Computational and Human Learning Models of Generalized Unsafety

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Abstract

The Generalized Unsafety Theory of Stress proposes that physiological markers of generalized stress impair learning of safe cues in stressful environments. Based on this model, chronic problems inhibiting physiological arousal lead to a heightened perception of threat, which involves experiencing anxiety symptoms without any obvious precipitating stressful or traumatic event. This investigation aims to determine the impact of stressor- versus context-related emotional learning on generalized unsafety, using a Pavlovian threat-conditioning paradigm. The difference in learning threatening cues ([CS+] paired with an aversive stimulus) compared to safety cues ([CS-] not paired with an aversive stimulus) was used as a proxy measure of generalized unsafety, as conceptualized by the GUTS model. This difference is expected to be moderated by individual differences in tonic cardiac regulation (i.e. heart rate variability). Lastly, a reinforcement learning model was used to predict skin-conductance learning data during stressor, stressor context and general contexts to determine which best predicts learning. Moreover, computationally-derived learning is expected to better predict skin-conductance learning in individuals with higher fear inhibition in comparison to those with low fear inhibition.

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General Audience Abstract

This study examined claims of a theory about how human bodies respond to stress and what this tells us about how anxiety develops in and affects the mind and body. The theory is named the Generalized Unsafety Theory of Stress (GUTS). Two main hypotheses from this theory were tested in this study: 1) the theory suggests that a person's feeling of safety is affected by the variation in their heart rate at rest, and 2) that a person's feeling of safety could be observed most accurately by their body's defense responses when they are experiencing a threatening situation that is objectively safe. Individuals experiencing anxiety often report being aware that they are safe, yet their heart rate remains elevated and palms remain sweaty. Most studies that have examined the body's defense response have focused almost solely on reactions to a threat by looking at the reactions of one or more organs that make up the body's defense-response systems (e.g., heart). Results of this study confirmed the unique GUTS perspective. Specifically, the heart rate's variation at rest affects the defense response (sweaty hands) during threatening and objectively safe contexts, which in turn, predicts a person's startle response during objectively safe contexts. These results confirm that there are measurable biological constraints that change the way people learn about and react to their environments, which is very important for understanding the development and maintenance of anxiety physiology and behavior. The way a person learns to associate emotional responses to certain cues in their environment, particularly threat and safety cues, were measured as defense responses in the body in response to a series of trials. Exploratory analyses examined human threat learning in

comparison with mathematically-generated learning in order to better model the processes whereby anxiety develops based on learning of threat and safety cues.

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Introduction

Prior research indicates similarities in associative learning across diagnoses, which raises the question of whether alternative approaches to symptom-based diagnoses are more appropriate for the study of anxiety and stressor-related pathology (Lang et al., 2016). Behavioral and biological models of stress reveal multiple similarities across features of anxiety and mood disorders (Barlow et al., 2014; Brown & Barlow, 1992; Davis et al., 2010; Lang, McTeague, & Bradley, 2016). For example, attention to threat, heightened defense responding, and physiological hyperarousal are common factors within several different anxiety disorders (Cisler & Koster, 2010; McTeague, Lang, & Bradley, 2016; Olatunji, Armstrong, McHugo, & Zald, 2013). Treatment implementation is a primary concern regarding behavioral similarities across diagnoses. Psychosocial and medical interventions are most commonly designed for specific diagnoses, instead of specific symptoms or impairments.

Neurophysiological measures in conjunction with threat-learning paradigms have aided in identifying mechanistic similarities between anxiety and stress-related pathology. Pavlovian threat conditioning (PTC) has been an advantageous paradigm for investigating features of maladaptive associative learning common in stress-related disorders (Davis et al., 2010). Examining individual differences in learning is an alternative to menu diagnoses with the goal of investigating etiological and maintaining factors of stress-related pathology (National Institute of Mental Health [NIMH], 2015). The NIMH has proposed an approach to studying psychopathology that shifts the focus from disorders to differences in neurophysiology and behavior, which can be used as translational treatment targets in future intervention studies (Blakey & Abramowitz, 2016; Deacon et al., 2013). Accordingly, neurobehavioral models have begun to provide parameters distinguishing acute-fearful, from chronic-anxious responses

(Grillon, 2002; Davis et al., 2010). However, this body of literature is in need of additional translational models with human subjects and clinical populations.

One transdiagnostic model of particular interest in the proposed study is the Generalized Unsafety Theory of Stress (GUTS; Brosschot, Verkuil, & Thayer, 2017). GUTS proposes that learning safety depends on physiological inhibitory systems such that low tonic physiological inhibition will be linked with increased physiological arousal during the absence of a threat. The present research proposal aims to validate this conceptualization of generalized unsafety (GU) using a combination of skin conductance, eyeblink startle reflexology, and computational indices of learning. A resting baseline of heart-rate variability will be examined as a measure of tonic inhibition of the stress response.

Traditional Diagnostic Perspectives

Wide-ranging pathological stress responses are split into discrete categories for the purpose of diagnosis, raising concerns in academic and medical communities that important transdiagnostic information is lost through use of these categorizations. Comorbidity is increasingly seen as the rule, rather than the exception, in diagnoses (Bromet, Kutov, & Luft, 2017; Flory & Yehuda, 2015; Spinhoven, Penninx, van Hemert, Rooij, & Elzinga, 2014; Wisco et al., 2016). National comorbidity data indicate that a diagnosis of an anxiety disorder increases the chance of a comorbid mood or anxiety disorder by seven times (Merikangas & Swanson, 2009). Another especially relevant example to the proposed project is the distinction between ‘stressor-related’ and ‘anxiety disorders’ in the DSM-5 (American Psychiatric Association, 2013). In a large sample of adults with diagnosis of posttraumatic stress disorder (PTSD), anxiety and depression were two times more likely to be concomitant conditions (Spinhoven et al., 2014). The same study revealed that physical and sexual abuse in childhood are linked with

increased symptoms of PTSD, Generalized Anxiety Disorder, Agoraphobia, Social Anxiety Disorder, Panic Disorder, and Major Depressive Disorder. A comorbid diagnosis accompanies approximately 80% of PTSD diagnoses, and two or more accompany 50% of PTSD diagnoses (Kilpatrick et al, 2013). Abundant evidence demonstrates the link between stressful life events and a wide array of psychological symptoms, and particularly those characteristic of mood, anxiety, and stress-related disorders (Kendler, Hettema, Butera, Gardner, & Prescott, 2003).

The Research Domain Criteria (RDoC) is a research initiative and investigative framework that aims to understand mental disorders as varying degrees of dysfunction in behavioral, cognitive, and neurophysiological domains. Anticipating the RDoC, van Praag and colleagues (1990) proposed a similar "functional pathology" approach to examining psychopathology, in which dysfunctional characteristics are the focus of clinical research. Basic domains of functioning, proposed by the RDoC (positive/negative valence, cognition, social systems, and physiological arousal), are examined in terms of genetic, cellular, behavioral and self-report measures to illuminate transdiagnostic individual-differences.

RDoC Perspective

Evidence systematized by the (RDoC) suggests that chronic stress exposure elicits responses reliably distinct from acute stress (NIMH, 2015). Regarding the negative valence domain, evidence suggests that acute- versus sustained-threat environments correspond with fearful versus anxious responding, respectively (NIMH, 2015). Findings regarding regulatory control and stress response suggest that chronically-elevated stress indices, particularly of the cardiovascular and endocrine systems, contribute to a generalized perception of 'unsafety'--even in relatively safe environments (Brosschot, Verkuil, & Thayer, 2016; Jovanovic et al 2012; McEwen, 2012). From this perspective, many individuals experiencing anxiety without a

recalled ontological event precipitating their condition are also at risk for developing trauma-related symptoms (Mol & Arntz, 2005).

Anticipation of threat engenders negatively conditioned environments, in which relatively neutral situations have some threat value that increases the stress response to seemingly innocuous events. Chronically-elevated physiological stress responses, particularly of the cardiovascular and endocrine systems, maintain a generalized perception of unsafety, even in relatively safe environments (Brosschot et al., 2016). Thus, generalized perceptions of unsafety may be better captured in safe, but negatively-conditioned contexts (Bouton, 2004; Brosschot et al., 2016; 2017). For example, stressor-related contexts (e.g., workplace, bullying colleagues, domestic violence) are ostensibly conditioned through stressful experiences, which are often not reported or specifically remembered (Goldsmith, Bouton, & Freyd, 2004; Otgaar, Muris, Howe, & Merckelbach, 2017). Moreover, experiencing anxiety symptoms over long periods of time could be construed as a form of chronic stressor, due to the concomitant continuous physiological hyperarousal. Neurobehavioral models of stress pathology demonstrate that individual variability in fronto-parietal activity--which inhibits of the body's default hypervigilant state during resting states--is linked with greater capacity to regulate stress responses, affect and attention (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). A model of generalized stress, as opposed to stressor-reactivity models, is needed to better understand the functional similarity across anxiety, stress and mood symptomatology in terms of inhibitory learning, gated by autonomic adaptivity and inhibition.

Autonomic Inhibition and Chronic Stress

Investigations of neurophysiological resting-states and stress responses converge on the consensus that the body’s default state is defensive (Davis et al., 2010; Smith, Thayer, Khalsa, &

Lane, 2017). If not for top-down regulation of the amygdala by the prefrontal regions, the hypothalamic-pituitary-adrenal (HPA) axis would be chronically activated (Jovanovic & Ressler, 2010; Friedman, 2007). The relative physiological cost of the default excitatory response to tonic inhibition is high (Kim et al., 2003). Accordingly, lack of inhibitory regulation over the default stress response system is concomitant with a parallel state of hyperarousal (Davis et al., 2010). Physiological stress-response models have traditionally conceptualized stress-response activity in terms of autonomic nervous system (ANS) and neuroendocrine responses (HPA) before and during a stressful task. However, more recent investigations have identified significant changes that occur in the interim between stressors, when the stress response should be inhibited (Jovanovic & Ressler, 2010).

Neurovisceral Integration (NVI). The Neurovisceral Integration model (NVI) of autonomic flexibility suggests that the ANS has a "set-point" of general arousal around which the body fluctuates, dependent upon individual factors and degree of stress exposure (Boyce & Ellis, 2005; Friedman, 2007). Physiological adaptation to stressful events is partially facilitated through autonomic negative feedback loops that re-engage inhibitory (e.g. parasympathetic) systems that return the body to a resting state when threat is not present, or when safety is perceived (Friedman, 2007; Thayer, & Ruiz-Padial, 2006). This adaptive process is also known as *inhibitory learning*, or *extinction,* in learning terms. It is proposed that traumatic incidents and chronic stress responses can transform this adaptive process, such that autonomic positive feedback loops (i.e. disinhibition) allow the default state to remain activated, thereby shifting the physiological set-point (i.e., allostasis).

Heart-rate variability (HRV). Analyses of beat-to-beat heart rate variability is a widely supported, non-invasive measure of top-down regulation of cognitive, behavioral and autonomic

outcomes (Brosschot et al., 2017; Thayer & Ruiz-Padial, 2006). Heart-rate variability is an indirect measure of tonic cardiac vagal activity, if measured during a resting baseline period (Berntson, Cacioppo, & Quigley, 1993). High HRV has been linked with increased capacity for stress coping as well as regulation of affect and attention (Bornstein & Suess, 2000; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996; Stifter & Fox 1990). Low HRV predicts impaired discriminatory learning (distinguishing between threatening and safe environments), decreased startle responding with repeated conditioning, and increased startle responding to unpredictable contexts (Gorka et al., 2013; Wendt et al., 2015). These findings support HRV as an individual-difference marker of tonic inhibition which can predict generalized stress symptoms.

Learning Models of Chronic Stress

The 'Extended-Amygdala' Hypothesis. Autonomic changes that occur in response to chronic threat may be the result of concomitant morphology in the central nervous system. Individual differences in defense responding, both diagnostically and in controlled laboratory settings, implicate neurological changes that distinguish chronic from acute threat (Davis et al., 2010; Sylvers, Lilienfeld, & Laprairie, 2011). Chronic threat training in rodents is shown to steadily increase bed nucleus of stria terminalis (BNST) activity, thereby initiating slower onset and longer-lasting startle responses (LeBow & Chen, 2016). The BNST acts as the primary receptor site for the mediational effects of corticotropin releasing hormone (CRH) on the rodent startle response. The role of CRH as a tonic regulator of stress serves to up- or down-regulate the overall stress response (Dabrowska et al., 2011; Gewirtz et al., 1998). Increased stress exposure increases BNST receptivity to CRH, thereby up-regulating fear-potentiated startle magnitude (Dabrowska et al., 2011; Walker, Toufexis, & Davis, 2003). For instance, rats exposed to

repetitive shocks displayed elevated startle responses in subsequent baseline measures (Gewirtz, Mcnish, & Davis, 1998).

Startle Magnitude as an Index of Inhibitory Fear Learning. Considering that startle is modulated by level of stress exposure, the startle response is a prime candidate for investigating variability in the anxiety symptomatology continuum in terms of learned responses to perceived threat and safety. Some argue that failure to condition a cue, particularly a safety cue, is indicative of contextual anxiety, due to the aversively conditioned context (Baas, Ooijen, Goudriaan, & Kenemans, 2008). "The organism cannot identify periods of danger and safety and remains in a chronic state of anxiety" (Grillon, 2002, p. 958).

The eyeblink startle response is a simple reflex that is subject to inhibition from higher brain input (Curzon, Zhang, Redek, & Fox, 2009; Koch & Schnitzler, 1997). *Startle potentiation* refers to the increase in startle magnitude during the presentation of a conditioned stimulus relative to baseline (Schmitz & Grillon, 2012; Jovanovic & Ressler, 2013). Startle response is modulated by the proximity of threat and by current emotional and motivational intensity, suggesting that startle is autonomically modulated, and specifically sensitive to the anxiogenic processes underlying fear and anxiety pathology (Dabrowska et al., 2011; Davis et al., 2010; Lang et al., 2016; McTeague, Lang, Wangelin, Laplante, & Bradley, 2012).

Generalized 'Unsafety' Theory of Stress (GUTS). According to GUTS, consistent exposure to unsafe contexts creates a chronically stressful environment, in which threat is overestimated and safety rarely perceived (Brosschot et al., 2016; 2017). With continued exposure, even periods of previously perceived safety become littered with hyperarousal and perseverative worry (Brosschot et al., 2010). From this perspective, the interim between specific stressors, as opposed to reactivity the stressors themselves, are superior predictors of pathology.

The GUTS perspective thus proposes an alternative conceptualization to traditional stress theory, shifting the focus from stressor-reactivity to generalized stress responses. According to GUTS, stress responses may become increasingly chronic when an individual is continuously re-exposed to a stressor context (e.g., workplace). The generalization of heightened stress responses to all contexts can occur from chronic exposure to actual stressors as well as when experiencing prolonged stress-response activation (Brosschot et al. 2016).

Similar to the allostatic load model (McEwen, 2012), GUTS attempts to explicate prolonged stress responses, in contrast to acute stress responses, by focusing on pathophysiological as well as social concomitants (i.e., loneliness) of chronic stress. GUTS extends the allostatic model by focusing on learning and appraisal mechanisms that have implications for psychological as well as physiological feedback loops that maintain resting state. More recent models of prolonged stress reactions suggest perseverative cognition as a mechanism to explain the chronic, hypervigilant states characteristic of anxiety (Brosschot, Gerin, & Thayer, 2006).

The perseverative cognition hypothesis proposes that rumination both preceding and following a stressor plays a role in maintaining a hypervigilant state, which eventually contributes to prolonged changes in cardiovascular, endocrinological, immunological, and neurovisceral activity (Brosschot et al., 2006; Ottaviani et al., 2016). Similarly, conceptualizations of both cognitive and autonomic inflexibility have been used to explain anxiety and prolonged stress symptoms, suggesting that inflexibility of thought and physiological response patterns contribute to habitual stress responses in a variety of contexts (Ottaviani, Medea, Lonigroa, Tarvainenc, & Couyoumdjian, 2015). Unconscious perseveration is conceived as physiological hyperarousal in the absence of worry or stressors, such as hyperaroused states

during sleep (Brosschot et al., 2010). For instance, lower resting HRV and longer latency to recover following stress have been observed in samples with prolonged stress symptoms, such as anxiety and PTSD (Friedman & Thayer, 1998; Norte et al., 2013).

Generalized Perception of Unsafety as a Learning Problem

Learning to associate environmental cues with contingent meaning (e.g., aversive or rewarding) is a key function of decision making and behavioral activation. Information from a new environment is "filtered" by an individual's perception of contingencies within the environment. According to the GUTS model, the appraisal of safety is a fundamental evaluation made in the presence of uncertain cues (Brosschot et al., 2016). This appraisal process manifests at both physiological and cognitive levels primed to perceive an environment as unsafe through experiences such a generalized trauma, recent life stressors, or physical health problems (Brosschot et al., 2016). However common, traumatic or stressful life events are not sufficient in explaining the multitude of psychological and physiological deficits linked with anxiety (Mol & Antz, 2004; Nuslock & Miller, 2016). Differences in learning to inhibit stress responses during threatening contexts may elucidate the process by which traumatic and stressful life events result in physiological and psychological conditions.

Historically, threat-learning paradigms have been implemented using human and rodent models to examine the neurobehavioral learning mechanisms that catalyze psychophysiological responses to stress and its anticipation. Evidence points to a degradation in associative learning as a potential pathogenic mechanism in the development and maintenance of anxiety-related psychopathology (Grillon, Ameli, Woods, Merikangas, & Davis, 1991; Jovanovic et al., 2005; Lissek & Güntürkün, 2004).

The Safety Signal Hypothesis. Explorations of inhibitory learning processes have led to the incorporation of 'safety signals' into threat conditioning models. Healthy individuals typically display inhibited responses to trials presented without aversive stimuli during aversive conditioning (Pavlov, 1928; Rescorla, 1969; Jovanovic et al., 2005). This inhibitory learning is also examined using a 'conditioned inhibition' paradigm in which safety signals are conditioned as inhibitors because they are never paired with threatening stimuli. Conditioned inhibition is indexed using the summation test derived from the Rescorla-Wagner (R-W) model (Rescorla & Wagner, 1972), and occurs when the safety signal dampens the fear response to excitatory stimuli (Christianson et al., 2012).

In aversive learning paradigms, conditioned inhibition is referred to as 'fear inhibition,' in that it captures the reduction of defense responses to the safety-conditioned stimulus (Christianson et al., 2012). The safety-signal hypothesis posits that fear-inhibition will be learned when a conditioned stimulus is repeatedly presented without the aversive stimulus during threat acquisition (Seligman, 1968; Seligman & Binik, 1977). Specifically, fear-inhibition is conditioned when an excitatory conditioned stimulus is presented in the presence of a familiar stimulus (i.e., safety signal or conditioned inhibitor) that was never paired with threatening or aversive stimuli.

Fear inhibition in response to real threat may be adaptive (e.g., facilitate an appropriate behavioral response). However, repeated use of safety-oriented coping strategies, especially in situations where threat is imagined, catalyzes a steady increase of anticipatory threat (Brosschot et al., 2017; Lovibond, Davis, & O'Flaherty, 2000). Failure to inhibit defense responses that are unchanging in response to informational and experiential inputs are another form of non-associative learning deficit evident in anxiety and stress-related disorders (Herman et al., 2005;

Jovanovic et al., 2012; LeDoux et al., 2017). One study demonstrated that individuals with severe PTSD displayed similar startle responses to both safety and threat cues, despite being aware of the contingency between safety signals and absence of the threat (Jovanovic, Kazama, Bachevalier, & Davis, 2012).

Discriminant-Conditioning Paradigms. Associative strength between stimuli acquire excitatory and/or inhibitory strengths that help guide future responses to these stimuli. In laboratory learning paradigms, the terms "excitatory" and "inhibitory" refer to how conditioned stimuli produce changes in the rate, or magnitude, of response. For example, a stimulus that is repeatedly paired with a shock will gain excitatory properties. As the contingency between the stimulus is strengthened, the predictive value of the stimulus is also strengthened, thereby promoting excitatory responding. Investigations of inhibitory learning processes have increased since the reconceptualization of extinction as an inhibitory learning process, such that the individual learns to inhibit their fear to a previously-threatening stimulus (Berman & Dudai, 2001; Craske et al., 2008).

Temporal Difference Prediction Errors

Predicting the future based on previously learned outcomes is a fundamental property of adaptive learning (Rogers, Hertzog, & Fisk, 2000). Associative learning principles are used to evaluate Pavlovian conditioning outcomes, because these paradigms provide for the examination of learning processes that unfold over time. Traditionally, learning models have been evaluated using mean-centered models that aggregate responses over conditioning trials and incidentally negate the importance of time in learning. Computational learning is conceptualized in terms of 'learning rules' that update expectations based on contingent factors of reward and/or threat within the learning environment. This type of expectancy-based learning model as prediction

error updating ([PE]; Li & McNally, 2014). For example, if an individual anticipates threat in association with a particular cue, and no threat is delivered, expectations are updated and fear will ostensibly be reduced in response to the next presentation of that cue (i.e. negative PE). Thus, safety cues presented in the absence of threat should begin to acquire an inhibitory value in contrast with excitation to threat cues.

The R-W model proposes a mathematical model that conceptualizes learning as the strength of association (V) between two or more stimuli, gated by the intensity of conditioned and unconditioned stimuli (i.e., CS and US) and updated during each trial (Rescorla & Wagner, 1972). Machine learning models have adapted the R-W framework to investigate temporal aspects of associative learning, in which associative values are fine-grained PEs preceding and during reinforcement, or omission thereof. For example, negative prediction errors are generated when aversive events are expected but do not occur (e.g., safety trials). Prediction-error terms serve as the 'learning rate,' which update during each time point sampled (Jensen et al., 2007).

Temporal-difference (TD) learning models are an adaptation of the R-W model that permit examination of learning in terms of prediction-error change during time points leading up to reward or threat delivery (Sutton, 1988). TD models have demonstrated superior capacity to predict reinforcement and fear learning in both human and nonhuman animals (Cole & McNally, 2007; Menon et al., 2007; Seymour et al., 2004; Spoormaker et al., 2011). Moreover, the strength of TD models over the R-W model is the incorporation of multiple response windows, surrounding the conditioned stimuli, which offers a more comprehensive account of the contextual factors influencing an individual's response to a conditioned cue. Moreover, the assumption that events experienced earlier will be learned at the expense of learning new information, as proposed by the R-W model, is also taken into account (*temporal primacy effect*;

Egger & Miller, 1962; Rescorla & Wagner, 1972). The model compares the PE—determined by the stimulus sequence (i.e. CS, US, inter-trial interval) prior to a particular trial--with actual behavioral or physiological outcomes on a trial-by-trial basis (Jensen et al., 2007; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003).

Proposed Study

The GUTS perspective proposes that tonic physiological regulation of the default stress response predicts impaired inhibitory learning (Brosschot et al., 2016). This perspective of chronic stress includes individuals experiencing anxiety without recalling any precipitating stressful or traumatic event (Brosschot et al., 2017). GUTS suggests that defense responses to actual stressors become generalized to stressor-related contexts and, eventually, all contexts (Figure 4). Because the GUTS perspective strongly invokes the default stress response as the mechanism of dysregulation, responses during "objectively neutral (but uncertain) periods" are argued to be more informative of both psychological and physiological concomitants of chronic stress, than are measures of reactivity to stressors (Brosschot et al., 2016; 2017, p. 5). Learning to inhibit the defense responses to safety cues is proposed to be moderated by the individual's level of neurovisceral integration, measured as resting HRV. This study aims to determine the differential impacts of the stressor reactivity versus context learning on generalized unsafety, moderated by individual differences in tonic physiological inhibition

Stressor vs. Context Learning. Discriminant threat conditioning provides an apt paradigm for examining differences in learning safe cues (CS-) during threatening contexts. In the current study, conditioned inhibition to a combined safety-threat cue is conceptualized as an index of GU (i.e., fear inhibition). During the test phase of conditioning, safety cues were presented in combination with a threatening cue, thereby creating an "objectively safe but

uncertain environment," as proposed by GUTS (Brosschot, 2018). Sampling skin conductance in response to the UCS omission and inter-trial intervals will account for generalization of defense responses to contexts beyond the eminent threat. To determine differential effects of the generalized sympathetic activation on safety learning (i.e. GU), skin-conductance responses to the UCS, UCS omission and inter-trial intervals will be used as predictors of fear inhibition. Sympathetic activity during inter-trial intervals and safety trials was used as an index of generalized stressor conditioning. The GUTS perspective assumes that context responses will predict greater changes in generalized unsafety, as compared with sympathetic responses to the stressor. However, differences in sympathetic activity to the context versus the stressor is not expected to display this trend in the population sampled for the present study, unless accounting for individual differences in physiological tonic inhibition.

Neurovisceral Conditions for Learning Unsafety. Neurovisceral inhibition of the default hyper-aroused state, measured using HRV, is proposed as a target index of tonic inhibitory regulation. To examine the role of tonic inhibition on the perception of unsafety (i.e. fear inhibition), hfHRV was examined as a moderator of conditioned responses on fear inhibition. According to GUTS, chronic dysregulation of physiological inhibition (i.e. low resting hfHRV) is sufficient to predict a heightened perception of unsafety. Abundant evidence supports resting HRV as a parasympathetic index of tonic vagal regulation of the heart (Thayer, Ahs, Fredrik, Sollers, & Wager, 2012). Moreover, increased fear inhibition is associated with greater resting hfHRV (Gorka et al., 2013; Wendt et al., 2015).

The conditional effects of resting hfHRV on the impact of stressor versus context learning will be examined. This combined model will examine how resting hfHRV modulates the effect to which stressor versus context conditioning impacts 'generalized perception of

unsafety,' or decreased fear inhibition, as it is operationally defined in this study. Individuals with low hfHRV were expected to fit the GUTS hypothesis that increased context conditioning predicts decreased fear inhibition (i.e. GU), whereas stressor responses will not significantly predict fear inhibition in this group. Conceptually, the more generalized defense response to the context surrounding the stressor, the more likely a perceptual bias toward perceiving objectively safe things to be unsafe, which is captured in the fear inhibition measure.

Predicted Learning Account of Stressor and Context Learning. Machine-learning algorithms adapted from the R-W associative learning rule provide an account of second-order and context learning by updating PEs at selected time-points during the conditioning paradigm. TDL models have displayed superior prediction of Pavlovian fear learning measured with autonomic activity and fMRI learning indices, in comparison to mean-comparison learning assessments (Jensen et al., 2007; Spoormaker et al., 2011). Computationally, TDL models presume that associative strength between the stimuli is updating at time-points between threat and safety trials, thereby providing a closer approximation of temporally-dependent learning.

The state of an individual's expectancy is presumed to change as the individual learns to temporally anticipate a threat (or absence, thereof), thus time points leading up to the threat will similarly begin to gain associative value. In the present study, a learning algorithm was implemented with two aims: 1) to determine which learning rule (i.e. prediction-error vectors updated during either UCS, UCS omission, or inter-trial intervals) best predicts skin-conductance learning, and 2) to determine the conditional effect of high and low fear inhibition on congruence between modeled and sympathetic learning values. A learning model that updates during inter-trial intervals, in addition to conditioned stimuli, was expected to provide a better account of actual learning than a model that only accounts for stressor learning. However, individuals with

low fear inhibition were expected to have less congruence between modeled and actual learning in comparison with those with high fear inhibition.

Method

Participants

A sample of 43 adults were recruited from the New River Valley community and the Virginia Tech student population. Participants were 18-50 years of age (M = 20.4, SD = 4.9), 86% female (n = 35), and 76% white (most participants were students participating for course credit). One participant was excluded from final analyses, as the EDA signal dropped out halfway through acquisition, making their data unusable in all analyses.

A screened sample of participants were recruited via social media and flyers distributed through the NRV and across the Virginia Tech campus. The proposed protocol has been approved by the Virginia Tech Institutional Review Board.

Screening and Laboratory Procedures

Exclusion criteria regarding major medical and hearing impairments was monitored using the Mind-Body Lab Health History Questionnaire (MBL-HHQ), which was administered through Qualtrics (see Appendix A). Cases were individually evaluated based on MBL-HHQ results before individuals were recruited to the lab. Individuals reporting cardiorespiratory and cardiovascular conditions (e.g., answering “yes” to the following: “circulatory problems,” “lung problems,” “cardiovascular disorder/disease”, “hyper/hypotension”) were excluded, due to the potential increased risk of heightened emotional or physiological reactivity to the stimuli presented during this study. Additionally, these individuals were excluded due to potential abnormal peripheral nervous system activity, which would propose substantial confounds to the sympathetic measures of threat conditioning in the proposed study (Taylor et al., 2006). Participants who report a history of seizures, epilepsy, neurological conditions or brain disorders were also excluded, due to their potential heightened sensitivity to the visual, auditory and tactile

stimuli. Finally, self-reported hearing impairments excluded participants, due to the auditory stimuli that are a central feature of the learning paradigm being examined in the proposed study.

Upon entering the study room, participants read and signed the informed consent form before beginning the lab protocols. Participants completed a short survey of recent health behavior (MBL-R-HHQ) to assure their recent abstention from caffeine, alcohol, vigorous exercise, and eating. Next, a hearing test, consisting of tones ranging from 12-22 kHz were administered to assure their hearing is within a normal range. A color-blindness test (online Enchroma color-blindness test) was also administered, as geometric shapes during the learning paradigm are different colors. Next, electrodes were attached for acquisition of physiological measures (i.e., electromyogram, electrodermal activity, electrocardiogram and respiration belt; Figure 1). Following electrode attachment, participants were asked to sit as quietly and calmly as possible while a five-minute baseline of all measures is taken.

Safety Learning Paradigm. The learning paradigm included three phases: 1) habituation, 2) acquisition, and 3) extinction. Habituation and acquisition trials were designed using the shapes and trials structure and order presented by Wendt and colleagues (2014; 2015) with the replacement of electric stimulation with an air blast, described in detail below. The researcher loaded the computer stimulus presentation program, informed subjects to begin the program, by pressing the spacebar after reading the instructions. Note that all further experimental instructions and stimuli were presented via Psychopy software on the lab PC. Researchers monitored subjects by looking through a two-way mirror from an adjacent room.

During the habituation phase, startle probes (auditory) and visual stimuli (colored geometric shapes) were presented without the aversive air blasts. This phase consisted of four startle probes, followed by presentation of each geometric shape (visual stimuli) with one startle

probe during each shape presentation. The startle stimulus consisted of a 40-ms burst of broadband noise with an intensity of 95 dB. The habituation phase was followed by the acquisition phase, where participants observed and ostensibly learned to associate pairs of shapes (i.e. cues; labeled here with letters A, B, and X) with the presence or absence of the threat stimulus (labeled here with +, with air blast or -, without air blast). Before acquisition, participants read instructions indicating that they may be able to identify shapes that are paired with the air-blast. At the end of each cue presentation, participants were asked to rate their certainty that an air-blast would occur on the next trial on a scale ranging from 0 'certain of no air-blast,' 1 'uncertain' and 2 'certain of air-blast.' During acquisition trials, pairs of cues A and X was followed by the threatening UCS (labeled CS+ trials), whereas B and X was not paired with an air blast (labeled CS- or safety trials). Before extinction, the researcher turned off the air compressor and verbally indicated to the participant that no more air blasts will be presented throughout the remaining trials. The researcher left the room and next the participant underwent extinction trials, during which the visual cues and startle probes were presented with no air blast stimulus (see Figures 3 and 4 for trial structure and order).

The aversive stimulus was a 200ms blast of air (approximately 140psi), generated by an air-compression tank, triggered by a solenoid valve with TTL inputs. Throat stimulation by air blast has been used as an aversive stimulus in clinical human populations with little to no risk (Jovanovic et al., 2009; 2012). Internal pressure of the device was maintained at 140psi via an air compressor (Jovanovic et al., 2005) and bursts of air were delivered by the release of a solenoid valve, triggered with a BIOPAC parallel-port unit (STP 100C amplifier) using the Psychopy experiment-builder software (Pierce, 2009, 2013). Air was funneled through a polyurethane tube that was 5-ft in length and ¼-inch in diameter, which terminated at a distance of 1 inch from the

throat (or top, external, center part of the throat) with air pressure output at approximately 140psi. The air blast is unpleasant, but not painful, and relatively mild when compared with the electric stimulation (i.e., mild shock) more frequently used in aversive conditioning paradigms (Grillon & Ameli, 1997).

Physiological Measures and Data Reduction

Electrodermal Activity (EDA). Skin conductance values were collected using electrodermal Ag-AgCl electrodes with NaCl electrolyte gel in the center (EL507, BIOPAC Systems Inc., Goleta, CA). Two EDA electrodes were attached to the distal phalange (e.g., top knuckle) of the index and middle fingers of the left hand. Signals were collected at 1000 Hz using Acqknowledge data acquisition software (BIOPAC Systems Inc.) installed on a Windows 10 desktop and amplified using the BIOPAC module for EDA collection. Acqknowledge software was also used for offline cleaning and visual inspection of EDA waveforms. Event markers, programmed into the stimulus presentation software, were used offline to identify time-points needed to calculate skin conductance response (SCR).

Skin Conductance Learning. EDA was analyzed in accordance with Schiller and colleagues (2008) as well as Spoormaker et al. (2011) to assess skin conductance level and responses. The criterion for an event-related response included a threshold amplitude of 0.02 microsiemens within a response window occurring two seconds following stimulus onset (Spoormaker et al., 2011). The 2-second delay is due to the time delay in skin conductance responses to stimuli presentation. Raw scores on all trials were baseline corrected and normalized using a square-root transformation and scaled to each individual's average normalized response to the UCS during CS+ trials. Responses not meeting the criteria described above will be coded as zero or unscorable.

SCRs were defined as the peak-to-peak amplitude difference in the largest difference in microsiemens. SCRs were sampled from the three following time windows: responses to the air-blast (UCS, 4s), air-blast omission (UCS omission, 4s), and to the startle probe during inter-trial intervals (ITIs; Figure 6). For regression and path analyses, SCRs were averaged using the last five windows for each response type (UCS, UCS omission and ITI) during acquisition. Averaging the final five responses from acquisition ostensibly captures learning effects from conditioning. Additionally, skin conductance to the first UCS presentation--to capture an individual value of maximum autonomic arousal due to the threat—was used to individually weight SCR scores for each response window.

Electromyogram (EMG). Startle potentiation was assessed using eye-blink strength, captured with electromyographic (EMG) signals. Three Ag/AgCl electrodes (11m diameter; Florida Research Instruments) filled with NaCl electrolyte gel were attached to the orbicularis muscle region and forehead (ground) using 12mm/4mm adhesive collars. The two active electrodes were placed approximately one centimeter beneath the right eye, targeting the orbicularis oculi (see Appendix A, Figure 1 for electrode placement configuration). Signals were be collected using the MP-150 BIOPAC amplifier and processed offline through the Acqknowledge data acquisition system.

Conditioned Inhibition of Eyeblink Startle Magnitude. The raw EMG signal was first amplified, using the EMG-amplification standard procedure provided by the Acqknowledge analysis system. Next, a high and low bandpass filter (28-500Hz) was applied to the amplified signal to eliminate extraneous movement and ambient electrical artifacts. Lastly, the signal was be averaged rectified, meaning positive and negative voltage values will be transformed into their absolute values, thereby smoothing the data and facilitating more accurate signal detection

(Blumenthal et al., 2005). Each startle response was analyzed using the peak amplitude of the blink reflex, which was derived from the 20-100ms time frame following stimulus onset relative to baseline (average baseline EMG level for the 50 ms immediately preceding stimulus onset). EMG magnitudes were standardized using within subject T-score conversions to normalize data and to reduce the influence of variability between subjects unrelated to psychological processes.

Safety-signal test trials (AB) were a combined CS+/CS- cue presented in the absence of the aversive stimulus. Responses to combined trials will be analyzed to determine an individual's level of conditioned inhibition (i.e. fear inhibition). Conditioned inhibition is distinguished from external inhibition in that responses to the safety cue are substantially different from excitatory cues, and therefore are learned inhibitory responses, not simply due to external factors (Christiansen et al., 2012). According to guidelines proposed by Christiansen and colleagues, inhibition achieved by conditioning a safety signal should be evaluated based on the change, or reduction, in the elicited response relative to response to an excitatory stimulus. This calculation is known as the *summation test* (Rescorla, 1969). The excitatory comparison value was the average startle magnitude of excitatory trials (CS+) divided by the mean startle magnitude of safety test trials (combined cue: CS+/CS-).

To capture the effects of conditioning and control for variability in startle responses, the last three trials of acquisition were averaged for CS+ trials (Jovanovic et al., 2009). Startle response values to the threat cue (CS+) and combined cue (CS+/CS-) accounted for individual variability. Specifically, a difference score was created between the CS startle and startle to the startle probe alone (i.e. ITI) within the same block of trials, which is considered a baseline value. The difference value is then divided by the startle probe alone and multiplied by one hundred (i.e. [(CS-ITI)/ITI]*100). Summation test values are used as an index of fear inhibition in

analyses. Larger, positive summation test values indicate greater fear inhibition; moreover, negative values indicate that average responses to the combined cue (i.e. safety test cue) were higher than responses to the threat cue (CS+). Fear inhibition scores in this sample were normally distributed so a mean-split was used to examine higher and lower levels of fear inhibition on predicted and actual learning.

Electrocardiogram (ECG) and Respiration. Baseline HRV measures were collected using an electrocardiogram (ECG), also using the BIOPAC and Acqknowledge systems. Peak-wave (R-wave) ranges from ECG were used to calculate high-frequency HRV (hfHRV), which is a frequency spectrum (0.12-0.40 Hz) corresponding to respiratory cardiac inputs at rest. A respiration belt (TP-TSD-201), transducing respiratory effort, was secured around participants' upper chest area. Respiration values will be used in analyses to check for its potential influence on hfHRV values.

High-Frequency Heart Rate Variability (HRV). For the proposed study, only baseline ECG measures were analyzed, in that the measure of interest is resting hfHRV. Interbeat-Intervals (IBIs), which are the temporal distance (ms) between each consecutive R-wave, were analyzed using spectral analysis in the form of a Fast-Fourier Transform (FFT) function in the Kubios HRV Standard software (Version 3.2.0, 2019, University of Eastern Finland). The FFT function derives power (ms^2) for a specific frequency band, 0.12-0.40, or hfHRV. For the sake of clarity, hfHRV will be referred to as only HRV in the statistical models and anticipated results. Resting HRV were assessed during the five-minute baseline window, prior to any study tasks. However, the baseline recording was only one minute for multiple participants, so a one-minute assessment of hfHRV was calculated.

Prediction Errors. Prediction errors were updated based on three trial types during acquisition--UCS, UCS omission, and inter-trial interval. Trials were arranged in the sequence presented to participants during conditioning. Thus, PEs were generated to capture stressor learning (UCS), stressor-context learning (UCS omission), and general-context learning (ITI).

The learning-rate parameter was manually set ($\alpha = 0.2$), which remains the same throughout each PE update. Reinforcement values are assigned as a 1 or 0 based on the presence or absence of the UCS (e.g., air-blast). As such, the UCS omission and ITIs have an r of 0 and yield negative PEs; whereas, instances of the UCS have an r of 1 and yield positive PEs. For the purpose of analyses, PEs generated based on the occurrence of the UCS were backed out of the full PE learning model to create a PE vector for stressor learning (12 instances). Similarly, PEs based on UCS omission (12 instances) and ITIs (12 instances) were backed out to create stressor-context and general context PE vectors.

$$EV_{t-1} + \alpha * (V_{t-1} - EV_{t-1})$$

Because the air blast always co-terminates with the CS+ shape cue, the same time window in the CS- trials provides an estimate of temporal expectancy of the stressor as well as a measure of stressor-context conditioning. Skin conductance sampled during safety trials provide a measure of sympathetic stressor-context conditioning because safety cues are composed of a threat cue (‘A’ in the AB safety trials), previously presented with the threat, and a safety cue, never before presented with a threat. Finally, inter-trial intervals provide an account of learning in the general context, in that GUTS argues that defense responses eventually generalize beyond the stressor contexts to all contexts. Specifically, generalization is proposed to occur more readily when an individual’s body and/or environment are “compromised,” or more frequently eliciting the defense response (Figure 4).

Results

The purpose of this investigation was to examine the effects of stressor versus context learning on fear inhibition as a proof-of-concept for 'generalized unsafety.' This perspective suggests that a generalized perception of unsafety is the inability to inhibit fear in safe environments, which is operationalized here as fear inhibition (i.e. reduction in startle magnitude in the presence of a safety signal). Furthermore, the GUTS perspective suggests that defense responses generalize beyond the stressor to stressor-contexts and eventually to the general context, which leads to a generalized perception of unsafety.

Participant learning outcomes were operationalized in three ways to capture stressor, stressor-context, and generalized responses: 1) as a response to the stressor, indexed with SCR in response to the UCS, 2) as response to the stressor context, which were indexed using SCRs during the omitted UCS, and 3) as a response to the generalize learning context, measured using SCR response to white noise during ITIs. These SCR values (averages of the last five trials of acquisition) were added as predictors of fear inhibition.

Three simple regressions were implemented to examine the effects of sympathetic arousal during these three response types on subsequent fear inhibition. As predicted, fear inhibition was not significantly predicted by SCRs in response to the stressor (B = -0.283, *ns*), the stressor context (B = -0.262, *ns*), nor the general learning context (B = -0.102, *ns*). Because marginally significant differences in fear inhibition were found by sex ($F(1, 41) = 3.6$, p = 0.065), such that males had lower fear inhibiton values on average (M = 1.29, SD = 0.198) than females (M = 1.56, SD = 0.331), these three regressions were run a second time with females only (Female n = 35). Similar to results found in the whole sample, fear inhibition was not

significantly predicted by sympathetic activity (SCRs) in response to the stressor (B = -0.385, *ns*), the stressor context (B = -0.485, *ns*), nor the general context (B = -0.597, *ns*).

According to GUTS, generalized stress responses (ITIs) were expected to predict the greatest variance in fear inhibition. However, this model is limited in testing the effects of stressor versus context learning on fear inhibition for two reasons: 1) context learning is explicitly not orthogonal to stressor responses, and 2) this statistical model does not examine individual differences. Specifically, risk factors that assess risk factors of generalized defense responding (e.g., resting hfHRV). The GUTS model suggests that defense responses during stressor-related and general contexts is an indicator of a generalized unsafety. Thus, variance in context responses should better differentiate 'compromised' versus 'healthy' individuals on indices such as resting hfHRV. Ostensibly, psychological measures such as worry or anxiety would work in the same way. To examine the moderating role of HRV on the predictive capabilities of stressor versus context conditioning, individuals were classified into higher versus lower hfHRV groups and regressions were run again.

Higher (1) and lower (0) baseline hfHRV levels were used in the "split file" function within SPSS data analysis software (IBM Corp., 2015). In the lower hfHRV group, SCRs during stressor context (B = -1.069, p = .011) and general context (B = -1.368, p = .010) inversely predicted fear inhibition, such that increased SCRs were linked with lower fear inhibition values. As predicted, SCRs to the stressor did not significantly predict fear inhibition (B = -0.835, p = .09), if using Fisher's alpha ($p < .05$) to test significance. In the higher hfHRV group, none of these relationships were significant. These findings confirm hypotheses, in that greater sympathetic arousal during stressor contexts and the general learning context is linked with decreased fear inhibition, but only in individuals with lower resting hfHRV.

Stressor responses were expected to have a positive relationship with fear inhibition, based results reported by Wendt et al., a positive correlation was expected between the stressor response and fear inhibition in the high HRV group (2015). However, Wendt did not use the same measure of fear inhibition as used in this study (i.e. conditioned inhibition). Moreover, this study used autonomic (SCR) learning indices during acquisition to predict fear inhibition in subsequent test trials; whereas, Wendt and colleagues used startle-response learning during acquisition (2015).

Prediction-Error Learning Model Comparison

Traditional methods of examining learning outcomes of conditioning typically use an average of the last few trials of acquisition, as was also done in the simple-regression results. Additionally, within-individual differences are neglected in simple-regression equations, whereas variable relationships are the focus. In this sample, differences in resting hfRHV result in changes in learning outcomes of SCR and fear inhibition. However, this information would be more meaningful if we could examine within-individual differences across the learning context as a function of between-individual factors, such as fear inhibition or resting hfHRV.

These limitations were addressed in three ways: 1) by generating three PE learning rules that represent stressor, stressor context, and general context, 2) by employing these PEs as predictors of SCRs derived from each trial and ITI presented during acquisition, and 3) examining these changes in learning by individual level of fear inhibition using Hierarchical Linear Modeling (HLM) software (Raudenbush & Bryk, 2001). This software permits the examination of hierarchically nested variables in which within-person variance can be examined as a function of person variables. For example, multiple instances of skin conductance regressed with predicted learning (PEs) across acquisition trials can be hierarchically-nested within

individual differences, such as fear inhibition. This is an improvement and addition to the previous statistical approach, as it includes learning indices that can be examined across acquisition and examined as a function of individual level of fear inhibition.

The purpose of creating PE learning vectors is to evaluate the importance of context learning both computationally and sympathetically. Moreover, the degree to which SCRs deviate from predicted learning may aid in revealing individual differences in fear inhibition, particularly deviation in context learning. The PE-learning model was manipulated to represent the response types of interest to the GUTS model: stressor only, stressor context, and general context learning, separately.

Model testing proceeded in three phases: unconstrained (null), intercepts-only, and intercepts-and-slopes-as-outcomes. Model comparisons focus on differences between the learning vector and less on individual differences. A final phase of model construction examines the effects of fear inhibition on computational and sympathetic learning indices.

Pavlovian Learning and PE Vector Models

To examine the effectiveness of PE learning rules in predicting SCR learning and whether this relationship changes by level of fear inhibition, HLM models were constructed with guidance from these sources (Raudenbush & Bryk, 2002; Singer & Willet, 2003; 2005; Woltman, Feldstain, MacKay, & Rocchi, 2012). First, three HLM models will be presented for the purpose of comparing three separate PE-learning vectors that represent stressor, stressor context, and general context learning in their capabilities in predicting skin-conductance learning. Of specific interest was the within-person relationship between SCRs (level-1 outcome variable) and PEs (level-1 predictor variable) representing trials across acquisition (12 UCSs, 12 UCS-omission windows, 12 ITIs per individual; Figure 6). Homogeneity of variances tests of

level-1 variance suggest that SCRs are homogeneously distributed within individuals across all trial types ($p > .500$).

Full-maximum likelihood models were implemented to examine both fixed and random effects between PEs and SCR learning during acquisition (see Tables 1-3). First, a "null," or non-conditional, model was generated by adding SCRs as a level-1 outcome variable to determine variability in SCRs without predictors in the model. Next, a random intercepts model was generated by adding stressor PEs as a predictor (level-1, uncentered) to examine the degree to which PEs predict SCRs for each learning rule. Predictor variables were uncentered because PE values are the same for each subject and a mean-detrended value of PEs would not be meaningful for the purposes of this investigation. Lastly, a level-2 predictor (uncentered) was added to examine the effects of fear inhibition on level 1 variance between SCRs and PEs.

Stressor PE Vector. A total of 473 SCRs responses were added to the intercept-only model and results confirmed that there are between-person differences (level-2) in stressor SCRs (level-1). The range of valid SCRs was 6-12 per individual. This model demonstrates that SCRs vary within and between individuals suggests that HLM (i.e., nested) modeling would be useful in explaining that variance ($X^2 = 197.327$, $p < .001$; Table 1). Stressor PEs, which were generated based on the occurrence of the UCS only, significantly and positively predicted SCRs ($\beta_{10} = 0.390$, $se = 0.40$, $p < .001$). This effect is a between-group regression coefficient (β_{10}), although heavily weighted by individual slopes derived from level-1 variance (Woltman et al., 2012). Covariance between the intercept, and slope is negative ($\pi_1 = -0.039$, $se = 0.011$), which indicates that individuals with lower stressor SCRs also display more agreement between SCRs and PEs. The intercept in this model represents the SCR grand mean. This finding argues that

individuals with lower sympathetic activation to the stressor, overall, are closer to computationally predicted learning that accounts stressor learning, alone.

Stressor-Context PE Vector. A total of 401 SCRs were entered as level-1 outcome variables. The range of valid SCRs was 6-12 per individual. The intercept-only model indicates that HLM nested modeling would be useful in explaining SCR variance ($X^2 = 231.696$, $p < .001$). Stressor-context PEs (UCS omission + UCS) positively predicted SCRs ($\beta_{10} = 0.843$, $se = 0.083$, $p < .001$). The covariance coefficient suggests that higher SCRs are associated with a larger slope, indicating greater agreement (Table 2). The higher coefficient (β_{10}) and lower deviance scores (i.e., model fit index) for the stressor-context model (Dev = -238.720) versus the stressor-only model (Dev = -513.332) both suggest that stressor-context PEs may be more capable of predicting SCRs. To evaluate this claim further, model comparison analyses were run in the form of a General Linear Model (GLM) comparison of β_{00} and β_{10} values from the stressor model as well as a chi-square analysis between deviance values. Findings vary, such that GLM results indicate significant differences between intercept and slope values between the stressor-only and stressor context models (Estimate = 0.765, $se = 0.050$, $p < .001$), whereas fit indices are not significantly different ($X^2 = 274.611$, $p = >.500$).

Within- and Between-Individual Variance. To examine the percentage of variance in SCRs attributable to the individual, an inter-class correlation (ICC) value was calculated for each PE-SCR model, using within and between variance residual values (Woltman et al., 2012). In the stressor-only model, the ICC value suggests that 25% of the variance in stressor SCRs are attributable to individual differences ($\tau_{00}/\tau_{00} + \sigma^2$), suggesting that the majority of variance (75%) may be better explained by a level-1 predictor, such as PEs. Indeed, with-person variance ($\sigma^2 =$

0.033) decreases with the addition of stressor-only PEs (σ^2 = 0.033, $R\varepsilon^2$ = 0.545[1]). However, between-person effects were significant for SCR intercepts-only (τ_0 = 0.011, *se* = 0.003, $p <$ .001) and for the PE-slopes model (τ_0 = 0.036, *se* = 0.070, $p <$ .001). In the stressor-context model, ICC value indicates that 77% of the variance in SCRs is attributable to individual differences, which indicates that variance in SCRs may be better explained with a between-person variable (e.g., fear inhibition) rather than a level-1 variables. Furthermore, between-person effects are significant at level 1 (τ_0 = 0.134, *se* = 0.003), although decreasing substantially with the addition of PE predictors (τ_0 = 0.022, *se* = 0.012).

General-Context PE Vector. Using the same method to examine general-context (ITI n = 439) PEs and SCRs yielded non-significant results (β_{10} = 0.356, *se* = 0.480). In fact, random nor fixed effects were significant, except for the intercept (β_{00} = 0.573, *se* = 0.186), which simply indicates that SCRs significantly deviate from the intercept (grand-mean SCR; Table 3). The reliability was also very low for the PE as (π_0 = 0.005); Raudenbush and Byrk report that reliability estimates below 0.05 may cause convergence in MLM software packages, such as HLM (2002).

First, to probe issues with the model within the variables being used, a model with reduced level-1 variance was employed. Using all ITI responses during acquisition may not reflect the aspects of context learning of interest to this study. Context learning, specifically generalized defense responses may be more evident after some conditioning trials. For this reason, only SCRs and PEs from the last half of acquisition were used in a second HLM model. Results indicate that PE significantly and negatively predicts SCRs (β_{10} = -0.641, *se* = 0.112)

[1] A pseudo effect size (Rε2) was derived from random-effects values that indicate within-individual variance (e.g., (intercepts-only σ^2 - intecepts-and-slopes σ^2)/intercepts-only σ^2; Singer & Willet, 2005; Woltman et al., 2012).

during ITIs. However, these results should be interpreted with caution, as the reliability estimate (π_0 = 0.006) for the slope was lower than is recommended (>0.05; Raudenbush and Byrk, 2002).

Full-Model PE Vectors. The general-context PE vector was expected to perform at least comparably to the stressor and stressor context vectors, but hypotheses were not confirmed. However, both stressor and stressor-context PE vectors performed significantly better when generated from the full PE model that included all trial types (Table 4). Specifically, the stressor-context PE vector model performed better than the previously tested stressor-context model in terms of overall variance predicted (β_{10} = 1.176, *se* = 0.128), as well as model fit (Dev = -188.155), although not significantly (X^2 = 50.566, *p* = >.500). The GLM intercept and slope comparison suggested that the stressor-context PE vector is an improvement upon the stressor-context only vector (Estimate = 1.614, *se* = 0.122, *p* < .001). Similarly, the stressor vector derived from the full model had significantly higher coefficients than those derived from the stressor-only model (Estimate = 0.342, *se* = 0.041, *p* < .001), but not in terms of model deviance (X^2 = 167.300, *p* = >.500).

When comparing the three proposed learning-rules in their capacity for predicting SCR learning, the stressor-context PE vector was expected to better predict SCRs than the stressor model. These hypotheses were confirmed regarding the stressor-context only PE vector as well as the stressor-context derived from the full model that included all trial types. Together, these results argue that the stressor-context learning predictions are superior in predicting Pavlovian conditioning in this sample and that this effect improves when the general-learning context is included in the PE model.

Predicted Learning and Fear Inhibition

The GUTS model suggests that the prevalence of threat responses in stressor-related contexts and general contexts will better distinguish healthy versus 'compromised' individuals than stressor responses, alone. The research question of interest is whether fear inhibition--a measure of discriminant learning--is inversely related to sympathetic activation in stress contexts and the general learning contexts. To examine the accuracy of computational predictions of sympathetic learning as a factor of fear inhibition level, individuals' level of fear inhibition was examined as a function of congruence between PEs and SCR learning using all learning rules, previously described. Five separate models were run examining the moderating role of fear inhibition (Tables 1, 2, 3, and 5).

However, the interaction effects of fear inhibition between PE predictors and SCRs were null for each model tested. Importantly, however, the fear inhibition group was negatively related to the intercept, which represents an individual SCR average. This suggests that individuals with lower fear inhibition also have greater sympathetic responses during the general learning context than those with higher fear inhibition, an effect that was not immediately evident in previous results using traditional regression methods.

Conditioning Effects on Context Arousal

Additional HLM models were run, using the last half of trials during acquisition to examine the same hypotheses regarding the effect of fear inhibition on PE-SCR congruence. Furthermore, these models will allow us to examine conditioned context effects further into acquisition (Table 6). As predicted, the context models both displayed significant moderation effects of fear inhibition on PE-SCR congruence. In terms of the magnitude of effect, the stressor-context model performed best (β_{11} = -0.731, *se* = 0.488); however, not in the direction

predicted. Specifically, fear-inhibition was negatively related to the PE slope, indicating that individuals with higher fear inhibition also display less agreement between SCRs and PEs. The general-context model is closest to predicted outcomes, regarding fear inhibition, such that higher fear inhibition is related with increased congruence between PEs and SCRs during the inter-trial intervals (β_{11} = -0.358, *se* = 0.234). Also as predicted, the stressor model did not display any significant effects of fear inhibition.

Discussion

Behavioral and cognitive models of fear and anxiety implicate inflexibility as a central feature of dysfunction, in that habitual defense responses become more frequent, while learning new information becomes more difficult. Similarly, the GUTS perspective argues that decreased discrimination between safety and threat results in generalization of the defense response. Lower fear inhibition scores provide an index of impaired discriminant learning, such that learned autonomic responses to the threat and safety cue do not differ greatly from each other. In both context-learning models, fear inhibition (group) negatively predicts SCRs, such that individuals with higher fear inhibition have higher skin conductance during the learning context than those with lower fear inhibition. Disregarding the effects of predicted learning models, the hypothesized effects of fear inhibition predicting higher sympathetic activity during learning contexts, rather than in response to stressors, was robustly confirmed by traditional and novel statistical approaches.

Prediction-error learning did not perform as well as anticipated in predicting differences in fear inhibition levels. However, the model comparisons confirmed hypotheses that predicted learning that incorporates aspects of the learning context have greater capacity to predict Pavlovian learning. Also, fear inhibition level did have the expected impact on the congruence between predicted and actual learning during the general learning context. This was not the case for the stressor-context model, which showed that higher fear inhibition predicted less agreement. Interestingly, people with higher skin conductance during the stressor context had less PE-SCR agreement. Although the stressor-context models predicted SCRs better than stressor or general context, the expected results regarding fear inhibition suggest that this model may not be useful in deciphering individual differences in Pavlovian learning.

Implications

These findings may have implications for treatment of stress and anxiety related disorders. Individual differences in context learning and fear inhibition may provide a more fine-grained learning approach to identifying learning-oriented treatment targets for chronic anxiety. Multiple variations of exposure therapy have been designed using updated conceptualizations of the learning processes involved, the investigation of which began with behavioral learning models (Deacon et al., 2013; McNally, 2007). Exposure therapy is likened to extinction conditioning, such that reminders of the feared stimulus or memory are ostensibly presented in the absence of the aversive outcome. Moreover, conditional effects of neurovisceral integration during resting state on fear inhibition will emphasize the importance of tonic physiological inhibition on learning to discriminate between safety and threat. Physiological treatment targets may be of increasing concern with the chronicity of stressors or related conditions (Afari et al., 2014).

Extinction learning was previously conceptualized to be an "un-learning" process in which the reminders are no longer associated with the aversive outcome. However, recently proposed models of exposure therapy emphasize inhibitory learning through updating predicted outcomes (Craske, Treanor, Conway, Zbozinek, & Vervilet, 2014). Traditional exposure treatments focus on habituation, or reduction of fear responses, which require the individual continue with an exposure until their fear response habituates to a predefined level of distress. In contrast, the inhibitory-learning approach focuses on violating threatening predictions of a particular exposure, such that the individual continues an exposure until the predicted outcome decreases to an individually predefined level. Updating prediction errors shifts the focus from

habituation-induced fear reduction to learning new outcomes which facilitates fear reduction through learned inhibition to previously fear cues and contexts.

The present investigation examines inhibitory learning in terms of safety-cue learning using both sympathetic skin-conductance and startle reflex as indices. Moreover, a classic assessment of conditioned inhibition is employed to examine safety-cued inhibition. These measures delve into the mechanisms of anxiety development, as opposed to re-learning methods which is the focus of extinction paradigms.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5).* Arlington: American Psychiatric Publishing.

Baas, J. M. P., Van Ooijen, L., Goudriaan, A., & Kenemans, J. L. (2008). Failure to condition to a cue is associated with sustained contextual fear. *Acta Psychologica, 127*(3), 581-592.

Barlow, D. H., Sauer-Zavala, S., Carl, J. R., Bullis, J. R., & Ellard, K. K. (2014). The nature, diagnosis, and treatment of neuroticism: Back to the future. *Clinical Psychological Science*, *2*(3), 344-365.

Berman, D. E., & Dudai, Y. (2001). Memory extinction, learning anew, and learning the new: dissociations in the molecular machinery of learning in cortex. *Science, 291*(5512), 2417-2419.

Berntson, G. G., Cacioppo, J. T., & Quigley, K. S. (1993). Respiratory sinus arrhythmia: lautonomic origins, physiological mechanisms, and psychophysiological implications. *Psychophysiology, 30*(2), 183-196.

Blakey, S. M., & Abramowitz, J. S. (2016). The effects of safety behaviors during exposure therapy for anxiety: Critical analysis from an inhibitory learning perspective. *Clinical Psychology Review, 49*, 1-15.

Blumenthal, T. D., Cuthbert, B. N., Filion, D. L., Hackley, S., Lipp, O. V., & Van Boxtel, A. (2005). Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology, 42*(1), 1-15.

Bornstein, M. H., & Suess, P. E. (2000). Child and mother cardiac vagal tone: Continuity, stability, and concordance across the first 5 years. *Developmental Psychology, 36*(1), 54.

Bouton, M. E. (2004). Context and behavioral processes in extinction. Learning & memory, 11(5), 485-494.

Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. An evolutionary–developmental theory of the origins and functions of stress reactivity. *Development And Psychopathology, 17*(2), 271-301.

Bremner, J. D., Narayan, M., Staib, L. H., Southwick, S. M., McGlashan, T., & Charney, D. S. (1999). Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *American Journal of Psychiatry, 156*(11), 1787-1795.

Brosschot, J. F., Gerin, W., & Thayer, J. F. (2006). The perseverative cognition hypothesis: A review of worry, prolonged stress-related physiological activation, and health. Journal of psychosomatic research, 60(2), 113-124.

Brosschot, J. F., Verkuil, B., & Thayer, J. F. (2017). Exposed to events that never happen: Generalized unsafety, the default stress response, and prolonged autonomic activity. *Neuroscience & Biobehavioral Reviews, 74*, 287-296.

Brosschot, J. F., Verkuil, B., & Thayer, J. F. (2016). The default response to uncertainty and the importance of perceived safety in anxiety and stress: An evolution-theoretical perspective. *Journal of Anxiety Disorders, 41*, 22-34.

Brosschot, J. F., Verkuil, B., & Thayer, J. F. (2010). Conscious and unconscious perseverative cognition: is a large part of prolonged physiological activity due to unconscious stress?. Journal of psychosomatic research, 69(4), 407-416.

Brown, T. A., & Barlow, D. H. (1992). Comorbidity among anxiety disorders: Implications for treatment and DSM-IV. *Journal of Consulting and Clinical Psychology, 60*(6), 835.

Campbell, D. T., & Fiske, D. W. (1959). Convergent and discriminant validation by the multitrait-multimethod matrix. *Psychological Bulletin*, 56(2), 81.

Christianson, J. P., Fernando, A. B., Kazama, A. M., Jovanovic, T., Ostroff, L. E., & Sangha, S. (2012). Inhibition of fear by learned safety signals: A mini-symposium review. *Journal of Neuroscience, 32*(41), 14118-14124.

Cisler, J. M., & Koster, E. H. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical Psychology Review, 30*(2), 203-216.

Clark, L. A., Cuthbert, B., Lewis-Fernández, R., Narrow, W. E., & Reed, G. M. (2017). Three approaches to understanding and classifying mental disorder: ICD-11, DSM-5, and the National Institute of Mental Health's Research Domain Criteria (RDoC). *Psychological Science in the Public Interest, 18*(2), 72-145.

Craske, M. G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., & Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. *Behaviour Research and Therapy, 46*(1), 5-27.

Dabrowska, J., Hazra, R., Ahern, T. H., Guo, J. D., McDonald, A. J., Mascagni, F., ... & Rainnie, D. G. (2011). Neuroanatomical evidence for reciprocal regulation of the corticotrophin-releasing factor and oxytocin systems in the hypothalamus and the bed

Grillonnucleus of the stria terminalis of the rat: implications for balancing stress and affect. *Psychoneuroendocrinology, 36*(9), 1312-1326.

Davis, M., Walker, D. L., Miles, L., & Grillon, C. (2010). Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacology, 35*(1), 105.

Friedman, B. H. (2007). An autonomic flexibility–neurovisceral integration model of anxiety and cardiac vagal tone. Biological psychology, 74(2), 185-199.

Gewirtz, J. C., Mcnish, K. A., & Davis, M. (1998). Lesions of the bed nucleus of the stria terminalis block sensitization of the acoustic startle reflex produced by repeated stress, but not fear-potentiated startle. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 22(4), 625-648.

Gillie, B. L., Vasey, M. W., & Thayer, J. F. (2015). Individual differences in resting heart rate variability moderate thought suppression success. *Psychophysiology, 52*(9), 1149-1160.

Gorka, S. M., Nelson, B. D., Sarapas, C., Campbell, M., Lewis, G. F., Bishop, J. R., ... & Shankman, S. A. (2013). Relation between respiratory sinus arrythymia and startle response during predictable and unpredictable threat. Journal of psychophysiology.

Grillon, C. (2002). Startle reactivity and anxiety disorders: aversive conditioning, context, and neurobiology. *Biological Psychiatry, 52*(10), 958-975.

Grillon, C., Ameli, R., Woods, S. W., Merikangas, K., & Davis, M. (1991). Fear-potentiated startle in humans: Effects of anticipatory anxiety on the acoustic blink reflex. *Psychophysiology, 28*(5), 588-595.

Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29*(8), 1201-1213.

IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Koch, M., & Schnitzler, H. U. (1997). The acoustic startle response in rats—circuits mediating evocation, inhibition and potentiation. *Behavioural Brain Research, 89*(1-2), 35-49.

Jovanovic, T., & Ressler, K. J. (2010). How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. *American Journal of Psychiatry, 167*(6), 648-662.

Jovanovic, T., Kazama, A., Bachevalier, J., & Davis, M. (2012). Impaired safety signal learning may be a biomarker of PTSD. *Neuropharmacology, 62*(2), 695-704.

Jovanovic, T., Keyes, M., Fiallos, A., Myers, K. M., Davis, M., & Duncan, E. J. (2005). Fear potentiation and fear inhibition in a human fear-potentiated startle paradigm. *Biological Psychiatry, 57*(12), 1559-1564.

Kendler, K. S., Hettema, J. M., Butera, F., Gardner, C. O., & Prescott, C. A. (2003). Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. *Archives of General Psychiatry, 60*(8), 789-796.

Kilpatrick, D. G., Resnick, H. S., Milanak, M. E., Miller, M. W., Keyes, K. M., & Friedman, M. J. (2013). National Estimates of Exposure to Traumatic Events and PTSD Prevalence Using DSM-IV and DSM-5 Criteria. Journal of traumatic stress, 26(5), 537-547.

Kim, H., Somerville, L.H., Johnstone, T., Alexander, A.L., Whalen, P.J., (2003). Inverse
amygdala and medial prefrontal cortex responses to surprised faces. *Neuroreport 14* (18),
2317–2322

Kindt, M., & Soeter, M. (2014). Fear inhibition in high trait anxiety. PloS one, 9(1), e86462.

Lang, P. J., McTeague, L. M., & Bradley, M. M. (2016). RDoC, DSM, and the reflex physiology of fear: A biodimensional analysis of the anxiety disorders spectrum. *Psychophysiology*, *53*(3), 336-347.

Lebow, M. A., & Chen, A. (2016). Overshadowed by the amygdala: the bed nucleus of the stria terminalis emerges as key to psychiatric disorders. Molecular psychiatry, 21(4), 450.Merikangas, K. R., & Swanson, S. A. (2009). Comorbidity in anxiety disorders. In Behavioral neurobiology of anxiety and its treatment (pp. 37-59). Springer Berlin Heidelberg.

LeDoux, J. E., Moscarello, J., Sears, R., & Campese, V. (2017). The birth, death, and resurrection of avoidance: A reconceptualization of a troubled paradigm. *Molecular Psychiatry*, *22*(1), 24.

Lissek, S., & Güntürkün, O. (2004). Maintenance in working memory or response selection?: Functions of NMDA receptors in the pigeon “prefrontal cortex”. *Behavioural Brain Research, 153*(2), 497-506.

Lovibond, P. F. (1992). Tonic and phasic electrodermal measures of human aversive conditioning with long duration stimuli. *Psychophysiology*, 29(6), 621-632.

Lovibond, P. F., Davis, N. R., & O'Flaherty, A. S. (2000). Protection from extinction in human fear conditioning. *Behaviour Research And Therapy*, *38*(10), 967-983.

McEwen, B. S. (2000). Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology*, *22*(2), 108-124.

McEwen, B. S., Eiland, L., Hunter, R. G., & Miller, M. M. (2012). Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress. *Neuropharmacology*, *62*(1), 3-12.

McEwen, B.S., Seeman, T., (1999). Protective and damaging effects of mediators of stress—elaborating and testing the concepts of allostasis and allostatic load. In: Adler, N.E., Marmot, M., McEwen, B., Stewart, J. (Eds.), *Socioeconomic Status and Health in Industrial Nations: Social, Psychological, and Biological Pathways, 896*, 30–47.

McTeague, L. M., Lang, P. J., Wangelin, B. C., Laplante, M. C., & Bradley, M. M. (2012). Defensive mobilization in specific phobia: Fear specificity, negative affectivity, and diagnostic prominence. *Biological Psychiatry*, *72*(1), 8-18.

Merikangas, K. R., & Swanson, S. A. (2009). Comorbidity in anxiety disorders. In *Behavioral Neurobiology of Anxiety and Its Treatment* (pp. 37-59). Springer, Berlin, Heidelberg.

Meuwly, N., Bodenmann, G., Germann, J., Bradbury, T. N., Ditzen, B., & Heinrichs, M. (2012). Dyadic coping, insecure attachment, and cortisol stress recovery following experimentally induced stress. *Journal of Family Psychology*, *26*(6), 937.

Mol, S. S., Arntz, A., Metsemakers, J. F., Dinant, G. J., Vilters-van Montfort, P. A., & Knottnerus, J. A. (2005). Symptoms of post-traumatic stress disorder after non-traumatic events: evidence from an open population study. *The British Journal of Psychiatry*, *186*(6), 494-499.

Nakagawa, S., & Cuthill, I. C. (2007). Effect size, confidence interval and statistical significance: a practical guide for biologists. *Biological Reviews, 82*(4), 591-605.

Olatunji, B. O., Armstrong, T., McHugo, M., & Zald, D. H. (2013). Heightened attentional capture by threat in veterans with PTSD. *Journal of Abnormal Psychology, 122*(2), 397.

Orr, S. P., Metzger, L. J., Lasko, N. B., Macklin, M. L., Peri, T., & Pitman, R. K. (2000). De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *Journal of Abnormal Psychology*, 109(2), 290.

Otgaar, H., Muris, P., Howe, M.L. and Merckelbach, H., 2017. What drives false memories in psychopathology? A case for associative activation. *Clinical Psychological Science, 5*(6), pp.1048-1069.

Pappens, M., Schroijen, M., Sütterlin, S., Smets, E., Van den Bergh, O., Thayer, J. F., & Van Diest, I. (2014). Resting heart rate variability predicts safety learning and fear extinction in an interoceptive fear conditioning paradigm. *PloS One, 9*(9), e105054.

Pavlov, I. P. (1928). *Lectures on conditioned reflexes, translated by WH Gantt.* International Publishers, New York.

van Praag, H. V., Asnis, G. M., Kahn, R. S., Brown, S. L., Korn, M., Friedman, J. H., & Wetzler, S. (1990). Nosological tunnel vision in biological psychiatry. *Annals of the New York Academy of Sciences, 600*(1), 501-510.ledou

Porges, S. W., Doussard-Roosevelt, J. A., Portales, A. L., & Greenspan, S. I. (1996). Infant regulation of the vagal "brake" predicts child behavior problems: A psychobiological model of social behavior. *Developmental psychobiology, 29*(8), 697-712.

Raudenbush, S. W., Bryk, A. S., & Congdon, R. (2001). *HLM for windows* (version 5.6. 4). Lincolnwood, IL: Scientific software international.

Raudenbush, S. W., & Bryk, A. S. (2002). *Hierarchical linear models: Applications and data analysis methods* (Vol. 1). sage.

Rescorla, R. A. (1969). Pavlovian conditioned inhibition. *Psychological Bulletin, 72*(2), 77.

Schmitz, A., & Grillon, C. (2012). Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). *Nature Protocols, 7*(3), 527.

Seligman, M. E., & Binik, Y. M. (1977). The safety signal hypothesis. *Operant-Pavlovian Interactions,* 165-187.

Shields, G. S., Bonner, J. C., & Moons, W. G. (2015). Does cortisol influence core executive functions? A meta-analysis of acute cortisol administration effects on working memory, inhibition, and set-shifting. *Psychoneuroendocrinology, 58*, 91-103.

Singer, J. D., & Willett, J. B. (2005). Growth curve modeling. *Encyclopedia of Statistics in Behavioral Science.*

Singer, J.D., & Willett, J.B. (2003). *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence*. New York: Oxford Press.

Sijbrandij, M., Engelhard, I. M., Lommen, M. J., Leer, A., & Baas, J. M. (2013). Impaired fear inhibition learning predicts the persistence of symptoms of posttraumatic stress disorder (PTSD). *Journal of Psychiatric Research*, *47*(12), 1991-1997.

Smith, R., Thayer, J. F., Khalsa, S. S., & Lane, R. D. (2017). The hierarchical basis of neurovisceral integration. *Neuroscience & Biobehavioral Reviews, 75*, 274-296.

Spinhoven, P., Penninx, B. W., van Hemert, A. M., de Rooij, M., & Elzinga, B. M. (2014). Comorbidity of PTSD in anxiety and depressive disorders: Prevalence and shared risk factors. *Child Abuse & Neglect*, *38*(8), 1320-1330.

Stifter, C. A., & Fox, N. A. (1990). Infant reactivity: Physiological correlates of newborn and 5-month temperament. *Developmental Psychology*, *26*(4), 582.

Sullivan, G. M., Apergis, J., Bush, D. E. A., Johnson, L. R., Hou, M. J. E. L., & Ledoux, J. E. (2004). Lesions in the bed nucleus of the stria terminalis disrupt corticosterone and freezing responses elicited by a contextual but not by a specific cue-conditioned fear stimulus. *Neuroscience*, *128*(1), 7-14.

Sylvers, P., Lilienfeld, S. O., & Laprairie, J. L. (2011). Differences between trait fear and trait anxiety: Implications for psychopathology. *Clinical Psychology Review*, *31*(1), 122-137.

Thayer, J. F., Åhs, F., Fredrikson, M., Sollers III, J. J., & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neuroscience & Biobehavioral Reviews*, *36*(2), 747-756.

Thayer, J. F., & Ruiz-Padial, E. (2006, April). Neurovisceral integration, emotions and health: An update. *In International Congress Series* (Vol. 1287, pp. 122-127). Elsevier.

Van Praag, H. M., Asnis, G. M., Kahn, R. S., Brown, S. L., Korn, M., Friedman, J. H., & Wetzler, S. (1990). Monoamines and Abnormal Behaviour a Multi-Aminergic Perspective. *The British Journal of Psychiatry*, *157*(5), 723-734.

Vansteenwegen, D., Vervliet, B., Iberico, C., Baeyens, F., Van den Bergh, O., & Hermans, D. (2007). The repeated confrontation with videotapes of spiders in multiple contexts

attenuates renewal of fear in spider-anxious students. *Behaviour Research and Therapy, 45*(6), 1169-1179.

Verkuil, B., Brosschot, J. F., de Beurs, D. P., & Thayer, J. F. (2009). Effects of explicit and implicit perseverative cognition on cardiac recovery after cognitive stress. *International Journal of Psychophysiology, 74*(3), 220-228.

Walker, D. L., Toufexis, D. J., & Davis, M. (2003). Role of the bed nucleus of the stria terminalis versus the amygdala in fear, stress, and anxiety. *European Journal Of Pharmacology, 463*(1), 199-216.

Wendt, J., Neubert, J., Koenig, J., Thayer, J. F., & Hamm, A. O. (2015). Resting heart rate variability is associated with inhibition of conditioned fear. *Psychophysiology*, *52*(9), 1161-1166.

Wisco, B. E., Miller, M. W., Wolf, E. J., Kilpatrick, D., Resnick, H. S., Badour, C. L., ... & Friedman, M. J. (2016). The impact of proposed changes to ICD-11 on estimates of PTSD prevalence and comorbidity. *Psychiatry Research, 240*, 226-233.

Woltman, H., Feldstain, A., MacKay, J. C., & Rocchi, M. (2012). An introduction to hierarchical linear modeling. *Tutorials in Quantitative Methods for Psychology*, *8*(1), 52-69.

Yehuda, R., Flory, J. D., Bierer, L. M., Henn-Haase, C., Lehrner, A., Desarnaud, F., ... & Meaney, M. J. (2015). Lower methylation of glucocorticoid receptor gene promoter 1F in peripheral blood of veterans with posttraumatic stress disorder. *Biological Psychiatry*, *77*(4), 356-364.

Zorawski, M., Blanding, N. Q., Kuhn, C. M., & LaBar, K. S. (2006). Effects of stress and sex on acquisition and consolidation of human fear conditioning. *Learning & Memory*, 13(4), 441-450.

Figure 1. The electrodes for measuring EMG will be placed on the eye, for ECG, on the chest and abdomen, and for EDA, on the fingers. The air-blaster will be placed around the neck, with the air-tube pointed directly at the neck, at approximately one inch from the throat.

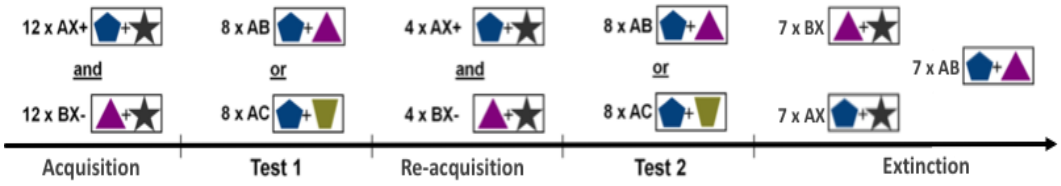

Figure 2. Trial type and order during acquisition, test, and extinction phases. Shapes were pseudo-randomized and counterbalanced between four trial orders--this is a representation of one trial sequence. Adapted from Wendt et al., 2015.

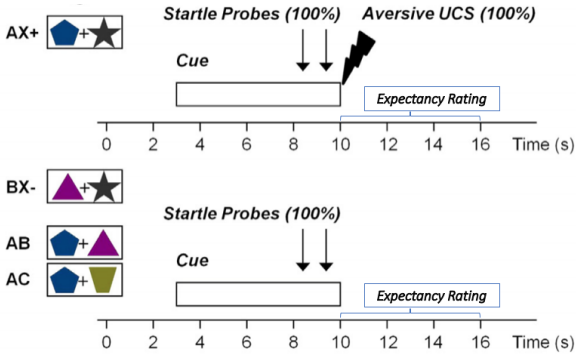

Figure 3. Trial structure of each trial type presented during acquisition and re-acquisition phases. This figure was adapted from Wendt et al., 2015.

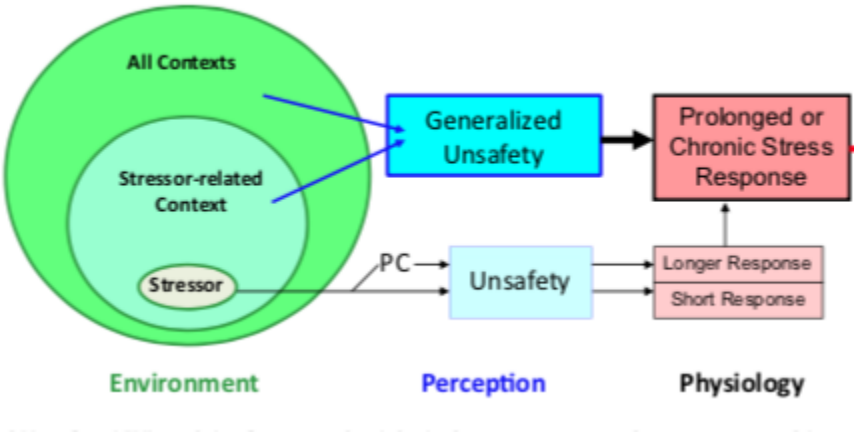

Figure 4. Proposed model of environmental conditioning underlying GU, which leads to chronic physiological responses (perseverative cognition [PC]). This figure is adapted from Brosschot et al. (2016) and does not include the disease component.

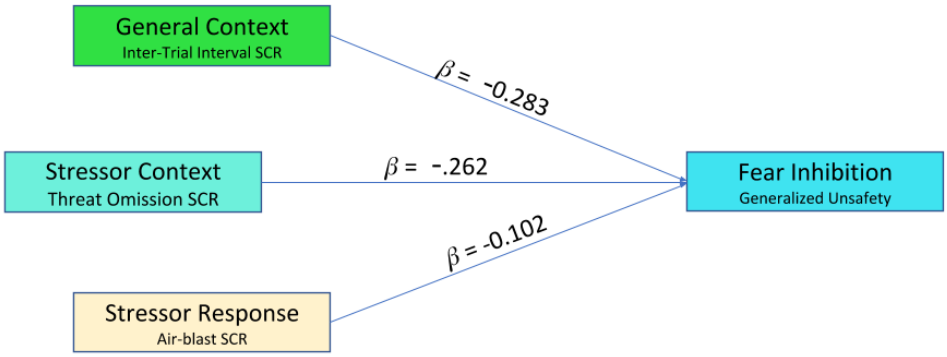

Figure 5. A multiple regression was implemented to examine stressor, stressor context and general context responses as predictors of fear inhibition.

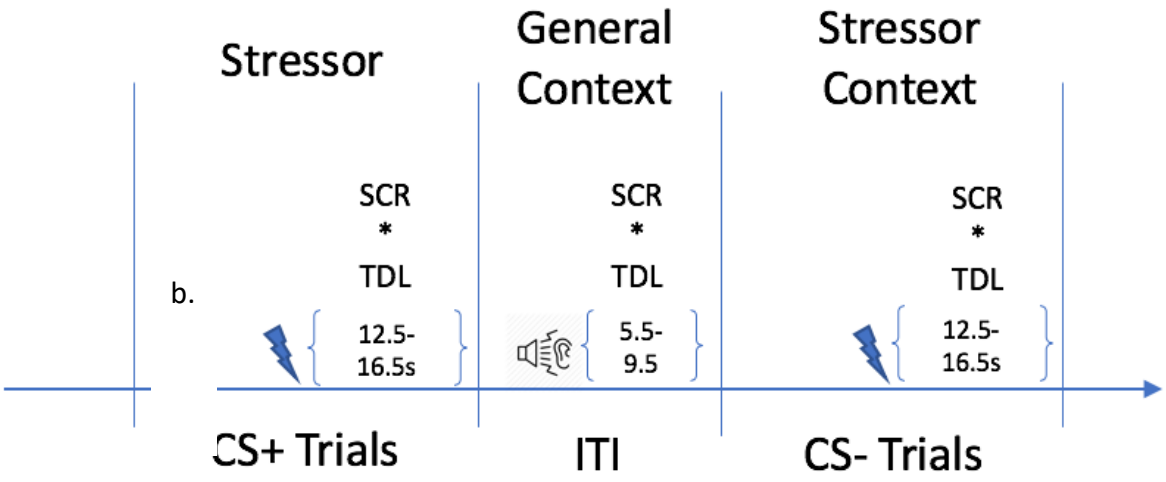

Figure 6. Sampling windows for SCR and TDL learning during acquisition.

Table 1. *Stressor-Only Model*

Parameter	Intercept-Only	Int. and Slopes	Outcomes
Outcome: SCR	none	L1: PE	L2: FI Group
(SCR) β_{00}	0.703***	0.550***	0.542***
se	*0.018*	*0.031*	*0.042*
Fear Inhibition β_{01}			0.016
se			*0.061*
PE β_{10}		0.390***	0.414***
se		*0.040*	*0.055*
Fear Inhibition β_{11}			-0.052
se			*0.079*
Within Person (σ^2)	0.033	0.015	0.015
se	*0.011*	*0.001*	*0.001*
Pseudo $R\varepsilon^2$		0.545	0.545
In initial status (SCR) π_0	0.011***	0.036***	0.036***
	0.003	*0.07*	*0.009*
In rate of change (PE) *r*		0.050***	0.050***
		0.224	*0.223*
Covariance π_1		-0.039***	-0.038***
		0.011	*0.010*
		Deviance Statistics	
Parameters (p)	3	6	8
Subjects (n)	42	42	42
Model Deviance	-212.260	-513.332	-514.032
AIC (Deviance + 2p)	-206.260	-501.332	-498.032
BIC (Deviance + ln(n) x p)	-201.047	-490.906	-484.131

significance levels: ***<.001, **.05, *.10

Table 2. *Stressor-Context Only Model*

Parameter	Intercept-Only	Int. and Slopes	Outcomes
Outcome: SCR	none	L1: PE	L2: FI Group
(SCR) β_{00}	0.426***	0.792***	0.655***
se	*0.023*	*0.037*	*0.194*
Fear Inhibition β_{01}			-0.175
se			*0.293*
PE β_{10}		0.843***	0.886*
se		*0.083*	*0.556*
Fear Inhibition β_{11}			-0.452
se			*0.842*
Within Person (σ^2)	0.039	0.025	0.025
se	*0.003*	*0.002*	*0.003*
Pseudo $R\varepsilon^2$		0.359	0.359
In initial status (SCR) π_0	0.134***	0.022***	0.027
	0.003	*0.012*	*0.200*
In rate of change (PE) *r*		0.010***	0.124
		0.100	*0.352*
Covariance π_1		0.029***	0.006
		0.025	*0.566*
		Deviance Statistics	
Parameters (p)	3	6	8
Subjects (n)	42	42	42
Model Deviance	90.243	-238.720	-97.341
AIC (Deviance + 2p)	96.243	-226.720	-81.341
BIC (Deviance + ln(n) x p)	101.456	-216.294	-67.440

significance levels: ***<.001, **.05, *.10

Table 3. *General-Context Model*

Parameter	Intercept-Only	Int. and Slopes	Outcomes
			L1: PE, L2: FI
Outcome: SCR	none	L1: PE	Group
(SCR) β_{00}	0.438***	0.444***	0.465**
se	*0.017*	*0.038*	*0.053*
Fear Inhibition β_{01}			-0.044*
se			*0.077*
PE β_{10}		**-0.016**	**0.067**
se		*0.086*	*0.136*
Fear Inhibition β_{11}			-0.107
se			*0.197*
Within Person (σ^2)	0.036	0.035	0.035
se	*0.013*	*0.003*	*0.003*
Pseudo Rε^2		0.028	0.028
In initial status (SCR) π_0	0.013***	0.016	0.016
	0.004	*0.014*	*0.014*
In rate of change (PE) *r*		0.012	0.002
		0.111	*0.043*
Covariance π_1		0.005	0.005
		0.033	*0.033*
		0.932	0.927
		Deviance Statistics	
Parameters (p)	3	6	6
Subjects (n)	42	42	42
Model Deviance	-154.989	-155.154	-155.709
AIC (Deviance + 2p)	-148.989	-143.154	-143.709
BIC (Deviance + ln(n) x p)	-143.776	-132.728	-133.283

significance levels: ***<.001, **.05, *.10

Table 4. *Full-Paradigm Predicted Learning Models*

Outcome: SCR	L1: PEstressor B	L1: PEstressorcont B	L1: PEgencontext B
(SCR) β_{00}	-0.075	0.786***	0.444***
se	0.089	0.037	*0.038*
PE β_{10}	0.984***	1.176***	-0.016
se	0.100	0.128	*0.086*
Within Person (σ^2)	0.023	0.029	0.035
se	0.002	0.002	*0.003*
In initial status (SCR) π_0	0.158***	0.016*	0.016
se	0.07	0.015	*0.014*
In rate of change (PE) *r*	0.140***	0.180*	0.012
se	0.224	0.424	*0.111*
Covariance π_1	-0.148***	0.021*	0.005
se	0.081	0.044	*0.033*
		Deviance Statistics	
# parameters (p)	6	6	6
# subjects (n)	42	42	42
Model Deviance	-346.032	-188.155	-155.154
AIC (Deviance + 2p)	-334.032	-176.155	-143.154
BIC (Deviance + ln(n) x p)	-323.606	-165.729	-132.728

significance levels: ***<.001, **.05, *.10

Table 5. *Fear-Inhibition Moderation of PE and SCR Learning*

	Stressor	Strssor Context	General Context
Outcome: SCR	L2: FI Group	L2: FI Group	L2: Fear FI Group
(SCR) β_{00}	-0.075***	0.655***	0.465**
se	*0.122*	*0.194*	*0.053*
Fear Inhibition β_{01}	-0.001	-0.175	-0.044*
se	*0.179*	*0.293*	*0.077*
PE β_{10}	0.987***	0.886*	0.067
se	*0.137*	*0.556*	*0.136*
Fear Inhibition β_{11}	-0.006	-0.452	-0.107
se	*0.200*	*0.842*	*0.197*
Within Person (σ^2)	0.025	0.025	0.035
se	*0.003*	*0.003*	*0.003*
In initial status (SCR) π0	0.159***	0.027	0.016
	0.074	*0.2*	*0.014*
In rate of change (PE) r1	*0.140***	0.124	0.002
	0.374	*0.352*	*0.043*
Covariance π1	*-0.148***	0.006	0.005
	0.082	*0.566*	*0.033*
		Deviance Statistics	
# parameters (p)	8	8	6
# subjects (n)	42	42	42
Model Deviance	-346.076	-97.341	-155.709
AIC (Deviance + 2p)	-330.076	-81.341	-143.709
BIC (Deviance + ln(n) x p)	-316.175	-67.440	-133.283

Table 6. *Reduced SCR and PE Model with Fear Inhibition Moderation*

	Stressor	Stressor Context	General Context
Outcome: SCR	L2: FI Group	L2: FI Group	L2: Fear FI Group
(SCR) β_{00}	-0.075***	0.719***	0.222**
se	*0.122*	*0.172*	*0.065*
Fear Inhibition β_{01}	-0.001	-0.395*	-0.161*
se	*0.179*	*0.258*	*0.100*
PE β_{10}	0.987***	0.714*	-0.480**
se	*0.137*	*0.325*	*0.158*
Fear Inhibition β_{11}	-0.006	-0.731*	-0.358*
se	*0.200*	*0.488*	*0.234*
Within Person (σ^2)	0.016	0.025	0.023
se	*0.002*	*0.003*	*0.003*
In initial status (SCR) π0	0.002***	0.033	0.018
	0.131	*0.152*	*0.022*
In rate of change (PE) r1	*0.140***	0.004	0.002
	0.374	*0.060*	*0.043*
Covariance π1	*-0.010***	0.010	0.005
	0.178	*0.282*	*0.052*
		Deviance Statistics	
# parameters (p)	8	8	8
# subjects (n)	42	42	42
Model Deviance	-346.076	-99.207	-146.76
AIC (Deviance + 2p)	-330.076	-83.207	-130.760
BIC (Deviance + ln(n) x p)	-316.175	-69.306	-116.859

Appendix A

Mind-Body Laboratory Health History Questionnaire (HHQ)

A very brief medical history must be obtained as part of the experimental protocol. It is very important that you be completely honest. This information will be kept strictly confidential.

1. What is your age, height, weight, and gender?

Age: _____ years

Height: _____ feet, _____ inches

Weight: _____ pounds

Sex: ___M ___F

2. Since birth, have you ever been hospitalized or had any major medical problems?

___ Yes ___ No

If Yes, briefly explain:

3. Have you ever experienced a concussion or lost consciousness due to a blow to the head?

___ Yes ___ No

If Yes, briefly explain:

4. Have you ever had problems that required you to see a counselor, psychologist, or psychiatrist?

___ Yes ___ No

If Yes, briefly explain:

5. Do you use tobacco products of any kind?

___ Yes ___ No

If Yes, describe what kind how often/much:

6. Have you ever been diagnosed with a psychological disorder?

___ Yes ___ No

If Yes, briefly explain:

7. Do you currently have or have you ever had any of the following?

___ Yes ___ No Strong reaction to cold weather

___ Yes ___ No Circulatory problems

___ Yes ___ No Tissue disease

___ Yes ___ No Skin disorders (other than facial acne)

___ Yes ___ No Arthritis

___ Yes ___ No Asthma

___ Yes ___ No Lung problems

___ Yes ___ No Cardiovascular disorder/disease

___ Yes ___ No Diabetes

___ Yes ___ No Hypoglycemia

___ Yes ___ No Hypertension (high blood pressure)

___ Yes ___ No Hypotension (low blood pressure)

___ Yes ___ No Hepatitis

___ Yes ___ No Neurological problems

___ Yes ___ No Epilepsy or seizures

___ Yes ___ No Brain disorder

___ Yes ___ No Stroke

If you responded Yes to any of the above conditions, briefly explain:

8. Have you ever been diagnosed as having:

___ Yes ___ No Learning deficiency or disorder

___ Yes ___ No Reading deficiency or disorder

___ Yes ___ No Attention deficit disorder

___ Yes ___ No Attention deficit hyperactivity disorder

___ Yes ___ No Autism Spectrum Disorder or Asperger's

9. Do you have:

___ Yes ___ No Claustrophobia (extreme fear of small closed spaces)

___ Yes ___ No Blood phobia (extreme fear of needles or blood)

___ Yes ___ No Fear of medical settings (e.g. hospital or doctor)

___ Yes ___ No Phobia of any type (if Yes, briefly explain:)

___ Yes ___ No Generalized anxiety disorder

___ Yes ___ No Anxiety disorder of any type (if Yes, briefly explain:)

If you responded Yes, briefly explain here:

10. List any over-the-counter or prescription medications you are currently taking:

11. List the symptoms that these drugs are treating

12. List any other medical conditions that you have or have had in the past:

13. What is your average daily caffeine consumption (approximate number of cups/glasses of coffee, tea, or caffeinated soda)?

14. What is your average weekly alcohol consumption (approximate number of alcoholic beverages)?

15. How many hours of sleep do you average per night?

16. On average, how often do you engage in physical activity for at least 30-minute sessions? (Circle one)

1- Never; 2- Rarely; 3-One to two days per week; 4-Three to four days per week; 5-Five to six days per week; 6-Seven days per week

17. Have you ever fainted? If so, explain. (When, what was likely to have caused it, how often does this occur?)