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Who is studied in de novo fear conditioning paradigms? An examination of demographic and stimulus characteristics predicting fear learning

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ABSTRACT

A common challenge in fear conditioning studies is that a relatively large proportion of individuals fail to acquire a differential conditioned skin conductance response (SCR). Researchers have identified demographic factors associated with poorer fear learning and explored the use of different fear conditioning paradigms across various populations. However, few studies have strategically aimed to enhance acquisition by manipulating the unconditioned stimulus (UCS). In the current manuscript, we examined whether demographic factors predicted failure to condition (n = 274) and explored whether modifications to the UCS enhanced fear learning (n = 143). Results indicated that race, but not age, education, or gender, predicted failure to condition. Stepwise logistic regression demonstrated that race was the most influential of these predictors; African Americans were less likely to acquire a conditioned SCR, compared to non-African Americans. Also, use of a compound UCS (i.e., electric shock combined with a scream noise) led to nearly double the rate of acquisition of a conditioned SCR. Hence, use of a compound UCS may provide a way to reduce the number of excluded individuals in studies of fear-conditioned SCR and thereby improve the representativeness of research samples.

1. Introduction

De novo fear conditioning is a commonly used procedure for investigating the etiology, maintenance, and treatment of anxiety disorders (Milad et al., 2014). In this procedure, a neutral stimulus (conditioned stimulus; CS+) is repeatedly paired with an aversive stimulus, such as a mild, electric shock (unconditioned stimulus; UCS), during acquisition. Evidence of successful conditioning is demonstrated when presentation of the CS+ produces a conditioned response, such as an increase in skin conductance (SC), when the UCS is no longer presented. This is often evaluated by comparing the magnitude of SC responses (SCRs) to the CS+ with SCRs to a stimulus (CS−) never paired with the UCS.

The fact that a substantial percentage of individuals fail to acquire a conditioned SCR is a challenging issue for fear conditioning researchers. At times, the rate of failure can approach 60% or more of the sample (e.g., Asthana et al., 2016: 19%; Fricchione et al., 2016: 53%; Guastella et al., 2007: 55%; Johnson and Casey, 2015: 37%; Otto et al., 2014: 43%; Schiller et al., 2013: 60%; Steinfurth et al., 2014: 50%; for review, Lonsdorf et al., 2017). This makes subject recruitment more difficult and limits representativeness of samples. Acquisition of conditioned fear responses can vary as a function of participant characteristics, with evidence for significantly decreased conditioned differential SCR among those with less education (Rosenbaum et al., 2015). Race is an additional factor, as lower rates of conditioned SCRs have been observed for African American, compared to non-African American, participants (Kredlow et al., 2017).

Meta-analyses suggest that the type of aversive stimulus (e.g., loud noise, aversive odor, painful pressure to the finger) used as the UCS does not significantly affect acquisition of a conditioned fear response (Lissek et al., 2005). However, comparisons between studies may mask specific interactive effects between populations and the aversive stimulus used as the UCS. For example, Lissek et al. (2008) found that using critical facial and verbal feedback as the UCS resulted in conditioned fear in social phobic, but not healthy individuals. This finding presumably reflects greater emotional sensitivity to the UCS in the socially anxious sample. Studies with children have used loud sounds, unpleasant photographs, and air puffs as UCSs, as ethical concerns preclude the use of more aversive stimuli (e.g., shock; Lau et al., 2008). Such alternative UCSs may tend to provoke minimal fear and thereby make conditioned responses more challenging to achieve. For this reason, Lau et al. (2008) developed and tested a protocol that involved the pairing of a facial photograph with a shrieking scream noise as the UCS, positing that this compound stimulus would be more effective and

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ecologically valid. The compound (face-scream) UCS produced better differential fear conditioning than other single UCSs (e.g., air puff, loud sounds, aversive pictures alone) in healthy and anxious children. In addition, Lau et al. (2008) found that the face-scream UCS was well tolerated as assessed by dropout rates.

Thus, the use of a compound, compared to a single, UCS may improve conditioning without increasing dropout rates. This strategy could be applied to adults by adding an additional UCS to that typically used (i.e., electric shock) in order to enhance conditioning. Another UCS variation that could enhance conditioning, but has not been explored, is the manipulation of shock duration. Although shock is the most common UCS used in fear conditioning studies, there is no standard guidance on shock duration (Lonsdorf et al., 2017) and studies vary considerably in durations used (e.g., Kredlow et al., 2016). To our knowledge, no studies have examined whether variations in shock duration impact conditioning.

In the current study, we examine whether previously identified demographic factors (Rosenbaum et al., 2015; Kredlow et al., 2017) would predict failure to acquire a differential conditioned SCR and whether enhancing the UCS by combining it with a secondary UCS or increasing its duration would influence acquisition of a differential conditioned SCR. We hypothesized that using a compound UCS and lengthening the UCS duration would both increase the acquisition of differential conditioned SCRs.

2. Methods

2.1. Participants

Participants consisted of healthy adults recruited from the Boston University undergraduate population ($n = 112$) and the community ($n = 42$), and anxious adults recruited from the community and a treatment clinic ($n = 137$). Individuals were excluded if they were taking medications that potentially could influence SC or conditioned fear. Specifically, individuals taking anticholinergic medications, clonidine, or benzodiazepines; and individuals not on a stable dose, or on an as-needed dose, of other psychotropic medications were excluded. Individuals with medical conditions that contraindicated fear conditioning procedures (e.g., severe heart disease, pregnancy) were also excluded. In addition, anxious participants were required to have greater than mild-to-moderate anxiety symptom severity as assessed by a Beck Anxiety Inventory score (Beck and Steer, 1990) above 15, or score on the Fear Questionnaire above 37 (Marks and Matthews, 1979). Anxious participants were also excluded if they: 1) met DSM-5 criteria for past or present bipolar or psychotic disorder, or substance-related disorder in the last three months (other than caffeine or nicotine use disorder); 2) endorsed current suicidality, homicidality, or self-destructive acts or urges; or 3) engaged in exposure therapy the week prior to, or during, study procedures. Participants were asked to refrain from caffeine and nicotine use for two hours prior to their study visits.

2.2. Study design

All procedures were approved by the Boston University Institutional Review Board. Participants completed a brief screening interview; eligible individuals then provided informed consent. Healthy participants were randomized to one of four fear-conditioning procedures as represented by a 2×2 factorial combination of shock duration and presence of a compound UCS: 1) a 500-msec shock ($n = 39$); 2) a 1000-msec shock ($n = 38$); 3) a 500-msec shock and concurrent scream noise ($n = 38$); or 4) a 1000-msec shock and concurrent scream noise ($n = 39$). All anxious participants received fear-conditioning with a 500-msec shock and concurrent scream noise as the UCS. Hence, only the healthy participants who were randomized to one of the four conditions contributed to the analyses of UCS characteristics. All participants contributed to analyses of demographic predictors of conditioning; anxiety status was used as a covariate. All other aspects of the assessment procedure were the same across participant groups as described below.

2.3. Fear conditioning procedures

2.3.1. Conditioned stimuli

Colored shapes (CS+ yellow circle, CS− white square for all participants) were used as the conditioned stimuli. The shapes were displayed on a computer monitor positioned 4 ft in front of the participant.

2.3.2. Unconditioned stimuli

The electric shock was set to an intensity level that the participant deemed to be “highly annoying but not painful” (0.2–4.0 mA) using the duration (500-msec or 1000-msec) that corresponded with the participant's randomization. Consistent with prior studies (e.g., Orr et al., 2000; Otto et al., 2007), the technician gave the following instructions: “For this experiment, you will set your own level of electric stimulation. You should choose a level that is highly annoying but not painful. I will start the electric stimulation at a very low level and gradually increase the level until you say “stop.” The level that you set for the electric stimulation will then be used throughout the remainder of the experiment.” The shock was generated by a Coulbourn Transcutaneous Aversive Finger Stimulator (Coulbourn Instruments, 2016) and delivered through electrodes attached to the second and third fingers of the participant's dominant hand. The scream noise was obtained from a lab which conducted fear conditioning studies in children with anxiety (Lau et al., 2008). The scream was 95 dB, 1 s in duration, and delivered by the experimenter manually through headphones at approximately the same time as the shock during acquisition. The scream noise was not used during the shock intensity selection procedures.

2.3.3. Conditioning context

All procedures took place in a sound-attenuated and electronically-shielded room. Participants were read a standard set of instructions that indicated that they “may or may not” see colored shapes and “may or may not” receive electric stimulation and/or hear an uncomfortable noise. Participants were attached to the shock electrodes and wore headphones throughout the experiment regardless of their randomization group. Participants were instructed to pay attention to the computer screen and try to figure out the relationship between the visually presented stimuli and the electric stimulation/noise.

2.3.4. Conditioning procedure

Participants completed a 5-min baseline recording period followed by habituation, which consisted of 5 CS+ and 5 CS− unreinforced presentations. Following habituation, the acquisition procedure consisted of 10 CS+ and 10 CS− presentations. Stimulus presentations were pseudorandom with no more than two consecutive presentations of the same stimulus type. The CS duration was 8 s and the inter-trial interval was 11 ± 1 s. Acquisition followed a 60% partial-reinforcement schedule, i.e., 6 of the 10 CS+ presentations were followed by the shock. For Groups 3 and 4, the concurrent scream noise was played on 5 of the 6 reinforced trials. The scream stimulus was presented on only 5, rather than all 6, of the reinforced trials in order to add an element of unpredictability, which has also been shown to enhance conditioning (Vansteenwegen et al., 2008).