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Title Page

Compound extinction: Using the Rescorla-Wagner model to maximize exposure therapy effects for anxiety disorders

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Abstract

Although exposure therapy is an effective treatment for anxiety disorders, fear sometimes returns following successful therapy. The Rescorla-Wagner model predicts that presenting two fear-provoking stimuli simultaneously (compound extinction) will maximize learning during exposure and reduce the likelihood of relapse. Participants were either presented with single extinction trials only or single extinction trials followed by compound extinction trials. Additionally, participants within each extinction group were randomized to caffeine or placebo ingestion prior to extinction to investigate the mechanism by which compound extinction may maximize learning (enhanced associative change or enhanced responding). Participants presented with compound trials demonstrated significantly less fear responding at spontaneous recovery compared with participants who received single extinction trials only. Ingestion of caffeine also provided some protection from spontaneous recovery (as measured by valence ratings). At the reinstatement test, only compound extinction trials predicted less fear responding; caffeine ingestion prior to extinction did not attenuate reinstatement effects.

Introduction

Although the evidence for the effectiveness of exposure therapy for phobias and anxiety disorders is extensive (e.g., Norton & Price, 2007), fear can sometimes return following successful exposure therapy (e.g., Craske & Mystkowski, 2006). Exposure therapy is believed to be the clinical proxy of extinction training and return of fear (ROF) following exposure therapy is consistent with occasions when a conditional stimulus (CS) re-elicits the conditional fear response (CR) following extinction: if tested in a different context than the extinction context (renewal; Bouton 1993), if tested after time has passed since extinction (spontaneous recovery; Baum, 1988), upon re-exposure to the unconditional stimulus (US) after extinction (reinstatement; Rescorla & Heth, 1975), or if the CS and US occur together again (rapid reacquisition; Kehoe & Macrae, 1997).

These phenomena suggest that extinction is *not* unlearning of the previously learned CS-US association; instead, extinction is hypothesized to involve new inhibitory learning (“CS-no US”) that then competes with the CS-US memory (e.g., Bouton, 1993). Poor retrievability of the CS-no US memory may explain ROF following exposure therapy. One method for reducing ROF is to enhance learning during extinction (i.e., facilitate learning of the CS-no US association) and the Rescorla-Wagner Model (Rescorla & Wagner, 1972) makes specific predictions for accomplishing this. A basic tenet of the model is that learning (during acquisition and extinction) is determined by the amount of surprise, defined as the discrepancy between what is expected to occur and what actually occurs. Surprise is maximized during the first few trials of acquisition or extinction (e.g., the US is especially surprising at the first trial of acquisition when the CS is neutral and expectation of an aversive event is 0). Subsequently, learning greatly

diminishes because expectation becomes closer to reality, thereby minimizing surprise. According to the Rescorla-Wagner model, one way to maximize learning during extinction (and thereby potentially offset ROF) is to repeatedly elevate US-expectancy which provides more opportunities for discrepancy between expectation and reality. This can be achieved by presenting two fear-provoking CSs simultaneously (i.e., compound extinction trials).

However, extant data indicate that compound extinction blocks, rather than enhances, extinction learning in animals (Pineno, Zilski, & Schachtman, 2007) and humans (Vervliet, Vansteenwegen, Hermans, & Eelen, 2007). These results are difficult to explain with elemental models of associative learning (e.g., the Rescorla-Wagner model) but may be explained with configural models of associative learning (e.g., Pearce, 1987) or configural extensions of elemental models (e.g., Rescorla & Wagner, 1972). Elemental models of learning posit that an individual will summate the predictive values of each individual stimulus within a collection of stimuli whereas configural models (e.g., Pearce, 1987), posit that an individual will process a collection of stimuli in a consolidated manner. In the case of compound trials during extinction, according to configural models, any new learning will be in regards to the compound stimulus rather than to each of the individual stimuli which comprise the compound. Thus, it seems that elemental processing of the CSs is required to maximize extinction learning during compound trials and previous studies of compound extinction may have unintentionally induced configural processing of stimuli during extinction, thereby blocking extinction learning regarding each individual CS. One method for facilitating elemental processing

of stimuli may be to present each CS on its own several times during extinction training prior to pairing two CSs together.

There is evidence to support the value of this method for enhancing elemental processing and maximizing extinction learning: Rescorla (2006) demonstrated that, in pigeons and rats, using both an appetitive paradigm (CS paired with food pellet US) and an aversive paradigm (CS paired with foot shock US), extinction learning was optimized when each CS underwent separate extinction and then the two CSs were presented together. Compared with animals that received single extinction trials only, animals that received the sequenced compound extinction trials demonstrated decreased spontaneous recovery and weaker reinstatement. These results have been replicated in a recent study in which rats presented with sequenced compound extinction trials demonstrated decreased spontaneous recovery at 1-week and 4-week follow-up testing compared with rats that received single extinction trials only (Janak & Corbit, 2011). Furthermore, in the study done by Rescorla (2006), the mechanism by which sequenced compound extinction trials enhances learning was also investigated: enhanced associative change (as predicted by the Rescorla-Wagner model) or enhanced responding (since two CSs are presented simultaneously, the organism is predicted to perform the conditional fear response at an enhanced level which can facilitate extinction learning by increasing adrenergic activity which has been shown to promote consolidation of emotional memories, Cain, Blouin, & Barad, 2004). Results indicated that the effectiveness of the sequenced compound trials in enhancing extinction learning was not simply due to elevated responding during extinction but rather due to enhanced associative change.

The present study aimed to investigate whether single CS extinction trials followed by compound CS trials optimizes extinction learning in humans and, if so, whether the results are attributable to enhanced associative change or enhanced responding. Following fear conditioning procedures, participants were randomly assigned to single extinction trials followed by compound extinction trials or single extinction trials only. Participants who received compound trials were hypothesized to demonstrate significantly higher fear responding and elevated US-expectancy throughout extinction but reduced return of fear at the spontaneous recovery and reinstatement tests one week following extinction. Additionally, within each extinction group, participants were randomly assigned to ingest caffeine or placebo prior to extinction training. Given that caffeine indirectly increases adrenergic activity, ingestion of caffeine was expected to elevate fear responding during extinction without increasing US-expectancy. Based on the findings of Rescorla (2006) and the predictions of the Rescorla-Wagner model, it was hypothesized that increased fear responding alone would not attenuate fear recovery at the spontaneous recovery and reinstatement tests. Thus, regardless of drug ingestion, it was predicted that the compound extinction groups would demonstrate less fear responding at spontaneous recovery and reinstatement compared with single extinction groups.

Method

Design

Participants were randomly assigned to one of four experimental groups according to a 2 (Extinction Group: single [S] or compound [C] stimulus trials) x 2 (Drug

Group: caffeine ingestion [C] or placebo ingestion [P]) design. The distribution of participants across the four groups was as follows: SP = 18, CP = 18, SC = 16, CC = 18.

Participants

Seventy participants (49 females, 21 males), with a mean age of 19.2 (range 18 to 23), were recruited through mass testing sessions from several Introduction to Psychology classes. Participants were from a variety of ethnic backgrounds: 32.9% Asian, 32.9% Caucasian, 18.6% Latino, 8.5% Biracial, 4.3% Middle Eastern, 1.4% Arab, 1.4% Indian. Participants were recruited if they: 1) scored in the top quartile of scores on the Behavioral Inhibition Scale (this was done to make the results more generalizable to individuals with a vulnerability to developing anxiety disorders); 2) on average, ingested between 100mg of caffeine per week and 500mg of caffeine per day and 3) were in the average range (18.5-24.9) for Body Mass Index. Exclusion criteria for study participation included 1) any heart, respiratory, or neurological problems, 2) current or a history of seizures, 3) pregnancy, and 4) current ingestion of drugs or medications which can interact with caffeine.

Measures

Self Report Questionnaires

Two self report measures were completed at Baseline: the Behavioral Inhibition Scale (BIS; Carver & White, 1994) and the Beck Depression Inventory (BDI; Beck, Steer, & Brown 1996). The 7-item BIS measures individual differences in the behavioral inhibition system, believed to regulate aversive motives in which the goal is to move away from something unpleasant (Carver & White, 1994). In the current sample, $\alpha = 0.84$. The Beck Depression Inventory is a widely used screening instrument for

depression with strong psychometric properties (e.g., Carmody, 2005). In the current sample, $\alpha = 0.92$.

Subjective Measures

Across all phases of the experiment (acquisition, extinction, and test), participants were asked to rate their expectancy of the scream-US during CS presentations. They were instructed to immediately record US-expectancy at the onset of each CS presentation. This expectancy was rated on a scale between -6 = “certain no noise” to +6 = “certain noise” with a midpoint of 0 = “uncertain.” Participants reported valence ratings for each CS from -50 = “very unpleasant” to +50 = “very pleasant” with a midpoint of 0 = “neutral” at four time points: immediately following acquisition, immediately following extinction, at spontaneous recovery, and following reinstatement.

Physiological Measures

Skin conductance responses (SCRs) were measured using a Biopac MP150 unit running Acqknowledge 4.0 software (Biopac Systems, Inc., Goleta, CA) with a GSR 100C amplifier set to direct current, a sensitivity of 5 $\mu\text{ohm/V}$, and a 1.0-Hz low-pass filter. SCRs were measured at each CS onset and provided a measure of fear arousal. Data were acquired at 200 samples per second.

To measure SCRs, two disposable 1 cm diameter AG-AgCl electrodes were placed on the distal phalanx of the index and middle fingers of the non-dominant hand. The magnitude of SCRs was calculated as the difference between the maximum skin conductance level (measured in microsiemens) within 1–6 seconds following CS onset and the mean skin conductance level within the 2-second period prior to CS onset. Amplitudes were range corrected using the largest response elicited by the US for each

individual participant. To do this, for each participant, SCRs to each US presentation were calculated as the difference between the maximum skin conductance level within 1-6 seconds following US-onset and the mean skin conductance level within the 2-second period prior to CS-onset (the CS which occurred immediately prior to that particular US presentation). For each participant, all SCRs to CSs were divided by that person's maximum SCR to the US. These range-corrected responses were then subjected to a square root transformation in order to normalize the distribution prior to statistical analysis. SCRs were rejected for a given CS presentation if behavioral observations indicated movement, including coughing and sneezing. SCRs were scored as zero for a given CS presentation when there was no observable peak in skin conductance level within 1-6 seconds following CS onset.

Apparatus and Stimuli

Three geometrical shapes (blue circle, red triangle, and green trapezoid) were used as the conditional stimuli (CSs). CSA always appeared on the left side of the screen and CSB always appeared on the right side of the screen; both were paired with the US during acquisition training. CS- always appeared in the middle of the screen and was never paired with the US. Which of the three geometrical shapes served as CSA, CSB, or CS- was counterbalanced across participants. The unconditional stimulus (US) was a 1-second scream presented binaurally through headphones at 82 decibels. Such auditory stimuli have successfully served as USs in previous studies (e.g., Lau et al., 2008). In fact, auditory USs have been found to demonstrate equivalent or superior conditioning effects as shock USs without the risk of causing pain or excessive anxiety (Neumann & Waters, 2006). Across different auditory US stimuli, a scream-US has been found to

produce more robust conditioning effects than a white noise-US (Joos, Vansteenwegen, & Hermans, 2012); thus a scream-US was utilized in the current study. Stimulus delivery was controlled by one computer which presented participants with the CSs and US through E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Physiological data acquisition was controlled by a second computer using Acqknowledge software (Biopac Systems, Inc., Goleta, CA, USA).

Procedure

The experiment consisted of several phases that were completed over the course of two days. Participants were asked to abstain from eating or drinking anything (except water) for 8 hours prior to the first day and were scheduled between 8am and 12pm. A trained research assistant described the study procedures, obtained informed consent, and administered the BIS and BDI. Electrodes for recording SCR were attached. Next, psychophysiological measures were recorded for a five-minute resting period during which participants were instructed to “please sit quietly and remain still” and left alone (the researcher monitored physiological data acquisition in a room adjacent to the experimental room). Next, participants were seated 3 feet in front of a 21” computer monitor placed at eye level which was used to display the CSs. They were asked to put on headphones and told they may sometimes hear a loud noise through the headphones. The researcher then trained participants on the US-expectancy scale and instructed them to rate their expectancy of the noise as soon as each shape appeared on the screen

Experimental phases are shown in Table 1. Across all phases, the CSs were presented in random order with the caveat that no more than two trials of each CS were presented sequentially and the inter-trial interval (ITI) varied across 20, 25, and 30

seconds (mean = 25 seconds). Participants first underwent *habituation*: four 8-second presentations of each CS. Next, participants underwent *acquisition*: eight 8-second presentations of each CS; during the last second of CSA and CSB presentation, the scream-US was presented through the headphones.

Insert Table 1

Following acquisition, participants removed the headphones and provided subjective valence ratings for each CS. Participants were given 4 oz of grapefruit juice which they knew may or may not contain 600 mg of crushed caffeine pills (this dosage was chosen because it has been shown to safely and reliably increase physiological arousal; Zoellner & Craske, 1999). The experimenter was blind to the participant's drug group assignment. Following ingestion of the juice, participants sat for 45 minutes (they were provided with magazines) to allow for optimal absorption of caffeine. Then, another 5-minute baseline was recorded prior to commencement of extinction training. During the *first phase of extinction*, all participants received eight 8-second presentations of CSA, CSB, and CS- without any US presentations. During the *second phase of extinction*, half of the participants within each drug group received eight 8-second trials of CSA while the other half received eight 8-second compound trials during which CSA and CSB appeared simultaneously next to each other on the screen. All participants also received eight 8-second trials of the CS-. Following extinction training, participants provided valence ratings for each CS.

On Day 2, participants provided valence ratings for each CS. Electrodes were then attached again for SCR recording and participants put on the headphones; they were also re-familiarized with the US-expectancy scale. The *test* phase consisted of eight 8-second presentations of CSA and CS-, presented in random order with the caveat that no more than two trials of each CS were presented sequentially and with ITIs ranging across 20, 25, and 30 seconds. Halfway through this test phase (i.e., following four CSA and four CS- presentations), all participants received one scream-US presentation during an intertrial interval (i.e., reinstatement). Upon completion of this phase, participants again provided subjective valence ratings for each CS.

Statistical Analyses

Baseline differences were examined using one-way ANOVAs; effect sizes reported for these analyses are partial eta squared. Regression analyses and their follow-up tests were conducted using hierarchical linear modeling (HLM; Raudenbush & Bryk, 2002). HLM is useful in analyzing repeated measures data (Level 1 data) nested within subjects (Level 2 data; Bryk, Raudenbush, & Congdon, 1996). HLM does not require the assumption of independence of observations, improves the estimate of effects within individual units, and has lower Type I error rates (Raudenbush & Bryk, 2002). HLM is essentially a program that conducts regressions and is capable of including fixed factors (i.e., independent variable) and multiple random factors (e.g., individuals). It was used in this study to examine change across time with repeated measures for each individual. T-tests were used to examine whether y-intercepts of the regression lines were significantly different from zero and whether differences between two regression lines (e.g., regression line for change in SCR to CSA in compound placebo group during extinction versus

regression line for change in SCR to CSA in single placebo group during extinction) were significant. To report effect sizes for these t-tests, Cohen's d was calculated using the following formula: $d = (t^2)/(\text{sqrt}(df))$ where t = t-test value and df = degrees of freedom.

Results

Baseline

The mean BIS score in this sample was 22.61 and the mean BDI score was 7.57. One-way ANOVAs revealed no significant differences among the four groups on the BIS ($F(3,69) = 0.25, p = 0.86, \eta_p^2 = 0.01$) or the BDI ($F(3,69) = 0.63, p = 0.60, \eta_p^2 = 0.03$). There were also no significant differences among the groups on age ($F(3,69) = 1.61, p = 0.20, \eta_p^2 = 0.07$), gender ($\chi^2(3, N = 70) = 5.22 (p = 0.16)$), or ethnicity ($\chi^2(21, N = 70) = 23.23 (p = 0.33)$).

Acquisition

Skin Conductance Response (SCR)

HLM analyses were conducted for SCRs to each conditional stimulus across the eight acquisition trials. For CSA and CSB, the intercept was significantly different from zero (CSA: $b = 0.28, t(61) = 4.60, p < 0.001, d = 1.18$; CSB: $b = 0.24, t(61) = 4.10, p < 0.001, d = 1.05$) indicating all participants demonstrated a skin conductance response higher than zero at the first trial of CSA and CSB. In addition, the slope was significantly different from zero and positive (CSA: $b = 0.03, t(439) = 3.08, p < 0.005, d = 0.29$; CSB: $b = 0.03, t(439) = 2.72, p < 0.01, d = 0.26$), indicating all participants demonstrated a significant increase in SCRs to CSA and CSB across acquisition, demonstrating the effects of fear conditioning. For CS-, the intercept was significantly different from zero ($b = 0.36, t(61) = 4.89, p < 0.001, d = 1.25$) and the slope was

significantly different from zero and negative ($b = -0.05$, $t(439) = -4.26$, $p < 0.001$, $d = 0.41$) indicating all participants demonstrated a significant decline in SCRs to CS- across acquisition. Thus, acquisition training was successful in that participants learned to demonstrate conditional fear responses to CSA and CSB and learned not to be fearful of the CS-.

Expectancy Ratings

HLM analyses were conducted for subjective US-expectancy ratings to each conditional stimulus across the eight acquisition trials. For CSA and CSB, the intercept was not significant indicating participants rated US-expectancy no different than zero (i.e., “uncertain”) at the first trial of CSA and CSB (p -values = 0.4 – 0.9). The slope was significantly different from zero and positive (CSA: $b = 0.49$, $t(355) = 3.03$, $p < 0.005$, $d = 0.32$; CSB ; $b = 0.42$, $t(355) = 2.34$, $p < 0.05$, $d = 0.25$) indicating all participants demonstrated a significant increase in US-expectancy ratings to CSA and CSB across acquisition, demonstrating the effects of fear conditioning. For CS-, there were no significant effects at the intercept and participants demonstrated no change in US-expectancy ratings across acquisition (p -values = 0.2 – 0.8). Thus, acquisition training successfully taught participants to expect the US when presented with CSA or CSB.

Pre-Acquisition Baseline to Pre-Extinction Baseline

A 2 (Drug Group: Placebo, Caffeine) x 2 (Time: Baseline prior to Habituation, Baseline prior to Extinction) ANOVA examined whether ingestion of caffeine impacted mean skin conductance levels during the baseline period. Results indicated a significant Time x Group interaction effect ($F(1,62) = 5.64$, $p < 0.05$, $\eta_p^2 = 0.08$). Tests of simple effects indicated that participants who ingested caffeine demonstrated a significant

increase in mean skin conductance level from pre-acquisition baseline to pre-extinction baseline ($F(1,62) = 9.01, p < 0.005, \eta_p^2 = 0.13$) whereas participants who ingested placebo demonstrated no change in mean skin conductance level ($F(1,62) = 0.13, p = 0.72, \eta_p^2 < 0.001$). Therefore, participants who ingested caffeine demonstrated a significantly higher level of arousal during extinction than participants who did not.

Extinction Phase 1

HLM analyses were conducted for SCRs and US-expectancy ratings during each CS trial across Extinction Phase 1. Participants were divided into caffeine versus placebo groups since drug ingestion was the only difference between participants during this phase.

Skin Conductance Response (SCR)

For CSA, the intercept was significantly different from zero ($b = 0.43, t(61) = 7.84, p < 0.001, d = 2.01$) and there was a significant difference between the caffeine group and the placebo group ($b = -0.14, t(61) = -2.02, p < 0.05, d = 0.52$) such that participants who ingested caffeine demonstrated significantly lower SCRs to CSA at the first trial of extinction compared with participants who ingested placebo. The slope of SCRs to CSA was significantly different from zero ($b = -0.05, t(439) = -6.30, p < 0.001, d = 0.60$) and the group slopes were significantly different from each other ($b = 0.03, t(439) = 3.19, p < 0.005, d = 0.30$) such that participants who ingested caffeine had a significantly flatter slope than those who ingested placebo (i.e., participants who ingested caffeine did not demonstrate a decline in SCRs to CSA across Extinction Phase 1 whereas participants who ingested placebo did demonstrate a decline in SCRs to CSA across this phase; see Figure 1).

For CSB, the intercept was significantly different from zero ($b = 0.40$, $t(61) = 6.09$, $p < 0.001$, $d = 1.56$) but there were no group differences at the intercept ($p = 0.35$). The slope of SCRs to CSB was significantly different from zero ($b = -0.04$, $t(439) = -4.52$, $p < 0.001$, $d = 0.43$) and the group slopes were significantly different from each other ($b = 0.03$, $t(439) = 1.92$, $p = 0.05$, $d = 0.18$) such that those participants who ingested caffeine had a significantly flatter slope than those who ingested placebo (i.e., participants who ingested caffeine did not demonstrate a decline in SCRs to CSB across Extinction Phase 1 whereas participants who ingested placebo did demonstrate a decline in SCRs to CSB across this phase).

For CS-, the intercept was significantly different from zero ($b = 0.24$, $t(61) = 6.13$, $p < 0.001$, $d = 1.57$) and the slope was significantly different from zero ($b = -0.02$, $t(439) = -4.83$, $p < 0.001$, $d = 0.46$) but there were no group differences (p -values = 0.4 – 0.9) indicating all participants demonstrated an SCR higher than zero to CS- at the first trial of Extinction Phase 1 and a significant decline in SCRs to CS- across Extinction Phase 1.

Expectancy Ratings

For CSA, the only significant finding was that the slope was significantly different from zero ($b = -0.23$, $t(488) = -2.25$, $p < 0.05$, $d = 0.20$), indicating all participants demonstrated a significant decline in US-expectancy ratings to CSA across the first phase of extinction (non-significant p -values = 0.4 – 1.0). For CSB, there were no significant findings although the slope approached significance ($b = -0.20$, $t(488) = -1.75$, $p = 0.08$, $d = 0.16$) indicating a decline in US-expectancy ratings to CSB across Extinction Phase 1 (non-significant p -values = 0.3 – 0.9). For CS-, the intercept was significantly different from zero ($b = -2.27$, $t(68) = -4.16$, $p < 0.001$, $d = 1.09$) and the

slope was also significantly different from zero ($b = -0.20$, $t(488) = -2.56$, $p < 0.05$, $d = 0.23$) indicating all participants demonstrated a significant decline in US-expectancy ratings to CS- across the first phase of extinction with no group differences at the intercept or in the slopes (p -values = 0.3 – 0.7).

Change from Extinction Phase 1 to Extinction Phase 2

Skin Conductance Response (SCR)

For CSA, a 4 (Group: SP, CP, SC, CC) x 2 (Time: Extinction Phase 1 Trial 8, Extinction Phase 2 Trial 1) repeated measures ANOVA revealed a significant effect of Time ($F(1,59) = 33.95$, $p < 0.001$, $\eta_p^2 = 0.37$), Group ($F(3,59) = 7.78$, $p < 0.001$, $\eta_p^2 = 0.28$), and Time x Group interaction ($F(3,59) = 9.00$, $p < 0.001$, $\eta_p^2 = 0.31$). CP and CC group participants demonstrated a significant increase in SCR from the last trial of Extinction Phase 1 to the first trial of Extinction Phase 2 (CP: $F(1,59) = 24.58$, $p < 0.001$, $\eta_p^2 = 0.29$; CC: $F(1,59) = 34.96$, $p < 0.001$, $\eta_p^2 = 0.37$) whereas SP and SC group participants did not (SP: $F(1,59) = 0.62$, $p = 0.43$, $\eta_p^2 = 0.01$; SC: $F(1,59) = 0.01$, $p = 0.94$, $\eta_p^2 < 0.001$). Thus, participants in the two compound extinction groups (CP and CC) demonstrated a significant increase in physiological fear response when first presented with the compound stimulus; see Figure 1.

Expectancy Ratings

For CSA, there was a significant effect of Time ($F(1,66) = 9.73$, $p < 0.005$, $\eta_p^2 = 0.13$) and Time x Group interaction ($F(3,66) = 5.68$, $p < 0.005$, $\eta_p^2 = 0.21$). CP and CC group participants demonstrated a significant increase in US-expectancy ratings from the last trial of Extinction Phase 1 to the first trial of Extinction Phase 2 (CP: $F(1,66) = 20.50$, $p < 0.001$, $\eta_p^2 = 0.24$; CC: $F(1,66) = 6.46$, $p < 0.05$, $\eta_p^2 = 0.10$) whereas SP and SC

group participants did not (SP: $F(1,59) = 0.03$, $p = 0.87$, $\eta_p^2 < 0.001$; SC: $F(1,59) = 0.71$, $p = 0.40$, $\eta_p^2 = 0.01$). Thus, participants in the two compound extinction groups (CP and CC) demonstrated a significant increase in US-expectancy rating when first presented with the compound stimulus.

Insert Figure 1

Extinction Phase 2

HLM analyses were conducted for SCRs and US-expectancy ratings during each CS trial across Extinction Phase 2.

Skin Conductance Response (SCR): CSA

For CSA, the intercept was significantly different from zero ($b = 0.18$, $t(61) = 2.54$, $p = 0.01$, $d = 0.65$) and there were significant group differences at this intercept ($b = 0.14$, $t(61) = 3.27$, $p < 0.005$, $d = 0.84$). There was no significant slope effect ($p = 0.34$) but there were significant group slope differences ($b = -0.01$, $t(439) = -2.60$, $p = 0.01$, $d = 0.25$). To more closely examine these group differences, pairwise HLM analyses were conducted.

SP versus CP: What is the impact of compound trials on extinction?

The intercept was not significantly different from zero ($p = 0.17$) but there were significant group differences at the intercept ($b = 0.64$, $t(29) = 5.14$, $p < 0.001$, $d = 1.91$) indicating CP group participants demonstrated a significantly higher SCR at the first trial of the second phase of extinction than SP group participants. There was no significant slope effect ($p = 0.14$) but there were significant group slope difference ($b = -0.05$, $t(215)$

= -2.69, $p < 0.01$, $d = 0.37$) indicating CP had a significantly steeper negative slope than SP. Thus, participants in the Compound Placebo group demonstrated significantly higher physiological fear responses to CSAB at the start of Extinction Phase 2 than Single Placebo group participants did to CSA and CP group participants demonstrated a steeper decline in SCRs to CSAB across this phase than did SP group participants to CSA.

SP versus SC: What is the impact of caffeine on extinction?

The intercept was not significantly different from zero ($p = 0.17$) but there were significant group difference at the intercept ($b = 0.07$, $t(30) = 2.01$, $p = 0.05$, $d = 0.73$) indicating SC group participants demonstrated a significantly higher SCR at the first trial of the second phase of extinction than SP group participants. Therefore, participants in the Single Caffeine group demonstrated significantly higher physiological fear responses to CSA at the start of Extinction Phase 2 than did Single Placebo group participants. There was no significant slope effect ($p = 0.14$) and no significant group slope differences ($p = 0.79$).

SC versus CC: What is the impact of caffeine on the difference between single and compound trials during extinction?

The intercept was significantly different from zero ($b = -0.78$, $t(30) = -2.57$, $p < 0.05$, $d = 0.94$) and there was a significant difference between the groups ($b = 0.48$, $t(30) = 3.58$, $p = 0.001$, $d = 1.31$) indicating CC group participants demonstrated a significantly higher SCR at the first trial of the second phase of extinction than SC group participants. Similarly, the slope was significantly different from zero ($b = 0.14$, $t(222) = 3.43$, $p < 0.001$, $d = 0.46$) and there was a significant difference between the groups ($b = -0.07$, $t(222) = -3.75$, $p < 0.001$, $d = 0.50$) indicating CC had a significantly steeper negative

slope than SC. Similar to the differences between groups CP and SP, Compound Caffeine group participants demonstrated significantly elevated physiological fear responses to CSAB at the start of Extinction Phase 2 than Single Caffeine group participants did to CSA and CC group participants demonstrated a steeper decline in SCRs to CSAB across this phase than did SC group participants to CSA.

Skin Conductance Response (SCR): CS-

For CS-, the intercept was significantly different from zero ($b = 0.12$, $t(61) = 2.66$, $p = 0.01$, $d = 0.68$) and there were significant group differences at this intercept ($b = 0.06$, $t(61) = 2.52$, $p < 0.05$, $d = 0.65$). There was no significant slope effect ($p = 0.72$) and no significant group slope differences ($p = 0.23$). To more closely examine the group differences at the intercept, pairwise HLM analyses were conducted.

SP versus CP: What is the impact of compound trials?

There were no significant findings for the intercept, group differences at the intercept, slope effect, or group slope differences (p -values = 0.1 – 0.7). Thus, there were no differences between Single Placebo and Compound Placebo group participants in physiological fear responding to CS- during Extinction Phase 2.

SP versus SC: What is the impact of caffeine?

The only significant finding was group difference at the intercept ($b = 0.16$, $t(30) = 3.27$, $p < 0.005$, $d = 1.19$) indicating SC group participants demonstrated a significantly higher SCR to CS- at the first trial of the second phase of extinction than SP group participants. Thus, Single Caffeine group participants demonstrated significantly higher physiological fear responses to CS- at the start of Extinction Phase 2 compared to Single

Placebo group participants. There were no significant effects for the intercept, slope, or group slope differences (p-values = 0.1 – 0.4).

SC versus CC: What is the impact of caffeine on the difference between single and compound trials?

The intercept was significantly different from zero ($b = 0.70$, $t(30) = 2.37$, $p < 0.05$, $d = 0.87$) but there were no significant group differences at the intercept ($p = 0.14$), indicating participants in both groups demonstrated SCRs higher than zero to CS- at the first trial of Extinction Phase 2. There was no significant slope effect ($p = 0.21$) and no significant group slope differences ($p = 0.41$). Thus, there were no differences between Single Caffeine and Compound Caffeine group participants in physiological fear responding to CS- during Extinction Phase 2.

Expectancy Ratings: CSA

For CSA, the intercept (i.e., the US-expectancy rating at the first trial of the second phase of extinction training) was significantly different from zero ($b = 1.41$, $t(68) = -2.18$, $p < 0.05$, $d = 0.53$) but there were no significant group differences ($p = 0.30$). The slope was significantly different from zero ($b = -0.27$, $t(488) = -2.84$, $p = 0.005$, $d = 0.26$) but there were no group slope differences ($p = 0.53$). Although this analysis did not reveal a significant group difference at the intercept, given the a priori hypothesis that compound versus single trials would have an impact on expectancy ratings, pairwise HLM analyses were conducted.

SP versus CP: What is the impact of compound trials on extinction?

Analyses revealed no significant intercept effect, group differences at the intercept, or slope effect (p-values = 0.1 – 0.2). However, there was a significant group

slope difference ($b = 0.52$, $t(250) = -3.59$, $p < 0.001$, $d = 0.45$) indicating that CP group participants had a significantly steeper negative slope than SP group participants. So, participants in the Compound Placebo group demonstrated a significantly greater decline in US-expectancy ratings (to CSAB) across Extinction Phase 2 than did Single Placebo group participants (to CSA).

SP versus SC: What is the impact of caffeine?

Analyses revealed no significant findings indicating no group differences between groups Single Placebo and Single Caffeine in US-expectancy ratings to CSA across Extinction Phase 2 (p -values = 0.1 – 1.0).

SC versus CC: What is the impact of caffeine on the difference between single and compound trials?

Analyses revealed that the intercept was significantly different from zero ($b = -9.13$, $t(32) = -2.54$, $p < 0.05$, $d = 0.90$) and there was a significant difference between the groups ($b = 3.28$, $t(32) = 2.35$, $p < 0.05$, $d = 0.83$), indicating that the mean expectancy ratings reported by CC group participants was significantly higher than reported by SC group participants. Thus, participants in the Compound Caffeine group reported significantly higher US-expectancy ratings to CSAB at the start of Extinction Phase 2 than did Single Caffeine group participants to CSA. There was no significant slope effect and no significant group slope differences (p -values = 0.1 – 0.3).

Expectancy Ratings: CS-

For CS-, the intercept was significantly different from zero in the negative direction ($b = -3.56$, $t(68) = -5.63$, $p < 0.001$, $d = 1.36$). There were no significant findings for group differences at the intercept, slope, or group slope differences (p -values

= 0.3 – 0.4). Pairwise HLM analyses also indicated the intercept was significantly different from zero in the negative direction (SP versus CP: $b = -3.30$, $t(34) = -4.26$, $p < 0.001$, $d = 1.46$; SP versus SC: $b = -3.30$, $t(32) = -4.26$, $p < 0.001$, $d = 1.51$; SC versus CC: $b = 0.70$, $t(30) = 2.37$, $p < 0.05$, $d = 0.87$). There were no group differences at the intercept, no significant slope effect, and no group slope differences (p -values = 0.2 – 0.7). Therefore, all participants provided US-expectancy ratings significantly negative from zero to CS- during Extinction Phase 2, indicating they did not expect to experience the US when presented with CS-.

Change from Endpoint of Extinction to Spontaneous Recovery Test

Skin Conductance Response (SCR)

For CSA, a 4 (Group: SP, CP, SC, CC) x 2 (Time: End of Extinction, Spontaneous Recovery Test) repeated measures ANOVA revealed a significant effect of Time ($F(1,59) = 13.64$, $p < 0.001$, $\eta_p^2 = 0.19$), Group ($F(3,59) = 3.31$, $p < 0.05$, $\eta_p^2 = 0.14$), and their interaction ($F(3,59) = 6.01$, $p = 0.001$, $\eta_p^2 = 0.23$). SP group participants demonstrated a significant increase in SCR from End of Extinction to Spontaneous Recovery ($F(1,59) = 27.94$, $p < 0.001$, $\eta_p^2 = 0.32$) whereas CP, SC, and CC group participants did not (CP: $F(1,59) = 0.29$, $p = 0.59$, $\eta_p^2 = 0.01$; SC: $F(1,59) = 3.12$, $p = 0.08$, $\eta_p^2 = 0.05$; CC: $F(1,59) = 0.91$, $p = 0.34$, $\eta_p^2 = 0.02$). So, participants in the Single Placebo group demonstrated significant spontaneous recovery of a previously extinguished physiological fear response while participants in the remaining three groups did not.

Expectancy Ratings

For CSA, Time was significant ($F(1,66) = 24.68, p < 0.001, \eta_p^2 = 0.27$) indicating all participants demonstrated a significant increase in US-expectancy ratings from End of Extinction to Spontaneous Recovery (Group: $F(3,66) = 2.06, p = 0.11, \eta_p^2 = 0.09$; Time x Group: $F(3,66) = 0.98, p = 0.41, \eta_p^2 = 0.04$). Thus, all participants demonstrated significant spontaneous recovery of a previously extinguished subjective fear response as measured by US-expectancy ratings.

Spontaneous Recovery Test

Skin Conductance Response (SCR)

A one-way ANOVA revealed a significant effect of Group at the first trial of CSA at one-week follow-up ($F(3,61) = 6.21, p = 0.001, \eta_p^2 = 0.19$; Figure 2). A series of independent-samples t-tests revealed that SCR was significantly higher in SP than CP ($t(30) = 4.67, p < 0.001, r = 0.65$) and in SP than CC ($t(30) = 2.78, p < 0.01, r = 0.45$). SP versus SC and SC versus CC revealed no significant differences (p-values = 0.1 – 0.3).

A one-way ANOVA revealed a significant effect of Group at the first trial of CS- at one-week follow-up ($F(3,63) = 2.68, p = 0.05, \eta_p^2 = 0.18$). A series of independent-samples t-tests revealed that SCR was significantly higher in SP than CP ($t(29) = 2.80, p < 0.01, r = 0.46$) and in SP than CC ($t(30) = 2.09, p < 0.05, r = 0.36$). SP versus SC and SC versus CC revealed no significant differences (p-values = 0.3 – 0.4).

Insert Figure 2

Expectancy Ratings

One-way ANOVAs revealed no significant Group effect at the first trial of CSA (Figure 3) or at the first trial of CS- at one-week follow-up (p-values = 0.4 – 0.8).

Valence Ratings

A one-way ANOVA revealed a significant effect of Group at one-week follow-up ($F(3,65) = 3.32, p < 0.05, \eta_p^2 = 0.13$). CSA was rated significantly more unpleasant in SP than CP ($t(34) = -2.69, p = 0.01, d = 0.92$) and in SP than SC ($t(31) = -2.79, p < 0.01, d = 1.00$). There was a trend for CSA to be rated more unpleasant in SP than CC ($t(34) = -1.93, p = 0.06, d = 0.66$). SC versus CC revealed no significant differences ($p = 0.25$). For CSB and CS-, there were no significant findings (p-values = 0.4 – 0.5).

Insert Figure 3

Reinstatement Test

Skin Conductance Response (SCR)

For CSA, a one-way ANOVA revealed a significant effect of Group at the first trial following reinstatement ($F(3,65) = 3.42, p < 0.05, \eta_p^2 = 0.18$; Figure 2). A series of independent-samples t-tests revealed that SCR was higher in SP than CP ($t(30) = 3.13, p < 0.005, d = 1.14$). For CS-, a one-way ANOVA revealed a nonsignificant trend towards a Group effect at the first trial following reinstatement ($F(3,63) = 2.40, p = 0.08, \eta_p^2 = 0.11$).

Expectancy Ratings

For CSA, there was a significant effect of Group at the first trial following reinstatement ($F(3,69) = 3.51, p < 0.05, \eta_p^2 = 0.14$; Figure 3). Independent samples t-test

revealed that expectancy ratings were significantly higher in SP than CP ($t(34) = 2.87, p < 0.01, d = 0.98$) and in CP than CC ($t(34) = -2.89, p < 0.01, d = 0.99$). SP versus SC and SC versus CC revealed no differences (p -values = 0.2 – 0.3). For CS-, there were no group differences ($F(3,69) = 1.70, p = 0.18, \eta_p^2 = 0.07$).

Discussion

This study tested the hypothesis that compound stimulus presentations during extinction would enhance extinction learning and lead to less recovery of conditional fear responding at spontaneous recovery and reinstatement tests. The mechanism was hypothesized to be enhanced discrepancy between expectation and reality (i.e., enhanced associative change) rather than enhanced conditional responding during extinction. As such, ingestion of caffeine was hypothesized to have no impact on recovery of fear. These results largely supported the study hypotheses.

Spontaneous Recovery

The impact of compound extinction trials

At spontaneous recovery, the Compound Placebo group demonstrated significantly lower fear arousal (i.e., SCRs) to CSA than Single Placebo, even though fear responding remained more elevated in the Compound Placebo group during extinction. This was also demonstrated in the difference from the end of extinction to spontaneous recovery: Single Placebo group participants demonstrated significant recovery of physiological fear responding whereas Compound Placebo group participants did not. Furthermore, Compound Caffeine demonstrated significantly less fear arousal (i.e., SCRs) to CSA at spontaneous recovery than did Single Placebo. Thus, regardless of drug group assignment, participants presented with compound trials during extinction

demonstrated significantly less physiological conditional fear responding to CSA than participants in the Single Placebo group at the one-week spontaneous recovery test.

Subjective valence ratings provided further evidence for the effectiveness of compound extinction trials in attenuating fear recovery. Compound Placebo group participants rated CSA as significantly less aversive at spontaneous recovery than did Single Placebo group participants. Compound Caffeine group participants also rated CSA as less aversive than Single Placebo participants although this trend did not quite reach significance.

US-expectancy data, however, did not converge with skin conductance and valence rating results. There is a body of literature indicating that subjective expectancy ratings sometimes do not converge with physiological indices of fear responding (McAndrew, Jones, McLaren, & McLaren, 2012). Most likely, this is due to expectancy ratings being influenced by a myriad of cognitive factors (e.g., Tune, 1964) whereas physiological indices are not. For example, participants may have based US-expectancy ratings at spontaneous recovery on a belief such as “I know this shape was paired with the sound last time; so, this time, maybe the other shape will be paired with the sound.”

In summary, both skin conductance responses and subjective valence ratings indicated compound extinction trials provided protection from spontaneous recovery effects one week following extinction training. This is consistent with findings reported by Rescorla (2006) and extends those findings to humans.

The impact of caffeine

Interestingly, valence ratings indicated some benefit to ingesting caffeine prior to extinction training: Single Caffeine group participants rated CSA as significantly less

aversive than Single Placebo group participants at spontaneous recovery. Caffeine ingestion led to enhanced conditional fear arousal during extinction; therefore, as predicted by the findings of Cain and colleagues (2004), enhanced fear responding (i.e., increased adrenergic activity) alone during extinction may enhance consolidation of extinction memories and thereby provide some protection against spontaneous recovery effects. However, there were no effects of SCR or US expectancy ratings.

Reinstatement

At the reinstatement test, among those who did not ingest caffeine, participants presented with compound extinction trials demonstrated significantly less conditional fear responding to CSA (as measured by skin conductance responses and US-expectancy ratings) than participants presented with single extinction trials only. Among those who ingested caffeine, there were no differences between compound and single extinction groups. Interestingly, Compound Placebo group participants demonstrated significantly lower US-expectancy ratings at reinstatement than Compound Caffeine participants. Taken together, these findings indicate that compound trials during extinction protected against reinstatement effects whereas ingestion of caffeine provided no protection against reinstatement.

Fear Responding to CS-

Group differences in fear responding to CS- at spontaneous recovery and reinstatement were unexpected and interesting. At spontaneous recovery, SCRs to CS- were significantly lower in both compound extinction groups than in the Single Placebo group. At reinstatement, SCRs to CS- were significantly lower in the Compound Placebo group than in both of the single extinction groups; furthermore, Compound Placebo

group participants demonstrated significantly lower US-expectancy to CS- than Single Placebo participants. Taken together, these findings indicate that compound extinction trials predicted lower fear responding to safety signals at one-week follow-up testing. A possible explanation for this derives from predictions of the Rescorla-Wagner model that each CS is comprised of several elements and there are shared common elements between stimuli. Thus, when two shape-CSs (CSA and CSB) were paired with the US, common elements shared between CSA, CSB, and CS- also became associated with the US eliciting some fear responding to the CS-. Participants in this study did indeed demonstrate some fear responding to CS- (although much greater responding to CSA and CSB). During extinction, it was logistically impossible to equate number of extinction trials, spacing of extinction trials, and stimuli presented between the compound and single groups; thus, participants in the compound extinction groups received twice as many CSB presentations during extinction. Therefore, any shared elements between CSB and CS- underwent twice as many extinction trials in the compound groups than in the single extinction groups which may explain the differences in fear responding to CS- at test.

Conclusion

Overall, these findings suggest that compound stimulus presentations during extinction enhance learning and provide protection from spontaneous recovery and reinstatement effects. In addition, enhanced associative change appears to largely explain the findings rather than enhanced fear responding alone since caffeine ingestion prior to extinction training provided limited protection against spontaneous recovery (only as measured by subjective valence ratings) and no protection against reinstatement. Thus,

compound extinction trials appear to enhance extinction learning by increasing expectancy of an aversive outcome which maximizes the discrepancy between expectation and reality, thereby driving learning as predicted by the Rescorla-Wagner model.

The current study yielded different results from a previous study of compound extinction in humans in which extinction learning was blocked when participants were presented with compound trials (Vervliet et al., 2007). Participants in that study may have processed the compound extinction trials as a new stimulus as predicted by configural models of learning (Pearce, 1987). In contrast, participants in the current study were first presented with single extinction trials of each CS+ shape before the two shapes were paired together for compound trials in an effort to activate elemental processing of the stimuli. At the conclusion of the study, participants in the compound extinction groups all stated they experienced the compound trials as two of the old shapes appearing together (i.e., they processed the compound trials elementally). Therefore, presenting fearful stimuli individually first prior to pairing them together seems imperative. These results are also in line with a body of literature demonstrating that additional extinction of a CS exhibiting any type of fear restoration deepens extinction learning (e.g., Hendry, 1982; Rescorla, 2006; Leung & Westbrook, 2012). It seems that any method for increasing expectancy of an aversive outcome during extinction provides opportunity for further learning regarding the CS-no US relationship and compound extinction trials are one technique for doing so.

Limitations

One potential limitation is that BIS scores were not as elevated as in individuals with anxiety disorders, perhaps making the results less generalizable to those with a vulnerability to develop anxiety disorders. However, BIS scores were still elevated above the mean reported in nonanxious samples and participants in this sample demonstrated significant fear conditioning indicating the results of extinction training should be relevant in enhancing the effectiveness of exposure therapy. A second possible limitation is that the US may not be as aversive as are the unconditional stimuli in the context of anxiety disorders. However, participants demonstrated significant physiological fear responding to the US indicating it was sufficiently aversive.

Clinical Implications

These results suggest the effects of exposure treatments for anxiety disorders may be enhanced if individuals are first exposed to one fear-provoking stimulus at a time and then exposed to two fear-provoking stimuli in compound. For example, in the treatment of panic disorder, individuals often conduct exposures to internal cues of panic attacks, then external cues of panic attacks, and then both simultaneously (e.g., Craske & Barlow, 2007). The current investigation provides a rationale for the effectiveness of such a paradigm. This can be done in the treatment of other anxiety disorders as well. For example, in exposure treatment for post-traumatic stress disorder, treatment effects should be enhanced by completing exposure to the trauma memory, exposure to situational reminders of the trauma, and then the combination of exposure to the trauma memory in the presence of situational reminders to the trauma. It will be important for future studies to replicate the findings reported here and to investigate whether compound stimulus presentations during exposure enhances treatment effectiveness in clinical

samples. More generally, these results indicate that exposure therapy may benefit from any method which restores fear responding to the anxiety-provoking stimuli and then subjects this restored fear to additional exposure therapy. This will be an important line of future research, especially given that it is quite different from how exposure therapy is traditionally conducted.

Future Directions

The most important future studies following from the results presented here would be to investigate whether sequenced compound stimulus presentations enhance the effectiveness of exposure therapy for anxiety disorders. This could easily be investigated in a sample of patients with Social Anxiety Disorder, Posttraumatic Stress Disorder, Panic Disorder, or Obsessive-Compulsive Disorder (OCD). For example, in a sample of patients with Panic Disorder, one group could be randomly assigned to complete exposures to interoceptive cues of panic attacks and separate exposures to external cues of panic attacks but never complete exposures to these cues in compound. The second group of patients would be randomly assigned to complete separate exposures to interoceptive cues, external cues, and then the two in compound. Comparing these groups on measures of Panic Disorder symptoms at post-treatment as well as follow-up assessments (ideally 3-month intervals for up to 18 months post-treatment) would indicate whether sequenced compound exposures truly predict better treatment outcomes. Additionally, patients could be assigned to ingest caffeine or placebo prior to exposures in order to assess the mechanism by which compound exposures enhance treatment effects, if they do.

Another line of important research would be to investigate the effectiveness of sequenced compound exposure when the two stimuli presented in compound do not predict the same aversive outcome. For example, a patient with OCD may have contamination-related feared stimuli such as doorknobs (i.e., the CSs) in which the feared aversive outcome (i.e., the US) is contracting an illness and accident-related feared stimuli such as checking the stove multiple times prior to leaving their home in which the feared aversive outcome is accidentally causing a fire. In this case, the USs are different: contracting an illness and causing a fire. It would be important to investigate whether sequenced compound exposures optimize treatment effects here. In the current investigation as well as all other investigations of compound extinction, the USs have been identical. According to the Rescorla-Wagner model, compound exposure is effective because presenting the fear-provoking stimuli in compound enhances expectation of the US which enhances discrepancy between expectation and reality thereby driving learning. It is not clear what happens when the USs are different. Presumably, compound exposure may still enhance treatment effects because expectation of an aversive event (regardless of what that event is) is enhanced when multiple fear-provoking stimuli are present simultaneously; however, it would be important for future studies to investigate this.

In sum, the most important future studies based on these results would investigate whether or not sequenced compound exposures can increase response rates and decrease relapse rates in the treatment of anxiety disorders. Such studies would provide vitally important information to clinicians regarding the ideal method for designing exposure exercises for their patients.

Authorship

All authors collaboratively developed the study concept and contributed to the study design. Development of the procedures manual, recruitment of subjects, data collection, and data analysis were performed by N.C.C. Data interpretation was performed by N.C.C. under the supervision of M.G.C. and with important contributions from B.V. N.C.C. drafted the paper and M.G.C. provided critical revisions. All authors approved the final version of the paper for submission.

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Table/Figure Captions

Table 1: Experimental phases completed during Day 1 and Day 2.

Figure 1: Slopes of skin conductance responses to CSA or CSAB across extinction. During Extinction Phase 1, participants were divided into Caffeine versus Placebo groups since drug ingestion is the only difference between participants during this phase.

Figure 2: Skin conductance responses to CSA at the spontaneous recovery and reinstatement tests.

Figure 3: Expectancy Ratings to CSA at the spontaneous recovery and reinstatement tests.