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Multiple fear-related stimuli enhance physiological arousal during extinction and reduce physiological arousal to novel stimuli and the threat conditioned stimulus

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Exposure therapy is a first line treatment of anxiety disorders, yet not all anxious individuals benefit in the short- or long-term highlighting a need for improvement. Whereas fears generalize easily to perceptually similar stimuli, fear extinction learning may not. Inclusion of multiple stimuli during extinction might enhance extinction retention, generalization of extinction learning to other novel stimuli, and fear reduction. Thirty-four unselected adults completed differential conditioning and extinction training in which one dog image conditional stimulus (CS+) was paired with an unconditional stimulus (US) (growl + scream), while a second dog image (CS-) was presented alone. During extinction, the Multiple group was exposed to unreinforced presentations of CS+ and CS- and two new dog images (i.e., M1; M2). The Control group was exposed to unreinforced CS+ and CS- matched on CS trial spacing to the Multiple group. During a generalization test, two new dog images were presented to both groups: GS Dog_Sim shared physical features with the CSs (encountered by both groups during extinction) and M2 (encountered only by the Multiple group during extinction), whereas GS Dog_Diff had distinctive physical features. During the extinction retest phase, the original CSs were presented unreinforced to both groups. During extinction, the Multiple group exhibited larger SCRs to both CSs compared to the Control group. During the generalization test, SCRs to GS Dog_Diff did not differ between groups, however, SCRs to GS Dog_Sim were smaller in the Multiple group than the Control group. SCRs were larger to GS Dog_Sim than GS Dog_Diff in the Control group whereas the inverse was found in the Multiple group. During the extinction retest, the Control group exhibited larger SCRs to the CS + than to the CS- whereas there was no significant difference in the Multiple group. The Multiple group rated both CSs as more unpleasant compared to the Control group after extinction, the generalization test phase and the extinction retest phase. Exposure to multiple stimuli enhanced generalized physiological arousal during extinction, yet reduced physiological arousal during subsequent exposure to novel stimuli and re-exposure to the CS+. Negative evaluations of both CSs seemed resistant to extinction with multiple feared stimuli, however, post-phase CS ratings may invoke recall of enhanced arousal during extinction and trial-by-trial CS evaluations should be assessed. Results suggest that multiple stimuli during exposure therapy may reduce physiological arousal to novel stimuli and the original feared stimulus after treatment.

1. Introduction

Anxiety disorders are among the most common and debilitating disorders with prevalence rates suggesting between 28 and 33% of people are likely to experience an anxiety disorder during their lifetime (Baxter, Scott, Vos, & Whiteford, 2013; Kessler et al., 2005, 2012). Anxiety disorders are highly comorbid and when untreated can lead to significant impairment (Goetzel, Hawkins, Ozminkowski, & Shaohung, 2003; Kessler et al., 1997; 2012). Exposure-based cognitive-behavioural therapy is a first line psychological treatment for anxiety disorders (James, James, Cowdrey, Soler, & Choke, 2015; Saavedra, Silverman, Morgan-Lopez, & Kurtines, 2010). Exposure therapy involves repeated and prolonged exposure to a feared stimulus in order to violate outcome expectancies, eliminate negative evaluations, and reduce fear (Craske

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et al., 2008; 2014). However, positive treatment-outcome rates hover around 60% and approximately half of those individuals who experience a successful post-treatment outcome are likely to relapse over time (Ginsburg et al., 2014; Loerinc et al., 2015). These findings highlight the need for further research to improve short- and long-term treatment outcomes.

Learning theories provide the dominant framework for understanding the development and treatment of anxiety disorders. They propose that anxiety develops via a number of learning-related pathways one of which is classical conditioning (Rachman, 1977). A fear response is induced in classical conditioning by pairing a neutral conditional stimulus (CS+; e.g., a shape) with an aversive unconditioned stimulus (US; e.g., a scream). Initially the CS does not elicit an emotional reaction. However, after repeated pairings of the CS and the US, this CS will elicit a conditioned response (CR), which may be characterised by increases in self-reported anxiety or in physiological responses such as skin conductance responses, relative to a control stimulus that was presented alone (CS-; e.g., Waters, Henry, & Neumann, 2009).

Research examining fear learning in anxious and non-anxious individuals suggests that pathological anxiety is associated with enhanced responding to the CS+ in single cue paradigms as well as a tendency to generalize fear responding to stimuli similar to the conditioned fear cue, including the CS-(e.g., Duits et al., 2015; Lissek, Powers, McClure, Phelps, Woldehawariat & Grillon, 2005; Pearce, 1987). For example, stimuli that share physical characteristics with the CS + can evoke a certain extent of conditioned responding (e.g., Lissek, Biggs, Rabin, Cornwell, Alvarez & Pine, 2008; Vervliet, Kindt, Vansteenwegen, & Hermans, 2010; Vervliet, Vansteenwegen, & Eelen, 2004; Vervliet, Vansteenwegen, Baeyens, Hermans, & Eelen, 2005). This generalization of fear can complicate psychological treatments. Extinction-based treatments involve repeated exposures to fear-evoking stimuli (i.e., the CS+) until fear declines (Lissek & Grillon, 2008). Exposure techniques are highly efficacious but previous research has shown that whereas acquisition of conditioned fear generalizes easily over perceptually similar stimuli, extinction of fear may not (e.g., Vervliet et al., 2005; Vervliet, Kindt, Vansteeenwegen, & Hermans, 2010).

Numerous studies have examined the generalization of fear extinction learning to other stimuli by including stimuli that are perceptually and/or conceptually similar to the CS+ during extinction, i.e., generalization stimuli (GSs) (e.g., Lissek & Grillon, 2008; Pappens, Schroijen, Van den Bergh, & Van Diest, 2015; Vervliet et al., 2010, 2005; Vervoort, Vervliet, Bennett, & Baeyens, 2014). For example, following an acquisition phase involving one shape (CS+) paired with shock and a second shape (CS-) presented alone, participants assigned to the extinction control group received four presentations each of the original CS+ and CS- without the US. The generalization group received four presentations of each of two GSs (GS1; GS2, without the US) and no presentations of the original CS+ and CS- (Vervliet et al., 2005). Generalization stimuli were categorically and perceptually similar to the CS+ and CS- (i.e., shapes). No differences were found between the groups during extinction. However, during test with the original CSs, the generalization group showed increased responding to the CS + compared to the CS- which was not observed in the extinction control group. Similar results have been found in studies of categorical fear extinction generalization, whereby fear to the original CS + did not decline following extinction with stimuli that were categorically similar to the CS+ (e.g., Vervoort et al., 2014). Thus, when the CS + *itself* is extinguished, extinction learning appears to persist with no differences between CSs observed at test. However, repeated presentation of stimuli that are perceptually or conceptually *similar* to the CS+ during extinction (in absence of the CS+) does not significantly reduce fear of the CS+. These differences have important practical implications given that exposure therapy is almost always conducted with generalization stimuli and not the original CS+.

It is also noteworthy that these studies assessed the generalization of fear extinction in test phases that included only the original CSs, but not novel stimuli that were distinct from the original CSs and GSs used during extinction (e.g., Pappens et al., 2015; Vervliet et al., 2005; 2010). Other studies that have examined fear extinction generalization to novel stimuli have found mixed evidence. Some have documented smaller responses to the CS+ and increasingly larger responses to GSs of increasing dissimilarity (e.g., Bass & Hull, 1934; Hovland, 1937; Myers & Davis, 2007) whereas other studies have found no evidence of extinction generalization as a function of stimulus similarity (e.g., Pappens et al., 2015). Furthermore, clinical analogue studies that compared responding to novel stimuli and the original CSs after exposure to either multiple feared stimuli (akin to multiple GSs) or the same feared stimulus (akin to a single GS given the original CS+ was not included in either condition) have found increased physiological and emotional reactivity during extinction, enhanced extinction generalization (i.e., less fear responding to novel stimuli post-extinction), and enhanced extinction retention (i.e., less fear responding to the original test stimulus) in the multiple stimulus group. For example, Rowe and Craske (1998) found more fear across exposure trials and a trend towards higher anxiety post-treatment in response to the original test spider, but also less fear to a novel spider in spider phobic adults exposed to four different spider stimuli during extinction compared to repeated exposure to the same spider. Similarly, Shiban, Schelhorn, Pauli, and Mühlberger (2015) found that exposure to multiple compared to a single spider stimulus produced stronger short- and long-term fear reductions.

It has been proposed that exposure to multiple feared stimuli during extinction/exposure therapy might enhance variability in emotional responding and sustain arousal and engagement during exposure sessions which may enhance extinction learning (e.g., Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Waters, Potter, Jamesion, Bradley, & Mogg, 2015). The precise mechanism(s) underlying increased reactivity during extinction/exposure therapy are unclear. Presenting multiple feared stimuli during extinction might increase arousal by facilitating attention and elaborative stimulus processing. This, in turn, may enhance learning that a wide array of stimuli that are directly (CS+) and indirectly (GSs due to CS + similarity but no direct conditioning) associated with threat (i.e., the US) are associated with safety (i.e., US absence; Waters & Craske, 2016). Thus, presenting multiple and varied stimuli might be one avenue for making learning during extinction more salient and memorable (cf. Bjork & Bjork, 1992), thereby strengthening the likelihood of retrieval of extinction memories and reduced fear upon subsequent exposure to novel stimuli (i.e., generalization test) or the original CS+ (i.e., extinction retest).

The present study aimed to determine the effects of conducting extinction trials with multiple stimuli (the original CSs and novel GSs) relative to extinction with the original CSs only on the generalization of extinction learning to novel stimuli and reactivity upon re-exposure to the original CSs. We tested the hypothesis that extinction training with multiple stimuli (i.e., CSs and GSs; Multiple condition) relative to extinction-*as*-usual with the original CSs only (Control condition) would (a) enhance physiological arousal (as indexed by skin conductance responses; SCRs) and emotional reactivity (as indexed by subjective anxiety ratings and CS evaluations) during extinction, and in turn, (b) result in lower physiological arousal and emotional reactivity to a new GS that is perceptually more similar to the original CSs and the extinction stimuli relative to a new GS that is perceptually more distinct to the extinction stimuli, and (c) result in lower physiological arousal and emotional reactivity to the original CS + at extinction retest. To enhance ecological validity and because abstract shape stimuli evoke low level processing in comparison to real life stimuli (Dunsmoor & Murphy, 2015) we utilised dog images as the CSs and GSs and an aversive growl coupled with a scream as the US.