measures include unconditional stimulus (US) expectancy, skin conductance response (SCR), and startle reflex. US Expectancy was measured on a 0-9 scale, where 0 = “Certain no electric shock”, 4.5 = “Uncertain,” and 9 = “Certain electric shock.” Error bars represent standard error. **Panels d-f** present model-based results in which latent intercepts, linear slopes, and quadratic slopes were estimated for acquisition and extinction. If quadratic slopes did not converge during model-based estimation, they were dropped and re-run with just intercepts and linear slopes. All models contain intercepts and linear slopes. Results show that our model-based results closely match the model-free results, suggesting the validity of our estimated latent intercepts, linear slopes, and quadratic slopes.

Latent Variable Modeling Produces Accurate Estimates of Acquisition and Extinction Intercepts, Linear Slopes, and Quadratic Slopes

See Figure 1d-f for aggregate results of our model-based estimations of latent intercepts, linear slopes, and quadratic slopes for acquisition and extinction across trials. Also, see Figure 2 for means, standard errors, and individual values of model-based intercepts and slopes. In all cases, the intercepts and linear slopes converged in the models. Additionally, quadratic slopes converged for 1) US expectancy CS+ acquisition, CS+ extinction, and CS- extinction, and 2) SCR CS+ acquisition. We saved all participants' model-estimated intercepts and slopes in the dataset to use in subsequent regressions and structural equation models to predict long-term fear (i.e., extinction test).

Visual inspection of Figure 1 shows that the model-free and model-based results are very similar, suggesting the validity of our model. Additionally, we correlated participants' latent acquisition and extinction intercepts with observed fear averaged across trials 1 and 2 in each phase. We found that the correlations were very high, ranging .732 to .940 (mean = .847): US expectancy (CS+ acquisition: $r = .732$; CS+ extinction: $r = .940$; CS- acquisition: $r = .779$; CS- extinction: $r = .904$), SCR (CS+ acquisition: $r = .879$; CS+ extinction: $r = .844$; CS- acquisition: $r = .799$; CS- extinction: $r = .755$), and startle reflex (CS+ acquisition: $r = .848$; CS+ extinction: $r = .892$; CS- acquisition: $r = .911$; CS- extinction: $r = .882$). Similarly, we correlated participants' latent acquisition and extinction linear slopes with their observed fear across trials 3 and 4 minus the average of trials 1 and 2 in each phase. We found the correlations were moderately positively

correlated, ranging .158 to .719 (mean = .413): US expectancy (CS+ acquisition: $r = .469$; CS+ extinction: $r = .676$; CS- acquisition: $r = .173$; CS- extinction: $r = .719$), SCR (CS+ acquisition: $r = .650$; CS+ extinction: $r = .276$; CS- acquisition: $r = .305$; CS- extinction: $r = .158$), and startle reflex (CS+ acquisition: $r = .301$; CS+ extinction: $r = .387$; CS- acquisition: $r = .388$; CS- extinction: $r = .458$).

Moreover, for all measures of fear, we found significant covariance between the model-based intercept and model-based linear slope for a given CS within a conditioning phase (e.g., covariance of CS+ acquisition intercept and CS+ acquisition linear slope was significant for US expectancy). The correlations between acquisition intercept and linear slope were high in two of three cases for the CS+ (US expectancy: $r = .972$; SCR: $r = .756$, startle reflex: $r = -.941$) and low for the CS- (US expectancy: $r = -.568$; SCR: $r = -.763$, startle reflex: $r = -.715$). The low intercept/linear slope correlation for acquisition CS+ startle reflex should be interpreted with caution, though, since the slope was overall very close to 0, had a very restricted range (range -.039 to -.007), and was highly invariant across participants. This led us to drop CS+ acquisition slope for startle reflex in subsequent models in order to maintain validity of our results. The correlations between extinction intercept and linear slope were low for the CS+ (US expectancy: $r = -.680$; SCR: $r = -.952$, startle reflex: $r = -.742$) and CS- (US expectancy: $r = -.471$; SCR: $r = -.981$, startle reflex: $r = -.674$). Thus, a higher acquisition intercept predicted a higher acquisition slope for the CS+ as measured by US expectancy and SCR (i.e., participants with higher initial fear had a faster acquisition rate), and a higher acquisition intercept predicted a lower acquisition slope for the CS- across all measures. Additionally, a lower extinction intercept predicted a flatter/higher extinction slope across both CSs and all measures (i.e., participants with lower fear

at the start of extinction had a flatter/higher slope, presumably because there was less room to decrease fear).

Figure 2. Means, Standard Errors, and Individual Values of Model-Based Estimates of Acquisition and Extinction Intercepts and Slopes for CS+ and CS-. Bars indicate means, error bars indicate standard error, and dots indicate individual datapoints from participants arranged in ascending order per an empirical cumulative distribution function. All models include an intercept and linear slope; if quadratic slope converged, it was included in figure or otherwise excluded. For startle reflex intercepts, all values were subtracted by 50 from their true values in order to visually scale the figure, but analyses included the true values.

When Alone in Regression, Higher Extinction Linear Slope Predicts Lower Long-Term Fear

First, to conceptually replicate previous experiments examining just CS+ extinction rate in its prediction of long-term CS+ fear (Brown et al., 2017; Bush et al., 2007; King et al., 2017, 2018; Reznikov et al., 2015), we entered extinction rate as the only predictor of extinction test fear in a regression. The results for all three measures of fear indicate that a flatter/higher extinction linear slope predicted less extinction test fear: US expectancy ($\beta = -.316$, $SE = .192$, $t(228) = -5.02$, $p < .001$), SCR ($\beta = -.230$, $SE = 2.050$, $t(213) = -3.45$, $p = .001$), and startle reflex ($\beta = -.242$, $SE = 1.446$, $t(223) = -3.72$, $p < .001$). This result is the opposite of those found in animal studies (Bush et al., 2007; King et al., 2017, 2018; Reznikov et al., 2015), which found that faster extinction rate predicted less extinction test fear.

For specificity, we assessed this with the CS- and found similar but less robust results. Flatter/higher extinction linear slope predicted lower extinction test fear as measured by SCR ($\beta = -.210$, $SE = 2.953$, $t(215) = -3.14$, $p = .002$) and startle reflex ($\beta = -.176$, $SE = 1.538$, $t(223) = -2.66$, $p = .008$) but not US expectancy ($\beta = -.070$, $SE = .294$, $t(222) = -1.04$, $p = .300$).

When Entered in Model with Extinction Intercept, Extinction Linear Slope No Longer Predicts Lower Long-Term Fear, But Higher Extinction Intercept Does

The findings in the previous paragraph could be interpreted to suggest that slower extinction rate predicts lower long-term fear for the CS+ and CS-. However, as stated previously, both acquisition intercept/linear slope and extinction intercept/linear slope were significantly covaried. The data shows that individuals with a lower extinction intercept also have a

flatter/higher slope. Thus, when entering just extinction slope into the model to predict long-term fear, this effect could be significant due to the intercept rather than the slope.

To investigate this, we conducted the same regressions but also included extinction intercept. The results strongly changed with both the CS+ and CS-. For the CS+, with all three measures of fear, extinction linear slope no longer predicted long-term fear: US expectancy ($\beta = -.045$, $SE = .201$, $t(228) = -.68$, $p = .497$), SCR ($\beta = -.217$, $SE = 5.615$, $t(213) = -1.19$, $p = .237$), and startle reflex ($\beta = -.070$, $SE = 1.827$, $t(223) = -.85$, $p = .395$). Instead, higher extinction intercept predicted higher extinction test fear with US expectancy ($\beta = .512$, $SE = .070$, $t(228) = 7.74$, $p < .001$) and startle reflex ($\beta = .272$, $SE = .132$, $t(223) = 3.30$, $p = .001$) but not SCR ($\beta = .014$, $SE = .412$, $t(213) = .08$, $p = .937$). Results were very similar for the CS-. Extinction linear slope did not predict extinction test fear: US expectancy ($\beta = .062$, $SE = .305$, $t(222) = .89$, $p = .373$), SCR ($\beta = -.177$, $SE = 13.578$, $t(215) = -.58$, $p = .565$), and startle reflex ($\beta = -.042$, $SE = 1.717$, $t(223) = -.57$, $p = .569$). Instead, higher extinction intercept predicted higher extinction test fear with US expectancy ($\beta = .335$, $SE = .081$, $t(222) = 4.81$, $p < .001$) and startle reflex ($\beta = .273$, $SE = .126$, $t(223) = 3.70$, $p < .014$) but not SCR ($\beta = .033$, $SE = .737$, $t(215) = .11$, $p = .914$). Thus, it appears that extinction intercept is a stronger predictor of CS+ and CS- long-term fear than extinction rate.

Structural Equation Models with Acquisition and Extinction Intercepts and Linear Slopes

Show that Acquisition Intercept is Strongest Predictor of Long-Term Fear

To further investigate specificity of effects, we included acquisition intercept, acquisition linear slope, extinction intercept, and extinction linear slope in the models in most cases. The only exception was the exclusion of acquisition linear slope for CS+ startle reflex. We did this

because there was very little variability in the estimation of this measure, which compromised its ability to be valid predictors (e.g., standard errors were extremely high when predicting CS+ extinction test startle reflex). Furthermore, to achieve greater validity in our analyses, we transitioned from regressions to structural equation modeling (SEM) in which variables were arranged in chronological order to predict each subsequent variable, ultimately ending with all variables predicting extinction test fear (e.g., acquisition intercept → acquisition linear slope → extinction intercept → extinction linear slope → extinction test fear). This was done separately for the CS+ and CS- for each measure of fear. In our SEM models, all “early” variables were given direct pathways to predict all subsequent variables (e.g., acquisition intercept directly predicted all subsequent variables). Previous experiments had not included or reported the effects of acquisition in predicting extinction test fear (Brown et al., 2017; Bush et al., 2007; King et al., 2017, 2018; Reznikov et al., 2015), which provides our analysis with a more specific evaluation of predictive variables than previous work.

Please see Table 1 for statistical details. Results showed that a higher total effect of acquisition intercept was the most robust predictor of higher extinction test fear for both the CS+ and CS- across all three measures of fear. This was complemented by direct effects of CS+ acquisition intercept predicting extinction test for US expectancy and startle reflex. There was also one significant negative indirect effect of acquisition rate predicting less extinction test US expectancy. Additionally, higher direct and total effects of extinction intercept predicted higher extinction test fear for the CS+ and CS- as measured by US expectancy. Thus, the results suggest that, for both the CS+ and CS-, acquisition intercept and extinction intercept are concurrent predictors of long-term fear with US expectancy, acquisition intercept becomes a predictor with SCR, and acquisition intercept replaces extinction intercept with startle reflex. Extinction rate

was not a significant predictor of extinction test fear with any measure, and acquisition rate had one indirect effect with US expectancy. Thus, the data emphasizes initial fear levels at the beginning of a phase (especially acquisition) in predicting extinction test fear rather than changes in fear levels within acquisition or extinction.²

Table 1. CS+/CS- Acquisition/Extinction Intercepts and Slopes Predicting Extinction Test Fear

CS	Predictor	Effect	US Expectancy					SCR					Startle Reflex				
			β	SE	Z	p	HB	β	SE	Z	p	HB	β	SE	Z	p	HB
CS+	Acq Intercept	Direct	.391	.379	2.38	.017	.025	.083	.270	0.85	.396	.050	.247	.180	2.55	.011	.017
		Indirect	.063	.362	0.40	.689	-	.116	.194	1.67	.096	-	.100	.138	1.35	.177	-
		Total	.454	.136	7.68	<.001	.017	.199	.192	2.87	.004	.050	.346	.117	5.50	<.001	.025
	Acq Slope	Direct	-.149	.796	-0.95	.342	-	.075	.454	0.81	.415	-	-	-	-	-	-
		Indirect	-.177	.371	-2.42	.016	.017	.023	.089	1.28	.201	.025	-	-	-	-	-
		Total	-.326	.843	-1.96	.050	.017	.098	.452	1.07	.284	.025	-	-	-	-	-
	Ext Intercept	Direct	.385	.076	5.41	<.001	.017	-.042	.432	-0.22	.827	.050	.104	.167	1.00	.317	.025
		Indirect	.017	.035	0.51	.607	-	.161	.389	0.93	.351	-	.019	.066	0.47	.641	-
		Total	.402	.068	6.34	<.001	.017	.119	.188	1.43	.152	.025	.123	.154	1.29	.199	.050
	Ext Slope	Direct	-.033	.196	-0.52	.606	-	-.175	5.772	-0.93	.351	-	-.038	1.820	-0.47	.640	-
		Indirect	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Total	same as Direct					same as Direct					same as Direct				
CS-	Acq Intercept	Direct	.170	.092	1.99	.047	.025	.091	.247	0.77	.443	.050	.258	.195	2.35	.019	.017
		Indirect	.075	.064	1.26	.209	-	.139	.202	1.44	.149	-	.092	.160	1.02	.306	-
		Total	.246	.070	3.78	<.001	.025	.230	.144	3.34	.001	.050	.350	.112	5.57	<.001	.017
	Acq Slope	Direct	.048	.545	0.61	.542	-	-.082	2.031	-0.82	.412	-	-.055	2.007	-0.71	.478	-
		Indirect	.063	.192	2.29	.022	.017	.036	.586	1.27	.205	.025	.007	.529	0.34	.738	.050
		Total	.111	.538	1.44	.151	-	-.045	1.970	-0.47	.640	-	-.049	1.944	-0.64	.521	-
	Ext Intercept	Direct	.259	.090	3.33	.001	.017	.014	.764	0.04	.966	.050	.068	.176	0.66	.510	.025
		Indirect	-.021	.037	-0.65	.515	-	.122	.735	0.40	.690	-	.015	.065	0.40	.687	-
		Total	.238	.082	3.36	.001	.017	.136	.209	1.56	.119	.025	.083	.163	0.87	.384	.050
	Ext Slope	Direct	.046	.307	0.65	.513	-	-.126	14.043	-0.40	.690	-	-.029	1.700	-0.40	.686	-
		Indirect	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Total	same as Direct					same as Direct					same as Direct				

Note: Significant results ($p < .05$) in **bold**. Significant results passing Holm-Bonferonni cutoff in gray and **bold**. "HB" = Holm-Bonferonni p-value cutoff. We corrected analyses for the same analysis across the three measures of fear, leading to cutoffs of .017, .025, and .050 in ascending order. "Acq" = acquisition; "Ext" = extinction. Unconditional Stimulus (US) Expectancy rated on 0-9 scale (0="Certain no electric shock," 4.5="Uncertain," and 9="Certain electric shock"), and "SCR" = skin conductance response.

² Studies 1-3 had a between-subjects mood induction condition (positive vs negative) before extinction. We conducted the same SEM analyses but inserted Mood Induction as a predictor before extinction intercept. Across the CS+ and CS- and all three measures of fear, Mood Induction did not have any significant direct, indirect, or total effects in predicting extinction test fear ($ps > .110$). Additionally, we evaluated potential multicollinearity within each model by running regressions including all predictors within a model and assessing the variance inflation factor (VIF; Thompson et al., 2017), where VIFs > 10 may indicate multicollinearity. All VIFs ranged 1.23 to 9.72, except for SCR CS- extinction intercept and extinction slope, which had VIFs of 21.61 and 21.37, respectively (total mean = 4.762). We thus re-ran these analyses excluding either SCR CS- extinction intercept or extinction slope and found that the results did not change (i.e., CS- acquisition intercept continued to significantly predict CS- extinction test SCR, but CS- extinction intercept and extinction linear slope remained non-significant). Thus, for congruency with other analyses, we present the results that include both SCR CS- extinction intercept and extinction slope in the model with the knowledge that results remain the same regardless of whether we include both or exclude one.

Discussion

The present report investigated individual differences in fear from four human fear conditioning studies. We estimated participants' latent acquisition intercept, acquisition slope, extinction intercept, and extinction for the CS+ and CS- for each measure of fear. Our model showed strong convergence with the real data and a wide distribution of estimated values. To conceptually replicate previous studies, we first evaluated the isolated effects of extinction rate on long-term changes in fear (measured one week after acquisition and extinction), hypothesizing that individuals with faster extinction would show less long-term fear. Subsequently, we built upon the previous literature by assessing the specificity of extinction rate by including other fear conditioning variables into the model: we included extinction intercept, and then we included acquisition intercept and acquisition slope. These analyses were conducted using structural equation modeling in which variables predicted each other in chronological fashion. We used a multi-modal approach to the measurement of fear during every trial, including unconditional stimulus (US) expectancy, skin conductance response (SCR), and startle reflex.

When assessed in isolation, our results showed that flatter/higher extinction slope (i.e., slower extinction) predicted less long-term fear with all three measures of fear for the CS+ and with two measures for the CS- (SCR and startle reflex). These results counter previous animal studies (Bush et al., 2007; King et al., 2017; Reznikov et al., 2015), which demonstrated that faster extinction rate predicted less long-term fear. However, flatter/higher extinction rate was significantly covaried with a lower extinction intercept. Thus, we entered extinction intercept into the model and found that extinction rate no longer predicted extinction test fear for the CS+ or CS-; instead, higher extinction intercept predicted higher extinction test fear with US

expectancy and startle reflex for the CS+ and CS- (but not SCR). Thus, the former extinction rate effect seems to be better explained by extinction intercept, ultimately leading to no effect of extinction rate.

We further expanded our extinction analyses to include acquisition intercept and acquisition slope. Results showed that higher acquisition intercept predicted higher extinction test fear with all three measures of fear, and higher extinction intercept predicted higher extinction test with US expectancy. Thus, in our most stringent analyses using acquisition intercept, acquisition slope, extinction intercept, and extinction slope to predict extinction test fear, the results suggest that higher acquisition intercept is the strongest predictor of long-term fear with some unique predictive ability from extinction intercept. This occurred with both the CS+ and CS-. In this latest model, there were no significant effects of extinction rate, and there was one negative indirect effect of acquisition rate with US expectancy. Our results thus emphasize the importance of starting fear (during acquisition and secondarily during extinction) in predicting long-term fear and de-emphasize rates of acquisition or extinction.

It is interesting that extinction rate had no effects above and beyond acquisition intercept, acquisition rate, or extinction intercept. On the one hand, this could suggest that the process of extinction is not critical to long-term fear reduction; on the other hand, it more likely reflects discord between level of fear expressed during extinction and associative mechanisms of inhibitory learning. It has long been recognized that the level of fear expressed during extinction is not an index of long-term learning and that fear at the end of extinction, as demonstrated herein, is not related to fear at test (Plendl & Wotjak, 2010). The same principle may apply to acquisition rate, as well. Interestingly, the effects of acquisition intercept, acquisition slope, extinction intercept, and extinction slope on long-term fear were very consistent between the

CS+ and CS-. This suggests that individuals who have high initial fear to a novel stimulus show elevated fear of that stimulus one week later – regardless of whether the stimulus becomes a danger or safety signal. This is consistent with meta-analyses showing that clinically anxious individuals have elevated fear of the CS+ (acquisition and extinction) and CS- (acquisition) compared to healthy controls (Duits et al., 2015; Lissek et al., 2005). Our results converge with the meta-analyses from a different angle, finding that elevated fear at the start of fear conditioning (rather than trait/clinical anxiety) is a strong predictor of long-term fear within the same task.

Clinically, our null extinction rate findings are consistent with data from exposure therapy – the clinical proxy of extinction – which shows that the amount of within-session fear reduction is not a reliable predictor of long-term fear (Brown et al., 2017; Plendl & Wotjak, 2010) nor necessary for positive outcomes from exposure therapy (Baker et al., 2010; Culver et al., 2012). Our finding that extinction rate is relatively non-predictive of long-term fear is neither supportive nor unsupportive of two major models of exposure therapy: the inhibitory learning model (Craske et al., 2014) and the habituation model (Foa & Kozak, 1986). The inhibitory learning model argues that elevated US expectancy during extinction will result in greater prediction error (and therefore greater long-term extinction learning) (Rescorla & Wagner, 1972), whereas the habituation model argues that fear reduction during extinction will result in greater long-term fear reduction. Thus, the inhibitory model favors elevated US expectancy during exposure (i.e., slower extinction rate), whereas the habituation model favors fear reduction during exposure (i.e., faster extinction rate). Our results suggest that extinction rate altogether is unimportant when assessed alongside initial acquisition fear, acquisition rate, and initial extinction fear, which poses a challenge for both models. One minor caveat from our data

should be interpreted with caution. Our analyses that included only extinction rate in the model suggested that slower extinction rate was predictive of less long-term fear. However, this was likely due to the covariance of extinction intercept and extinction rate, where lower intercept was predictive of flatter/slower extinction rate. When entered in the model together, extinction intercept was the only significant predictor of long-term fear. Even further, when acquisition factors were entered in the model, acquisition intercept became the strongest predictor of long-term fear, followed by extinction intercept. Thus, our results indicate that relatively greater focus in clinical settings could be placed on preventing/mitigating acquisition of fear. For example, the therapist could de-emphasize the rate of fear reduction during exposure and instead focus on and discuss initial fear levels across therapy sessions.

There were a few limitations of the present study. First, while the four studies in this report were largely similar, there were minor differences in methods. Second, three of the studies contained mood inductions between acquisition and extinction, which were not of theoretical interest in the present manuscript. However, analyzing the data with and without the mood induction produced very similar results. Third, acquisition and extinction were conducted on the same day, which may have reduced excitatory learning via “unlearning” mechanisms (Myers et al., 2006) and thus reduced the fear observed one week later at test. Fourth, we chose a baseline correction approach to SCR calculations (Sjouwerman et al., 2021) in which negative SCRs were coded as zeros. This is one of the commonly used SCR techniques in which negative SCRs are coded as zero because they reflect the skin conductance habituation drift (which is typically not of theoretical interest in fear conditioning experiments) and because we used square root transformation of the data, which requires coding negative values as zero (the same limitation occurs with log transformations). However, the frequency with which SCRs using baseline

correction are zero or negative tends to occur in descending order of $CS^- > CS^+ > US$ (Sjouwerman et al., 2021), which was the case in our data, as well (CS^- : 59.71% of trials; CS^+ : 46.83%; US : 3.48%). Despite the potential limitation of this SCR calculation, our SCR results for a) acquisition, extinction, and extinction test, and b) the association of acquisition/extinction intercept/slope with extinction test are cross-validated with the US expectancy and startle reflex measures. This consistency is encouraging and suggests that the SCR results are valid and informative. Lastly, our experiments model a one-week interval between extinction and test. It is unclear how these results would extend over longer periods of time or multiple sessions of extinction, which would be relevant for exposure treatment of anxious individuals.

In conclusion, the present study suggests that fear at the start of acquisition of fear conditioning is the strongest predictor of fear one week later, followed by fear at the start of extinction. Flatter/slower extinction rate initially predicted lower long-term fear when entered in the model alone, which countered previous studies (Bush et al., 2007; King et al., 2017; Reznikov et al., 2015). However, this effect was no longer significant when including extinction intercept or when additionally including acquisition intercept and acquisition slope. These results were consistent across both the CS^+ and CS^- , suggesting that individuals who are initially fearful of a stimulus will be afraid of it later – regardless of whether the stimulus becomes a danger signal or safety signal.

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Conflict of Interest

The authors declare no conflict of interest.