

To Avoid or Not to Avoid: The Role of Neuroticism and Trauma, Predictability Information, and
Hormones on Fear Generalization

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Abstract

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Fear generalization is a key construct for understanding why some individuals struggle to feel safe in objectively non-threatening situations. Although fear is generally adaptive, danger cues can proliferate when conditioned fear spreads to similar but innocuous stimuli (Lissek, 2012). Individuals with higher neuroticism are more likely to react negatively to stressful life events (Uliaszek et al., 2009) and a combination of high neuroticism and trauma exposure may confer greater risk for fear overgeneralization (Parslaw, Jorm, Christiansen, 2006). Increasing the availability of predictability information decreases stress (Grillon et al., 2008; 2009), and manipulating the content of such information (e.g. danger versus safety information) may influence appraisals of ambiguous generalization stimuli. Additionally, women are disproportionately affected by anxiety-based disorders (McLean, Asnaani, Litz, & Hoffman,

2011), and low estradiol hormone levels have been implicated as a possible risk factor for maladaptive fear responding (Glover, Jovanovic, & Norrholm, 2011). Seventy-seven women, selected for either high stress load (high neuroticism + trauma exposure) or low stress load (low neuroticism + no trauma exposure), underwent a fear acquisition and generalization task. Using the well-established "Screaming Lady" paradigm (Lau et al., 2008), two female neutral faces served as conditioned danger (CS+) and safety (CS-) cues, the former paired and the latter unpaired with a loud scream paired with a fearful face (unconditioned stimulus; US). Participants were then randomized to receive either danger or safety cue predictability information. The spread of fear to generalization stimuli (GS 1-4), which consisted of female faces morphed on a continuum between conditioned danger and safety, was measured via online risk ratings of GS and behavioral avoidance of GS. Salivary levels of estradiol and progesterone were measured prior to the fear generalization task. As expected, individuals with high stress load showed overgeneralized fear and avoidance patterns to the most ambiguous stimuli at the end of the task, pointing towards effects of high neuroticism and trauma exposure on the *persistence* of overgeneralized responding. The provision of safety cue information protected low stress load individuals from overgeneralized avoidance of ambiguous stimuli, but did not alter responding for the high stress load individuals. The present study highlights clinical implications for optimizing current treatments, exploring the potential utility of safety cue information, and proactively increasing resilience and preventing future psychopathology by strategically targeting preclinical transdiagnostic factors, such as neuroticism, that increase vulnerability for overgeneralized fear responding after negative life events.

Introduction

Although fear is a remarkably adaptive response to threat, fear can be maladaptive when it persists even though danger does not. Fear overgeneralization, a tendency to extend conditioned fear responses to stimuli that resemble conditioned danger cues but are objectively not dangerous, represents one avenue for maladaptive fear responding. Although the capacity to broadly generalize fear is considered to be functionally adaptive, as organisms are more likely to survive by learning to avoid potentially dangerous stimuli (e.g., Mineka, 1992), fear generalization that is overly broad may lead to excessive threat detection, even in the face of innocuous cues (Dunsmoor, Mitroff, & LaBar, 2009).

Fear generalization can be conceptualized on a generalization gradient, where a conditioned fear response spreads to increasingly dissimilar stimuli (Armony, Servan-Schreiber, Romanski, Cohen, & LeDoux, 1997; Lissek et al., 2008). Whereas classical conditioning (Pavlov, 1927) may lead a woman who is assaulted by a man to fear that man following an attack, fear generalization may lead that same woman to also fear other cues, such as men with similar physical characteristics, men in general, or even all people. This overgeneralization of fear may prevent her from interacting with others and leaving her house and may lead to functional impairment and diminished quality of life. Thus, fear generalization has been proposed as an underlying process potentially driving exacerbated fear responding in anxiety-based mental disorders (e.g., Lissek, 2012). Indeed, anxious individuals may react fearfully to stimuli that do not in fact signal danger but bear resemblance to conditioned danger cues, leading to a proliferation of danger cues and an inability to identify and utilize safety signals (e.g., Jovanovic et al. 2010).

Although generalization has been well documented within the animal literature (e.g., McLaren & Mackintosh, 2002; Pavlov, 1927; Pearce, 1987), the study of fear generalization in humans has only recently grown in the past decade (see Dunsmoor & Paz, 2015; Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2014). A well-established fear generalization paradigm uses ten rings of gradually increasing size as conditioned stimuli and generalization stimuli (Lissek et al., 2008), where the largest or smallest rings serve as the conditioned danger cue (CS+) or conditioned safety cue (CS-), the former paired and the latter unpaired with an aversive unconditioned stimulus (US). Generalization stimuli (GS), represented by eight intermediately sized rings forming a continuum of similarity between the CS+ and CS-, create the generalization gradient. Using this paradigm, patients with anxiety-based disorders, such as panic disorder (Lissek et al., 2010) and generalized anxiety disorder (GAD; Lissek et al., 2014b), social anxiety disorder (Ahrens et al., 2016), and posttraumatic stress disorder (PTSD; Morey et al., 2015; Thome et al., 2017), relative to healthy controls, consistently show fear overgeneralization. Consistent with this, higher self-reported state and trait anxiety have been associated with poorer discrimination between CS+ and GS that closely approximate CS+ (Haddad, Pritchett, Lissek, & Lau, 2012b) and with specific brain activation patterns that look similar to patterns observed with impaired fear acquisition and extinction (Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011). Fear generalization is often indexed by the steepness of a generalization gradient as stimuli become increasingly dissimilar to the CS+, with healthy participants producing steep quadratic decreases in fear, as opposed to anxious participants who produce flatter, shallower, linear decreases in fear, indicative of greater generalization to stimuli resembling the CS+ (Lissek et al., 2008).

Fear generalization has been tested with a variety of stimuli, including faces (e.g., Dunsmoor et al., 2009; Garcia & Zoellner, 2017; Glenn, Lieberman, & Hajcak, 2012), shapes (e.g., Lissek et al., 2008), sounds (Norrholm et al., 2014), and colors (Dunsmoor & LaBar, 2013). Furthermore, fear generalization has been shown to spread both perceptually and conceptually, with studies showing generalization across categories (e.g., animals; Dunsmoor, Martin, & LaBar, 2012) and semantic meaning (e.g., “broth” to “soup”; Boyle, Roche, Dymond, & Hermans, 2015). Neural activation patterns using these tasks mirror fear generalization gradients, with showing a positive gradient in the bilateral insula to stimuli approximating CS+ and a negative gradient in the ventromedial prefrontal cortex to stimuli approximating CS- (Dunsmoor, White, & LaBar, 2011; Lissek et al., 2014a). There are also fear generalization theories that emphasize the role of the hippocampus in pattern completion versus pattern separation, wherein an excitatory conditioned response occurs in response to sufficient overlap between a GS and CS+ while an inhibitory response occurs with insufficient overlap (Gluck & Myers, 1993; Lange et al., 2017). Accordingly, fear generalization may engage a similar brain network underlying fear learning and fear inhibition processes (Dymond et al., 2014). Overall, this breadth of research points to fear generalization as a robust phenomenon with strong effects observed across different stimuli and paradigms.

Personality traits may be critical to the understanding of fear generalization. Neuroticism, a personality trait associated with an increased tendency to experience negative, distressing emotions in response to threat, loss, and frustration (Lahey, 2009), is robustly associated with a variety of mental and physical health problems, including anxiety and mood disorders (Lahey, 2009; Maluoff, Thorsteinsson, & Schutte, 2005, Watson, Gamez, & Simms 2005). Neuroticism is thought to be a highly heritable personality trait that is also influenced by some of the same

genes associated with clinical anxiety and features of depression (Hettema et al., 2006; Abdellaoui et al., 2018). Genetic contributions of neuroticism are estimated to predict between 40% and 60% of the variance in the expression of the trait (Bouchard & Loehlin, 2001; Clark, Watson, & Mineka, 1994; Kendler, Prescott, Myers, & Neale, 2003), with evidence that neuroticism remains relatively stable in adulthood after it emerges in childhood (Eaton, Krueger, & Oltmanns, 2011; Roberts & Mroczek, 2008). Neurobiological studies in samples with high neuroticism show genetically mediated hyper excitability to threatening stimuli and difficulty downregulating arousal in the absence of threat, also supporting the notion that neuroticism has a strong genetic component (Keightley et al., 2003; Stein, Simmons, Feinstein, & Paulus, 2007; Westlye, Bjornebekk, Grydeland, Fjell, & Walhovd, 2011, Pezawas et al., 2005). Of particular interest to the study of fear generalization, which involves the spread of conditioned fear to novel stimuli containing elements of both danger and safety cues, neuroticism increases the likelihood of experiencing negative affect in response to uncertainty and ambiguity (Barlow, Sauer-Zavela, Carl, Bullis, & Ellard, 2013). Consistent with this, Lommen, Engelhard, and van den Hout (2010) found that individuals with high levels of neuroticism were more likely to avoid generalization stimuli after a fear conditioning task compared to participants with low neuroticism. This suggests that neuroticism may prompt individuals to take more of a “better safe than sorry” approach, by using a lower threshold for detecting danger when confronted with ambiguous stimuli (Lommen et al., 2010). This may reflect interpretation and judgment biases wherein, according to signal detection theory, individuals with higher neuroticism are simply willing to accept false alarms in order to avoid missing danger signals (Calvo & Castillo, 2001; Eysenck & Derakshan, 1997; Eysenck, MacLeod, & Mathews, 1987). Although a recent study did not find a strong relationship between neuroticism and higher fear generalization

(Arnaudova, Kryptos, Effting, Kindt, & Beckers 2017), they did find that high neuroticism was associated with higher stimulus recognition, possibly reflecting higher vigilance during the task. It has also been proposed that some fear generalization paradigms may suffer from an overly “strong situation” (Lissek, Pine, & Grillon, 2006; Pittig, Treanor, LeBeau, & Craske, 2018), wherein group differences fail to emerge due to robust learning and limited individual variability. Still, other studies have found associations between fear generalization and neuroticism-related constructs such as trait anxiety (Wong and Lovibond, 2018) and distress endurance (van Meurs Wiggert, Wicker, & Lissek, 2014). Thus, trait neuroticism may affect fear overgeneralization.

Neuroticism, however, would likely have little impact on mental health outcomes in the absence of a strong association between higher neuroticism and more frequent and intense negative reactions to stressful life events (Lahey, 2009). Indeed, individuals with high levels of neuroticism are both more likely to experience stressful events (e.g., Kendler, Gardner, & Prescott, 2003; Suls & Martin, 2005) and more likely to develop anxiety and depression in response to negative life events (e.g., Parslaw, Jorm, Christiansen, 2006; Uliaszek et al., 2009). In fact, Barlow and colleagues (2014) theorize that neuroticism likely arises out of a combination of genetic factors, which make individuals susceptible to hyper reactivity to stress, paired with environmental life stress or trauma, particularly at critical developmental stages (Gunnar & Quevedo, 2007; Lanius, Frewen, Vermetten, & Yehuda, 2010). Extended to the trauma literature, Parslaw and colleagues (2006), in a large prospective epidemiological study, found that higher neuroticism prior to a natural disaster was strongly associated with higher PTSD symptoms and contributed significantly to overall symptom severity. This is consistent with emerging research showing fear overgeneralization in samples with PTSD (Morey et al., 2015, Thome et al., 2017) and the presence of classic symptoms of generalized fear in PTSD, such as responding with

strong emotional and physiological arousal to cues that merely bring to mind or bear resemblance to the trauma (Pole, 2007). This overgeneralization of fear responding, and often subsequent avoidance of generalized, non-dangerous trauma-related cues, can be detrimental for trauma survivors due to the propagation of fear caused by not only innocuous CSs present at the time of the trauma but also related generalization stimuli (GS) not present at the time of the trauma (US). However, the notion that trauma is a necessary but not sufficient condition for developing PTSD captures the importance of genetic, biological, or otherwise heritable conditions that provide an important context for that stressful life events (Dell’Osso & Carmassi, 2011). In fact, a term *p factor* has been coined (Caspi et al., 2014) that represents general psychopathology and is believed to have strong genetic and environmental components, including neuroticism. This p factor also further highlights the potential importance of transdiagnostic examinations of common factors, such as neuroticism, consistent with a growing recognition of the need in the field towards looking across mental disorders, using a variety of units of analysis, and paying closer attention to uncovering complex etiologies of phenotypes (Cuthbert, 2014; Sanislow et al., 2010). According to Caspi and colleagues (2014), “uncovering the etiology of p factor will require measurements across genetic, neural, cognitive, and environmental domains” (p. 17). Thus, exploring the combination of heritable and environmental factors, such as trait neuroticism and prior trauma exposure, represent an important future direction for fear generalization research.

The degree to which individuals feel they can predict outcomes may buffer stress for individuals prone to anxious responding. Animals not only prefer predictable over unpredictable US (e.g., shock) but experience worse physiological and behavioral outcomes in the context of unpredictable stressors than when stressors are predictable (Mineka & Kihlstrom, 1978).

Unpredictable threat has been associated with increased anxiety, behavioral avoidance, and startle response in healthy samples (Grillon, Baas, Cornwell, & Johnson, 2006) and with higher anxiety symptoms in clinical samples (Grillon et al., 2008; 2009). Although instrumental fear learning represents one avenue for acquiring predictability information via fear-relevant associations, Rachman (1977) posited other indirect pathways such as verbal instructions, such as with parental warnings and news reports of dangerous situations (Pittig et al., 2018). In fact, verbal transmission of threat can cause fearful behavior of novel stimuli in children (Field, 2006; Field, & Lawson, 2003); and verbal instructions about a CS-US contingency can provide sufficient conditions for fear acquisition in adults (e.g., Bublatzky et al., 2017, 2014; Olsson & Phelps, 2007; Schmitz & Grillon, 2012). Consistent with this, several studies have demonstrated comparable fear learning acquired through direct versus indirect experiences (Olsson & Phelps, 2004; Raes et al., 2014; Mertens et al., 2015), such that receiving predictability information appears to be an effective way of acquiring fear. Furthermore, communication of negative or threatening information can bias fear-related appraisals (e.g., Barrett, Rapee, Dadds, & Ryan, 1996; Field & Lester, 2010; Muris, Zwol, Huijding, & Mayer, 2010) and anxiety levels can be manipulated by training individuals to interpret ambiguous situations in either threatening or non-threatening ways (Mathews & Mackintosh, 2000). In fact, training individuals to interpret inherently ambiguous situations more positively has been shown to reduce anxiety in adults in healthy and clinically anxious samples (Murphy, Hirsch, Mathews, Smith, & Clark, 2007; Beard & Amir, 2008). Interpretation information about danger versus safety cues may be especially relevant to the construct of fear generalization, as generalization stimuli are by definition ambiguous and susceptible to various threat potential appraisals. Consistent with this, instructional manipulations have been shown to impact the generalization of conditioned fear

(Vervliet et al., 2010), even after controlling for direct learning via fear acquisition (Ahmed & Lovibond, 2015), suggesting that fear learning may be a complex process that involves both direct learning experiences as well as higher-order cognitive rules or beliefs about a CS-US relationship. Additionally, enhancing stimulus discrimination by training participants to detect perceptual differences between danger and safety cues mitigated fear generalization (Ginat-Frolich, Klein, Katz, & Shechner, 2017; Lommen et al., 2017). Although there is controversy in the literature regarding the utility of safety information in extinguishing fear (e.g., Craske et al., 2008), some argue that the strategic and judicious use of safety information can help individuals to adaptively appraise threat and generalize that learning (e.g., Levy & Radomsky, 2014). A critical review of the effects of safety behaviors highlights the possibility of safety information in facilitating approach behavior, promoting an individual's sense of control, and generalizing non-threat associations and inhibitory learning (see Blakey & Abramowitz, 2016). Therefore, it is very likely that manipulating the content of predictability information, specifically about predictors of danger or safety via relevant instructions, may differentially impact the spread of fear.

Another important factor that may predict fear generalization is sex hormones. Estradiol and progesterone, specifically, have been implicated in fear learning processes across both rodent and human research (see reviews Garcia, Walker, & Zoellner, 2018; Glover, Jovanovic, & Norrholm, 2015; Maeng & Milad, 2015). In rodents, extinction recall is superior when female rats undergo extinction in the proestrus phase, when estradiol and progesterone are high (e.g., Chang et al., 2009), and inferior during the metestrus phase, when estradiol and progesterone are low (e.g., Chang et al., 2009; Milad, Igoe, Lebron-Milad, & Novales, 2009; Rey, Lipps, & Shansky, 2014). In humans, women with higher estradiol exhibit better fear extinction recall

compared to women with lower estradiol (e.g., Graham & Milad, 2013; Milad et al., 2010; Zeidan et al., 2011). In addition to hormonal effects, menstrual phase effects may also be associated with fear learning, such that the women in the early follicular phase, characterized by low estradiol and progesterone, exhibit poorer fear inhibition compared to women in the luteal menstrual phase when estradiol and progesterone are higher (Glover, 2013; Pineles et al., 2016). Estrogen receptors are abundantly expressed in the hippocampus (Weiser, Foradori, & Handa, 2008), a brain region involved in fear learning processes, consistent with theories that estradiol may function by increasing consolidation and expression of extinction learning memory (Milad & Quirk, 2012; Sotres-Bayon, Sierra-Mercado, Pardilla-Delgado, & Quirk, 2012). Although there is increasing interest in examining naturally fluctuating levels of sex hormones such as estradiol and progesterone in the context of related fear learning constructs such as fear acquisition (e.g., Inslicht et al., 2013), fear inhibition (Glover et al., 2013), fear extinction (Glover et al., 2012; Merz et al., 2012), and fear extinction recall (e.g., Graham & Milad, 2013; Milad et al., 2010; Zeidan et al., 2011), there are no studies to date examining these hormones in fear generalization. This is a particularly important area of research given that women are disproportionately affected by anxiety and traumatic stressor related disorders (Kessler et al., 1995; McLean, Asnaani, Litz, & Hoffman, 2011) and experience longer courses of illness and higher functional impairment than men (e.g., Breslau et al., 1998; McLean & Anderson, 2009; McLean et al., 2011). Although men also have fluctuating levels of sex hormones, their relatively low and stable levels of estradiol and progesterone and higher levels of testosterone complicate sex-based comparisons (Milad et al., 2010). Thus, effects of estradiol and progesterone on fear learning may be better examined in samples with women with higher and lower hormone levels, or at different menstrual phases, than in samples comparing women to men.

Recently, Garcia and Zoellner (2017) used a novel fear generalization paradigm to examine the interaction between neuroticism and predictability on the generalization of fear. Participants with varying levels of neuroticism were randomized to high and low predictability conditions, where participants in the high predictability condition were given explicit information about the US, and participants in the low predictability condition were simply left to figure out the US contingency on their own. This manipulation was designed to examine the effect of increasing predictability of danger and whether it buffered or exacerbated anxious arousal. Individuals with higher neuroticism who received predictability information reported higher risk ratings of, and greater attentional bias toward, the most ambiguous stimuli on the generalization gradient than individuals with lower neuroticism. Even when stimuli were safer and were rated as such, individuals with higher neuroticism who received predictability information showed stronger attentional bias toward neutral not previously presented stimuli than individuals with lower neuroticism, demonstrating hypervigilance even in the presence of safety cues. Although inconsistent with neuroticism being associated with a greater intolerance for uncertainty, unfamiliarity, and ambiguity (e.g., Barlow et al., 2013), it is possible that the predictability information in this study simply exacerbated a tendency to react with greater negative affect to ambiguous stimuli. It is also possible that the provision of both CS+ and CS-relevant predictability information confounded differential effects regarding the fear-relevance or safety-relevance of predictability information. In line with emerging safety signal research (Jovanovic, Kazama, Bachevalier, & Davis, 2012; Lissek et al., 2005), these findings point to more response variability on the safety end of the generalization gradient, arguing for a more careful study of how information about safety, in comparison to information about danger, specifically may alter fear generalization.

One important limitation of many fear conditioning and fear generalization studies to date is an exclusive focus on measuring passive-emotional rather than active-behavioral effects of fear, such as actual avoidance behavior (van Meurs et al., 2014). Although avoidance historically has been a key construct implicated in prominent theories conceptualizing the etiology of anxiety and stressor-based disorders (e.g., Craske et al., 2008; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Foa & Kozak, 1986), the behavioral construct of avoidance has also historically been hard to measure in so far that it is characterized by the *absence* of behavior. However, if fear learning abnormalities, including fear overgeneralization, are believed to underlie functionally impairing anxiety and traumatic-stressor related disorders (Lissek et al., 2005), then it is essential to not only measure appraisals and physiological responses to fear-eliciting stimuli but also the specific maladaptive behaviors that excessive fear supposedly motivates (Craske, Hermans, & Vervliet, 2018). Behavioral avoidance of feared stimuli remains a hallmark symptom that cuts across the anxiety- and traumatic stressor-related disorders and can be maladaptive to the extent that it restricts engagement in activities and prevents corrective learning experiences that could otherwise disconfirm negative expectations (Foa & Kozak, 1986; Mineka, 1979). Individuals who exhibit fear overgeneralization may also experience more functionally impairing avoidance behavior simply due to the proliferation of perceived fearful stimuli. Indeed, several researchers (e.g. Boyle et al., 2015; Declercq and DeHouwer, 2009; Lommen et al., 2010; van Meurs et al., 2014) have found that avoidance behavior generalizes to ambiguous stimuli and can be used as an index of fear generalization. Behavioral avoidance has been measured using various laboratory paradigms such as a virtual farmer computer game (van Meurs et al., 2014), a symbolic generalization task (e.g., Dymond, Schlund, Roche, De Houwer, & Freeguard, 2012), a semantic generalization task (e.g., Boyle et al., 2015), a stimulus

discrimination avoidance task (Lommen et al., 2017), and other tasks that measure generalized avoidance after a fear conditioning task (e.g., Arnaudova, Kryptos, Effting, Kindt, & Beckers, 2017; Cameron et al., 2015). In these tasks, avoidance was measured by assessing the frequency of adaptive approach behavior in the context of variable levels of potential threat (e.g., van Meurs et al., 2014) or by measuring keyboard avoidance responses to novel, ambiguous stimuli associated with previously threatening stimuli that were either symbolically related (Dymond et al., 2012), semantically related (Boyle et al., 2015), or perceptually related (Arnaudova et al., 2017; Cameron, Schlund, & Dymond, 2015; Lommen et al., 2017). The avoidance task employed by Boyle et al., is particularly simple and straightforward, wherein participants undergo fear conditioning, during which the US is unavoidable, and are later told that they can press a key (e.g., space bar) to avoid the US during a test phase where generalization stimuli are presented. This avoidance task successfully elicits measurable avoidance behavior with a range of responding, without inadvertently producing a ceiling effect due to the low response cost of exclusively avoiding all stimuli. These behavioral avoidance tasks show promise as paradigms that may have convergent validity with other measures of fear generalization as well as real-world avoidance.

Accordingly, the next critical steps are to build on the existing fear generalization literature by examining the combined effects of neuroticism plus prior trauma exposure, explore differential effects of predictability information about both danger and safety cues, measure the critical and often neglected construct of fear-motivated avoidance behavior, and examine the degree to which estradiol and progesterone predict the generalization of fear. In the current study, women were selected for having a higher stress load, characterized by high neuroticism and prior trauma exposure, or lower stress load, characterized by low neuroticism and no trauma exposure.

High and low stress load groups were chosen to represent transdiagnostic categories made up of potentially heritable neuroticism and environmental trauma exposure components that may increase vulnerability for fear overgeneralization (Barlow et al., 2014). Danger cue and safety cue predictability information was systematically manipulated to increase the salience of either the danger cue contingency or the safety cue contingency, based on prior work highlighting the potential importance of safety cue processing (Garcia & Zoellner, 2017) and research suggesting that manipulating information can modulate fear appraisals and individuals can be trained to interpret ambiguous situations more positively (Beard & Amir, 2008; Mathews & Mackintosh, 2000). The fear generalization task included a fear acquisition phase followed by a generalization test phase with key outcomes of subjective risk ratings, reaction times, and physiological arousal during online risk rating trials, and accuracy and reaction times during active behavioral avoidance trials. Key psychopathology constructs, including depression, anxiety, experiential avoidance, and intolerance of uncertainty will be examined as possible predictors of fear generalization, given their strong overlap with neuroticism (Carleton, 2016; Barlow et al., 2014; Lahey, 2009) and the need to link active avoidance during fear-eliciting tasks to real world avoidance (van Meurs et al., 2014). Finally, estradiol and progesterone will be measured in a female sample to expand emerging evidence for a protective role of estradiol on adaptive fear learning process to the fear generalization literature (see Garcia & Zoeller, 2017) and to explore the related yet understudied possible influence of progesterone in women.

Based on evidence for greater fear overgeneralization in samples with anxiety disorders (Ahrens et al., 2016; Lissek et al., 2010; 2014b; Morey et al., 2015; Thome et al., 2017) and associations between higher neuroticism and higher posttraumatic stress symptoms after traumatic events (Maluoff et al., 2005; Parsaw et al., 2016), it was hypothesized that individuals

with high stress load would show increased fear generalization, as evidenced higher online risk ratings, higher skin conductance response, and higher behavioral avoidance to ambiguous generalization stimuli compared to individuals with low stress load. Based on evidence that instructional manipulations can impact fear generalization (e.g., Vervliet et al., 2010; Ahmed & Lovibond, 2015) and that training participants to discriminate safety cues from danger cues can mitigate the spread of fear (Ginat-Frolich et al., 2017; Lommen et al., 2017), it was hypothesized that individuals who are given safety cue information would also show decreased fear generalization to ambiguous stimuli than individuals who are given danger cue information. It was also hypothesized that individuals with high neuroticism and trauma exposure who were given danger cue information would show greater fear generalization than individuals with low neuroticism and no trauma exposure who were given safety cue information.

As for predictors of the excessive spread of fear, it was hypothesized that higher levels of self-reported psychopathology (e.g., depression, anxiety, PTSD) and related constructs (e.g., intolerance of uncertainty) would predict higher fear generalization to ambiguous stimuli, given that fear generalization is associated with a broad range of psychopathology (Ahrens et al., 2016; Lissek et al., 2010; Lissek et al., 2014; Morey et al., 2015; Thome et al., 2017). It was further hypothesized that higher self-reported behavioral and experiential avoidance would be associated with higher active behavioral avoidance on the fear generalization task. Finally, given that women with lower estradiol and women in the follicular menstrual phase show maladaptive fear learning (e.g., Glover et al., 2015), it was hypothesized that lower estradiol levels would predict higher fear generalization to ambiguous stimuli than women with higher levels of estradiol levels. Due to minimal investigations to date on the influence of progesterone levels on fear

learning (Garcia et al. 2018), there were no *a priori* hypotheses about the direction of the effect of progesterone levels on fear generalization.

Method

Participants

Seventy-seven women between 18 and 40 years of age participated in the study. Participants were recruited from the community in a large metropolitan city via flyers and online advertisements looking for women who “stress out easily” or “handle stress well.” Participants were fluent in English and had self-reported normal or corrected-to-normal hearing and vision. Participants who were pregnant or regularly taking medications such as sedative-hypnotics, benzodiazepines, or beta-blockers were excluded due to confounds with hormones and substances that are known to interfere with fear learning. Participants with irregular menstrual cycles or hormonal contraceptive use were not excluded in order to preserve the generalizability of the findings. Participants were selected for high neuroticism on the Eysenck Personality Questionnaire - Revised Neuroticism (EPQ-RN; Eysenck, Eysenck, & Barrett, 1985) and for prior trauma exposure based on the presence of lifetime exposure to at least one DSM-5 Criterion A traumatic event (Kessler, 1995). The other half were selected for low neuroticism and no lifetime trauma exposure. Of the 86 women who initiated study participation, nine participants were removed from the study due to ending the study prematurely ($n = 2$), technical malfunction ($n = 3$), or not understanding the task instructions ($n = 4$). The final sample ($N = 77$) was comprised of participants in the high stress load / danger cue condition ($n = 19$), high stress / safety cue condition ($n = 23$), low stress load / danger cue condition ($n = 18$), low stress load / safety cue condition ($n = 17$). See Table 1 for sample characteristics.

Study Design

This study used a mixed-subjects design, with between-subject factors of group (high neuroticism/trauma exposure; low neuroticism/no trauma exposure) and predictability information manipulation condition (danger cue, safety cue), and within-subjects variables of stimulus type (CS+, GS1-4, CS-). Predictor variables for exploratory hormonal analyses were hormone levels for estradiol and progesterone. Primary dependent variables were online risk ratings (response, reaction time, skin conductance response (SCR), and behavioral avoidance (accuracy, reaction time).

Materials

Stimuli. Two female neutral faces from the NimStim Set of Facial Expressions (Tottenham et al., 2009) served as the conditioned danger cue (CS+) and the conditioned safety cue (CS-), the former paired and the latter unpaired with an aversive unconditioned stimulus (US). The US was a loud scream (Lau et al., 2008), 1s and 95 dB, delivered through high fidelity professional reference headphones (Maico, TDH-39-P) and a fearful face, made by the same woman serving as the CS+, immediately after CS+ offset on reinforced trials. This “screaming lady” paradigm provides a strong conceptual association between the CS+ and the US and has high ecological validity, as humans are highly biologically prepared to fearful screaming faces (e.g., Haddad, Xu, Raeder, & Lau, 2012a). The generalization stimuli (GS1, GS2, GS3, GS4) were gradually morphed versions of the CS+ and CS- (“Morpheus Photo Morpher”, n.d.), forming a continuum of similarity between CS+ and CS- in order to examine fear responses across a generalization gradient (Garcia & Zoellner, 2017). See Figure 1. Conditioned and generalization stimuli were presented on a white background and measured approximately 7” tall and 5” wide.

Screaming lady fear generalization paradigm. This task was adapted based on existing paradigms (Boyle et al., 2015; Garcia & Zoellner, 2017) and was programmed on E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

Baseline. A baseline phase consisted of six trials of a neutral stimulus that would later become a conditioned fear cue (CS+) and six trials of a neutral stimulus that would later become a conditioned safety cue (CS-). These stimuli were included to control for exposure to future conditioned stimuli. These stimuli were randomly presented for 2s, with 4s inter-trial intervals (ITIs) on a white screen.

Fear acquisition. Twelve trials of the conditioned fear cue (CS+) and twelve conditioned safety cue (CS-) trials were presented. The image used for the CS+ and CS- was counterbalanced across participants. Stimuli were randomly presented for 2s, with 4s ITIs on a white screen. The CS+ was immediately followed by the US (1s) 75% of the time in order to maximize learning from a partial reinforcement schedule (Haddad, Lissek, Pine, & Lau, 2011). The remaining trials culminated with a white screen for 1s.

Acquisition learning was assessed via US expectancy and fear ratings. The CS+ or CS- was randomly presented without the US and participants were provided with the following instructions: “Rate the likelihood of hearing a loud scream on a scale of 1-7 (1 = extremely unlikely, 7 = extremely likely)” and “Rate how afraid you are of this face on a scale of 1-7 (1 = not at all afraid, 7 = highly afraid). The response terminated the image. Both US expectancy and fear ratings were provided for both CS+ and CS-, for a total of four ratings.

Distracter task. A brief visuospatial distracter task was used to provide separation between acquisition and test phases of the study for 10 min. The shapes of different states were presented and participants were asked to identify the name of state via written free response.

Information manipulation. In order to examine the differential effects of safety cue versus danger cue predictability information on fear generalization, content of predictability information was manipulated. Predictability information that highlighted the danger cue contingency (CS+) was given to participants randomized to the danger cue condition. Predictability information that highlighted the safety cue contingency (CS-) was given to participants randomized to the safety cue condition.

The danger cue predictability information read: *"Sometimes people struggle to recognize threat. This face [image of CS+] will give you danger information, signaling a high likelihood of a loud scream."*

The safety cue predictability information read: *"Sometimes people struggle to recognize safety. This face [image of CS-] will give you safety information, signaling a low likelihood of a loud scream."*

Fear generalization test. This test phase was modeled on Garcia and Zoellner (2017) and Boyle et al. (2015) and was designed to measure the degree to which fear spreads across a continuum of similarity between CS+ and CS-. The test phase consisted of alternating online risk rating blocks and avoidance blocks for all six test stimuli (CS+, GS1-4, CS-).

Online risk ratings. Online risk ratings were collected to assess subjective risk of how likely the image would be followed by a loud scream (US) for each stimulus (e.g., Lissek et al., 2010). Three online risk rating blocks consisted of six trials each for a total of 18 trials. All six test stimuli (CS+, CS-, GS1-4) were assessed within a given block. Stimuli were randomly presented for 4s, followed by a prompt "*Level of Risk?*" which remained on the screen until a rating was made. Ratings were made on a 7-point Likert scale (1 = *no risk*, 7 = *high risk*). Risk ratings for CS+ were immediately followed by the US 100% of the time, to prevent extinction of

conditioned learning. All trials culminated with a 4s ITI on a white screen. No trials were excluded for reaction times shorter than 150 ms.

Avoidance task. This task was modeled after Boyle et al. (2015) and was designed to assess active, behavioral avoidance of feared stimuli. Behavioral avoidance responses were collected during the test phase to assess the degree to which participants expected and wished to avoid the US. An initial behavioral avoidance training block instructed participants that they could now avoid the US at the appropriate time. Ten conditioned danger cues (CS+) and 10 conditioned safety cues (CS-) were randomly presented for 4s. The US was avoided by pressing the spacebar during the 4s that the CS+ appeared on the screen. Pressing the spacebar during this time cancelled the US 100% of the time but did not remove the CS+ from the screen. If the spacebar was not pressed during this period, it was followed by the US 100% of the time. No feedback was given to participants, and spacebar presses to CS- were not acknowledged.

The avoidance training block led straight into the first avoidance test block without warning (Boyle et al., 2015). Two behavioral avoidance blocks consisted of 12 trials each, for a total of 24 trials, and were presented in between the 3 online risk rating blocks. All 6 test stimuli (CS+, GS1-4, CS-) were assessed twice within a given block, 4 times in total. As with the training phase, stimuli were randomly presented within blocks for 4s, during which participants had the option to press the spacebar to cancel the US. CS+ trials were immediately followed by the US 100% of the time when not avoided with a spacebar press, in order to prevent extinction of the conditioned fear (Haddad et al., 2012b).

The dependent variables for the behavioral avoidance task were the mean accuracy of avoidance responding for each stimulus and mean reaction times during avoided trials from stimulus onset until spacebar press. Accurate trials were defined as pressing the spacebar during

CS+ trials, or abstaining from pressing the spacebar on all other trials (CS-, GS 1-4). Reaction time data was analyzed by comparing avoidance reaction time on accurately avoided trials (CS+) to inaccurately avoided trials aggregated across CS- and GS1-4. No trials were excluded for reaction times shorter than 150 ms.

Subjective Units of Distress (SUDs) ratings. Subjective Units of Distress were assessed at four time points: before and after fear acquisition, and before and after the fear generalization test phase. Ratings were based on current distress made on a 100-point scale (0 = *most relaxed you've ever been*, 100 = *most distressed, uncomfortable, or anxious you've ever been*).

Post-test ratings. US expectancy and fear ratings for test stimuli (CS+, GS1-4, CS-) were assessed after the fear generalization test. US expectancy trials assessed the likelihood of the US following each test stimulus and fear rating trials assessed how afraid participants were of each stimulus. Both US expectancy (1 = *extremely unlikely*, 7 = *extremely likely*) and fear ratings (1 = *not at all afraid*, 7 = *highly afraid*) were provided for six stimuli (CS+, GS1-4, CS-), for a total of 12 ratings, and stimuli were randomly presented without the US. Distress levels to the US were also assessed to examine how upsetting participants found the US to be on average, at its peak, and by the end of the task, (1 = *not at all distressed*, 7 = *highly distressed*). Finally, degree of predictability was assessed to measure how well participants felt that they could overall predict the US contingency, given the manipulation of the type of predictability information, (1 = *couldn't predict*, 7 = *always predict*).

Self-report Questionnaires

Eysenck Personality Questionnaire - Revised Neuroticism (EPQ-RN; Eysenck et al., 1985). The 24-item EPQ-RN scale assesses negative trait emotionality, including unstable mood, high reactivity to emotional stimuli, anxiety, and depression. Responses are dichotomous (1 = *no*,

2 = *yes*), with higher total scores indicating higher levels of neuroticism. The 24-item version of this measure was used instead of the 12-item short form version to yield a wider range of participant scores. The EPQ-R has demonstrated good internal consistency ($\alpha = .85 - .88$, Eysenck et al., 1985), and the N scale has shown good test-retest reliability ($r = .89$, Eysenck & Eysenck, 1991). High and low neuroticism criteria, used for group selection in this study, were determined based on female population norms for the EPQ-RN (Eysenck et al., 1985; Garcia & Zoellner, 2017), with the high neuroticism group endorsing a minimum score of ≥ 13 (+1 SD), and the low neuroticism group endorsing a maximum score of ≤ 8 (-1 SD).

PTSD Scale-Self-Report for DSM-5 (PSS-SR-5; Foa et al., 2016). The PSS-SR-5 is a 24-item self-report measure used to assess prior trauma exposure and subsequent PTSD symptoms. The PSS-SR-5 uses a 10-item trauma screen to identify prior exposure to traumatic events and assesses the severity of DSM-5 PTSD symptoms related to the event causing the most distress in the last month. The trauma screen asks participants whether they have experienced a DSM-5 Criterion A traumatic event (e.g., serious life threatening illness, physical assault, sexual assault, military combat/lived in a war zone, child abuse, serious accident, or natural disaster). The PSS-SR-5 includes 20 questions assessing symptom severity on a 5-point Likert scale (0 = *not at all*, 4 = *six or more times a week/severe*), and scores are calculated by summing responses, with higher scores indicating higher PTSD severity. The PDS-5 has excellent test-retest reliability ($r = .90$) and good convergent validity with the PTSD Checklist ($r = .90$) and the PTSD Symptom Scale—Interview Version for DSM-5 (PSSI-5; $r = .85$; 2016).

Life-Stressor Checklist - Revised. (LSC-R; McHugo et al., 2005). The LSC-R is a 30 item self-report measuring stressful life events over the lifespan that includes both high severity traumatic events (e.g., Have you ever been abused or physically attacked by someone you know?

Did you ever have sex when you didn't want to because someone forced you in some way or threatened to harm you if you didn't?), as well as less severe stressful life events (e.g., Have you ever had serious money problems? Did your parents ever separate or divorce while you were living with them?). The LSC-R was included to thoroughly assess for a range of stressful life events that could contribute to environmental stress load. LSC-R scores were calculated by summing responses, with higher scores indicating a higher number of life-stressor events. The LSC-R has demonstrated good test-retest reliability (McHugo et al., 2005) and good convergent validity in PTSD (Brown, Stout, & Mueller, 1999; Gavrilovic, Lecic-Tosevski, & Knezevic, 2002; Kimerling et al., 1999; Wolfe & Kimerling, 1997).

Posttraumatic Avoidance Behavior Questionnaire (PABQ; Van Minnen & Hagenaars, 2010). The PABQ is a 25-item self-report measuring trauma-related avoidance behavior (e.g., avoiding visual trauma reminders, being alone, intimate relationships) on a 4-point Likert scale (1 = *almost never* to 4 = *almost always*). The PABQ was included to explore the relationship between active avoidance on the fear generalization task and real-life trauma-related avoidance in the high stress load group only. PABQ scores were calculated by summing responses, with higher scores indicating more severe avoidance. The questionnaire has good test-retest validity ($r = .87 - .78$) and convergent validity with PTSD symptom severity ($r = .77 - .56$; Van Minnen & Hagenaars, 2010).

Brief Experiential Avoidance Questionnaire (BEAQ; Gámez et al., 2013). The BEAQ, a shortened version of the Multidimensional Experiential Avoidance Questionnaire (MEAQ; (Gámez et al., 2011), is a 15 item self-report measuring experiential avoidance, on a 6-point Likert scale (1 = *strongly disagree* to 6 = *strongly agree*; Gámez et al., 2013). The BEAQ was included to explore the broader construct of experiential avoidance, which is made up of general

cognitive, emotional, and behavioral avoidance, across all participants with high and low stress load. BEAQ scores were calculated by summing responses, with higher scores indicating more severe avoidance. The BEAQ shows convergent validity with other measures of avoidance, divergent validity with measures of neuroticism, and has high internal consistency (Gámez et al., 2013, 2011).

Beck Depression Inventory-II (BDI-II; Beck, Steer, Ball, & Ranieri, 1996). The BDI-II is a 21-item self-report rating inventory that measures characteristic attitudes and symptoms of depression in the last two weeks on a 4-point Likert scale with anchors that vary for each item (e.g., 0 = *I do not feel sad*; 3 = *I am so sad or unhappy I can't stand it*). The BDI was included to assess for depression which frequently co-occurs with neuroticism, anxiety, PTSD, and is also strongly linked with maladaptive avoidance patterns. BDI-II scores were calculated by summing responses, with higher scores indicating more severe depression. The BDI-II has good convergent validity with the Hamilton Psychiatric Rating Scale for Depression ($r = .71$, Beck et al., 1996).

State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983). The STAI is a 40-item self-report measure of anxiety that assesses both state (temporary; STAI-S) anxiety and trait (long-standing; STAI-T) anxiety scales rated on a 4-point Likert scale (1 = *not at all*, 4 = *very much so*). The STAI was included to assess for general anxiety which frequently co-occurs with neuroticism, depression, and PTSD, and is also strongly linked with maladaptive avoidance patterns. The STAI-S measures how participants feel “right now” whereas the STAI-T measures how they “generally feel.” The STAI-S and STAI-T are separately scored by summing responses, with higher scores indicating greater anxiety. The STAI-T has demonstrated both good test-retest reliability ($r = .73 - .86$; Spielberger et al., 1983) and good convergent validity ($r = .52 - .80$;

Spielberger et al., 1983).

Intolerance of Uncertainty Scale-12 (IUS-12; Carleton, Norton, & Asmundson, 2007).

The IUS, a 12-item short-form of the original 27-item Intolerance of Uncertainty Scale, measures reactions to uncertainty, ambiguous situations, and the future (e.g., “Unforeseen events upset me greatly.”) on a 5-point Likert scale (1 = *not at all characteristic of me*, 5 = *entirely characteristic of me*). The IUS was included to assess the degree to which participants can tolerate uncertainty given that the fear generalization task is, by definition, ambiguous and uncertain. The IUS is calculated by summing a total score from all items, with higher total scores indicating higher degrees of intolerance. The IUS-12 has a strong correlation with the original 27-item scale ($r = .96$) and has demonstrated high internal consistency ($\alpha = .91$) and good convergent validity with the Beck Anxiety Inventory ($r = .57$), Penn State Worry Questionnaire ($r = .54$) and Generalized Anxiety Disorder Questionnaire ($r = .61$, Carleton et al., 2007).

Demographics and Medical Questionnaire. This questionnaire includes questions about age, ethnicity, education level, height and weight, current psychotropic and other medications, visual and auditory impairments, recent caffeine use and sleep patterns, menstrual cycle length and regularity, recent hormonal contraceptive use, and reproductive status. These variables served as exclusion criteria or were assessed as covariates in the analyses.

Physiological Measures

Skin conductance response (SCR). Skin conductance responding was assessed as a measure of physiological arousal during the “screaming lady” fear generalization paradigm. Participants’ hands were gently wiped with clean cotton balls and no water. Two disposable snap electrodes (EL507-10) pre-gelled with isotonic gel were placed adjacently on the volar surfaces of distant phalanges of the pointer and middle fingers on the non-dominant hand and secured

with surgical tape. Skin conductance data was collected using Biopac's MP150 Data Acquisition System (Biopac Systems, Inc.) running Acknowledge 4.2 software. A Galvanic Skin Response module (GSR100C) with gain set to $10 \mu\Omega/V$, low pass filter set to 1 Hz, and high pass filter set to DC was used to collect skin conductance data in the range of 0-100 microsiemens (μS). The signal was sampled at 1 kHz in AcqKnowledge.

Skin conductance response was defined as the maximum increase in skin conductance occurring between 1s and 4s after stimulus onset, after correcting for mean baseline skin conductance level during the last second of the prior ITI (Cacioppo, Tassinary, & Berntson, 2007; Dawson, Schell, & Filion, 1990). Negative responses were not calculated but were included as zero responses (Boyle et al., 2015). Responses were recorded in microSiemens (μS) and were square root transformed to normalize positively skewed and leptokurtotic skin conductance data (Boyle et al., 2015).

Salivary estradiol and progesterone. Salivary estradiol and progesterone assays have been shown to provide reliable, non-invasive assessment of menstrual cycle status (Gandara, Leresche, & Mancl, 2007; Gröschl, 2008). We collected salivary sex hormone levels due to strong evidence for association between lower estradiol and maladaptive fear learning process and critical need to further explore progesterone. Saliva samples were collected via the SalivaBio's Passive Drool Method ("Salimetrics") to avoid interference effects commonly caused by absorbing saliva with cotton materials or more invasive collection methods such as measuring hormones from urine, serum, or plasma (Shirtcliff, Granger, Schwartz & Curran, 2001). Approximately 2mL was collected in order to have sufficient saliva for analyses. Participants were instructed to allow saliva to pool in mouth, and then with their head tilted forward, gently force saliva through a saliva collection aid into a collection viral. Saliva was

stored at -20 degrees C. Saliva samples were sent to the Kirschbaum biopsychology laboratory in Dresden, Germany, for analysis. Salivary hormone levels outside of expected ranges, 0.8–14.3 pg/mL for estradiol and 28–446 pg/mL for progesterone, were excluded (Soni, Curran & Kamboj, 2013). Eight participants had salivary estradiol levels that were outside of this range, and a separate eight participants had salivary progesterone levels outside of the range; these values were removed for analyses.

Procedure

Participants were screened over the telephone and assessed for exclusion criteria, such as pregnancy, uncorrected visual or hearing impairments, and regular use of sedative-hypnotics, benzodiazepines, or beta-blockers. Participants were also assessed for Criterion A trauma exposure based on seven highly traumatic events (Kessler, 1995) including: combat, sexual assault, physical assault, serious life-threatening accident, serious natural disaster, physical threats, and witnessing someone being badly injured or killed. Potentially eligible participants were emailed a link to take the EPQ-RN and LSC-R questionnaires online. Neuroticism scores on the EPQ-RN and trauma exposure reported on the phone screen were used to select for high and low stress load groups, and the LSC-R was used to corroborate trauma exposure from the phone screen. Eligible participants were then scheduled to come to the laboratory. Study procedures were scheduled to start between 8 am and 9 am to account for diurnal rhythms in gonadal hormone levels (Bao et al., 2003).

Study procedures took place in a sound attenuated room equipped with a PC computer, 18-inch color monitor Windows XP software, and sound attenuating Maico TCH-39-P headphones. Participants were seated at the computer with a viewing distance of approximately 18 inches. Participants were provided informed consent, after which they provided saliva

samples for 2 min. Participants then completed the self-report questionnaires (Demographics and Medical, PSS-SR-5, PABQ, BEAQ, BDI-II, STAI, IUS, CUDIT).

Participants were given headphones to wear over their ears and sensors were placed on their non-dominant hand. Subjective distress (SUDs) scale were explained as a thermometer that goes from 0-100, *“where zero is the most relaxed you’ve ever been and 100 is most distressed, uncomfortable, or anxious you’ve ever been.”* Participants were asked to report their (SUDs) prior to the fear acquisition phase: *“What is your current SUDs level?”* Participants then underwent a 2 min baseline period and were given the following instructions: *“Please relax your body and focus on your breath for 2 minutes.”* After that, participants underwent a habituation phase, during which they were exposed to neutral stimuli that would later serve as CS+ and CS- and were given the following instructions: *“Now you will see some faces. Please pay attention to each of the images that appear on the screen in front of you”*. Participants then underwent fear acquisition to CS+ and CS-, during which the US was paired with CS+, and received the following instructions: *“In this next phase of the task, some faces will be followed by a loud scream. Please continue to pay attention to each of the images that appear on the screen in front of you.”* Participants then provided post-acquisition US expectancy and fear ratings for the CS+ and CS-. US expectancy ratings showed an image of the stimulus in question and prompted participants with: *“Rate the likelihood of hearing a loud scream on a scale of 1-7.”* Fear ratings also showed an image of the stimulus in question and prompted participants with: *“Rate how afraid you are of this face on a scale of 1-7.”* Participants were then asked to state their subjective distress (SUDs) after the fear acquisition phase.

This was followed by a 10 min distractor task involving the identification of U.S. states. Participants were then randomized to a predictability information condition, such that they

received information that either enhanced the predictability of the danger cue contingency (CS+) or the safety cue contingency (CS-).

Participants in the danger cue predictability information condition were told: *"Sometimes people struggle to recognize threat. This face [image of CS+] will give you danger information, signaling a high likelihood of a loud scream."*

Participants in the safety cue predictability information condition were told: *"Sometimes people struggle to recognize safety. This face [image of CS-] will give you safety information, signaling a low likelihood of a loud scream."*

Participants were asked to state their subjective distress (SUDs) prior to the fear generalization test phase. The fear generalization test phase then began with the following prompt: *"Now you will see more faces!"* Participants completed alternating online risk ratings blocks and avoidance task blocks with trials for conditioned stimuli (CS+ and CS-) and generalization stimuli (GS1, GS2, GS3, GS4), for a total of five test blocks. Participants began by completing the first block of online risk ratings, followed by avoidance training and the first block of avoidance test trials, followed by the second block of online risk ratings, followed by the second block of avoidance test trials, and finally the third block of online risk ratings.

During risk rating blocks, participants were shown all each test stimulus and asked to respond to the following prompt: *"Level of Risk?"* During the first avoidance task block, participants were taught that they could avoid the US with the following instructions: *"You will now have the opportunity to avoid further loud fearful screams in your ears. You can avoid the screams by pressing spacebar in response to the appropriate face at any time. At the start of the second avoidance task block, participants were given the following instructions: "Remember, you can avoid loud fearful screams in your ears by pressing spacebar at the appropriate time."*

After the end of the fear generalization test, participants provided post study ratings. Participants were asked US expectancy and fear ratings for all six test stimuli. US expectancy ratings showed an image of the stimulus and prompted participants with: *“Rate the likelihood of hearing a loud scream on a scale of 1-7.”* Fear ratings also showed an image of the stimulus and prompted participants with: *“Rate how afraid you are of this face on a scale of 1-7.”* Next, participants reported their average, peak, and end-of-task distress: *“On average, how distressed were you by the loud scream you heard through the headphones; What was your highest level of distress in response to the loud scream you heard through the headphones; By the end of the task, how distressed were you by the loud scream you heard through the headphones?”* Finally, participants reported the degree to which they could predict the US: *“How well did you feel you could predict when the scream would occur?”* Participants were then asked to state their subjective distress (SUDs).

See Figure 2 for a flow diagram of the study. Upon completion of study procedures, participants were debriefed and received forty dollars.

Data Analysis

Power analyses. Fear generalization studies examining interactions between group (anxious, healthy) and stimulus type (GS1-4) typically have medium effect sizes ranging from $d = 0.44 - 0.51$ on psychophysiological measures and large effect sizes ranging from $d = 0.91 - 0.92$ on measures of online risk ratings (Lissek et al., 2010; 2014b). Studies examining the effect of predictability information on fear learning have found medium to large effect sizes ranging from $d = 0.50 - 0.60$ (Davies & Craske, 2015; Shankman, Robinson-Andrew, Nelson, Altman, & Campbell, 2011). Studies examining low versus high estradiol on fear extinction and extinction recall have found medium to large effects of estradiol ranging from $d = 0.47 - 1.03$, respectively

(Glover et al., 2012; Zeidan et al., 2011). Taken together, estimated effect sizes for the hypothesized main effects of group (high neuroticism/trauma exposure, low neuroticism/no trauma exposure), information condition (danger cue, safety cue), and estradiol on fear generalization are consistently medium to large. Sample size estimates for main effects with two groups, six measurements that are moderately associated ($r = .23$), power = .80, and $\alpha = .05$ suggest that 26 participants were needed to detect a large effect ($f = .35$), 48 for a medium effect ($f = .25$), and 128 for a small to medium effect ($f = .15$).

In our previous study examining the interaction between neuroticism and predictability on fear generalization (Garcia & Zoellner, 2017), there were between medium and large effect sizes on fear generalization measured by attentional bias scores ($r = .40 - .45$) and online risk ratings ($r = .41$). A study examining the interaction between anxious groups and predictability on fear learning found medium effect sizes ranging from $d = 0.45 - 0.50$ (Nelson, Hodges, Hajcak, & Shankman, 2015). Taken together, we estimated medium to large effect sizes for the interaction effect of group x information condition. Sample size estimates for an interaction effect with four conditions, six measurements that are moderately associated ($r = .23$), non-sphericity correction = .42, power = .80 and $\alpha = .05$, were 40 participants to detect a large effect ($f = .35$), 72 participants for a medium effect ($f = .25$), and 192 participants for a small to medium effect ($f = .15$). Accordingly, we selected a final sample size of 80, with 20 participants per cell, to be able to observe at least a medium size effect.

General data reduction. Data was screened prior to analysis to ensure accuracy of entered data and check for missing values. Less than 1% of the data was missing and data was checked for univariate and multivariate outliers. Data was also checked for parametric test assumptions such as normally distributed data, homogeneity of variance, and independence

(Tabachnick & Fidell, 2007).

Variables known to be associated with fear learning and physiological arousal such as height and weight, room temperature, medication use, smoking, caffeine use and sleep patterns were evaluated as potential covariates in the analyses. Due to no significant differences between groups and conditions, they were not included as covariates (Tabachnick & Fidell, 2007). As expected, there were no differences between the danger cue versus safety cue predictability information conditions on age, ethnicity, education, or psychopathology measures such as neuroticism (EPQ-R-N), exposure to stressful life events (LSC-R), PTSD severity (PSS-SR-5), depression severity (BDI-II), trait anxiety (STAI-T), state anxiety (STAI-S), or intolerance of uncertainty (IUS). Similarly, high and stress load groups also did not differ on age, ethnicity, or education. Thus, these variables were also not included as covariates in the analyses.

Analytic strategy. Repeated measures analysis of variance (ANOVA) was used to examine main effects and interaction effects of group, predictability information condition, and test stimulus on fear generalization. Repeated measures ANOVAs were used instead of multivariate analysis of variance due to the a priori expectation that dependent variables would move somewhat independently of each other and not be sufficiently correlated for use of MANOVA (Tabachnick & Fidell, 2007). Responses across blocks were examined separately for online risk ratings (first, middle, last block), skin conductance response (first, middle, last block), and avoidance (first, last block), due to the expectation that dependent measures would change across repeated presentations, given that learning likely continued even in the test phase.

The main analytic strategy utilized 2 (Group: high stress load; low stress load) x 2 (Predictability Information Condition: danger cue; safety cue) x 6 (Stimulus Type: CS+, CS-, GS1-4) repeated measures ANOVAs examining fear generalization as the dependent variables

for online risk ratings (response, reaction time, skin conductance response) and behavioral avoidance (accuracy, reaction time). Significant main effects and interactions were followed up with simple effects analyses.

Simultaneous linear regressions were used to examine whether self-reported psychopathology measures predicted the fear generalization dependent variables: online risk responses and avoidance accuracy to the most ambiguous stimuli (GS2, GS3). Due to multicollinearity issues with trait and anxiety (STAI-T) and neuroticism (EPQ-R-N), only depression (BDI), state anxiety (STAI-S), experiential avoidance (BEAQ), and intolerance of uncertainty (IUS) were entered simultaneously into the model. Pearson correlations were used to examine the relationship between posttraumatic avoidance behavior (PABQ) and online risk responses and avoidance accuracy to the most ambiguous stimuli (GS2 and GS3). Similar simultaneous linear regressions were used to examine the effects of baseline continuous estradiol and progesterone levels on fear generalization. Since there were no high versus low stress load group differences on either estradiol or progesterone levels, group membership was not included in the analysis.

Results

As expected, there were group differences between the high stress load group and low stress load group across psychopathology measures, such that participants in the high stress load group reported higher neuroticism ($d = 4.80$), higher exposure to stressful life events ($d = 1.63$), higher experiential avoidance ($d = 1.09$), higher depression severity ($d = 1.32$), higher trait anxiety ($d = 2.05$), higher state anxiety ($d = 1.49$), and higher intolerance of uncertainty ($d = 1.23$). See Table 1.

Fear Acquisition Phase

Post-Acquisition: US expectancy. As anticipated, participants correctly learned the US contingency. When examining post-acquisition US likelihood ratings, where higher scores reflect higher perceived likelihood of the US following conditioned stimuli (CS+ or CS-), there was a main effect of test stimulus, $F(1,75) = 436.52, p < .001$, such that US expectancy ratings were higher for CS+ ($M = 5.38, SD = 1.18$) compared to CS- ($M = 1.73, SD = 1.06$), $d = 2.37$.

Post-Acquisition: Fear ratings. When examining post-acquisition fear ratings, where higher scores reflect higher fear of conditioned stimuli (CS+ or CS-), there was a main effect of test stimulus, $F(1,75) = 48.06, p < .001$, which was modified by a group x test stimulus interaction, $F(1,75) = 9.21, p = .003$. To examine the two-way interaction, we examined test stimuli separately. The high stress load group reported higher fear of CS+ ($M = 3.60, SD = 1.64$) than those in the low stress load group ($M = 2.86, SD = 1.67$), $d = 0.53$. There was no significant group difference on CS-.

Fear Generalization Test

See Table 2 for raw mean and standard deviations for online risk rating responses and avoidance accuracy across high and low stress load groups and danger and safety cue predictability information conditions. See Table 3 for correlations among main fear generalization measures.

Online risk ratings responses. We examined online risk ratings, where higher scores reflect higher perceived levels of risk of the US occurring, across test stimuli (CS+, GS1-4, CS-) in the first, middle, and last block.

First block. There was a main effect of test stimulus in the first block, $F(5, 365) = 139.99, p < .001$. Simple effects showed that participants rated GS1 ($M = 5.09, SD = 1.84$) as riskier than GS2 ($M = 4.22, SD = 1.81$), $d = 0.54$, GS2 as riskier than GS3 ($M = 2.18, SD = 1.30$), $d = 0.94$,

and GS3 as riskier than GS4 ($M = 1.55$, $SD = 0.93$), $d = 0.58$. There were no significant main or interaction effects of group or predictability information condition.

Middle block. There was a similar main effect of test stimulus in the middle block, $F(5, 365) = 212.46$, $p < .001$, and no other main effects or interactions.

Last block. There was a similar main effect of test stimulus in the last block, $F(5, 365) = 215.01$, $p < .001$, which was modified by a group x test stimuli interaction, $F(5, 365) = 2.56$, $p = .03$. To examine the two-way interaction, test stimuli were examined separately. For GS2, those in the high stress load group ($M = 3.62$, $SD = 2.07$) rated GS2 as riskier compared to those in the low stress load group ($M = 2.69$, $SD = 1.73$), $d = 0.49$. There was a similar group difference on GS3, such that those in the high stress load group ($M = 2.48$, $SD = 1.80$) rated this stimulus as riskier compared to those in the low stress load group ($M = 1.77$, $SD = 0.94$), $d = 0.49$. In other words, at the end of the generalization task, participants in the high stress load group rated the most ambiguous generalization stimuli as riskier than those in the low stress load group. See Figure 3.

Online risk ratings reaction times. We examined reactions times for online risk ratings to test stimuli (CS+, GS1-4, CS-), where longer reaction times potentially reflect greater degree of uncertainty, in the first, middle, and last blocks.

First block. There was a main effect of test stimulus in the first block, $F(5, 365) = 8.71$, $p < .001$. Participants had faster reaction times to GS1 ($M = 2.72$, $SD = 1.46$) compared to CS+ ($M = 3.37$, $SD = 2.44$), $d = 0.64$, GS1 than GS2 ($M = 3.45$, $SD = 1.83$), $d = 0.34$, GS3 ($M = 2.94$, $SD = 1.58$) than GS2, $d = 0.28$, and GS4 ($M = 2.33$, $SD = 1.48$) than GS3, $d = 0.37$. In general, participants responded faster as stimuli became increasingly dissimilar to CS+. There were no significant main or interaction effects of group or predictability information condition.

Middle block. There was a similar main effect of test stimulus in the middle block, $F(5, 365) = 5.34, p < .001$. There was also a main effect of predictability, $F(1, 73) = 12.91, p = .001, d = 0.46$, such that those given danger cue predictability information ($M = 1.55, SD = .99$) had faster reaction times than those given safety cue predictability information ($M = 2.07, SD = 1.23$).

Last block. There was a similar main effect of test stimulus in the last block, $F(5, 365) = 3.22, p = .01$. There was also a main effect of group, $F(1, 73) = 6.39, p = .01, d = 0.32$, such that those in the high stress load group ($M = 1.31, SD = 0.81$) had faster reaction times compared to those in the low stress load group ($M = 1.67, SD = 1.37$).

In summary, danger cue predictability information was associated with faster reaction times, or lower perceptions of ambiguity, than safety cue predictability information when rating stimuli in the middle block. However, high stress load was associated with faster reaction times than low stress load in the last block.

Online risk ratings: Skin conductance responses (SCRs). SCR was measured during online risk ratings to test stimuli (CS+, CS-, GS1-4), where higher responses reflect greater physiological arousal or fear, in the first, middle, and last block.

First block. There were no significant main effects or interactions for group, predictability information condition, or test stimulus in the first block.

Middle block. Similarly, there were no significant main effects or interactions for group, predictability information condition, or test stimulus in the middle block.

Last block. There was a main effect of test stimulus, $F(5, 360) = 2.40, p = .04$, modified by a trend-level group X test stimuli interaction, $F(5, 360) = 2.00, p = .08$. To examine the two-way interaction, test stimuli were examined separately. There was a significant group difference

on CS+ such that those in the high stress load group ($M = 0.22$, $SD = 0.32$) showed higher physiological arousal compared to those in the low stress load group ($M = 0.10$, $SD = 0.16$), $d = 0.47$. No other comparisons approached significance. In other words, by the end of the task, participants in the high stress load group showed higher physiological arousal or fear to the CS+ relative to the participants in the low stress load group.

Avoidance trials: Accuracy. We examined accuracy of avoidance trials to test stimuli (CS+, GS1-4, CS-), where higher accuracy was defined as avoiding CS+ and not avoiding other test stimuli (CS-, GS1-4), in the first and last blocks.

First block. There was a main effect of test stimulus in the first block, $F(5, 365) = 94.31$, $p < .001$. Participants had higher accuracy on CS+ ($M = .94$, $SD = .23$) than GS1 ($M = .14$, $SD = .31$), $d = 1.66$, GS2 ($M = .47$, $SD = .46$) than GS1, $d = 0.73$, GS3 ($M = .73$, $SD = .40$) than GS2, $d = 0.71$, and GS4 ($M = .92$, $SD = .23$) than GS3, $d = 0.57$. In other words, accuracy was lowest on GS1 and gradually increased as generalization stimuli approached CS-. There were no other significant main effects or interactions of group, predictability information condition, or test stimuli.

Last block. There was a similar main effect of test stimulus in the last block, $F(5, 365) = 69.75$, $p < .001$, modified by group X predictability X test stimulus interaction, $F(5, 365) = 2.35$, $p = .04$. See Figure 4. To examine the three-way interaction, we examined predictability conditions separately. In the danger cue predictability information condition, there were no main effects or interaction of group and test stimulus. However, in the safety cue predictability information condition, there was a significant main effect of group, $F(1, 38) = 503.67$, $p = .03$, $d = 0.49$, with those in the high stress load group having lower avoidance accuracy ($M = .67$, $SD = .36$) compared to those in the low stress load group ($M = .82$, $SD = .24$). In other words, by the

end of the task, participants in the high stress load group who were given safety cue predictability information showed more maladaptive avoidance behavior compared to those in the low stress load group who were given safety cue predictability information. The danger cue predictability information condition, on the other hand, mitigated stress load group effects on avoidance behavior.

Avoidance trials: Reaction times. Reaction times to accurately avoided trials (CS+) and inaccurately avoided trials (GS1-4, CS-), where longer reaction times potentially reflect greater degree of uncertainty, were examined in the first and last block.

First block. There was a main effect of test stimulus, $F(1, 67) = 4.19, p = .05$. Simple effects showed that participants responded more quickly to CS+ trials ($M = .79, SD = .31$) than non-CS+ trials ($M = 0.88, SD = .40$), $d = 0.22$. In other words, participants took more time when making an inaccurate response to non-CS+ stimuli than when making a correct avoidance response to CS+.

Last block. There were no significant main effects, interactions of group, predictability information condition, or test stimulus.

Self-reported distress throughout fear generalization task. Subjective units of distress (SUDs) were examined before and after fear acquisition and before and after the generalization test phase, where higher scores reflect higher levels of distress. There was a main effect of time, $F(3, 216) = 15.67, p < .001$. Participants reported lower SUDs before fear acquisition ($M = 31.25, SD = 20.28$) compared to after fear acquisition ($M = 22.77, SD = 18.28$), $d = 0.69$. Participants also reported lower SUDs before the fear generalization test ($M = 29.37, SD = 20.67$) compared to after the test ($M = 23.51, SD = 20.67$), $d = 0.40$.

There was also a main effect of group, $F(1, 72) = 180.76, p < .001$, such that participants

in the high stress load group reported higher SUDs ($M = 31.71$, $SD = 20.97$) compared to participants in the low stress load group ($M = 20.74$, $SD = 15.69$), $d = 0.59$. In summary, the high stress load group consistently reported higher subjective levels of distress than the low stress load group.

Post-Test Ratings

Mirroring the post-acquisition ratings, US expectancy and fear ratings were assessed for each stimulus (CS-, GS1-4, CS+) after the fear generalization test. These questions measured the degree to which participants expected the screaming lady (US) after each stimulus and how afraid participants were of each stimulus. Furthermore, retrospective general distress ratings were used to assess how distressing participants found US to be on average, by the end of the test, and at its peak. Finally, retrospective predictability was assessed by asking participants to report how well they felt they could predict the occurrence of the US.

Post-Test: US expectancy. When examining post-test US expectancy ratings, where higher scores reflect a higher expectation of the US following test stimuli (CS+, GS1-4, CS-) after the task, there was a main effect of test stimulus, $F(5, 365) = 287.34$, $p < .001$. US expectancies were higher on CS+ ($M = 6.65$, $SD = 0.77$) than GS1 ($M = 5.14$, $SD = 2.07$), $d = 0.77$, GS1 than GS2 ($M = 3.14$, $SD = 1.94$), $d = 0.95$, GS2 than GS3 ($M = 1.83$, $SD = 1.13$), $d = 0.72$, GS3 than GS4 ($M = 1.21$, $SD = 0.47$), $d = 0.59$, and GS4 than CS- ($M = 1.05$, $SD = 0.28$), $d = 0.35$. In summary, US expectancies gradually declined across the entire generalization gradient. There were no other significant main effects or interactions of group, predictability information, or test stimuli.

Post-Test: Fear ratings. When examining post-test fear ratings, where higher scores reflect higher fear of test stimuli (CS+, GS1-4, CS-) after the task, there was a main effect of test

stimulus, $F(5, 365) = 246.25, p < .001$. Participants reported higher fear of CS+ ($M = 5.99, SD = 1.51$) than GS1 ($M = 5.21, SD = 1.87$), $d = 0.73$, GS1 than GS2 ($M = 3.45, SD = 1.81$), $d = 1.20$, GS2 than GS3 ($M = 2.09, SD = 1.15$), $d = 0.96$, GS3 than GS4 ($M = 1.44, SD = 0.80$), $d = 0.55$. In summary, post-test fear ratings gradually declined across nearly the entire generalization gradient. There were no other significant main effects or interactions of group, predictability condition or test stimuli.

Post-Test: US distress. US distress ratings, where higher scores reflect greater distress caused by the US, were measured in three ways: average distress, end distress, and peak distress. There were no significant main effects or interactions for group or predictability condition.

Post-Test: Predictability. When examining the degree to which participants felt that they could predict the US contingency, where higher scores reflect higher perceived predictability, there was a main effect of predictability information condition, $F(1, 73) = 5.23, p = .03, d = 0.55$. Participants who received danger cue predictability information condition reported higher perceived predictability ($M = 5.24, SD = 1.06$) compared to participants who received safety cue predictability information ($M = 4.58, SD = 1.34$). In other words, although all participants received some kind of predictability information, those that received information about the danger cue reported higher perceived predictability.

Psychopathology and Sex Hormones Predicting of Fear Overgeneralization

Simultaneous linear regression was used to examine whether psychopathology factors (i.e., BDI-II, STAI-S, BEAQ, IUS) predicted online risk ratings and avoidance accuracy in the last block to the most ambiguous stimuli (GS2 and GS3). A Pearson correlation was used to examine whether posttraumatic avoidance behavior (PABQ) was associated with the same key dependent variables.

Psychopathology predicting online risk ratings. When examining whether depression (BDI-II), state anxiety (STAI-S), experiential avoidance (BEAQ), intolerance of uncertainty (IUS), predicted online risk ratings in the last block for GS2, the overall model was significant, $R^2 = .13$, $F(72) = 2.69$, $p = .04$. Specifically, higher intolerance of uncertainty predicted higher online risk ratings to GS2, $b = .39$, $t(72) = 2.74$, $p = .01$.

When examining whether depression, state anxiety, experiential avoidance, and intolerance of uncertainty predicted online risk ratings in the last block for GS3, the overall model was again significant, $R^2 = .23$, $F(72) = 5.51$, $p = .001$. Specifically, this was again driven by higher intolerance of uncertainty predicting online risk ratings to GS3, $b = .07$, $t(72) = 3.42$, $p = .001$.

Posttraumatic avoidance behavior (PABQ), in the high stress load group, was not strongly associated with online risk ratings in the last block to GS2 ($r = .09$) or GS3 ($r = -.01$). In summary, higher intolerance of uncertainty was associated with higher risk ratings to the most ambiguous stimuli in the last block.

Psychopathology predicting avoidance accuracy. When examining whether depression (BDI-II), state anxiety (STAI-S), experiential avoidance (BEAQ), intolerance of uncertainty (IUS), predicted avoidance accuracy in the last block for GS2, the overall model was not significant.

When examining whether the same measures predicted online risk ratings in the last block for GS3, the overall model was significant, $R^2 = .15$, $F(72) = 3.08$, $p = .02$. However, this was not driven by any specific measure.

When examining whether posttraumatic avoidance behavior (PABQ) in the high stress load group was associated with avoidance accuracy in the last block, there was a significant

correlation, $r = -.34$, $p = .03$, such that higher posttraumatic avoidance behavior was significantly associated with lower avoidance accuracy on GS3. Although the relationship between posttraumatic avoidance behavior and avoidance accuracy on GS2 was not significant, the pattern was consistent ($r = -.16$). In summary, higher posttraumatic avoidance behavior was associated with poorer avoidance accuracy to the most ambiguous stimuli in the last block.

In summary, higher intolerance of uncertainty predicted higher online risk ratings to the most ambiguous stimuli (GS2 and GS3) and higher posttraumatic avoidance behavior was associated with poorer avoidance accuracy on GS3.

See Table 4 for correlations among self-report psychopathology measures. See Tables 5 and 6 for correlations among self-report measures and online risk ratings and avoidance accuracy in the fear generalization test. In general, higher psychopathology was associated with higher online risk ratings and lower avoidance accuracy on one of the most highly ambiguous stimuli (GS3).

Sex hormones predicting online risk ratings. Simultaneous linear regression was used to examine whether estradiol and progesterone predicted online risk ratings and avoidance accuracy in the last block to the most ambiguous stimuli (GS2 and GS3).

When examining whether estradiol and progesterone predicted online risk ratings in the last block for GS2, the overall model was not significant. When examining GS3, however, the overall model had trend-level significance, $R^2 = .09$, $F(2, 58) = 2.69$, $p = .07$. Specifically, progesterone predicted online risk ratings for GS3, $b = .26$, $t(60) = 2.09$, $p = .04$, such that higher progesterone predicted higher online risk ratings for GS3 in the last block.

Sex hormones predicting avoidance accuracy. When examining the degree to which estradiol and progesterone predicted avoidance accuracy in the last block for GS2, the overall

model was not significant. However, the model was significant when examining estradiol and progesterone predicting avoidance accuracy in the last block for GS3, $R^2 = .10$, $F(2, 58) = 3.23$, $p = .05$. Specifically, progesterone predicted avoidance accuracy for GS3, $b = -.32$, $t(60) = -2.52$, $p = .01$, such that higher progesterone predicted lower avoidance accuracy for GS3 in the last block.

Overall, higher progesterone predicted higher online risk ratings and lower avoidance accuracy for the most ambiguous stimuli. Estradiol, on the other hand, did not strongly predict online risk ratings or avoidance accuracy. See Table 7 for correlations among estradiol, progesterone, online risk ratings, and avoidance accuracy in the fear generalization test. There was no association between estradiol and progesterone levels ($r = -.03$); and, as seen in the Table 7, higher progesterone was associated with higher online risk ratings to GS3.

Discussion

Fear generalization is a key construct for understanding why some individuals struggle to feel safe in objectively non-threatening situations. Although generalization of fear can be an adaptive phenomenon in helping individuals steer clear of dangerous situations, overgeneralization can lead to excessive and persistent fear of innocuous stimuli and situations. As expected, individuals with high levels of neuroticism and prior trauma exposure, relative to individuals with low neuroticism and no prior trauma exposure, showed fear appraisal and avoidance patterns consistent with fear overgeneralization, particularly to the most ambiguous stimuli. Importantly, this finding only emerged towards the end of the fear generalization task, suggesting that a combination of high neuroticism and trauma exposure may predispose individuals to the *persistence* of overgeneralized responding. Whereas participants regardless of neuroticism levels and trauma history responded similarly at the beginning of the task, a

combination of high neuroticism and trauma exposure was associated with an enduring overestimation of threat and behavioral avoidance. As expected, there were also differential effects of receiving predictability information that highlighted either danger cue or safety cue information, such that the provision of safety cue information may have helped protect low stress load individuals from persistent overgeneralized avoidance but either backfired or was an insufficient intervention for the high stress load individuals. The present study laid important groundwork for elucidating the potential utility of providing safety-enhancing information to mitigate maladaptive fear responding and highlights clinical implications for preventatively targeting preclinical transdiagnostic constructs, such as neuroticism and intolerance of uncertainty, that increase vulnerability for fear overgeneralization.

Fear overgeneralization in individuals with high neuroticism and prior trauma exposure is consistent with a growing body of literature pointing to fear overgeneralization as a transdiagnostic feature of anxiety based disorders (Dymond et al., 2015). Although fear generalization has been documented in other clinical samples such as panic disorder (Lissek et al., 2010), generalized anxiety disorder (Lissek et al., 2014), social anxiety disorder (Ahrens et al., 2016), and PTSD (Morey et al., 2015; Thome et al., 2017), this is the first study to examine neuroticism in the context of stressful life events. This critical and much needed examination across trait and stressor domains (Caspi et al., 2014) is particularly important, given the strong association between higher neuroticism and more frequent and intense negative reactions to stressful life events (Lahey, 2009). It is possible that the presence of high neuroticism and prior stressful life events represent non-clinical transdiagnostic vulnerability factors that collaboratively predispose individuals to later maladaptive responding. In fact, this may begin to explain why a recent study did not find an effect of neuroticism alone on fear generalization

(Arnaudova et al., 2017), although another one did (Lommen et al., 2010). It is possible that neuroticism *in the context of prior trauma* magnifies information processing impairments such as fear overgeneralization, consistent with the notion that the deleterious effect of high neuroticism lies specifically in maladaptive responses to threat, stress, and ambiguity (Kendler, Gardner, & Prescott, 2003; Suls & Martin, 2005; Parslaw, Jorm, & Christiansen, 2006; Uliaszek et al., 2009). This study extends the current literature by putting forth somewhat of a “two-hit” hypothesis, wherein highly heritable trait neuroticism paired with trauma exposure predisposes individuals to fear overgeneralization in an ambiguous, fear-eliciting task.

Excessive fear itself is not nearly as problematic as the maladaptive and life-impairing avoidance behavior it often motivates (Craske et al., 2018). This research adds to the fear generalization literature by measuring not only the spread of fear, but also the spread of unnecessary avoidance of harmless stimuli that contain aspects of both a conditioned danger cue and a conditioned safety cue, in line with previous studies (Boyle et al., 2015; van Meurs et al., 2014; Lommen et al., 2010). Importantly, overgeneralized avoidance in this study was associated with a *persistent* behavioral avoidance pattern, consistent with fear and avoidance patterns implicated in anxiety and stressor-related disorders (Craske et al., 2018). In other words, initial avoidance of a novel and possibly dangerous stimulus is not necessarily impairing and may even be adaptive; however, rigid and relentless avoidance behavior in the absence of danger can transform avoidance into a maladaptive response (Kryptotos, Effting, Kindt, & Beckers, 2015). Consistent with definitions of anxiety- and stressor-based disorders being characterized by marked and persistent fear that is excessive or unreasonable (American Psychiatric Association, 2013), persistent avoidance can be thought of as a cardinal transdiagnostic symptom that likely also contributes to recovery failure, or the inability to extinguish fear over time, by preventing

the ability to acquire corrective inhibitory learning (Foa & Kozak, 1986). In fact, posttraumatic resiliency does not necessarily involve the absence of fear and avoidance, but rather the ability to “bounce back” after fearful events (Zoellner & Feeny, 2014). The present study points to maladaptive fear overgeneralization as a problem of persistence, reflecting a failure to adapt over time, given that differences emerged in the final test block after repeated opportunities to learn that GS stimuli are harmless. However, the excessive avoidance behavior only occurred in the high stress load individuals within the safety cue predictability information condition. Although the safety cue information condition was hypothesized to reduce the spread of fear, this hypothesized effect only benefitted low stress load individuals. We will begin by discussing this effect in the safety cue condition and then discuss reasons for why this effect may have been mitigated when participants were given danger cue information.

Current theories accounting for pathways to overgeneralized fear and avoidance may elucidate why the safety cue manipulation did not have the intended effect of reducing the spread of fear on the high stress load group. For instance, several studies point to poor discrimination between conditioned danger cues and safety cues (Haddad et al., 2012; Lissek et al., 2005), poor safety transfer from safety cues to ambiguous stimuli (Jovanovic et al., 2012; Sijbrandij et al., 2013), or deficits in using contextual information to modulate fear responding (Levy-Gigi et al., 2015; van Rooij et al., 2015; Waters & Craske et al., 2016). In the present study, both danger cue and safety cue information conditions were designed to enhance predictability information, but only the latter was expected to specifically aid with safety transfer by enhancing safety cue salience. However, contrary to our hypotheses, it was precisely in the safety cue condition only that the high stress load individuals showed more overgeneralized avoidance compared to the low stress load group. On the one hand, it is possible that the safety cue information was

unhelpful to the high stress load individuals, consistent with extinction-based theories (Craske et al., 2008; 2014; Foa & Kozak, 1986) that highlight the iatrogenic nature of safety behaviors, defined as actions performed to prevent, escape, or minimize feared outcomes or associated distress (Blakey & Abramowitz, 2016). According to prominent inhibitory learning theories (Bouton, 2004; Rescorla & Wagner, 1972), safety behaviors prevent the acquisition and generalization of corrective, inhibitory learning by reducing the maximum violation of negative expectancies. If this is the case, then the provision of safety cue information may have inadvertently blocked more adaptive fear appraisals and behaviors for the high stress load individuals.

However, others argue that safety behaviors are not ubiquitously problematic and that judicious use of safety cues may facilitate approach behavior and even promote the generalization of non-threat associations (Levy & Radomsky, 2014; Rachman et al., 2008). In fact, the present finding that individuals with high neuroticism and prior trauma exposure avoided more than individuals with low neuroticism and no trauma exposure when given information about the safety cue may highlight a deficit in utilizing, or trusting, safety cue information. This difficulty incorporating safety information when appraising and avoiding ambiguous situations may explain why the low stress load individuals benefitted from safety cue information whereas the high stress load individuals did not. It could be that individuals with higher neuroticism and prior trauma exposure have a higher resistance to feeling safe, or simply more experiences from their lives contradicting feelings of safety. They may have simply needed a stronger safety cue manipulation, either by way of more detailed information (i.e., about the generalization stimuli themselves to further disambiguate the US contingency) or more frequent repetition of the safety cue information (i.e., across multiple trials). This is in line with the notion

that learning to fear is easy, but learning not to fear is harder (Bolles, 1972; Bouton, 2004). For example, a person who is bitten (US) by a dog (CS+) probably doesn't need more than that single interaction to fear that dog (CS+), but may need multiple positive interactions with a different dog (CS-) in order to effectively discriminate between danger and safety cues, which requires the successful incorporation, storage, and retrieval of safety-relevant information. During such exposures, it may be useful for individuals to take note of subtle safety cues (e.g., smaller size, no teeth showing, tongue hanging out, and wagging tail) and use that safety cue information to reappraise the threat of the situation. However, exposure therapists may choose not to point out these safety signals that disambiguate the situation out of fear of botching the exposure, which theoretically relies on maximizing the violation of negative expectancies (e.g., Craske et al., 2008). Findings from the present study, showing that highlighting safety cue information helped low stress load individuals but did not help high stress load individuals, are either consistent with theories of iatrogenic safety behaviors (e.g., Craske et al, 2008) or simply highlight a need for additional coaching with high stress load individuals in how to notice, utilize, and generalize safety information.

In contrast to how safety cue information shifted avoidance responding, there were no differences between high and low stress load individuals when given danger cue information. A possible explanation for the mitigation of this effect is that the danger cue information represented a "strong situation," defined as a context in which there is unambiguous threat and the strength of the task or manipulation inadvertently masks group differences that would otherwise emerge (Lissek, Pine, & Grillon, 2006). On the flip side, weaker experimental situations may increase variability in responding and thus may be more likely to elicit differences in anxious arousal. Indeed, participants in the present study characterized the danger cue

condition as a “stronger” condition than the safety cue condition, in that participants randomized to receive danger cue information reported higher resulting levels of predictability compared to those who were randomized to receive safety information. There may be something inherently stronger about threat-relevant information compared to information that is not relevant to threat, which fits with adaptive, evolutionary survival strategies for facilitating the detection of threat in order to avoid danger (Bar-Haim et al., 2007). Further, there is strong evidence for higher attentional bias towards threat in individuals with higher anxiety (Bar-Haim et al., 2007; Cisler & Kostner, 2010; Fani et al., 2012) as well as evidence that individuals with higher neuroticism are simply more willing to accept false alarms in order to avoid missing danger signals (Calvo & Castillo, 2001; Eysenck & Derakshan, 1997; Eysenck et al., 1987). In sum, the danger cue information may have been a strong enough situation to obscure differences between high and low stress load individuals. The safety cue condition may have provided a weak enough situation to allow the high stress load individuals to show overgeneralized patterns of fear and avoidance, relative to low stress load individuals.

Individuals who received danger cue information had faster response styles when appraising stimuli, as did high stress load individuals. Reaction times may serve as an index of threat uncertainty, wherein faster times reflect greater certainty and slower times reflect greater uncertainty (Lissek et al. 2010; 2014). Adaptive responding to ambiguous stimuli may involve slower responses, whereas maladaptive responding, characterized by poor discrimination between danger and safety cues, may involve faster responses. Consistent with this, both individuals who received danger cue information, as well as individuals with high stress load, had faster responses, indicative of quicker appraisals even in the face of ambiguity. However, these effects were independent of one another and not interactive. It is noteworthy that the

individuals who were given danger cue predictability information essentially mirrored the high stress load individuals. Conversely, the manipulation of providing safety cue information caused individuals to slow down in their appraisals and behave more like low stress load individuals. This could have interesting clinical implications, given that clinicians cannot easily change an individual's trait neuroticism or prior exposure to traumatic life events, but they can certainly change their approach in coaching an individual to slow down when appraising situations. Although fast responding in the face of danger is adaptive and involuntary (Bar-Haim et al., 2007), there may be opportunities for teaching individuals to slow down and check speedy reactions to ambiguous stimuli that are unlikely to be harmful.

Individuals with higher neuroticism and prior trauma exposure also had higher self-reported anxiety, depression, experiential avoidance, and intolerance of uncertainty compared to individuals with lower neuroticism and no prior trauma. In fact, strong correlations between neuroticism and the aforementioned constructs may point to neuroticism as a central, higher order construct across the psychopathology measures (Barlow et al., 2014). Although this research is in line with prior work linking higher neuroticism and fear overgeneralization (Lommen et al., 2010), negative affect in response to uncertainty and ambiguity (Barlow et al., 2013), and more intense negative reactions to stressful life events (Lahey et al., 2009; Parslow et al., 2006; Uliaszek et al., 2009), the present research speaks to more than just a relationship between neuroticism, trauma exposure, and fear generalization. Notably, there were moderate and consistent associations between higher avoidance and risk appraisals of the most ambiguous stimuli (GS3), specifically, and higher depression, trait anxiety, state anxiety, PTSD, behavioral and experiential avoidance, and intolerance of uncertainty. This is consistent with growing evidence for information processing abnormalities in anxiety and stress-related disorders on the

safety side of the spectrum (e.g., Garcia & Zoellner, 2017; Jovanovic et al., 2012; Lissek et al., 2005), suggesting that maladaptive fear responding is not so much characterized by hyperreactivity to danger cues but rather difficulty differentiating danger cues from safety cues. However, there were no significant associations between psychopathology and risk appraisals and avoidance behaviors in the presence of the safety cue itself (CS-) in the present study, highlighting the particularly strong relationship for ambiguity, rather than safety per se.

The emphasis on interpretation of ambiguous stimuli is further highlighted by the consistently moderate relationship between higher intolerance of uncertainty and higher risk appraisals and lower avoidance behavior for nearly the full gamut of ambiguous stimuli. In other words, there was a robust relationship between intolerance of uncertainty, a trait characterized by misinterpreting ambiguous events as threatening and overestimating risk (Butler & Mathews, 1987), and maladaptive responses to the uncertain stimuli. Intolerance of uncertainty is associated with anxiety-based disorders (Dugas, Gagnon, Ladouceur, & Freeston, 1998; Tolin, Abramowitz, Brigidi, & Foa, 2003; Boelen & Reijntes, 2009) and to higher post extinction return of fear (Dunsmoor, Campese, Ceeceli, LeDoux, & Phelps, 2015). In the present study, higher intolerance of uncertainty was strongly associated with higher neuroticism, questioning the divergent validity of intolerance of uncertainty as a unique predictor of fear overgeneralization. However, in a recent fear generalization study, intolerance of uncertainty predicted attenuated attention to generalization stimuli, possibly reflecting avoidant strategies in the face of uncertain and distressing stimuli (Nelson, Weinberg, Pawluk, Gawlowska, & Poudfit, 2015). In sum, there were highly consistent associations between higher psychopathology-related constructs and exaggerated fear and avoidance responding to the most ambiguous stimuli, as well as evidence

pointing to the possibility of neuroticism as a higher-order transdiagnostic factor and potentially unique contributions of intolerance of uncertainty.

A critical and unique undertaking of the present research was to test whether active avoidance behavior in the fear generalization task mapped on to self-reported avoidance in daily life. Experiential avoidance, reflecting multiple facets of avoidance across cognitive, emotional, and behavioral domains, was not only moderately higher in individuals with high neuroticism and prior trauma exposure, compared to those with low neuroticism and no prior trauma, but it was also slightly to moderately associated with higher active behavioral avoidance of the most ambiguous stimuli. Posttraumatic avoidance behavior, on the other hand, was not strongly associated with overgeneralized avoidance. However, this measure was only administered to the high stress load individuals due to its specificity to avoidance following trauma exposure. While it is possible that the broader construct of experiential avoidance, including emotional and cognitive avoidance, was more predictive of fear generalization, the measure was only given to half of the sample and there may not have been sufficient variability in posttraumatic avoidance behavior among those with high neuroticism plus trauma exposure to reveal a strong relationship with fear overgeneralization. Overall, the present study shows a sturdy relationship between self-reported experiential avoidance in real life and avoidance behavior in the task, in line with studies linking avoidance behavior as an index of fear over generalization (e.g., Boyle et al., 2015; Declercq & DeHouwer, 2009; Lommen et al., 2010; van Meurs et al., 2014).

Another critical extension of the fear learning literature was to examine estradiol and progesterone as predictors of fear overgeneralization, given that women are disproportionately affected by anxiety and traumatic stressor related disorders (Kessler et al., 1995; McLean et al., 2011) and sex hormones have been implicated in fear extinction processes (see Garcia et al.,

2018). In the present study, there was no strong relationship between estradiol and fear generalization, which is inconsistent with robust protective effect of higher estradiol on processes such as fear extinction and fear-extinction recall (e.g., Graham & Milad, 2013; Milad et al., 2010; Zeidan et al., 2011). Interestingly, it was higher salivary progesterone that predicted both higher fear and excessive avoidance the most ambiguous stimuli. This is consistent with some evidence for higher PTSD re-experiencing symptoms during the luteal phase (high estradiol and progesterone) in clinical samples (Bryant et al., 2011; Ferec & Cahill, 2009; Ferree et al., 2011; Soni et al., 2013). Although the analyses in the present study may be confounded by hormonal contraceptive use and irregular cycling, the pattern of results did not change when examining naturally and regularly cycling women only. Although hormone based interventions have the potential to provide relatively non-invasive optimization of exposure based treatments, the literature is far from conclusive regarding the estradiol and progesterone effects on fear learning processes.

This study had limitations that are worth discussing. Although neuroticism and trauma exposure constructs were intentionally combined to form stress load groups, this removes the ability to separate out their unique effects and contributions. However, it is difficult and perhaps not useful to isolate the effects of high neuroticism and trauma exposure, given their high degree of natural co-occurrence. Similarly, the choice to include two predictability information conditions neglects a third, control condition of no predictability information. However, a prior study previously examined the effect of danger cue predictability versus no predictability information and found effects of predictability information that required further exploration via breaking down the components of danger cue contingency versus safety cue contingency predictability information (Garcia & Zoellner, 2017). Although the present study included a

community sample with high neuroticism and trauma exposure, participants, on the average, did not have high rates of psychopathology, though a number of participants scored well within a clinical range. Further, there were no structured clinical interviews to assess for PTSD, mood, or anxiety disorders, which could have provided more precise clinical assessments. However, the use of high and low stress load groups selected on neuroticism scores helped to achieve sufficient variability on related psychopathology measures to capture reliable associations and predictors of fear overgeneralization. Some analyses were also likely underpowered and had unequal cell sizes, which may have obscured more small to moderate associations and impacted the generalizability of the present findings. Given that predictability information was expected to modify danger cue and safety cue expectancies, it would have been helpful to re-administer the post-acquisition US expectancy and fear ratings after the predictability information manipulation to examine potential changes in fear acquisition prior to the fear generalization task. However, it would have been impractical to assess for US contingencies immediately after providing predictability information, and US contingencies and fear ratings were assessed a second time at the end of the fear generalization task. Further, the predictability manipulation clearly had an effect on the fear generalization test phase independent of the fear acquisition phase. Although the avoidance phase was an innovative addition to the present study, the avoidance task did not incentivize participants *not* to avoid. In other words, there was no penalty to playing it safe and pressing the spacebar at every avoidance trial. However, participants did not routinely employ this strategy, despite the absence of a negative consequence of exclusively avoiding. Importantly, there is a growing literature suggesting that studying fear-driven avoidance behavior in the absence of reward-driven approach drives provides an incomplete understanding of real world avoidance where approach-avoid conflicts commonly exist (see Kirlic, Young, Aupperle, 2017).

Another limitation was the use of a differential conditioning task (CS+ and CS-), as opposed to single cue conditioning (CS+), that may have weakened the manipulation of enhancing predictability information about a single cue by inadvertently but inherently providing information about both cues. Yet, differential conditioning to both danger and safety cues was an optimal choice for creating a clear generalization gradient to test learning in both directions. Finally, although both hormone levels and menstrual cycles were assessed, the inclusion of women with irregular cycles and using hormonal contraceptives may have obscured the ability to detect effects. However, including these women increases the generalizability of the findings, given the high rates of contraceptive use in women of childbearing age.

It will be important to continue exploring the effect of safety cue predictability information. Namely, further investigating whether the presence of safety cue information led to unhelpful and possibly even iatrogenic effects or was simply insufficient and a more powerful intervention with more detailed and repeated safety information was required. A follow up study may involve testing multiple versions of safety cue and danger cue predictability information conditions to explore the effect of more active coaching (e.g., “This face has red hair”), slowing processing speed (e.g., prompting individuals to slow down and reappraise automatic thoughts), or repeated presentations of the same predictability information. However, as observed in the present study and a prior study (Garcia & Zoellner, 2017), and consistent with extinction based theories underlying exposure therapies (Craske et al., 2008), predictability information also has the potential to backfire, such that well-intentioned information can be used in unanticipated ways or not at all.

Finally, a clinically relevant continuation of the present research involves exploring the generalization of extinction learning. Given that gold-standard exposure therapies often do not

get to target the full spectrum of stimuli in a fear network and instead end up focusing on the most feared stimuli, it is crucial to harness what is known about the spread of fear learning and apply this to what needs to be known about the *spread of corrective inhibitory learning*, to maximize the reach of clinical interventions beyond the learning that is directly achieved during therapy sessions. Although evidence based treatments for anxiety and stressor related disorders are highly effective with large effects and gains maintained over time (Schneider, Arch, Wolitzky-Taylor, 2015; Watts et al., 2013), one of the challenges may be with the generalization of this exposure learning, which largely depends on the ability for extinction to generalize to the many anxiety producing cues that simply cannot be targeted due to feasibility limitations and time constraints (Craske et al., 2018). Future research may adapt the current paradigm by randomizing participants to either a fear extinction or distraction task phase in between fear acquisition and fear generalization phases, allowing for examination of fear responding along a similar generalization with either an extinguished cue or a danger cue. Future clinical studies may explore ways of promoting stimulus differentiation (Haddad et al., 2012; Lissek et al., 2005), safety transfer (Jovanovic et al., 2012; Sijbrandij et al., 2013), and use of contextual information to modulate fear responding (Levy-Gigi et al., 2015; van Rooij et al., 2015; Waters & Craske, 2016) in a clinical setting to enhance current psychotherapy interventions. This may involve manipulations targeting active therapist coaching in generalizing successful extinction learning or explicitly pointing out shared features between extinguished fear cues and related cues in other areas of life.

Another clinical implication of the current research is on the prevention of psychopathology by targeting pervasive fear overgeneralization patterns before a trauma or stressful event even occurs. An important first step is identifying individuals who may be

particularly vulnerable to fear overgeneralization. Based on the current study, and in line with previous work (e.g, Lommen et al., 2010), trait neuroticism poses a general vulnerability for maladaptive responding even in the absence of an expressed mental disorder phenotype, such as PTSD or depression. It will be important to continue exploring non-clinical transdiagnostic constructs, such as experiential avoidance and intolerance of uncertainty (Carleton, 2016), to more precisely identify those who are most susceptible to overgeneralized fear responding. Critical next steps will be intervening on fear overgeneralization tendencies, perhaps by treating associated pre-clinical factors themselves. Some have recommended screening for neuroticism during routine medical visits (Widiger, 2017) and a promising transdiagnostic unified protocol has shown promise in treating neuroticism (Wiliamowska et al., 2010). Finally, based on the current study, further elucidating the potential utility and effectiveness of training individuals to strategically notice, utilize, and generalize safety information in their environment may also provide innovative targets for transdiganostic interventions aimed at evading psychopathology and increasing the likelihood of resiliency in the event of future negative life events.

The present research showed that individuals with high neuroticism and prior trauma exposure overgeneralized fear and avoidance to the most ambiguous stimuli at the end of the task, pointing towards a pattern of maladaptive *persistence* of overgeneralized responding. This study also experimentally tested the utility of providing safety-enhancing information, despite widely held clinical beliefs that safety information is iatrogenic for adaptive fear learning. Although providing information about the safety cue reduced the likelihood of avoiding the most ambiguous stimuli for individuals with low neuroticism and no prior trauma exposure, the manipulation did not alter responding for individuals with high neuroticism and prior trauma exposure. This may have been due to iatrogenic effects of providing safety information or may

suggest that high stress load individuals simply needed a stronger intervention via more detailed or more repetitive safety cue information. Although behavioral avoidance is difficult to study, this research adds to the literature by showing that fear-motivated avoidance behavior can overgeneralize, as exemplified in this ambiguous, fear-eliciting generalization task. Future work will need to elucidate the utility of safety cue information in assisting with information processing as well as the utility in exploring how to harness what is known about fear overgeneralization into maximizing the generalization of adaptive extinction learning. Clinical applications may involve directly targeting preclinical transdiagnostic factors that increase vulnerability for overgeneralized fear responding, such as neuroticism and intolerance of uncertainty, in order to increase resiliency and proactively circumvent risk for later pathology.

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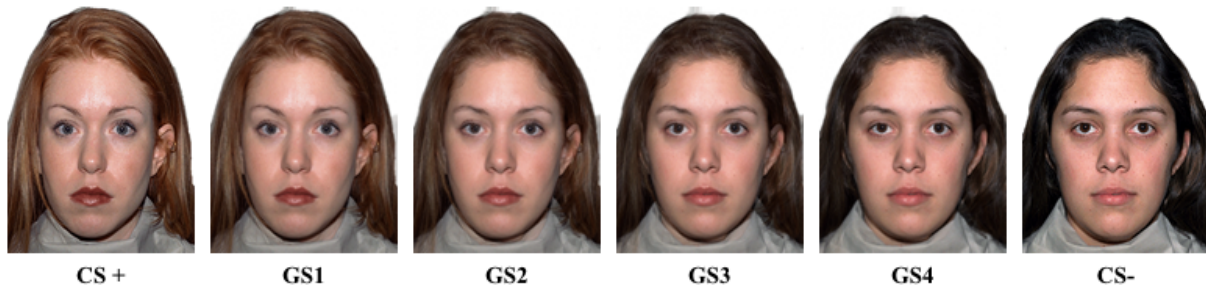
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Figure 1. *Generalization Gradient with Conditioned Stimuli (CS+, CS-) and Generalization Stimuli (GS1-4)*



Note. Conditioned stimuli (CS+ and CS-) will be counterbalanced. Conditioned fear was designed to decrease from right to left across this gradient. Images obtained from NimStim Set of Facial Expressions (Tottenham et al., 2009)

Figure 2. *Study flowchart*

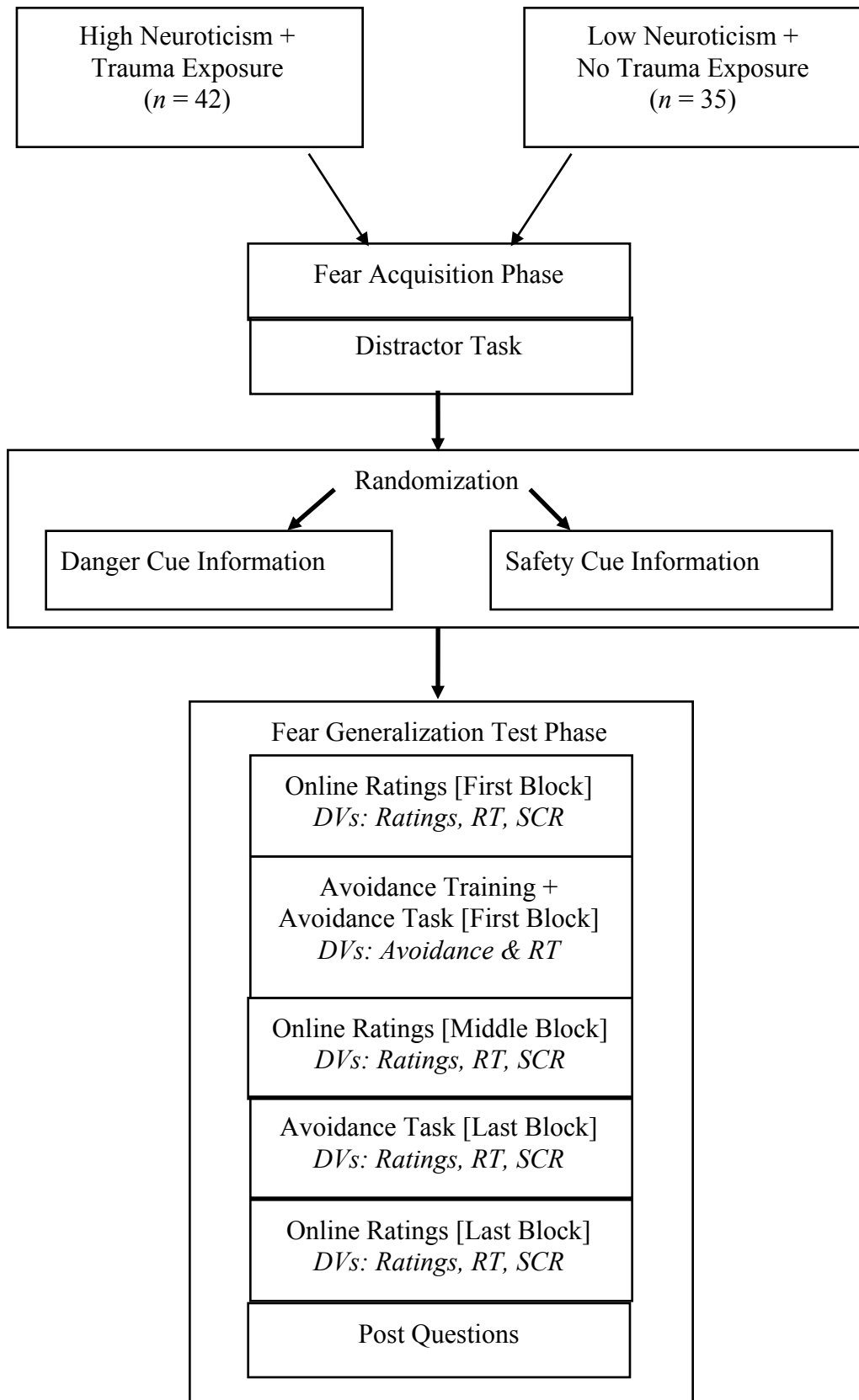
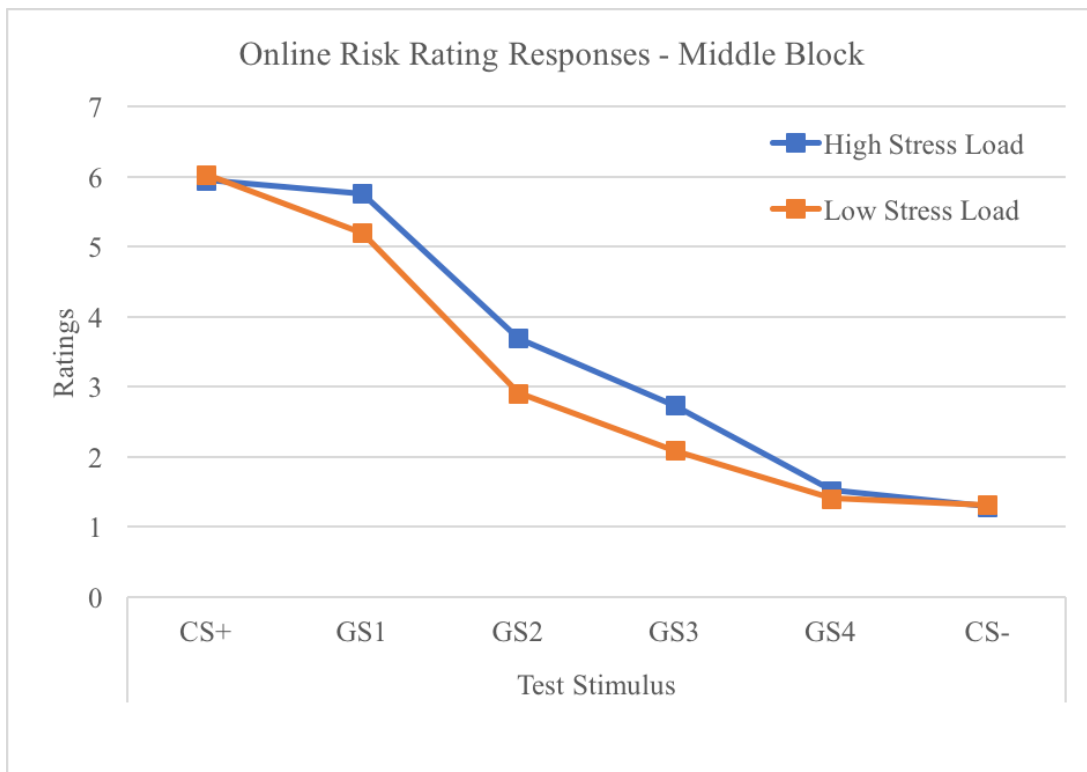
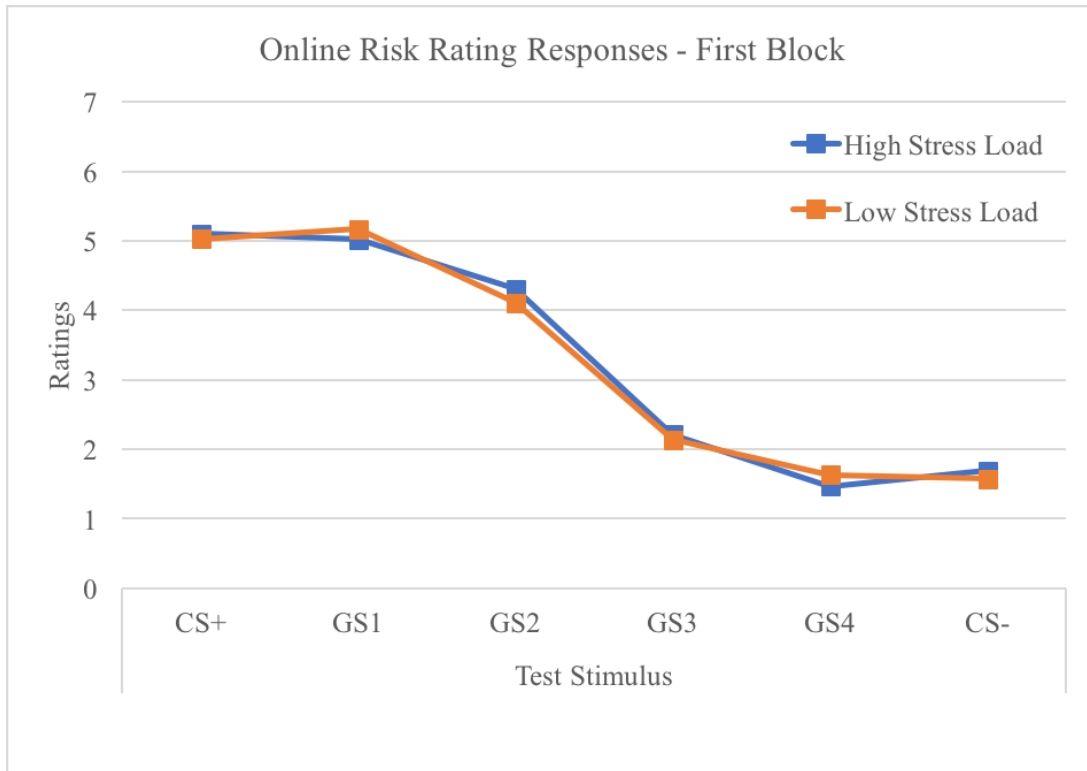


Figure 3. Online risk rating responses: Group by predictability by test stimulus interaction across blocks



Online Risk Rating Responses - Last Block

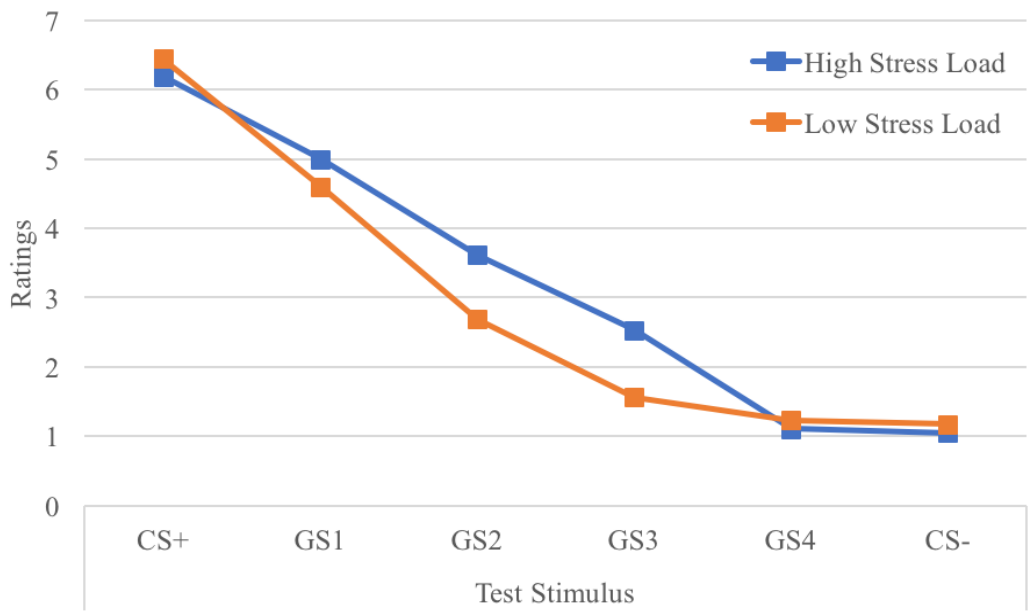
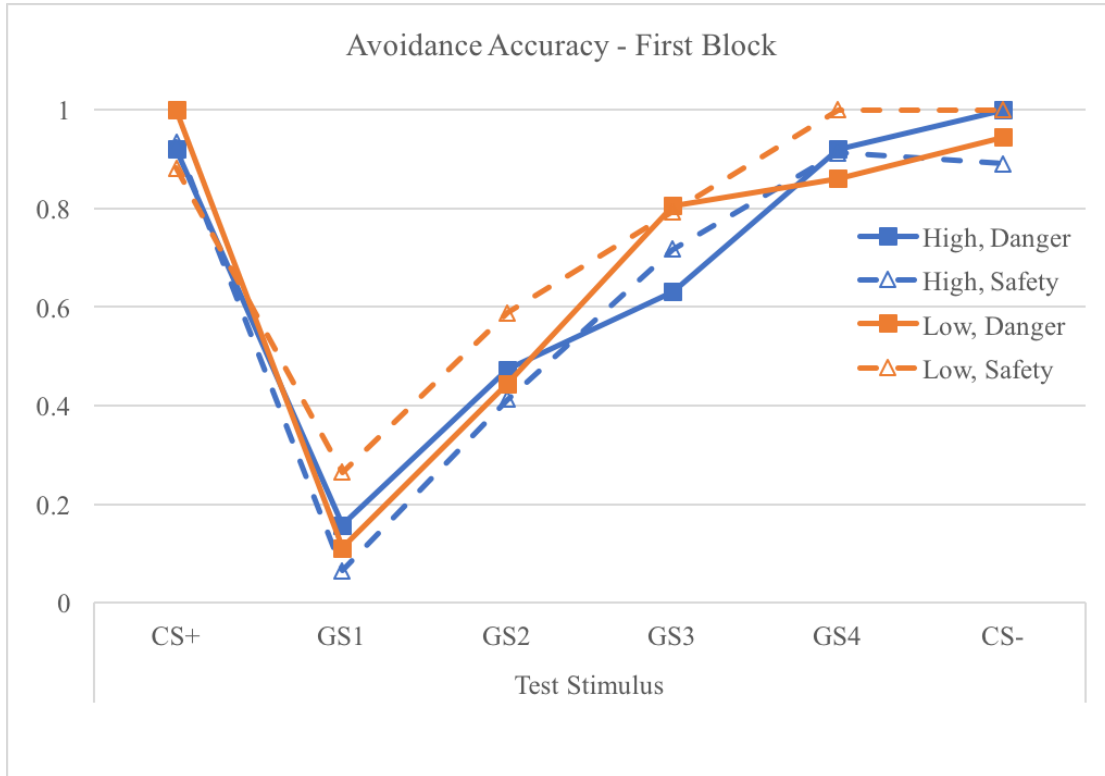


Figure 4. Avoidance accuracy: Group (high and low stress load) by predictability (danger versus safety information) by test stimulus interaction



Avoidance Accuracy - Last Block

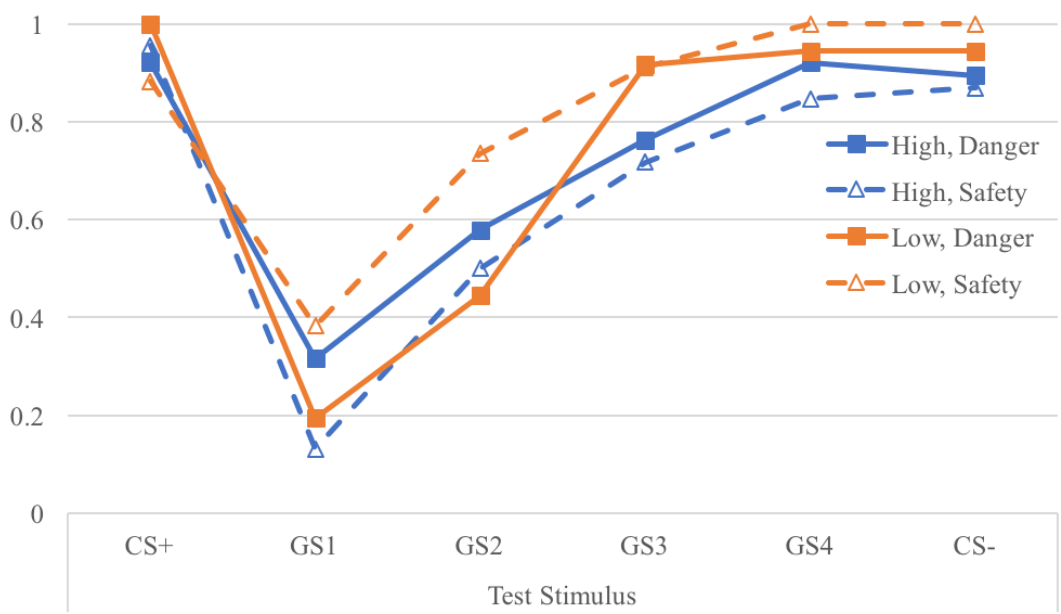


Table 1. *Baseline characteristics: Danger and safety cue predictability information conditions & high and low stress load groups*

| | High Stress Load | | | | Low Stress Load | | | |
|-------------------------------|------------------|-----------|-----------------|-----------|-----------------|-----------|-----------------|-----------|
| | Danger Cue | | Safety Cue | | Danger Cue | | Safety Cue | |
| | <i>(n = 19)</i> | | <i>(n = 23)</i> | | <i>(n = 18)</i> | | <i>(n = 17)</i> | |
| | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> |
| Age (years) | 24.16 | 5.47 | 23.26 | 4.71 | 22.00 | 4.00 | 21.76 | 3.70 |
| Ethnicity (% Caucasian) | 36.8% | | 65.2% | | 38.9% | | 35.3% | |
| Education (years) | 15.37 | 2.14 | 14.91 | 2.00 | 15.00 | 2.54 | 14.59 | 2.67 |
| Neuroticism (EPQ-RN) | 18.32 | 3.62 | 17.73 | 2.72 | 3.94 | 2.41 | 5.53 | 2.03 |
| Life Stressors (LSC-R) | 9.01 | 4.61 | 9.65 | 4.92 | 3.33 | 3.34 | 2.88 | 1.76 |
| PTSD Severity (PSS-SR-5) | 19.28 | 11.86 | 23.05 | 18.14 | | | | |
| Depression (BDI-II) | 15.11 | 9.81 | 17.29 | 13.67 | 3.72 | 3.06 | 5.24 | 4.97 |
| Behavioral Avoidance (PABQ) | 43.53 | 11.75 | 44.14 | 13.17 | | | | |
| Experiential Avoidance (BEAQ) | 54.26 | 9.44 | 50.04 | 6.77 | 42.50 | 7.27 | 44.88 | 6.56 |
| Trait Anxiety (STAI-T) | 50.89 | 9.55 | 51.09 | 11.60 | 29.33 | 7.35 | 33.18 | 9.55 |

| | | | | | | | | |
|-------------------------------|-------|------|-------|-------|-------|------|-------|------|
| State Anxiety (STAI-S) | 42.68 | 7.82 | 42.70 | 11.31 | 27.67 | 6.81 | 30.82 | 9.40 |
| Intolerance Uncertainty (IUS) | 33.26 | 8.84 | 36.00 | 9.84 | 22.50 | 6.16 | 27.29 | 6.17 |

Note. PTSD Severity measure was only give to the high stress load group ($n = 42$); EPQ-RN = Eysenck Personality Questionnaire - Revised - Neuroticism. LSC-R = Life Stressor Checklist – Revised. PSS-SR-5 = Posttraumatic Diagnostic Scale for DSM 5. BDI-II = Beck Depression Inventory-II. PABQ = Posttraumatic Avoidance Behavior Questionnaire. BEAQ = Brief Experiential Avoidance Questionnaire. Figures STAI-T = State-Trait Anxiety Inventory-Trait. STAI-S = State-Trait Anxiety Inventory-State. IUS = Intolerance of Uncertainty.

Table 2. Main outcomes: Danger and safety cue predictability information conditions & high and low stress load groups

| | High Stress Load | | | | Low Stress Load | | | |
|-----------------------|------------------|-----------|------------|-----------|-------------------|-----------|-------------------|-----------|
| | Danger Cue | | Safety Cue | | <i>Danger Cue</i> | | <i>Safety Cue</i> | |
| | (n = 19) | | (n = 23) | | (n = 18) | | (n = 17) | |
| | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> |
| US Expectancy Ratings | | | | | | | | |
| CS+ | 5.47 | 0.70 | 5.18 | 1.23 | 5.33 | 1.28 | 5.59 | 1.46 |
| CS- | 1.32 | 0.67 | 1.35 | 0.83 | 1.67 | 1.19 | 1.88 | 1.46 |
| Fear Ratings | | | | | | | | |
| CS+ | 3.74 | 1.48 | 3.48 | 1.78 | 2.67 | 1.78 | 3.06 | 1.56 |
| CS- | 1.53 | 1.17 | 1.43 | 1.08 | 1.94 | 1.26 | 2.12 | 1.36 |
| Online Risk Ratings | | | | | | | | |
| CS+ | 5.84 | 1.50 | 5.67 | 1.52 | 6.06 | 1.33 | 5.61 | 1.24 |
| GS1 | 5.30 | 1.66 | 5.23 | 1.46 | 4.94 | 1.67 | 5.04 | 1.62 |
| GS2 | 4.02 | 1.72 | 3.75 | 1.44 | 3.04 | 1.38 | 3.45 | 1.22 |

| | | | | | | | | |
|--------------------|------|------|------|------|------|------|------|------|
| GS3 | 2.47 | 1.16 | 2.48 | 1.26 | 1.74 | 0.77 | 2.28 | 0.99 |
| GS4 | 1.37 | 0.57 | 1.54 | 0.91 | 1.35 | 0.66 | 1.55 | 0.77 |
| CS- | 1.32 | 0.64 | 1.49 | 0.85 | 1.28 | 0.65 | 1.43 | 0.69 |
| Avoidance Accuracy | | | | | | | | |
| CS+ | .88 | .24 | .90 | .21 | .96 | .07 | .83 | .32 |
| GS1 | .24 | .34 | .10 | .24 | .15 | .30 | .32 | .41 |
| GS2 | .53 | .44 | .46 | .44 | .44 | .43 | .66 | .39 |
| GS3 | .70 | .40 | .72 | .37 | .86 | .30 | .85 | .28 |
| GS4 | .92 | .15 | .89 | .30 | .90 | .24 | 1.0 | 0.0 |
| CS- | .95 | .10 | .88 | .31 | .94 | .24 | .98 | .03 |

Note. CS+ = danger conditioned stimulus; CS- = safety conditioned stimulus; GS1-4 = generalization stimulus on a continuum of danger (GS1) to safety (GS4). US Expectancy Ratings: rated after acquisition on a scale of 1 (*extremely unlikely to be followed by US*) to 7 (*extremely likely to be followed by US*). Fear Ratings: rated after acquisition on a scale of 1 (*not at all afraid*) to 7 (*extremely afraid*). Online Risk Ratings: collected during the fear generalization test and rated on a scale of 1 (*no risk*) to 7 (*high risk*). Avoidance Accuracy: collected during the fear generalization test on a scale of 0 (*not accurate*) to 1 (accurate), where accuracy was defined as avoiding CS+ and not avoiding all other test stimuli (CS-, GS1-4). *p < .05

Table 3. *Associations among fear generalization test online risk ratings and avoidance accuracy*

| Variable | 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. | 10. | 11. | 12. | 13. |
|---------------------|-------|-------|-------|-------|-------|-------|-------|------|------|------|------|-----|-----|
| Online Risk Ratings | | | | | | | | | | | | | |
| 1. CS+ | -- | | | | | | | | | | | | |
| 2. GS1 | .73* | -- | | | | | | | | | | | |
| 3. GS2 | .41* | .66* | -- | | | | | | | | | | |
| 4. GS3 | .36* | .55* | .60* | -- | | | | | | | | | |
| 5. GS4 | .11 | .18 | .29* | .61* | -- | | | | | | | | |
| 6. CS- | .12 | .18 | .33* | .58* | .93* | -- | | | | | | | |
| Avoidance Accuracy | | | | | | | | | | | | | |
| 7. CS+ | .44* | .43* | .20 | .26* | .07 | .09 | -- | | | | | | |
| 8. GS1 | -.27* | -.59* | -.40* | -.37* | -.19 | -.18 | .70* | -- | | | | | |
| 9. GS2 | -.05 | -.31* | -.48* | -.37* | .27* | .27* | -.39* | .56* | -- | | | | |
| 10. GS3 | -.07 | -.24* | -.35* | -.40* | -.28* | -.28* | -.23* | .37* | .69* | -- | | | |
| 11. GS4 | .05 | -.01 | -.12 | -.27* | -.44* | -.43* | -.11 | .21 | .39* | .62* | -- | | |
| 12. CS- | .11 | .05 | -.08 | -.19 | -.39* | -.40* | -.07 | .15 | .32* | .53* | .88* | -- | |

Note. CS+ = aversive conditioned stimulus; CS- = safety conditioned stimulus; GS1-4 = generalization stimulus on a continuum of danger to safety; Online Risk Ratings: collected during the generalization test and rated on a scale of 1 (*no risk*) to 7 (*high risk*); Avoidance Accuracy: collected during the fear generalization test on a scale of 0 (*not accurate*) to 1 (accurate), where accuracy was defined as avoiding CS+ and not avoiding all other test stimuli (CS-, GS1-4). * $p < .05$.

Table 4. *Associations among self-report measures of psychopathology*

| Variable | 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. |
|----------------------------------|-------|------|------|------|------|------|------|------|----|
| Self-Report Measures | | | | | | | | | |
| 1. Neuroticism (EPQ-R-N) | -- | | | | | | | | |
| 2. Life Stress (LSC-R) | .63* | -- | | | | | | | |
| 3. PTSD (PSS-SR-5) | .39* | .64* | -- | | | | | | |
| 4. PTSD Avoidance (PABQ) | .18 | .65* | .79* | -- | | | | | |
| 5. Avoidance (BEAQ) | .50* | .38* | .06 | .26 | -- | | | | |
| 6. Depression (BDI-II) | .63* | .56* | .61* | .43* | .51* | -- | | | |
| 7. Trait Anxiety (STAI-T) | .79* | .54* | .50* | .30 | .57* | .83* | -- | | |
| 8. State Anxiety (STAI-S) | .70* | .46* | .35* | .31 | .57* | .70* | .83* | -- | |
| 9. Intolerance Uncertainty (IUS) | -.62* | .49* | .40* | .43* | .47* | .57* | .57* | .69* | -- |

Note. PTSD measures (PSS-SR-5 and PABQ) were only given to the high stress load group ($n = 42$); EPQ-R-N = Eysenck Personality Questionnaire - Revised - Neuroticism. LSC-R = Life Stressor Checklist - Revised. PSS-SR-5 = Posttraumatic Diagnostic Scale for DSM 5. PABQ = Posttraumatic Behavioral Avoidance Questionnaire. BEAQ = Brief Experiential Avoidance Questionnaire, BDI-II = Beck Depression Inventory-II. STAI-T = State-Trait Anxiety Inventory-Trait STAI-S = State-Trait Anxiety Inventory-State. IUS = Intolerance of Uncertainty; * $p < .05$.

Table 5. *Associations among online risk ratings and self-report psychopathology measures*

| Online Risk Ratings | CS+ | GS1 | GS2 | GS3 | GS4 | CS- |
|----------------------------------|-----|------|------|------|------|------|
| Self-Report Measures | | | | | | |
| Neuroticism (EPQ-R-N) | .01 | .13 | .26* | .29* | .04 | .07 |
| Life Stress (LSC-R) | .03 | .12 | .13 | .15 | .02 | -.07 |
| PTSD (PSS-SR-5) | .14 | .12 | .01 | .24 | .24 | .20 |
| PTSD Avoidance (PABQ) | .10 | .15 | -.06 | .27 | .08 | .01 |
| Avoidance (BEAQ) | .09 | .22* | .23* | .30* | .11 | .09 |
| Depression (BDI-II) | .14 | .10 | .11 | .14 | -.03 | -.01 |
| Trait Anxiety (STAI-T) | .06 | .11 | .14 | .22 | -.03 | -.04 |
| State Anxiety (STAI-S) | .02 | .08 | .17 | .35* | .13 | .09 |
| Intolerance of Uncertainty (IUS) | .15 | .35* | .30* | .41* | .01 | .01 |

Note. CS+ = aversive conditioned stimulus; CS- = safety conditioned stimulus; GS1-4 = generalization stimulus on a continuum of danger to safety; Online Risk Ratings: collected during the generalization test and rated on a scale of 1 (*no risk*) to 7 (*high risk*); PTSD measures (PSS-SR-5 and PABQ) were only give to the high stress load group ($n = 42$); EPQ-R-N = Eysenck Personality Questionnaire - Revised - Neuroticism. LSC-R = Life Stressor Checklist – Revised. PSS-SR-5 = Posttraumatic Diagnostic Scale for DSM 5. PABQ = Posttraumatic Behavioral Avoidance Questionnaire. BEAQ = Brief Experiential Avoidance Questionnaire, BDI-II = Beck Depression Inventory-II. STAI-T = State-Trait Anxiety Inventory-Trait STAI-S = State-Trait Anxiety Inventory-State. IUS = Intolerance of Uncertainty; * $p < .05$.

Table 6. *Associations among avoidance accuracy and self-report psychopathology measures*

| Avoidance Accuracy | CS+ | GS1 | GS2 | GS3 | GS4 | CS- |
|----------------------------------|------|-------|------|-------|------|------|
| Self-Report Measures | | | | | | |
| Neuroticism (EPQ-R-N) | .03 | -.16 | -.16 | -.32* | -.15 | -.12 |
| Life Stress (LSC-R) | .04 | -.18 | -.20 | -.33* | -.10 | -.12 |
| PTSD (PSS-SR-5) | .15 | -.19 | -.13 | -.23 | -.04 | -.07 |
| PTSD Avoidance (PABQ) | .14 | -.16 | -.20 | .27 | .02 | .02 |
| Avoidance (BEAQ) | -.03 | -.03 | -.16 | -.34* | -.12 | -.08 |
| Depression (BDI-II) | -.03 | .01 | -.09 | -.29* | -.03 | -.04 |
| Trait Anxiety (STAI-T) | -.04 | .02 | -.04 | -.22 | -.04 | -.05 |
| State Anxiety (STAI-S) | -.10 | .02 | -.12 | -.31* | -.18 | -.18 |
| Intolerance of Uncertainty (IUS) | .09 | -.26* | -.15 | -.29* | -.05 | -.02 |

Note. CS+ = aversive conditioned stimulus; CS- = safety conditioned stimulus; GS1-4 = generalization stimulus on a continuum of danger to safety; Avoidance Accuracy: collected during the fear generalization test on a scale of 0 (*not accurate*) to 1 (*accurate*), where accuracy was defined as avoiding CS+ and not avoiding all other test stimuli (CS-, GS1-4). PTSD Severity measure was only give to the high stress load group ($n = 42$); EPQ-R-N = Eysenck Personality Questionnaire - Revised - Neuroticism. LSC-R = Life Stressor Checklist – Revised. PSS-SR-5 = Posttraumatic Diagnostic Scale for DSM 5. PABQ = Posttraumatic Behavioral Avoidance Questionnaire. BEAQ = Brief Experiential Avoidance Questionnaire, BDI-II = Beck Depression Inventory-II. STAI-T = State-Trait Anxiety Inventory-Trait. STAI-S = State-Trait Anxiety Inventory-State. IUS = Intolerance of Uncertainty; * $p < .05$.

Table 7. *Associations among sex hormone levels and online risk rating responses.*

| Variable | Estradiol | Progesterone |
|---------------------|-----------|--------------|
| Online Risk Ratings | | |
| 1. CS+ | -.03 | -.08 |
| 2. GS1 | .01 | -.03 |
| 3. GS2 | .08 | .14 |
| 4. GS3 | .10 | .19 |
| 5. GS4 | .14 | .05 |
| 6. CS- | .09 | .01 |
| Avoidance Accuracy | | |
| 7. CS+ | -.22 | -.11 |
| 8. GS1 | .01 | .12 |
| 9. GS2 | -.07 | -.06 |
| 10. GS3 | -.04 | -.26* |
| 11. GS4 | .05 | -.12 |
| 12. CS- | .12 | .02 |

Note. CS+ = aversive conditioned stimulus; CS- = safety conditioned stimulus; GS1-4 = generalization stimulus on a continuum of danger to safety; Online Risk Ratings: collected during the generalization test and rated on a scale of 1 (*no risk*) to 7 (*high risk*). Avoidance Accuracy: collected during the fear generalization test on a scale of 0 (*not accurate*) to 1 (*accurate*), where accuracy was defined as avoiding CS+ and not avoiding all other test stimuli (CS-, GS1-4). * $p < .05$.