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Neural Substrates of Fear Generalization and Its Associations with Anxiety and Intolerance of Uncertainty

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NEURAL SUBSTRATES OF FEAR GENERALIZATION AND ITS ASSOCIATIONS WITH ANXIETY AND INTOLERANCE OF UNCERTAINTY

by

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ABSTRACT

NEURAL SUBSTRATES OF FEAR GENERALIZATION AND ITS ASSOCIATIONS WITH ANXIETY AND INTOLERANCE OF UNCERTAINTY

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Under the Supervision of Professor Christine L. Larson, Ph.D.

Fear generalization - the tendency to interpret ambiguous stimuli as threatening due to perceptual similarity to a learned threat – is an adaptive process. Overgeneralization, however, is maladaptive and has been implicated in a number of anxiety disorders. Neuroimaging research has indicated several regions sensitive to effects of generalization, including regions involved in fear excitation (e.g., amygdala, insula) and inhibition (e.g., ventromedial prefrontal cortex). Research has suggested several other small brain regions may play an important role in this process (e.g., hippocampal subfields, bed nucleus of the stria terminalis [BNST], habenula), but, to date, these regions have not been examined during fear generalization due to limited spatial resolution of standard human neuroimaging. To this end, the proposed project utilized high resolution spatial resolution of 7T fMRI to (1) characterize the neural circuits involved in threat discrimination and generalization, and (2) examine modulating effects of trait anxiety and intolerance of uncertainty on neural activation during threat generalization. In a sample of 31 healthy undergraduate students, significant positive generalization effects (i.e., greater activation for stimuli with increasing perceptual similarity to a learned threat cue) were observed in the visual cortex, thalamus, habenula and BNST, while negative generalization effects were observed in the dentate gyrus, CA1, CA3, and basal nucleus of the amygdala. Associations with individual differences were limited, though greater generalization in the insula and primary

somatosensory cortex was correlated with self-reported anxiety. Overall, findings largely support previous neuroimaging work on fear generalization and provide additional insight into the contributions of several previously unexplored brain regions.

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BLA	Basolateral amygdala
BNST	Bed nucleus of the stria terminalis
BOLD	Blood oxygen level dependent
CMN	Centromedial nucleus
CS+	Conditioned threat stimulus
CS-	Conditioned safety stimulus
fMRI	Functional magnetic resonance imaging
fROI	Functional region-of-interest
DG	Dentate gyrus
gPPI	Generalized psychophysiological interaction
GS	Generalization stimulus
IUS	Intolerance of Uncertainty Scale
LDS	Linear departure score
PTSD	Posttraumatic stress disorder
ROI	Region of interest
STAI-T	State-Trait Anxiety Inventory-Trait Version
vmPFC	Ventromedial prefrontal cortex

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Neural Substrates of Fear Generalization and its Associations with Anxiety and Intolerance of Uncertainty

Fear generalization is an adaptive process that enables an organism to respond appropriately to novel, possibly harmful, stimuli based on the presence of similar features to a learned threat. However, this process can prove maladaptive when individuals *over*generalize and exhibit fear responding to environmental cues that actually signal safety. Overgeneralization of fear has oft been neglected scientifically in human studies; however, it has profound clinical significance and is implicated in the pathophysiology of several psychiatric disorders, including anxiety and posttraumatic stress disorder (PTSD; Lissek et al., 2008; Lissek, et al., 2014b; Lissek, Rabin, & Heller, 2009; Morey et al., 2015). A better understanding of the complexities of fear generalization and the neural circuitry instantiating the behavior is likely to provide important insight into the pathophysiology of these disorders and potentially aid in the development of novel treatment targets.

Emerging research has shed light on the basic neural processes supporting fear generalization. Experimental paradigms typically utilize a Pavlovian conditioning design to condition participants to an initially neutral threat cue (conditioned stimulus; CS+) by presenting it with a naturally aversive stimulus (unconditioned stimulus; US), such as electric shock; after conditioning, a series of generalization stimuli (GSs) that parametrically vary in perceptual similarity to the CS+ are introduced (Dunsmoor, Mitroff, & LaBar, 2009; Lissek et al., 2008). Such designs allow for examination of the psychophysiological responses that follow a generalization gradient that tracks the degree of perceptual similarity to the threat cue. The slope of these generalization gradients can be examined to assess the degree of generalization across subjects. In healthy controls, gradients typically show most robust fear responding to the CS+,

with a fairly steep, quadratic decline in fear as the GSs decrease in similarity to the CS+, reflecting an appropriate balance of excitatory versus inhibitory processes (Asok, Kandel, & Rayman, 2019; Dunsmoor et al., 2009; Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011; Lissek et al., 2014a). However, when overgeneralization occurs, these gradients assume a more linear or convex shape, indicating safe GSs are perceived as threatening (see *Figure 1*)

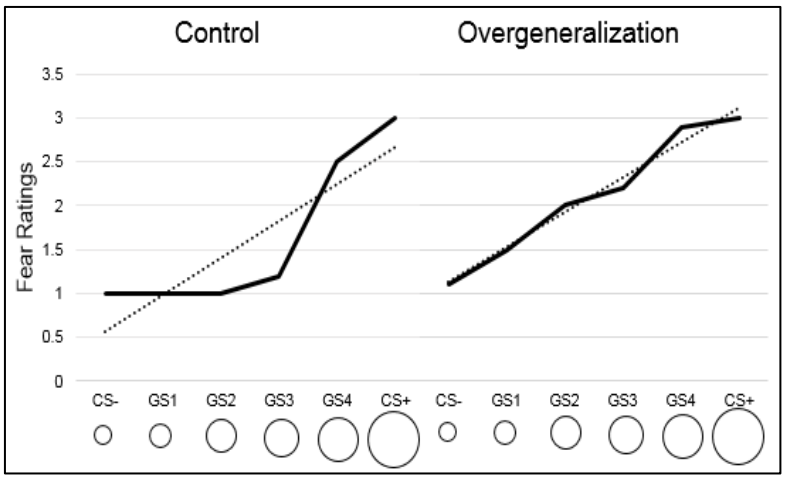

Figure 1. Example generalization findings. In healthy controls (left), generalization gradients typically depict most robust fear responding to the CS+, with a sharp, quadratic decline as stimuli decrease in similarity to the CS+. When overgeneralization occurs (right), gradients are more linear or convex in shape.

Neuroimaging research has elucidated a number of brain regions sensitive to effects of generalization. For instance, regions implicated in fear excitation – including the insula, dorsal anterior cingulate cortex (dACC), thalamus, periaqueductal grey (PAG), caudate, and ventral tegmental area (VTA) – demonstrate positive generalization gradients, wherein neural activation increases with increasing similarity to threat. On the other hand, regions involved in fear inhibition – including the ventromedial prefrontal cortex (vmPFC) and precuneus – demonstrate negative generalization gradients, wherein activation *de*creases with increasing similarity to threat (Dunsmoor et al., 2009; Lissek et al., 2014b; Spalding, 2018). The hippocampus has also been established as a region important for generalization for its roles in both memory formation

and pattern separation (Lissek et al., 2014a; Yassa & Stark, 2011), with hippocampal activation typically demonstrating negative generalization gradients (Lissek et al., 2014b).

However, many of the regions implicated in the process of fear generalization are heterogeneous in nature and relatively large in size; as such, there may be important structural and/or functional subdivisions that differentially contribute to threat generalization. Animal research, for instance, has provided substantial insight into different functional correlates of various anatomical regions – such as the hippocampus and amygdala - when segregated into more refined subregions (Fox, Oler, Tromp, Fudge, & Kalin, 2015; Strange, Fletcher, Henson, Friston, & Dolan, 1999; Zimmerman, Rabinak, McLachlan, & Maren, 2007). Such findings suggest that it may be vitally important to examine these subdivisions in humans in order to more finely characterize the neural circuitry supporting fear generalization. To this end, utilizing advantages afforded by ultra high field/high resolution neuroimaging may help to more reliably characterize the role of several regions -including the hippocampal subfields, amygdala subnuclei, bed nucleus of the stria terminalis, and habenula - during the process of fear generalization.

Hippocampus

Extensive research has implicated the hippocampus as a critical site for the formation of new associative memories, underscoring its importance for learning threat contingencies (Izquierdo, Furini, & Myskiw, 2016; Sanders, Wiltgen, & Fanselow, 2003). Moreover, lesions of the hippocampus and its cortical inputs have been shown to increase threat generalization (Bucci, Saddoris, & Burwell, 2002; Solomon & Moore, 1975; Wild & Blampied, 1972). Neural models of generalization are largely grounded in the hippocampus (e.g., Lissek, 2012), based on hippocampal-dependent processes subserving stimulus discrimination via pattern separation and

completion (McHugh et al., 2007; Rolls, 2013; Yassa & Stark, 2011). Thus, in the context of incomplete or ambiguous sensory information, sufficient overlap between a novel stimulus and learned threat cue leads to pattern completion in the hippocampus and subsequent engagement of structures involved in fear excitation (e.g., amygdala, insula); however, if neural representations of these stimuli are more distinct, the hippocampus initiates pattern separation and recruits structures involved in fear inhibition (e.g., vmPFC; Lissek et al., 2012).

Importantly, pattern separation and completion processes are attributed to different subfields of the hippocampus. Animal research has pointed to the dentate gyrus as the site for pattern separation, with lesions of the dentate gyrus shown to impair separation-dependent memory (Amaral, Scharfman, & Lavenex, 2007). Interestingly, human neurogenesis has been identified in the dentate gyrus (Eriksson et al., 1998; Kempermann et al., 2018). Some animal research has suggested that newly formed neurons in the dentate gyrus support pattern separation (Clelland et al., 2009; Glover, Schoenfeld, Karlsson, Bannerman, & Cameron, 2017). For instance, rats with ablated neurogenesis demonstrate impairment in discriminating between stimuli close in space, despite intact associative learning and an ability to correctly discriminate when stimuli are more spatially dissimilar (Clelland et al., 2009). Although research examining dentate gyrus function in humans is relatively scarce – largely limited by difficulties in clearly defining spatial boundaries of hippocampal subfields - emerging research has demonstrated a bias toward pattern separation in the dentate gyrus/CA3 subfield, while the CA1 subfield is biased toward pattern completion (Bakker, Kirwan, Miller, & Stark, 2008; Dimsdale-Zucker et al., 2018; Lacy et al., 2011) . Given this research, treating the hippocampus as a homogenous region may not adequately characterize the complex, neural processes supporting stimulus generalization.

Amygdala and Bed Nucleus of the Stria Terminalis

The amygdala has been less consistently implicated in fear generalization, despite a rich history of research that has well-documented the region's role in the detection and regulation of threat responding (Davis, 1992; LeDoux, 2003). Within the amygdala, the lateral nucleus (LA) has been proposed as a key site of plasticity for fear learning and memory (Goosens & Maren, 2001). Sensory information via thalamic inputs is received by the basolateral amygdala (BLA) where it is integrated with contextual information to establish threat contingencies. This information is then transmitted to the central amygdala (CeA) where it is forwarded to other regions, such as the striatum, to mediate behavior (e.g., fight-or-flight response; Janak & Tye, 2015). The amygdala shares strong anatomical and functional connections with the bed nucleus of the stria terminalis (BNST; Avery et al., 2014; Torrisi et al., 2015), an understudied region also implicated in threat responding (Davis, Walker, Miles, & Grillon, 2010; Lebow & Chen, 2016). Together with the CeA, the BNST is considered part of an anatomically defined macrostructure of several small, tightly interconnected regions referred to as the extended amygdala (Shackman & Fox, 2016; Tyszka & Pauli, 2016). While the CeA has been thought to mediate more immediate, phasic responding to an identifiable threat (i.e., 'fear'), the amygdala's lateral nuclei and BNST are thought to support more sustained apprehensive states (i.e., 'anxiety'; Davis et al., 2010; Klumpers, Kroes, Baas, & Fernández, 2017; Shackman & Fox, 2016).

Insufficient spatial resolution has limited reliable characterization of the functional roles of these divisions of the amygdala and its neural neighbors. Animal work has provided some useful insight into how these regions may be implicated in generalization. For instance, following aversive conditioning, primates display altered tuning curves in the BLA that are

associated with reduced stimulus discrimination (Resnik & Paz, 2015). In rats, BLA activity is higher when stimulus features resemble a learned threat (Grosso, Santoni, Manassero, Renna, & Sacchetti, 2018), and defensive responding to ambiguous threat cues is modulated by BNST activation (Goode, Ressler, Acca, Miles, & Maren, 2019). Emerging human research has also begun to disentangle the BNST's role in threat processing, demonstrating that the BNST is activated during anticipation of unpredictable threat (Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011) and tracks threat proximity (Somerville, Whalen, & Kelley, 2010). Functional connectivity studies – both at rest and during threat-based tasks – have shown overlapping and distinct functional connections of the BNST and CeA (Gorka, Torrisi, Shackman, Grillon, & Ernst, 2018; Tillman et al., 2018; Torrisi et al., 2015; 2018; Weis et al., 2019). No studies to date have examined how these circuits contribute to the process of fear generalization in humans. Although the role of the amygdala remains unclear within the larger body of generalization research, considering the broader amygdaloid complex and its subdivisions may help to provide clarification. Specifically, there may be differential contributions of amygdala subnuclei and/or the BNST to fear generalization that fail to be observed with a more homogenous functional perspective of the amygdala. For instance, ambiguity related to the perceptual similarity of a stimulus to a threat may drive BNST activation during generalization, while increased generalization may be observed uniquely in the BLA (rather than the CeA). Thus, utilizing the spatial resolution advantages offered by 7T ultra high-field resolution will be instrumental for delineating the precise neural processes within the amygdaloid complex during generalization.

Habenula

The habenula, a region proposed to play a pivotal role in enabling adaptive behavior related to both threat and reward, may also play a key role in generalization. The habenula serves

as an important interface between core affective regions and the brainstem (Boulos, Darcq, & Kieffer, 2017; Epstein, Hurley, & Taber, 2018), and has critical structural and functional connections with the medial prefrontal cortex, ACC, and hippocampus (Ely et al., 2016; Shelton, Becerra, & Borsook, 2012; Torrisi et al., 2017). Researchers have proposed the habenula's core role is in signaling the occurrence of negative events and integrating information about internal states and external context, in order to modulate or adapt behavior (Boulos et al., 2017; Epstein et al., 2018; Salas, Baldwin, de Biasi, & Montague, 2010). Neuronal recordings in the habenula have demonstrated increased activity in response to behaviorally salient negative events, such as threat cues (Hikosaka, 2010; Matsumoto & Hikosaka, 2007). In humans, habenula activation is observed in response to conditioned threat cues (Hennigan, D'Ardenne, & McClure, 2015; Lawson et al., 2017). Thus, the habenula may play a role in integrating information about a learned threat in order to flexibly respond (i.e., by either generalizing or discriminating between stimuli). However, measuring only about 15-36 mm3 in volume in humans (Lawson, Drevets, & Roiser, 2013), most studies examining neural activity related to threat learning and prediction have largely ignored the habenula. In addition, in both human and animal research, no studies to date have examined the habenula during fear generalization.

Clinical Relevance of Generalization

Therefore, utilizing ultra high-field 7T neuroimaging will likely provide important insight into the complex neural mechanisms implicated in fear generalization. Importantly, a better basic science understanding of this process may have substantial clinical implications. While fear generalization is an adaptive process - allowing individuals to flexibly respond to novel threat based on similarity to a previously learned threat - evidence suggests that this process goes awry in anxiety disorders and becomes maladaptive, such that individuals respond fearfully to cues

that actually confer safety (Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015; Lissek, 2012). Clinical observations clearly illustrate how this overexpression of fear in the context of safety can cause profound distress and impairment in an individual's daily functioning. For example, an assaultive trauma survivor may experience an intense emotional and physiological reaction triggered by seeing someone who resembles their attacker. Overgeneralized fear may also contribute to avoidance of activities that provide positive reinforcement or are instrumental to daily living. For instance, an individual with panic disorder who has a single panic attack while driving may generalize their fear response from this event to novel situations, potentially leading them to avoid driving-related activities altogether, including driving or riding as a passenger in a motor vehicle.

Experimental work has implicated overgeneralization of fear across a number of anxiety-related pathologies, including panic (Lissek et al., 2009), generalized anxiety (Cha et al., 2014; Lissek et al., 2014b), social anxiety (Ahrens et al., 2016) and posttraumatic stress disorders (Lissek & van Meurs, 2015; Thome et al., 2018). Neuroimaging work with clinical samples is more rare. Recent work has demonstrated PTSD patients show increased generalization in the insula, hippocampus, vmPFC, and caudate (Kaczkurkin et al., 2017; Morey et al., 2015). Generalized anxiety disorder has been linked to aberrant functioning of the vmPFC and mesocorticolimbic system during fear generalization (Cha et al., 2014; Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2013).

More broadly, anxious pathology has been frequently associated with abnormalities in brain regions relevant to fear generalization. Meta-analyses, for instance, have implicated aberrancies within regions critical for fear excitation and inhibition, such as the insula, amygdala, and vmPFC, in anxiety disorders (Etkin & Wager, 2007). Decreased hippocampal volume has

been observed in PTSD and social anxiety disorder, with high-resolution data suggesting that this volume reduction may be localized to the DG and CA3 (Hayes et al., 2017; Wang et al., 2010). Given the role of the DG in pattern separation, this finding may relate to overgeneralization observed in these populations. Indeed, some have proposed that impairment in pattern separation – and deficient neurogenesis in the DG – as an endophenotype for anxiety disorders (Besnard & Sahay, 2016; Kheirbek, Klemenhagen, Sahay, & Hen, 2012). Anxiety, therefore, may be related to a bias for pattern completion, wherein anxious individuals overgeneralize new information to fit an existing representation of threat.

Evidence also exists to suggest that the functioning of regions including amygdala subnuclei, BNST, and habenula may be altered in individuals with anxiety disorders. For example, altered functional connectivity of the BLA, but not CEA, has been demonstrated to differentiate PTSD patients from trauma-exposed controls (Brown et al., 2014). Compared to healthy controls, patients with anxiety disorders (GAD) demonstrate increased BNST activation during conditions of uncertainty (Yassa, Hazlett, Stark, & Hoehn-Saric, 2012). Hyperactivation of the habenula has been related to anxiety and defensive responding in rats and zebrafish (Mathuru & Jesuthasan, 2013; Pobbe & Zangrossi, 2008); though limited, emerging human research suggests habenular dysfunction is observed in depression, which is highly comorbid with anxiety (Lawson et al., 2017; Yoshino et al., 2018). Together, these findings warrant further examination of how these regions are recruited during anxiety-relevant processes, such as fear generalization, in humans.

It is also important to consider how non-clinical levels of anxiety may modulate fear generalization. Most research to date has focused on examining generalization between patient and control populations, rather than focusing on individual difference factors. Several studies

have examined generalization as related to trait anxiety, although findings have been somewhat inconsistent; some studies have suggested trait anxiety is related to overgeneralization (Haddad, Xu, Raeder, & Lau, 2013; Wong & Lovibond, 2018), while others have failed to find an association (Arnaudova, Krypotos, Effting, Kindt, & Beckers, 2017; Torrents-Rodas et al., 2013).

To this end, it may also be useful to examine anxiety-relevant transdiagnostic constructs that may more specifically encapsulate the cognitive processes playing into fear generalization, such as intolerance of uncertainty. Intolerance of uncertainty is an individual difference factor that captures the extent to which an individual experiences distress or anxiety in response to unpredictable or ambiguous information (Buhr & Dugas, 2002; Ladouceur, Gosselin, & Dugas, 2000). Intolerance of uncertainty has been extensively implicated in the etiology and maintenance of anxiety (Correa, Liu, & Shankman, 2019; Dugas, Gagnon, Ladouceur, & Freeston, 1998; Osmanağaoğlu, Creswell, & Dodd, 2018; Shihata, McEvoy, Mullan, & Carleton, 2016). When presented with ambiguous stimuli, those who are more intolerant of uncertainty may excessively worry about possible negative outcomes and exhibit a propensity to overgeneralize their threat response. Indeed, recent behavioral research has indicated a relationship between intolerance of uncertainty and fear generalization. Higher intolerance of uncertainty has been shown to be uniquely associated with threat generalization (Bauer et al., 2020; Morriss, Macdonald, & van Reekum, 2016; Nelson, Weinberg, Pawluk, Gawlowska, & Proudfit, 2015). In addition, individuals with high intolerance of uncertainty are more likely to perceive ambiguous stimuli as threatening and engage in avoidance behavior to avoid the perceived threat (Hunt, Cooper, Hartnell, & Lissek, 2019). Notably, these effects appear driven

by stimuli in the middle of the CS+ to CS- generalization continuum, which are inherently the most ambiguous stimuli due to their equidistance to both threat and safety cues.

While intolerance of uncertainty and trait anxiety are highly correlated (Sexton & Dugas, 2009), intolerance of uncertainty may be particularly insightful in examining generalization, as the construct is theoretically well-aligned with the psychological and cognitive processes occurring while viewing generalized stimuli. No studies, to date, have examined how intolerance of uncertainty modulates neural responding during fear generalization. However, intolerance of uncertainty has been linked to aberrant responding in brain regions implicated in generalization, such as hyperactivation of the amygdala and insula during anticipation of uncertain threat (Sarinopoulos et al., 2010; Shankman et al., 2014; Tanovic, Gee, & Joormann, 2018). Hyperactivity of the BNST has also been proposed as a neural correlate of higher intolerance of uncertainty (Grupe & Nitschke, 2013; Tanovic et al., 2018).

Aims:

In sum, research on the neural activity supporting fear generalization in humans has been sparsely studied despite its clinical relevance to anxious pathologies. Critically, from a basic science perspective, current understanding of fear generalization in humans has been limited by shortcomings of neuroimaging technology; specifically, the spatial resolution of standard fMRI acquisition has constrained the ability to delineate the unique contributions of small neural regions or subdivisions implicated in generalization and threat responding. While emerging work has demonstrated multiple anxiety disorders are marked by behavioral and neural aberrancies related to fear generalization, a better understanding of the precise neurobiological mechanisms involved in fear stimulus discrimination may ultimately help to inform novel, targeted

treatments. As such, the current study had several aims designed to understand the basic neural processes implicated in fear generalization, as well as their correlates with self-reported anxiety.

Aim 1: Utilize the high spatial resolution of 7T fMRI to characterize the neural circuits supporting threat discrimination and generalization.

Hypotheses: (1) GSs more similar to the CS+ will have increased activation of the hippocampal CA1 subfield; (2) GSs more similar to the CS- will have increased activation of the hippocampal dentate gyrus/CA3 subfield; (3) positive generalization gradients will be observed in the BNST, amygdala, habenula, dACC, thalamus, caudate (4) negative generalization gradients will be observed in prefrontal regions (vmPFC) and precuneus/posterior cingulate cortex. For functional connectivity analyses, we hypothesized that the dentate gyrus would demonstrate increased coactivation with inhibitory regions (e.g., vmPFC), while the CA1 would demonstrate increased functional connectivity with excitatory regions (e.g., amygdala, insula) for GSs more similar to the CS+.

Aim 2: Examine the effects of trait anxiety and intolerance of uncertainty on neural activation to generalized threat stimuli.

Hypotheses: Trait anxiety and intolerance of uncertainty will be associated with overgeneralization (i.e., less steep generalization gradient) of the conditioned threat cue in regions sensitive to generalization, including the BNST, habenula, and CA1.

Method

Participants

Forty-one undergraduate students were recruited from the University of Wisconsin – Milwaukee research subject pool. Participants were eligible for the study if they were between

the ages of 18 and 55, right-handed, and English-speaking. Exclusion criteria included contraindications to MRI (e.g., irremovable metal in body, pregnancy, claustrophobia), use of specific medications (antipsychotics, anticonvulsants, mood stabilizers), and history of head trauma, neurological conditions (e.g., epilepsy), psychosis, or bipolar disorder. One participant was excluded due to technical error (no shocks were administered during the task), and nine subjects failed the post-task contingency awareness test and were excluded from further analysis, resulting in a final analyzable N of 31. Sample characteristics are summarized in *Table 1.*

	Mean (SD) / n (%)
Sex	
Female	20 (64.5%)
Male	11 (35.5%)
Age	22.61 (3.95)
Race/Ethnicity	
White, non-Hispanic	21 (67.7%)
African-American	5 (16.1%)
Hispanic	3 (9.7%)
Asian/Pacific Islander	1 (3.2%)
Other/Unknown	1 (3.2%)
STAI-T	37.68 (8.55)
IUS	59.55 (16.21)
Factor 1	28.71 (6.98)
Factor 2	30.84 (8.51)

Table 1. Sample characteristics (n=31). STAI-T, State-Trait Anxiety Inventory – Trait; IUS, Intolerance of Uncertainty Scale

Procedure

Participants filled out an online prescreen through the research subject pool portal to assess for initial eligibility and provide a code to sign up for a study slot. After signing up, participants were contacted by study personnel to complete a phone screen to confirm MRI safety. Study participation included a series of functional and structural MRI scans, blood draw, and battery of self-report questionnaires. Participants were compensated with course credit and cash payment for their participation. Participants provided written informed consent. All study

procedures were approved by the University of Wisconsin-Milwaukee and Medical College of Wisconsin Institutional Review Boards.

Shock Work-Up

Prior to completing the fMRI generalization task, participants completed a shock work-up to determine the level of electrical stimulation (i.e., shock) used for the task at an individually-titrated aversive level. Shocks were delivered through a Psychlab system (Contact Precision Instruments, Cambridge, MA). Two electrodes were placed approximately two inches above the participant's left ankle. Starting at a low level of electrical stimulation (~.6mA, duration=500ms), a series of shocks were delivered. After each individual shock, participants were asked to make a 0 to 10 rating (0 = "didn't feel anything"' 10 = "painful, but tolerable"). Participants were informed that the level set should be "painful, but tolerable" and would be used throughout the task.

Generalization Task

The generalization task consisted of two phases: acquisition and generalization. During acquisition, participants were conditioned to the threat (CS+) and safety (CS-) cues. The acquisition phase consisted of a total of 20 trials (10 CS+, 10 CS-) in which the participant was presented with Gabor patch angled at either +15° or -15° offset from 0° (*Figure 2*). The stimulus established as the CS+ co-terminated with shock (100% reinforcement). Stimuli were counterbalanced such that for half of the participants, the +15° Gabor patch was the CS+, while for the other half the -15° stimulus was the CS+. Stimulus presentation was presented in a pseudorandomized order such that the same stimulus was presented a maximum of two consecutive trials. Stimuli appeared on the screen for 5000-ms. Participants viewed a fixation during inter-trial intervals (ITI) for 5000 to 9000-ms (average duration 7000-ms).

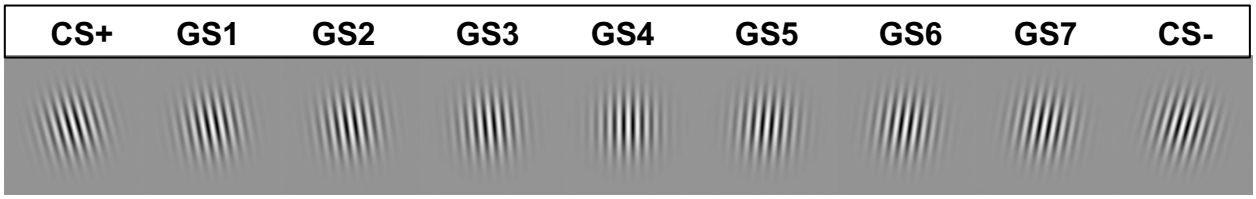

Figure 2. Generalization stimuli (GS). From left to right, Gabor patch angle of orientation at -10°, -8°, -5°, 0°, +5°, +8°, and +10° offset from 0°. The -15° and +15° degree stimuli were used as the CS+ and CS-, counterbalanced across participants.

During the generalization phase, a series of 7 novel generalization stimuli (i.e., GSs) were introduced that varied in degree of similarity to the CS+ and CS-. GSs consisted of Gabor patches at -10°, -8°, -5°, 0°, +5°, +8°, and +10° offset from 0° (*Figure 2*). The generalization phase consisted of 168 trials spread across three task runs. During each run, participants were presented with 6 trials of each GS and CS for 5000-ms. To prevent extinction, an additional 2 reinforced trials of the CS+ were included in each run. Thus, the generalization phase includes a total of 18 trials of each GS and the CS- and 24 trials of the CS+ (25% reinforcement). Stimuli were presented in a randomized order. ITI duration varied from 2000 to 5000-ms (average duration 3500-ms).

Throughout both task phases, participants were instructed to make online behavioral ratings to evaluate perceived risk of the stimuli. For each trial, 1000-ms post-stimulus onset, participants were prompted with the text "Level of risk?" To make a 1-3 Likert rating (1 = "no risk"; 3 = "high risk") on a button box about the likelihood of being shocked at the end of the trial. After responding, the number selected turned red on the screen; stimuli remained on the screen for the remainder of the 5000-ms stimulus presentation. The task design is depicted in *Figure 3.* In addition, following the final generalization run, participants were presented with both the CS+ and CS- side-by-side on the screen and asked to indicate by button press which stimulus predicted the shock.

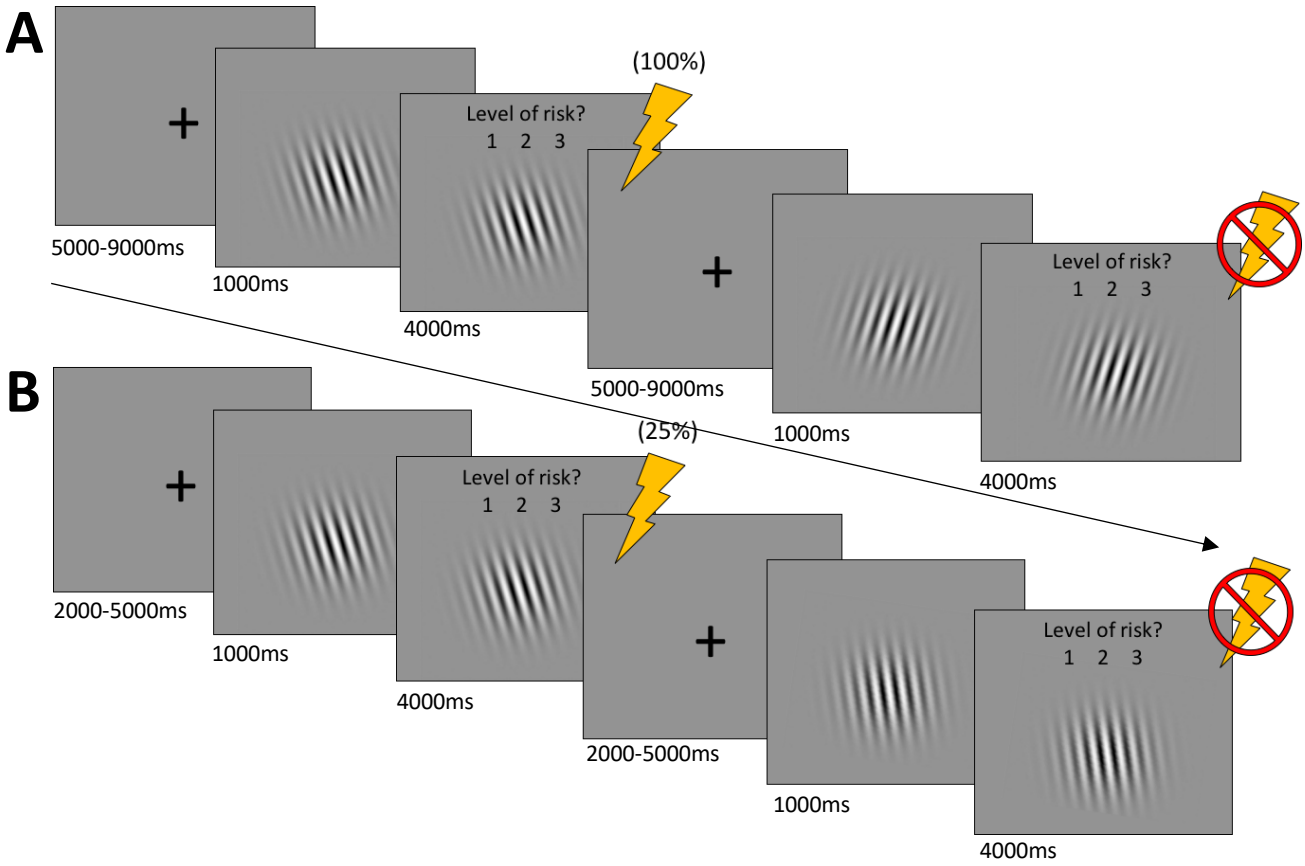

Figure 3. Generalization task design. During acquisition (A), participants presented with 10 trials each of CS+ (co-terminated with shock on 100% of trials) and CS-. During generalization (B), participants presented with 18 trials each of the CS+ (unreinforced), CS-, and 7 generalization stimuli (GSs) that vary in orientation from the CSs. An additional 6 trials of the reinforced CS+ were presented to prevent extinction.

Trait Anxiety

Trait anxiety was measured using the Trait version of the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger, 1983). The STAI consists of 20 self-report items rated on a four-point scale. The STAI has demonstrated good psychometric properties, including high test-retest reliability and internal consistency (Barnes, Harp, & Jung, 2002).

Intolerance of Uncertainty

Intolerance of uncertainty was measured using the Intolerance of Uncertainty Scale (IUS; Freeston et al., 1994; Buhr & Dugas, 2002). The IUS consists of 27 self-report items rated on a five-point scale. The IUS measures the extent to which an individual is able to tolerate uncertainty in ambiguous situations, beliefs about the emotional and behavioral consequences of uncertainty, and attempts to control the future. The IUS has demonstrated good internal consistency, test-retest reliability, and convergent/divergent validity with measures of anxiety, depression, and worry (Buhr & Dugas, 2002).

MRI data acquisition

Anatomical. Imaging data were collected on a 7.0 Tesla MR950 General Electric scanner (GE Healthcare, Waukesha, WI). Whole-brain high-resolution T1-weighted anatomical images were acquired using a BRAVO gradient echo sequence with the following parameters: TR/TE = 8.012/3.784s; FOV: 220; flip angle = 5°; thickness = .8mm; matrix = 276 x 276; voxel size = 0.43 x 0.43 x 0.80mm. A high-resolution, T2-weighted structural scan covering the hippocampus was collected in order to create regions-of-interest (ROIs) based on parcellation of the hippocampal subregions. For the hippocampus anatomical scan, oblique images were acquired coronally, angulated perpendicular to the long axis of the hippocampal formation: TR/TE = 10000/30.66; FOV: 85; voxel size = 0.4297 x 0.4297 x 2mm.

Functional. Partial-brain functional T2*-weighted EPI scans were acquired in an axial orientation with the following parameters: TR/TE = 2500ms/24ms; flip = 73°; FOV = 220; matrix = 224 x 224; thickness = 1.8mm; voxel size = 0.8594 x 08594 x 1.8mm. Partial-brain coverage was optimized to take advantage of the high resolution capabilities of the 7T scanner and prioritize a priori ROIs of the study aims, including the amygdala, BNST, hippocampus, and

insula. Scan coverage was determined on an individual subject basis by placing the most inferior slice to cover the most ventral part of the hippocampus (*Figure 4)*. An additional single-volume EPI scan with reverse phase encode polarity was collected after the task to correct for susceptibility-related distortion during image processing.

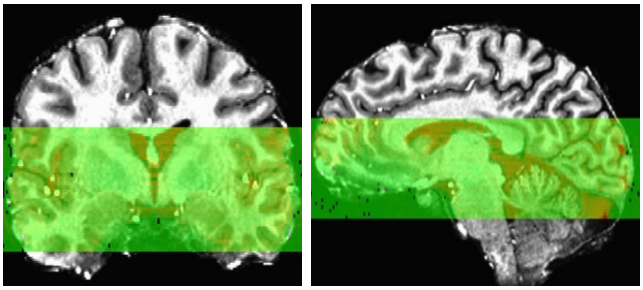

Figure 4. Example EPI partial coverage from a representative subject.

Preprocessing

Data were analyzed using Analysis of Functional Neural Images (AFNI) software (Cox, 1996). In preprocessing, the first three volumes were removed to allow for scanner equilibration, and volumes with excessive motion (>.2mm) and/or outliers (>10% of voxels in the volume identified as outliers) were excluded from further analyses. Due to greater sensitivity to distortion at ultra-high field, remaining EPI volumes were distortion corrected by warping to a middle space with the reverse phase encode polarity scan. EPI volumes were co-registered to the first functional volume, aligned to the subject's anatomy, and converted to percent signal change. A blur of 2mm FWHM was applied to the data. For whole brain group analyses, data were normalized to template (MNI152). Single subject BOLD responses were modeled with regressors for each condition type (acquisition: CS+, CS-; generalization: CS+, GS1, GS2, GS3, GS4, CS-) for each voxel in the functional dataset. Motion parameters were included as regressors of no interest. To examine generalization of threat – rather than safety - analysis of GSs focused on stimuli (GS1-3) expected to generalize to the threat stimulus based on their angle

of orientation, along with GS4 (i.e, the vertical stimulus which was dissimilar from both the CS+ and CS-).

ROI definition

Functional ROIs. The acquisition run was used to define functional ROIs sensitive to differential conditioning (e.g., Lissek et al., 2014). Data were preprocessed as described above; however, a 4mm –rather than 2mm – smoothing kernel was used to blur the data in order to produce more meaningful clusters. Whole brain analyses of the CS+ vs. CS- contrast were conducted using a voxelwise probability of $p < .001$ and cluster probability of $p < .05$. Estimated blur of the final EPI dataset was calculated using 3dFWHMx. Average auto-correlation function (ACF) parameters were entered into 3dClustSim to correct for multiple comparisons and estimate probability of obtaining clusters of a particular size ($p<.05$, $k>217$).

Hippocampal subfields. Subjects' native space T1 and T2 weighted structural scans were entered into Automatic Segmentation of Hippocampal Subfields (ASHS) software for hippocampal parcellation. Segmentation was performed using the Magdeburg 7T young adult protocol (Berron et al., 2017). ASHS has been validated in 7T data where it has demonstrated comparable accuracy with manual segmentation (Giuliano et al., 2017). The segmentation protocol failed for one participant, who was subsequently excluded from hippocampal analyses.

Amygdala subnuclei. Freesurfer version 6.0 was used for automated segmentation of amygdala subnuclei (basal, lateral, and centromedial) from subjects' native space T1 anatomical volume (Saygin et al., 2017).

BNST. The BNST ROI was defined in MNI space by the probabilistic segmentation mask constructed by Theiss and colleagues (2017).

Habenula. Based on average coordinates from a meta-analysis of the human habenula (Lawson et al., 2013), spherical ROIs with a radius of 2mm were created in MNI space for the left (-2.8, -24.4, 2.3) and right (4.8, -24.1, 2.2) habenula. The left and right habenula ROIs were combined for a bilateral habenula mask.

fMRI activation

Beta weights during the generalization phase were averaged across voxels within the functional and a priori ROIs and plotted across the conditioned (i.e., CS+, CS-) and generalization (i.e., GS1, GS2, GS3, GS4). A series of one-way ANOVAs with six levels (CS+, GS1, GS2, GS3, GS4, CS-) were conducted to examine generalization effects on threat stimulus processing and were followed by tests of linear and quadratic components, as appropriate. Statistical threshold was set at $\alpha = .05$.

Functional connectivity

To examine whether functional connectivity of the hippocampus varied as a function of condition, a generalized psychophysiological interaction (gPPI) was conducted. Preprocessing steps followed the same overall protocol as the activation analyses, with a blur of FWHM=4mm. Subject-specific dentate gyrus and CA1 ROIs were used as seeds. The time series of these seeds was extracted for each generalization run, detrended, and convolved with a gamma impulse response function. Resulting time series were used to create interaction regressors for each condition. Functional connectivity maps were created through deconvolution that included the original regressors (i.e., condition, motion) along with the second-order interaction regressors. For whole brain group analysis, beta values for interaction regressors of interest (i.e., CS+, GS1, GS2, GS3, GS4, CS-) were entered into 3dANOVA for each seed separately to examine whether

connectivity of the dentate gyrus and CA1 varied by condition, using a voxel-wise probability of $p < .001$ and cluster-wise probability of $p < .05$.

Associations with individual differences in anxiety.

Consistent with prior work in human fear generalization research (see van Meurs et al., 2013, Kaczkurkin et al., 2017; Lange et al., 2019), linear departure scores (LDS) were calculated to correlate with individual difference factors (i.e., STAI-T and IUS). The LDS assesses the degree to which an individual subject's generalization gradient deviates from linearity and is derived from the following equation: LDS = (GS1 + GS2 + GS3)/3 – (CS+ - GS4)/2. In this equation, the second expression refers to the theoretical midpoint if the gradient were perfectly linear, while the first expression represents the average response to the three generalized threat stimuli, which may fall above (positive departure), below (negative departure), or at (zero departure) the theoretical linear midpoint. In the current study, the GS4 (i.e., the vertical GS) was used in place of the CS-, as it represents a distinct, dissimilar stimulus from the CS+ and we did not expect a linear relationship to extend across the entire dimension of threat (GS1-3) and safety (GS5-7) generalization stimuli. As such, the LDS represents a single, quantifiable index of generalization. Positive LDS values represent shallow, convex gradients, while negative LDS values represent steep, concave gradients (see *Figure 1)*, with positive and negative departures indicating stronger and weaker generalization, respectively. For each functional and a priori ROI, extracted averaged beta weights were used to generate a LDS for that ROI and were correlated with STAI-T and IUS scores.

Behavioral data. Levels of conditioning during acquisition and generalization were assessed with paired samples t-tests to compare risk ratings to the CS+ vs. CS-. Risk ratings during generalization were analyzed with a one-way, repeated measures ANOVA with six levels

(CS+, GS1, GS2, GS3, GS4, and CS-) and followed by tests of linear and quadratic components. An LDS was also calculated for perceived risk ratings during the generalization task and correlated with STAI-T and IUS scores. Statistical threshold was set at $\alpha = .05$ for all tests.

Sex differences. Sex differences related to fear generalization, anxiety, and relevant neurobiological structure and function have been reported. For instance, female rats demonstrate faster fear generalization (Lynch, Cullen, Jasnow, & Riccio, 2013), and prevalence of anxiety is consistently higher in females (Breslau, Davis, Andreski, Peterson, & Schultz, 1997; Kessler et al., 1994; McLean, Asnaani, Litz, & Hofmann, 2011). Structural neuroimaging has also indicated that the BNST is sexually dimorphic (Allen & Gorski, 1990), and hippocampal volume is associated with sex hormone levels (e.g., estrogen; Protopopescu et al., 2008; Woolley, 1998). Given these findings, it is reasonable to expect sex differences in proposed analyses. Additional analyses to examine whether neural responses underlying fear generalization differ between males and females were conducted; however, as the sample is primarily female (28 female, 13 male), these tests are insufficiently powered and were exploratory in nature.

Results

Behavioral

Acquisition. Paired samples t-tests demonstrated significantly higher perceived risk for the CS+ (M=2.75, SD=.37) compared to the CS- (M=1.34, SD=.49) during conditioning, $t(30)=10.74$, $p<.001$. There were no significant differences in reaction time between the conditioned stimuli ($p=.36$). STAI trait anxiety was significantly correlated with higher perceived risk of the CS- ($r=.474$, $p=.007$). There was a marginal positive association of CS- ratings with IUS ($r=.332$, $p=.07$). There were no significant correlations between STAI or IUS with CS+ ratings or reaction times for either stimulus.

Generalization. Conditioned fear was maintained during the generalization runs, as evidenced by significantly higher perceived risk for the CS+ (M=1.80, SD=.61) compared to the CS- (M=1.15, SD=.25), $t(30)=5.55$, $p<.001$. A repeated measures ANOVA revealed significantly increased risk ratings from the CS- to GS4 to GS3 to GS2 to GS1 to CS+, $F(5,26)=22.49$, $p<.001$, indicating generalization of conditioned fear. Follow-up comparisons indicated both linear, $F(1,30)=31.52$, $p<.001$, and quadratic, $F(1,30)=4.78$, $p=.03$, components to the generalization gradient. There was also a significant effect of condition on reaction time, $F(5,26)=2.96$, $p=.01$, with a significant quadratic component, $F(1,30)=4.95$, $p=.03$, indicating increased reaction time for generalization stimuli in the middle of the generalization continuum (e.g., GS2, GS3).

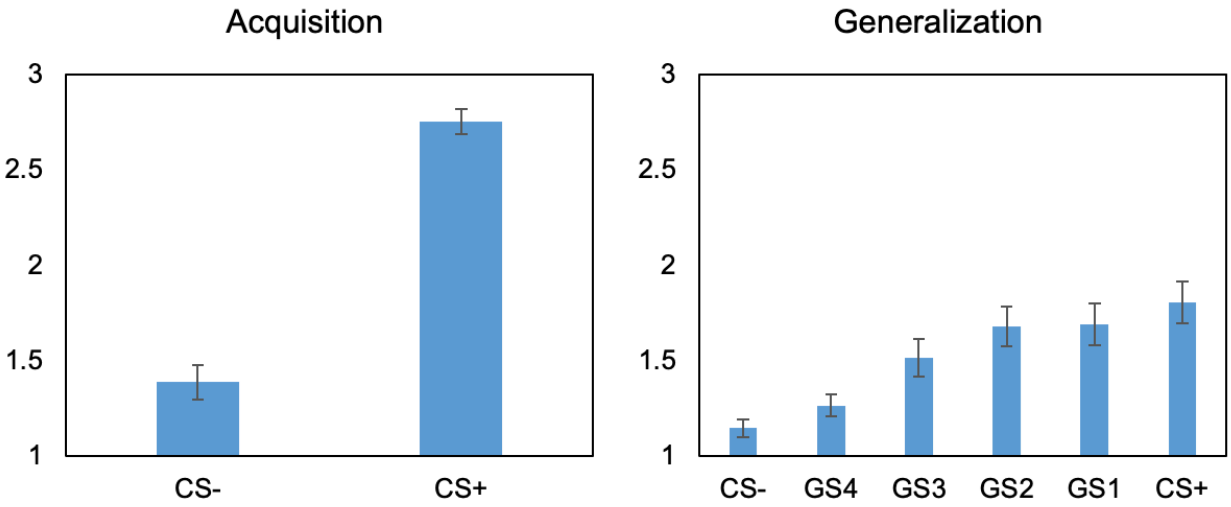

Figure 5. Online ratings of perceived risk (1-3) to the conditioned threat (CS+) and safety (CS-) cues and generalization stimuli (GSs) during acquisition and generalization task phases. Error bars represent standard error of the mean.

fMRI activation.

fROIs. Using a voxel-wise $p<.001$ and cluster threshold of $p<.05$, 13 clusters emerged that demonstrated increased activation for the CS+ relative to the CS- (*Table 2*). No clusters emerged that demonstrated increased activation for the CS- relative to the CS+.

			MNI coordinates			
	Region	**k**	**x**	**y**	**z**	**t**
1	Visual cortex/lingual gyrus	2142	0	-77	-4	4.91
2	Visual cortex/lingual gyrus	1211	-16	-102	1	4.72
3	R insula	1120	45	-7	11	5.64
4	Cuneus	477	25	-96	31	4.82
5	L insula	490	-34	-15	-4	4.12
6	R inferior parietal lobule/somatosensory cortex	489	51	-30	18	4.57
7	Somatosensory cortex/posterior insula	423	-51	-7	13	5.07
8	L inferior parietal lobule/somatosensory cortex	331	-47	-35	28	4.33
9	Somatosensory cortex	327	60	-3	14	4.60
10	Fusiform gyrus	284	25	-63	-10	4.60
11	Cuneus	245	17	-82	26	4.69
12	R thalamus	236	13	-26	17	4.48
13	L thalamus	218	-4	-16	2	5.13

Table 2. Significant clusters for contrast CS+ > CS- during acquisition phase with voxel-wise threshold $p < .001$ and cluster size corrected threshold of $p < .05$.

Generalization effects.

fROIs. Full results of the within-subjects generalization tests for all fROIs and a priori ROIs are presented in *Table 3.* During the generalization phase, activation within several fROIs demonstrated positive generalization gradients, with strongest activation to the CS+ with gradually decreasing activation to the GS1, GS2, GS3, GS4, and CS- as stimuli were increasingly dissimilar to the CS+ (see *Figure 6*). Specifically this pattern was noted in both of the visual cortex fROIs (cluster 1: $F(3.382, 26) = 3.516$, $p = .014$; cluster 2: $F(3.397, 26) = 2.97$, $p = .03$) and thalamus fROIs (cluster 12: $F(3.796, 26) = 4.7$, $p = .002$; cluster 13: $F(5,26) = 3.855$, $p = .003$). Follow-up tests of linear and quadratic components of these effects indicated significant linear, but not quadratic, effects in the more posterior visual cortex cluster (2), $F(1,30) = 6.139$, $p = .019$, right thalamus, $F(1,30) = 16.134$, $p < .001$, and left thalamus, $F(1,30)$

= 15.817, $p < .001$. For the other cluster in the visual cortex (1), both linear, $F(1,30) = 7.054$, $p = .013$, and quadratic, $F(1,30) = 5.039$, $p = .032$, were significant.

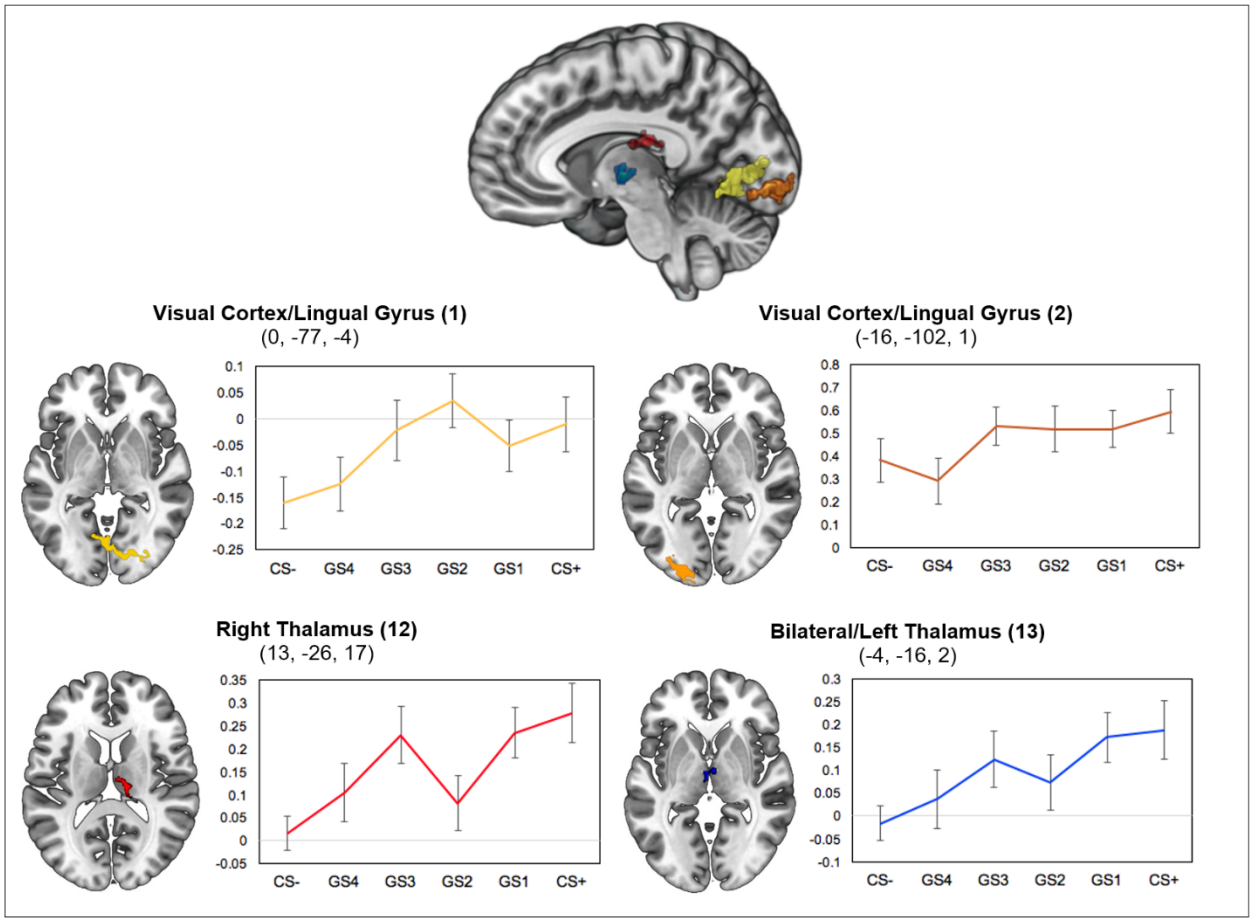

Figure 6. Functional regions-of-interest (fROIs) demonstrating significant effects during threat generalization. Numbers in parentheses correspond to the cluster numbers presented in Table 2. Parameter estimates represent signal averaged across the fROIs for the conditioned threat (CS+) and safety (CS-) cues, along with generalization stimuli (GSs). Error bars represent standard error of the mean.

Hippocampal subfields. Negative generalization gradients, with strongest activation to the CS- with gradually decreasing activation to the GS4, GS3, GS2, GS1, and CS+ as stimuli were increasingly similar to the CS+, were observed in the dentate gyrus, $F(5,25) = 2.919$, $p = .015$, CA3, $F(5,25) = 2.778$, $p = .02$, and CA1, $F(5,25) = 2.46$, $p = .036$ (*Figure 7*). For all subfields, follow-up tests indicated significant linear, but not quadratic effects in these regions

(dentate gyrus: $F(1,29) = 8.868$, $p = .006$; CA3: $F(1,29) = 6.422$, $p = .017$; CA1: $F(1,29) = 11.756$, $p = .002$).

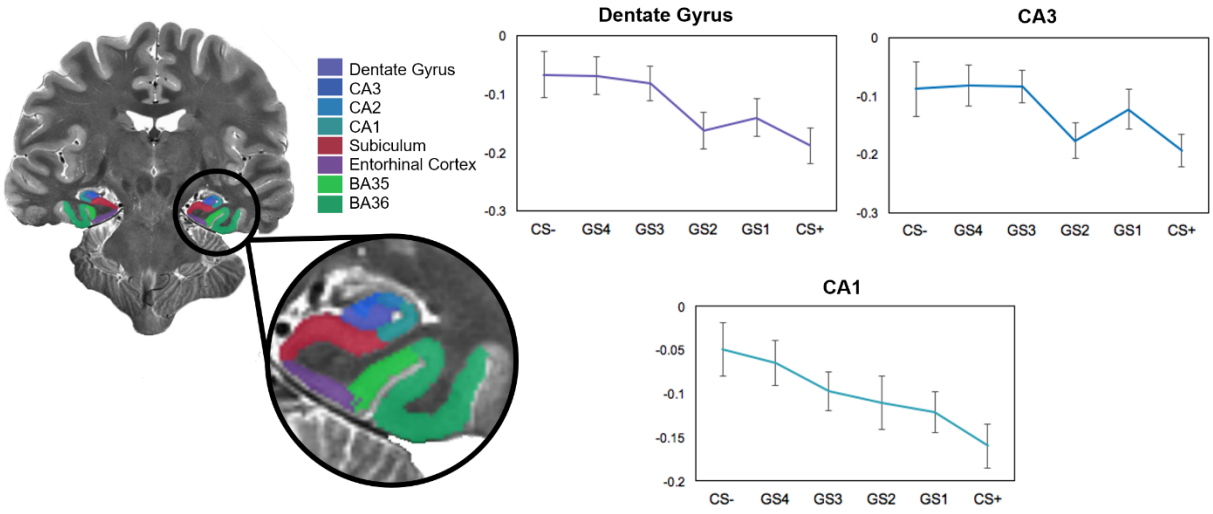

Figure 7. Hippocampal segmentation of a representative subject presented on T2-weighted anatomical scan. Significant negative generalization effects were observed in the dentate gyrus CA3, and CA1. Parameter estimates represent signal averaged across the hippocampal subfields for the conditioned threat (CS+) and safety (CS-) cues, along with generalization stimuli (GSs). Error bars represent standard error of the mean.

Amygdala subnuclei. There was a marginally significant negative generalization gradient observed in the basal nucleus of the amygdala, $F(3.809, 25) = 2.301$, $p = .066$, with a

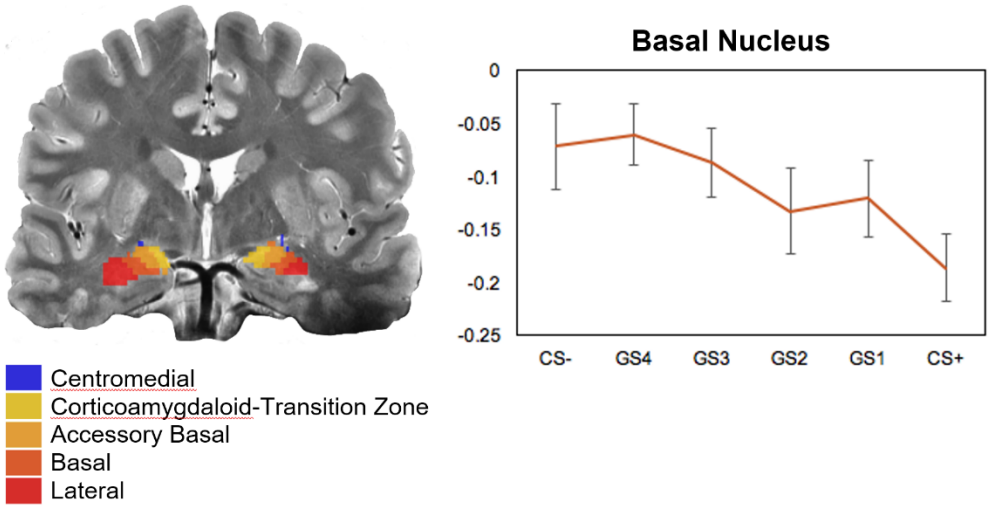

Figure 8. Segmentation of amygdala subnuclei for a representative subject presented on T2-weighted anatomical scan. Marginally significant ($p = .066$) negative generalization effects were observed in the basal nucleus. Parameter estimates represent signal averaged across the hippocampal subfields for the conditioned threat (CS+) and safety (CS-) cues, along with generalization stimuli (GSs). Error bars represent standard error of the mean.

significant linear, but not quadratic, component, $F(1,29) = 8.94$, $p = .006$ (*Figure 8*). There were no significant generalization effects observed in the lateral or centromedial subnuclei.

BNST. Significant generalization was observed in the BNST, $F(5,26) = 2.963$, $p = .014$; however, follow-up tests revealed that activation within the BNST was neither linear ($p = .082$) nor quadratic ($p = .208$) in nature (*Figure 9*).

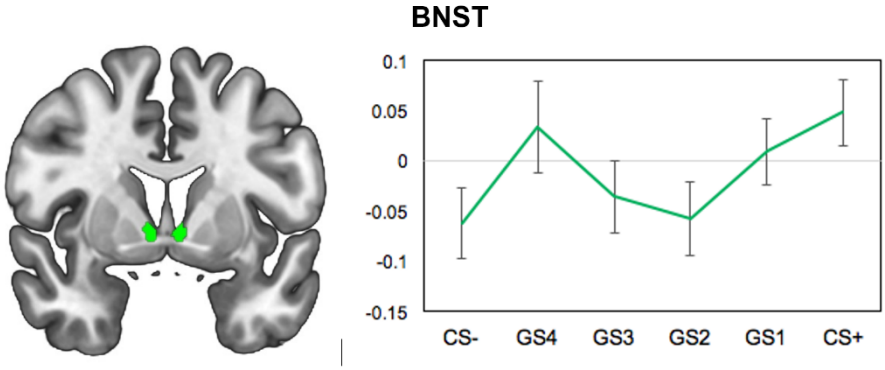

Figure 9. Bed nucleus of the stria terminalis (BNST) ROI defined in MNI space using probabilistic segmentation mask (Theiss et al., 2017). Parameter estimates represent signal averaged across the BNST for the conditioned threat (CS+) and safety (CS-) cues, along with generalization stimuli (GSs). Error bars represent standard error of the mean.

Habenula. A significant positive generalization gradient was observed in the habenula, $F(5,26) = 3.926$, $p = .002$, with a significant linear component to this effect, $F(1,30) = 8.465$, $p =$

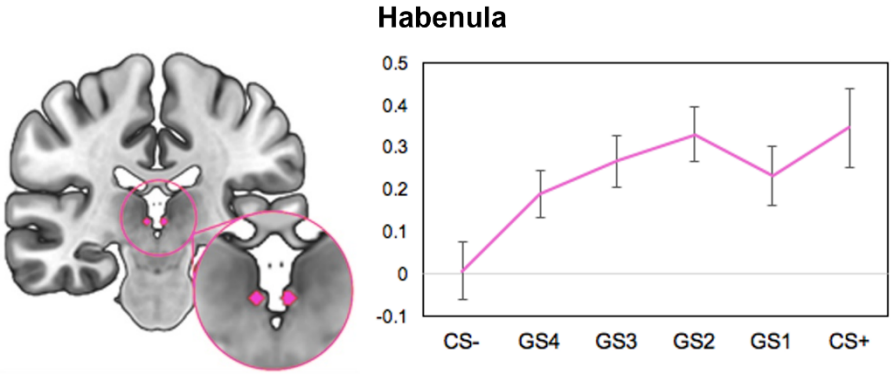

Figure 10. Bilateral habenula ROI defined in MNI space as spheres with 2mm radius around coordinates for the left (-2.8, -24.4, 2.3) and right (4.8, -24.1, 2.2) habenula (Lawson et al., 2013). There was a significant positive linear effect of generalization. Parameter estimates represent signal averaged across the mask for the conditioned threat (CS+) and safety (CS-) cues, along with generalization stimuli (GSs). Error bars represent standard error of the mean.

.007 (*Figure 10*). The quadratic component was marginally significant, $F(1,30) = 3.109$, $p = .088$.

Sex differences. There was a marginally significant stimulus X sex interaction on activation of the right thalamus, $F(3.741,26) = 2.183$, $p = .08$. No other regions demonstrated significant stimulus X sex interactions.

ROI	**F**	**p**
fROIs		
Visual cortex/lingual gyrus (1)	3.516	0.014
Visual cortex/lingual gyrus (2)	2.97	0.03
Cuneus (4)	0.686	0.566
Cuneus (11)	1.4	0.227
Fusiform gyrus (10)	1.189	0.319
R insula (3)	0.525	0.757
L insula (5)	0.367	0.871
R inferior parietal lobule/somatosensory cortex (6)	0.345	0.754
L inferior parietal lobule/somatosensory cortex (8)	1.333	0.264
Somatosensory cortex/posterior insula (7)	0.903	0.481
Somatosensory cortex (9)	1.229	0.303
R thalamus (12)	4.7	0.002
L thalamus (13)	3.855	0.003
Hippocampal subfields		
Dentate gyrus	2.919	0.015
CA1	2.46	0.036
CA3	2.778	0.02
Amygdala, BNST, & Habenula		
Basal amygdala	2.301	0.066
Lateral amygdala	1.329	0.255
Centromedial nucleus	1.511	0.19
BNST	2.963	0.014
Habenula	3.926	0.002

Table 3. Results of repeated measures ANOVAs for functional (fROIs) and a priori regions of interest. Results are clustered by region with fROI cluster numbers in parentheses corresponding to those denoted in Table 2.

Functional connectivity.

Results of the whole brain 3dANOVAs for the dentate gyrus and CA1 revealed no significant effect of condition on functional connectivity of the seeds with the rest of the brain. Exploratory examination of individual contrasts between stimuli revealed stronger connectivity between the CA1 and left middle temporal gyrus (-61, -31, 4; k = 84 & -68, -37, 2; k =47) and right amygdala (24, 5, -26; k = 71) for the CS+ relative to all GSs. More specifically, there was greater CA1 to right amygdala connectivity when presented with the CS+ vs the GS3 (24, 5, -26; k = 43) and GS4 (25, 5, -26; k = 47). There was also greater connectivity between the CA1 and left anterior cingulate cortex (-5, 50, -1; k =79) and thalamus (1, -12, 13; k = 41) for the GS1 vs. the GS4. None of these clusters survived cluster-level corrections.

Associations with individual differences.

Trait anxiety. Significant associations with individual differences are presented in *Figure 11*. Higher STAI trait anxiety was positively correlated with linear departure scores (i.e., greater generalization) in the primary somatosensory cortex, r = .39, p = .03 (cluster 9). STAI scores were not correlated with any other ROIs.

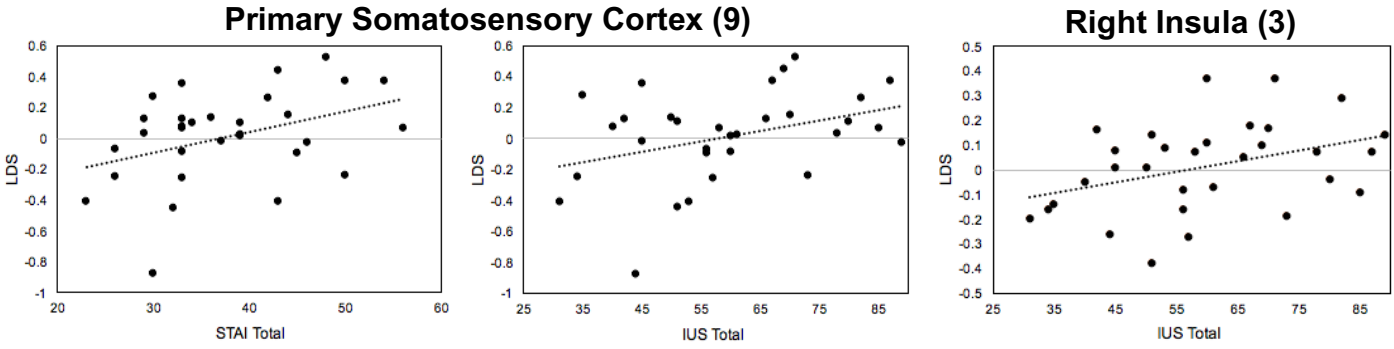

Figure 11. Scatterplots depict significant associations of self-reported trait anxiety (STAI) and intolerance of uncertainty (IUS) with linear departure scores (LDS) for regions-of-interest. The LDS was calculated by extracting averaged beta weights for each ROI and condition and entering them in the formula: LDS = (GS1+GS2+GS3)/3 – (CS+ - GS4)/2. Positive and negative LDS values represent stronger and weaker generalization, respectively. STAI and IUS scores were positively correlated with generalization in the primary somatosensory cortex (60, -3, 14; cluster 9). IUS was also positively correlated with generalization in the right insula (45, -7, 11; cluster 3).

Intolerance of uncertainty. Total IUS was positively correlated with linear departure scores in the right insula (cluster 3; $r = .379$, $p = .036$) and primary somatosensory cortex (cluster 9; $r = .373$, $p = .039$). IUS scores were not correlated with any other ROIs.

Discussion

In a sample of healthy young adults, the current study sought to characterize the neural processes contributing to the generalization of conditioned fear. Supporting prior work, neural signal tracked along gradients for a conditioned threat stimulus and perceptually similar stimuli in several key brain regions (e.g., thalamus, hippocampus). Moreover, the novel use of high-resolution 7T fMRI provided improved spatial resolution that highlighted the importance of previously uninvestigated small neural regions (e.g., habenula) during threat stimulus generalization.

Analysis of the initial conditioning run revealed a diffuse network of regions – including the insula, inferior parietal lobule, and somatosensory cortices - that exhibited greater activation for the threat versus safety cue; however, when novel generalization stimuli were introduced, only regions within the visual cortex and thalamus exhibited significant generalization, with the BOLD response tracking along degree of similarity to the CS+. While many view the amygdala as the brain's fear center, supporting arousal in response to threatening stimuli (Davis, 1992; LeDoux, 2003), sensory input (e.g., a visual cue) is transmitted to the amygdala along thalamic mediated paths (Das et al., 2005; Shi & Davis, 2001). As such, early perceptual processing plays an important role in fear generalization. Psychophysiological studies have demonstrated enhanced visuocortical activation for stimuli associated with threat (Armony & Dolan, 2001; Miskovic & Keil, 2013; Vuilleumier & Driver, 2007). The current findings suggest a possible

tuning effect, where this enhanced visual processing is perhaps weighted depending on degree of similarity to the learned threat cue.

Notably, in the current study, we also found a significant effect of generalization in the basal nucleus of the amygdala. The basolateral nucleus receives visual input from higher-order visual association cortices (Pessoa & Adolphs, 2010; Shi & Davis, 2001) and is thought to be a convergence zone for affective modulation of sensory information (Shi & Davis, 2001). In addition, feedback loops between the lateral and basal nuclei of the amygdala may modulate visual processing (Freese & Amaral, 2005; Pessoa & Adolphs, 2010). Interestingly, in contrast to hypotheses, the effect of generalization in the basal amygdala was negative, such that there was *less* activation as stimuli were increasingly similar to the CS+. Previous work has found similar negative generalization gradients in the amygdala/hippocampus (Kaczkurkin et al, 2017). Together with the generalization findings in the earlier parts of the processing stream (i.e., visual cortex, thalamus), it is possible that the amygdala is less necessary for further processing as the response has already been modulated by more basic sensory regions. Despite its prevalence in models of fear and anxiety (Davis, 1992; Etkin & Wager, 2007), the role of the amygdala has not been clearly delineated in fear generalization; neuroimaging studies have mostly failed to reveal generalization gradients within the amygdala (Greenberg et al., 2013; Lange et al., 2019), though altered functional connectivity of the amygdala (including with visual areas) may be important (Morey et al., 2015; Dunsmoor et al., 2011; Lissek et al., 2014).

The current study provides further support for the importance of the hippocampus during fear generalization. The hippocampus has been proposed as the heart of neural models of fear generalization (Lissek et al., 2014). Specifically, sensory information is relayed via the thalamus and higher order visual cortices to the hippocampus, where – depending on the degree of overlap

between a novel, ambiguous stimulus and learned threat cue – a pattern completion or separation process occurs that facilitates invocation or inhibition of the fear response. Consistent with hypotheses, the dentate gyrus and CA3 (implicated in pattern separation; Clelland et al., 2009; McHugh et al., 2007; Rolls, 2013; Yassa & Stark, 2011) both demonstrated significant negative generalization effects, such that there was increased activation within these subfields as stimuli were increasingly *dis*similar from the CS+, suggesting pattern separation was occurring. In the context of fear generalization, these findings suggest that the dentate gyrus and CA3 play an active role in discriminating between stimuli that are perceptually similar to a learned threat cue.

On the other hand, contrary to hypotheses, a similar negative effect was also observed in the CA1. Functional studies of the hippocampal subfields in humans are limited, though evidence has suggested that the CA1 is biased towards pattern completion (Bakker et al., 2008; Lacy et al., 2011; Dimsdale-Zucker et al., 2018). Although in the current study, functional connectivity of the DG and CA1 did not significantly vary as an effect of condition, examination of individual contrasts provide some hints that the CA1 is perhaps engaging in pattern completion; the CA1 demonstrated stronger coactivation with the amygdala for the CS+ compared to more dissimilar GSs (i.e., GS3 and GS4), as well as with the thalamus and ACC for the GS1 vs. GS4. These effects were small and did not survive corrections, but do fit with the theory that the CA1's pattern completion process facilitates engagement of fear excitatory structures to produce anxious arousal. That said, it is unclear why the activation of the CA1 was less robust as stimuli were more similar to the CS+. Rodent models propose a complex picture of hippocampal subfield function, suggesting that the CA3 may facilitate both pattern completion and separation depending on the degree of overlap between a novel stimulus and its existing neural schema (Guzowski et al., 2004). As the CA3 outputs to the CA1, the consequences of

dynamic competition within the CA3 may have additional downstream effects on computations within the CA1 that may (or may not) lead to pattern completion. Recent evidence has also shown that lesions of the CA1 impair pattern separation in humans (Hanert, Pedersen, & Bartsch, 2019). Thus, the CA1 may also have a dynamic function and support both matching and discrimination, and this role may be influenced by the input it receives from the CA3. Few neuroimaging studies, though, have examined pattern separation and completion in humans with sufficient spatial resolution to reliably distinguish between subfields. In addition, other studies have found study of this process to be even more complex given an inherent association of these mechanisms with memory processes of encoding and recall (Aimone, Deng, & Gage, 2011; Hunsaker and Kesner, 2013). Suggesting that the CA1 is primed for pattern completion may, therefore, be an overly simplistic representation of its function. Future work would benefit from probing the unique and shared functions within and between human hippocampal subfields and downstream structures; a clearer model of these mechanisms is essential for understanding how things may go awry in pathological anxiety.

Significant generalization of the conditioned threat stimulus was also observed in the bilateral habenula. The habenula is thought to play an important role in signaling the occurrence of salient negative events in order to modulate behavior adaptively (Boulos et al., 2017; Epstein et al., 2018; Salas et al., 2010). While prior research in humans has demonstrated activation of the habenula in response to conditioned threat cues (Hennigan et al., 2015; Lawson et al., 2017), this study is the first to show that this activation generalizes to perceptually-similar cues in a linear fashion. The current findings suggest that, as stimuli become more similar to a learned threat, habenular response increases. Given that the habenula is thought to modulate experience-dependent emotional behavior (Boulos et al., 2017; Epstein et al., 2018; Salas et al., 2010), this

may have important implications (e.g., by influencing approach-avoidance behaviors to perceived threats). This has important clinical relevance, as avoidance is a key behavioral feature of anxiety disorders. Abnormal activation of the habenula may perhaps reflect errors in threat prediction that subsequently contribute to maladaptive behavioral and emotional response (e.g., avoidance, fear). The habenula is part of a complex, diffuse network that includes prefrontal (Ely et al., 2016; Shelton et al., 2012; Torrisi et al., 2017) and brainstem (Boulos et al., 2017; Epstein et al., 2018) regions that may give rise to these responses. Although in the current study we did not observe modulation of the habenula based on individual differences in anxious traits, future studies would benefit from consideration of the habenula in psychopathology to better understand its role.

Clarifying the effects of anxiety on BNST activity may also be critical. In the current study, although there was a main effect of stimulus, it was difficult to interpret the meaning of this effect given that it was neither linear nor quadratic in nature. The BNST is thought to be particularly related to sustained threat-related arousal, i.e., anxiety (Davis et al., 2010; Klumpers et al., 2017; Shackman & Fox, 2016). Indeed, greater activation was observed for stimuli most similar to the CS+, suggestive of apprehension about the threat cue. More robust activation was also noted for the GS4. Given that the vertical orientation of the GS4 was dissimilar from both the conditioned threat and safety cues, it is possible that it was perceived as more ambiguous; therefore, increased BNST activation for this stimulus may be consistent with increased anxious apprehension during uncertain threat (Alvarez et al., 2011).

Surprisingly, effects of individual differences in anxiety on fear generalization within the brain were sparse. Overgeneralization of fear has been observed across a number of anxiety disorders (Ahrens et al., 2016; Cha et al., 2014; Lissek et al., 2009; Lissek et al., 2014b; Thome

et al., 2018). Moreover, emerging research has suggested that this overgeneralization is also reflected in the brain regions supporting this process (Cha et al., 2014; Greenberg et al., 2013; Kaczkurkin et al., 2017; Morey et al., 2020). In the current study, trait anxiety was related only to greater generalization (as defined by LDS) in the primary somatosensory cortex, while intolerance of uncertainty was related to greater generalization within the right insula and primary somatosensory cortex. These findings are, however, consistent with prior work in clinical populations. Cha and colleagues (2014) observed less discrimination within somatosensory areas in GAD patients compared to controls, possibly reflecting violations of shock expectancy under uncertainty, while PTSD symptoms are associated with increased generalization in the insula (Kaczkurkin et al., 2017; Morey et al., 2020).

It is possible that individual difference findings were limited in the current study due to having a relatively healthy sample; overgeneralization may be more robust in samples with clinical anxiety (Stegmann et al., 2019). Indeed, studies examining whether anxiety traits are associated with overgeneralization are mixed, with some studies demonstrating it is (Haddad, Xu, Raeder, & Lau, 2013; Wong & Lovibond, 2018), while others have failed to find an effect (Arnaudova, Krypotos, Effting, Kindt, & Beckers, 2017; Torrents-Rodas et al., 2013; Zaman et al., 2019). A recent meta-analysis found that there is a small positive effect of anxious traits on generalization (Sep, Steenmeijer, & Kennis, 2019). Although a useful metric that has validated clinical correlates (Lange et al., 2019; van Meurs et al., 2014), the linear departure score is also a somewhat crude measure that may not adequately characterize potentially meaningful intraindividual patterns of responding (e.g., poor differentiation between conditioned threat and safety cues). Notably, recent work has utilized data-driven clusterizing approaches to characterize individual patterns of behavioral fear generalization (Stegmann et al., 2019).

Diverging from classic perspectives on fear generalization (which typically distinguish between linear and quadratic generalization gradients), this study found five distinct response patterns characterizing generalization; importantly, a pattern defined by a linear gradient with high arousal and low CS-differentiation had the highest levels of self-reported anxiety. In our sample, trait anxiety was highly correlated with greater perceived risk of the CS-, consistent with the notion that pathologic anxiety may be characterized by elevated fear responding to safety cues (Duits et al., 2015; Gazendam, Kamphuis, & Kindt, 2013). Utilizing data-driven approaches to define more nuanced patterns of responding during generalization, therefore, may be important for understanding how anxiety traits relate to behavioral and neural fear generalization, and whether a distinct "at risk" group exists.

Taken together, these findings provide further support for extant work suggesting important roles of regions such as the hippocampus and thalamus in fear generalization, while also shedding light on several regions (such as the habenula) which were previously unexplored. That said, the current findings diverge from prior work in several notable ways. The functionally derived ROIs in the current study were similar to those identified in other fear generalization and conditioning neuroimaging studies (Dunsmoor et al., 2011; Lissek et al., 2014). These studies, however, have found substantially more of the regions identified to be sensitive to effects of generalization (e.g., insula, inferior parietal lobule; Lissek et al., 2014; Kaczkurkin et al., 2017), whereas our findings observed generalization effects only within the visual cortex and thalamus. In the current study, the threat cue was reinforced on 100% of CS+ trials. It is possible, therefore, that some of the identified ROIs relate to sensory/perceptual processing that is less relevant to the generalization test. Other studies have utilized reinforcement rates ranging from 62.5 (Dunsmoor et al., 2011) to 80% (Lissek et al., 2014), allowing trials where the BOLD signal is

contaminated by electrical stimulation to be discarded. Of course, introducing variable reinforcement schedules adds another layer of uncertainty to the paradigm; underlying theoretical models and prior work in fear conditioning suggest that threat reinforcement rates have profound effects on learning and recall of threat contingencies (Grady et al., 2016; Wagner, Siegel, & Fein, 1967) and may be moderated by individual differences in anxiety (Chin et al., 2014; Lonsdorf & Merz, 2017). Given that uncertainty may be a key mechanism contributing to fear generalization (Hunt et al., 2019; Morriss et al., 2016; Nelson et al., 2015), it is important to understand the implications of initial threat predictability when later introducing ambiguous stimuli.

Further diverging from prior work, results of the current study revealed consistently linear – rather than quadratic – generalization effects. In both animal (Honig & Urcuioli, 1981) and human (Lissek et al., 2008) samples, quadratic gradients generally reflect an adaptive degree of generalization. Linear gradients, on the other hand, are typically observed in clinical samples (Kaczkurkin et al., 2017; Lissek et al., 2010; Lissek et al., 2014), consistent with behavioral phenotypes suggestive of overgeneralized threat responding in anxious pathologies (Dymond et al., 2015; Lissek et al., 2008; Lissek, 2012). The current sample comprised healthy young adults, yet generalization gradients were more similar to those previously found in clinical samples. The reason for this is unclear. One possibility relates to the stimuli used; previous studies have typically utilized simple geometric shapes (e.g., circles [Lissek et al., 2014; van Meurs et al., 2014], rectangles [Cha et al., 2014; Greenberg et al., 2013]) faces (Dunsmoor et al., 2011), and conceptual categories (e.g., animals/tools; Morey et al., 2020). Gabor patches have been used infrequently in other aversive stimulus generalization paradigms (Koban et al., 2017; McTeague et al., 2015). In the current paradigm, stimuli varied an average of 3.33 degrees from the next

most similar stimulus; this narrow difference may have made the task quite challenging compared to alternative stimuli (e.g., circles [Lissek et al., 2014; van Meurs et al., 2014]) or similar stimuli with greater steps between stimuli (e.g., ± 10 degrees [McTeague et al., 2015]). Interestingly, a study by Koban and colleagues (2017) found a similar linear generalization effect for conditioned pain modulation using similar stimuli (i.e., Gabor patches varying by ± 4 degrees). It is possible that smaller steps in perceptual change between conditioned and generalization stimuli biases generalization gradients towards different shapes; future work examining this idea in a systematic fashion would be beneficial, as it may influence how we conceptualize quadratic and linear gradients as adaptive and (potentially) pathologic, respectively.

The current study is limited in several aspects. First, the sample comprises relatively healthy, young adults. While this has allowed us to contribute to the growing literature about the neural bases of fear generalization, it has limited generalizability to other populations. In particular, given the proposed clinical relevance of threat generalization in psychiatric disorders (Dunsmoor & Paz, 2015; Dymond et al., 2015; Lissek, 2012), future translational work is critical, as there may be important clinical implications (e.g., prediction of psychopathology onset, potential treatment target). Additionally, while partial coverage scans allowed us to optimize high spatial resolution for our small a priori regions of interest (e.g., hippocampal subfields, habenula), we were unable to examine regions previously implicated in fear generalization (e.g., dorsomedial prefrontal cortex [Lissek et al., 2014; Kaczkurkin et al, 2017]) as they were outside of the functional scan coverage. Finally, individuals vary in their low-level perceptual discrimination abilities (Ward et al., 2017). Although research suggests that generalization effects cannot be fully explained by individual differences in perceptual

discriminability (Guttman & Kalish, 1956; Onat & Buchel, 2015), there may still be important effects on generalization (Dunsmoor & Paz, 2015; Struyf et al., 2015; Zaman et al., 2020). Indeed, studies have found generalization is related to perceptual errors (i.e., misclassification of generalization stimuli as the CS+; Zaman et al., 2019), though it remains unclear whether such errors are effects of true perceptual differences or reflect higher-order cognitive processes (e.g., memory biases; Mitte, 2008). As such, future studies would benefit from additional procedures (e.g., discrimination threshold testing) that allow for consideration of these differences in analyses.

Overall, these findings largely support previous work on the neurobiological bases of fear generalization and make a compelling case for further examination of regions (e.g., habenula, hippocampal subfields) that have been poorly studied due to technological restraints of standard neuroimaging parameters. Key differences (e.g., linear shaped gradients), however, suggest that our current understanding of fear generalization and its neural substrates is incomplete. Fear generalization, therefore, remains a promising area of study. Further work is certainly warranted in order to disentangle the complexities of this process, particularly given generalization's strong clinical relevance. In fact, emerging work has shown that perceptual discrimination training can reduce avoidance behavior and decrease arousal in anxious populations (Ginat-Frolich et al., 2019; Lommen et al., 2017), suggesting generalization may be a useful, modifiable treatment target. Being able to better link behavioral and clinical phenotypes to the brain's function is certain to provide further insight that will aid in developing and optimizing effective treatments.

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Weis, C. N., Huggins, A. A., Bennett, K. P., Parisi, E. A., & Larson, C. L. (2019). High-resolution resting-state functional connectivity of the extended amygdala. *Brain Connectivity, 9*(8), 627-637.

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Curriculum Vitae

Ashley A. Huggins, M.S.

Education

2020 – 2021 **Charleston Consortium Psychology Internship**
Medical University of South Carolina / Ralph H. Johnson VA Medical Center
Predoctoral Psychology Intern, Neuropsychology
Research Preceptor: Lisa McTeague, Ph.D.

2015 – 2021 **University of Wisconsin – Milwaukee**
Ph.D. Clinical Psychology
Advisor: Christine Larson, Ph.D.
Dissertation: *Neural substrates of fear generalization and its associations with anxiety and intolerance of uncertainty* (defended 5/28/2020)

2018 **University of Wisconsin – Milwaukee**
M.S. Psychology
Advisor: Christine Larson, Ph.D.
Thesis: *Moderating effects of harm avoidance on resting state functional connectivity of the anterior insula*

2013 **University of Southern California**
B.A. Psychology (minor: French)
Advisor: Stanley Huey, Jr., Ph.D.
Thesis: *Yoga for the head and heart: Effects of yoga on depression and cardiac functioning*

Research

2020 – Present **Brain Stimulation Division**
Medical University of South Carolina
PI: Lisa McTeague, Ph.D.
Projects: *Charleston Resilience Monitoring (CHARM) Study*
Intelligence Biometrics for PTSD
tDCS-Augmented Prolonged Exposure Therapy

2015 – Present **Affective Neuroscience Lab**
University of Wisconsin – Milwaukee
PI: Christine Larson, Ph.D.
Projects: *Acute Neurocognitive-Affective Predictors of Chronic Post-Trauma Outcomes*
High Resolution Imaging of Neural Systems Subserving Aberrant Fear Regulation
Milwaukee Trauma Outcomes Project (MTOP) Consortium
Developing Effective Response Inhibition Training for Symptom Relief in OCD

2013 – 2015 **Chicago Lab of Emotion and Physiology**
University of Illinois – Chicago
PI: Stewart Shankman, Ph.D.
Projects: *Family Study of Reward and Threat Sensitivity in Internalizing Psychopathology*

2012 – 2013 **Genetics of Post-Traumatic Stress Disorder**
Los Angeles County + University of Southern California Medical Center
PIs: John Briere, Ph.D. & Randye Semple, Ph.D.

2011 **Lotto Lab**
London Science Museum & University College London
PI: Richard Clarke, Ph.D.

2011	**Baby & Child Rebel Lab** *University of Nevada – Las Vegas* PI: Jennifer Rennels, Ph.D.
2010 – 2011	**Articulated Thoughts in Simulated Situations (ATSS) Lab** *University of Southern California* PI: Gerald Davison, Ph.D.

Clinical Experience

2020 – 2021	**Ralph H. Johnson VA Medical Center** Psychology Intern, Traumatic Brain Injury (TBI) Service & Neuropsychology Clinic
2020 – 2021	**Medical University of South Carolina** Psychology Intern, Neuropsychology Clinic & Tobacco Treatment Program
2019 – 2020	**Clement J. Zablocki VA Medical Center** Practicum Student, Neuropsychology
2018 – 2019	**Medical College of Wisconsin** Practicum Student, Adult Neuropsychology
2017 – 2020	**UWM Psychology Clinic** Student Therapist
2016 – 2017	**UWM Psychology Clinic** Practicum Student, Assessment

Peer-Reviewed Publications

(*) denotes joint first authorship (**) denotes shared senior authorship

1. Weis, C. N.*, Webb, E. K.*, **Huggins, A. A.**, Kallenbach, M., Miskovich, T. A., Fitzgerald, J. M., Bennett, K. P., Krukowski, J. L., deRoon-Cassini, T. A.**, & Larson, C. L.** (in press). Reliability of hippocampal subfield measurement using FreeSurfer in a longitudinal study of PTSD. *NeuroImage.*
2. Ritchay, M. M., **Huggins, A. A.,** Wallace, A. L., Larson, C. L., & Lisdahl, K. M. (in press). Resting state functional connectivity in the default mode network: Relationships between cannabis use, gender, and cognition in adolescents and young adults. *NeuroImage: Clinical.*
3. Webb, E. K., Weis, C. N., **Huggins, A. A.,** Parisi, E. A., Bennett, K. P., Miskovich, T. A., Hanson, J., deRoon-Cassini, T. A.**, & Larson, C. L.** (2021). Neighborhood disadvantage is associated with stable deficits in neurocognitive functioning. *Health and Place, 67*, 102493.
4. **Huggins, A. A.,** Harvey, A. M., Miskovich, T. A., Lee, H., & Larson, C. L. (2020). Resting state functional connectivity of supplementary motor area associated with skin-picking symptom severity. *Journal of Obsessive-Compulsive and Related Disorders, 26,* 100551.
5. Webb, E. K.*, **Huggins, A. A.*,** Belleau, E. L., Taubitz, L., Hanson, J. L., deRoon-Cassini, T. A.**, & Larson, C. L.** (2020). Altered resting-state functional connectivity of periaqueductal gray subregions associated with posttraumatic stress disorder symptom severity. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 5*(9), 891-900.
6. Weis, C. N., **Huggins, A. A.,** Bennett, K. P., Parisi, E. A., & Larson, C. L. (2019). High resolution resting state functional connectivity of the extended amygdala. *Brain Connectivity, 9,* 627-637.
7. **Huggins, A. A.,** Weinberg, A., Gorka, S. M., & Shankman, S. A. (2019). Blunted neural response to gains versus losses associated with both risk-prone and risk-averse behavior in a clinically diverse sample, *Psychophysiology, 56*, e13342.
8. **Huggins, A. A.,** Belleau, E. L., Miskovich, T. A., Pedersen, W. S., & Larson, C. L. (2018). Moderating effects of harm avoidance on resting state functional connectivity of the anterior insula, *Frontiers in Human Neuroscience, 12*, 447.
9. **Huggins, A. A.**, Gorka, S. M., & Shankman, S. A. (2018). The moderating role of gender on the association between childhood trauma and risk-taking propensity. *Graduate Student Journal of Psychology, 17*, 5-17.

10. Lieberman, L., Stevens, E. S., Funkhouser, C. J., Weinberg, A., Sarapas, C., **Huggins, A. A.**, & Shankman, S. A. (2017). How many blinks are necessary for a reliable startle response? A test using the NPU-threat task. *International Journal of Psychophysiology, 114*, 24-30.
11. Lieberman, L., Liu, H., **Huggins, A.A.**, Katz, A.C., Zvolensky, M.J., & Shankman, S.A. (2016). Comparing informant- and self-reports of personality to laboratory indices of emotional responding as criterion variables. *Psychophysiology, 53*, 1386-1397.
12. Lieberman, L., Gorka, S. M., **Huggins, A. A.**, Katz, A. C., Sarapas, C., & Shankman, S. A. (2016). Agreement between self and informant-reported ratings of personality traits: The moderating effects of major depressive and/or panic disorder. *Journal of Nervous and Mental Disease, 204*, 306-313.
13. Gorka, S. M., **Huggins, A. A.**, Fitzgerald, D. A., Nelson, B. D., Phan, K. L., & Shankman, S. A. (2014). Neural response to reward anticipation in those with and without panic disorder. *Journal of Affective Disorders, 164*, 50-56.

Publications Under Review & In Preparation

Fitzgerald, J. M.*, Webb, E. K.*, Weis, C. N., **Huggins, A. A.**, Bennett, K. P., Miskovich, T. A., Krukowski, J. L., deRoon-Cassini, T. A.**, & Larson, C. L.** (in revision). *Hippocampus resting-state functional connectivity forecasts individual PTSD symptoms: A data-driven approach.*

Huggins, A. A., Weis, C.N., Parisi, E. A., Bennett, K. P., & Larson, C. L. (in revision). *Neural substrates of human fear generalization: A 7T-fMRI investigation*.

Huggins, A. A., Fitzgerald, J. M., Webb, E. K., Weis, C. N., Bennett, K. P., Parisi, E. A., Krukowski, J., deRoon-Cassini, T. A., & Larson, C. L. (in prep). *Hippocampal activation during fear extinction predicts PTSD symptom severity in after acute traumatic injury.*

Huggins, A. A., Davis, M., Joseph, J., Bustos, N., Danielson, C., & McTeague, L. (in prep). *Associations between socioeconomic disadvantage and neural responsivity to predictable and unpredictable threat in youth.*

Hunt, J. C., Larsen, S., Fitzgerald, J. M., **Huggins, A. A.**, Geier, T. J., Chesney, S. A., Larson, C. L., & deRoon-Cassini, T. A. (in revision). *Network analysis of DSM-5 PTSD symptoms following traumatic injury.*

Parisi, E. A., Webb, E. K., Sellnow, K., **Huggins, A. A.,** Weis, C. N., Bennett, K. P., deRoon-Cassini, T. A., & Larson, C. L. (in prep). *Negativity bias mediates the relationship between adverse life events and future PTSD symptom severity.*

Webb, E. K.*, Weis, C. N.*, **Huggins, A. A.,** Fitzgerald, J. M., Bennett, K. P., Bird, C., Parisi, E. A., Kallenbach, M., Krukowski, J., deRoon-Cassini, T. A.**, & Larson, C. L.** (under review). *Neural impact of neighborhood socioeconomic disadvantage in traumatically-injured adults.*

Weis, C. N., Bennett, K. P., **Huggins, A. A.,** Parisi, E. A., Gorka, S. M., & Larson, C. L. (in revision). *Functional connectivity of the periaqueductal grey during rest and uncertain threat using high resolution 7-Tesla MRI.*

Weis, C. N., **Huggins, A. A.,** Miskovich, T. A., Fitzgerald, J. M., Bennett, K. P., Krukowski, J. L., Webb, E. K., deRoon-Cassini, T. A.**, & Larson, C. L.** (in revision). *Acute white matter integrity post-trauma predicts chronic PTSD symptoms.*

Presentations

Poster Presentations

(*) denotes conference moved to virtual format due to COVID-19 pandemic

1. **Huggins, A. A.**, Fitzgerald, J., Weis, C. N., Hanson, J., Webb, E. K., Bennett, K. P., Parisi, E. A., deRoon-Cassini, T. A., & Larson, C. L. (2021, May). *Neural activation during fear extinction acutely post-trauma predicts chronic PTSD severity.* Poster presented at the European Meeting of Human Fear Conditioning, virtual.
2. **Huggins, A. A.**, Fitzgerald, J., Weis, C. N., Hanson, J., Webb, E. K., Bennett, K. P., Parisi, E. A., deRoon-Cassini, T. A., & Larson, C. L. (2021, April). *Neural activation during fear extinction acutely post-trauma predicts chronic PTSD severity.* Poster presented at the 76th annual meeting of the Society of Biological Psychiatry, virtual.

3. **Huggins, A. A.,** Weis, C. N., Parisi, E. A., Bennett, K. P., & Larson, C. L. (2020, June). *High-resolution 7T-fMRI of human hippocampal subfields during fear generalization.* Poster presented at the 26th annual meeting of the Organization for Human Brain Mapping, Montreal, Canada.*

4. **Huggins, A. A.,** Weis, C. N., Fitzgerald, J. M., Hanson, J., Bennett, K. P., Parisi, E. A., Webb, E. K., deRoon-Cassini, T. A., & Larson, C. L. (2020, May). *Contingency awareness and neural response to threat: Associations with acute traumatic distress and childhood trauma.* Poster presented at the 75th annual meeting of the Society of Biological Psychiatry, New York, NY.*

5. Fitzgerald, J. M., **Huggins, A. A.,** Weis, C. N., Hanson, J., Bennett, K. P., Parisi, E. A., Webb, E. K., Larson, C. L., & deRoon-Cassini, T. A. (2020, May). *Differences in endocannabinoids relate to intact fear learning after traumatic injury*. Poster presented at the 75th annual meeting of the Society of Biological Psychiatry, New York, NY.*

6. Weis, C. N., **Huggins, A. A.,** Bennett, K. P., Parisi, E. A., & Larson, C. L. (2020, May). *Dynamic functional connectivity of the periaqueductal grey in response to predictable and unpredictable threat using 7-Tesla MRI.* Poster presented at the 75th annual meeting of the Society of Biological Psychiatry, New York, NY.*

7. Webb, E. K., Weis, C. N., Sellnow, K., **Huggins, A. A.,** deRoon-Cassini, T., & Larson, C. L. (2020, May). *Neighborhood disadvantage is associated with smaller amygdala size and altered amygdala functional activity*. Poster presented at the 75th annual meeting of the Society of Biological Psychiatry, New York, NY.*

8. Kallenbach, M. D., **Huggins, A. A.**, Larson, C. L., & deRoon-Cassini, T. A. (2019, November). *Effects of civilian trauma on executive functioning*. Poster presented at the 35th annual meeting of the International Society for Traumatic Stress Studies, Boston, MA.

9. Weis, C. N., **Huggins, A. A.,** Bennett, K. P., Parisi, E. A., & Larson, C. L. (2019, October). *Resting state functional connectivity of the human periaqueductal grey using 7-Tesla MRI.* Poster presented at the 49th annual meeting of the Society for Neuroscience, Chicago, IL.

10. **Huggins, A. A.,** deRoon-Cassini, T., & Larson, C. L. (2019, September). *Intolerance of uncertainty associated with reduced heart rate variability in acute trauma survivors.* Poster presented at the 59th annual meeting of the Society for Psychophysiological Research, Washington, DC.

11. **Huggins, A. A.,** Weis, C. N., Parisi, E. A., Bennett, K. P., & Larson, C. L. (2019, June). *Trait anxiety associated with differences in BOLD activation during fear generalization task.* Poster presented at the 25th annual meeting of the Organization for Human Brain Mapping, Rome, Italy.

12. Weis, C. N., **Huggins, A. A.,** Bennett, K. P., Parisi, E. A., & Larson, C. L. (2019, June). *High resolution resting state functional connectivity of the extended amygdala.* Poster presented at the 25th annual meeting of the Organization for Human Brain Mapping, Rome, Italy.

13. Webb, E. K., **Huggins, A. A.,** Belleau, E. L., Taubitz, L., Hanson, J. L., deRoon-Cassini, T. A., & Larson, C. L. (2019, May). *Periaqueductal gray resting state functional connectivity prospectively predicts posttraumatic stress symptom severity.* Poster presented at the 74th annual meeting of the Society of Biological Psychiatry, Chicago, IL.

14. Hunt, J., Fitzgerald, J. M., Weis, C. N., **Huggins, A. A.,** Hanson, J. L., Isely, K. A., & Larson, C. L. (2019, May). *Classification of mild traumatic brain injury from resting state fMRI: A graph theory approach.* Poster presented at the 74th annual meeting of the Society of Biological Psychiatry, Chicago, IL.

15. Parisi, E. A., Weis, C. N., **Huggins, A. A.,** Bennett, K. P., Hajcak, G., & Larson, C. L. (2019, May). *Amygdala and hippocampal activation to conditioned stimuli during extinction following threat avoidance.* Poster presented at the 74th annual meeting of the Society of Biological Psychiatry, Chicago, IL.

16. Weis, C. N., **Huggins, A. A.,** Miskovich, T. A., Fitzgerald, J. M., Bennett, K. P., deRoon-Cassini, T. A., & Larson, C. L. (2019, May). *White matter integrity in individuals at-risk for PTSD development: A longitudinal investigation.* Poster presented at the 74th annual meeting of the Society of Biological Psychiatry, Chicago, IL.

17. Weis, C., **Huggins, A. A.,** Bennett, K. P., Parisi, E. A., & Larson, C. L. (2018, November). *High resolution functional connectivity in anxiety*. Poster presented at the 48th annual meeting of the Society for Neuroscience, San Diego, CA.

18. **Huggins, A. A.**, Harvey, A. M., Yaroch, M., Greskoviak, R., Larson, C. L., & Lee, H. (2018, May). *Resting state functional connectivity of supplementary motor area associated with skin-picking symptom severity.* Poster presented at the 73rd annual meeting of the Society of Biological Psychiatry, New York, NY.

19. **Huggins, A. A.**, deRoon-Cassini, T. A., & Larson, C. L. (2017, November). *Associations between exposure to childhood trauma and acute post-trauma symptom severity in adulthood.* Poster presented at the 33rd annual meeting of the International Society for Traumatic Stress Studies, Chicago, IL.

20. Harvey, A. M., Yaroch, M. R., Pendleton, A. M., **Huggins, A. A.**, Miskovich, T. A., Larson, C. L., & Lee, H. (2017, November). *The association between response inhibition and skin-picking symptoms.* Poster presented at the 51st annual meeting of the Association for Behavioral and Cognitive Therapies, San Diego, CA.

21. **Huggins, A. A.,** Belleau, E. L., Miskovich, T. A., Pedersen, W. S., & Larson, C. L. (2017, May). *Altered functional connectivity between right insular cortex and default mode regions associated with perceived stress and anxiety during undergraduate students' finals week.* Poster presented at the 72nd annual meeting of the Society of Biological Psychiatry, San Diego, CA.

22. Lieberman, L., Liu, H., **Huggins, A. A.**, Gorka, S. M., Sarapas, C., & Shankman, S. A. (2015, May). *Informant-reports but not self-reports of personality predict psychophysiological indices of positive and negative emotional responding*. Poster presented at the 27th annual meeting for the Association for Psychological Science, New York, NY.

23. **Huggins, A. A.**, Gorka, S. M., Hodges, A. M., DeLizza, A. A., & Shankman, S. A. (2014, September). *The association between childhood abuse and risk-taking behavior: the moderating effect of gender*. Poster presented at the 28th annual meeting of the Society for Research in Psychopathology, Evanston, IL.

24. Sarapas, C., Liu, H., **Huggins, A. A.**, DeLizza, A. A., Hodges, A. M., & Shankman, S. A. (2014, September). *Biased attention to threat and familial risk for anxiety disorders*. Poster presented at the 28th annual meeting of the Society for Research in Psychopathology, Evanston, IL.

25. Lieberman, L., DeLizza, A. A., **Huggins, A. A.**, Katz, A. C., Campbell, M., & Shankman, S. A. (2014, September). *Self-informant agreement on ratings of personality traits: the moderating effects of major depressive and/or panic disorder*. Poster presented at the 28th annual meeting of the Society for Research in Psychopathology, Evanston, IL.

26. Hodges, A. M., Sarapas, C., Katz, A. C., **Huggins, A. A.**, DeLizza, A. A., & Shankman, S. A. (2014, September). *Is anxiety sensitivity a familial risk factor for panic disorder?* Poster presented at the 28th annual meeting of the Society for Research in Psychopathology, Evanston, IL.

27. Gorka, S. M., **Huggins, A. A.**, Fitzgerald, D. A., Nelson, B. D., Phan, K. L., & Shankman, S. A. (2014, September). *Neural response to reward anticipation in those with depression with and without panic disorder*. Poster presented at the 54th annual meeting of the Society for Psychophysiological Research, Atlanta, GA.

28. Katz, A. C., **Huggins, A. A.**, Hodges, A. M., & Shankman, S. A. (2014, March). *Effect of comorbid post-traumatic stress disorder and panic disorder on defensive responding*. Poster presented at the 2014 annual conference of the Anxiety and Depression Association of America, Chicago, IL.

29. **Huggins, A. A.** (2013, May). *Yoga for the head and heart: the effects of yoga on depression and cardiac functioning*. Poster presented at the 2013 University of Southern California Undergraduate Research Symposium, Los Angeles, CA.

Oral Presentations

30. Webb, E. K., Weis, C. N., Bennett, K. P., **Huggins, A. A.**, Parisi, E. A., Miskovich, T. A., Kallenbach, M., Krukowski, J., Fitzgerald, J., deRoon-Cassini, T. A., & Larson, C. L. (2021, April). *Neural impact of neighborhood disadvantage in traumatically-injured adults: A multi-modal investigation.* Oral paper to be presented at the 76th annual meeting of the Society of Biological Psychiatry, virtual.

31. Hunt, J. C., Larsen, S., **Huggins, A. A.,** Geier, T. J., Fitzgerald, J. M., Chesney, S. A., Larson, C. L., & deRoon-Cassini, T. A. (2019, November). *A network analysis of the Clinician Administered PTSD Scale for the DSM-5 in a sample of adult traumatic injury survivors.* Oral paper to be presented at the 35th annual meeting of the International Society for Traumatic Stress Studies, Boston, MA.

32. Fitzgerald, J. M., **Huggins, A. A.,** Miskovich, T.A., & Larson, C. L (2019, September). *Contribution of updating emotional conflict monitoring to emotion dysregulation in trauma-exposed individuals*. Big Question talk presented at the 59th annual meeting of the Society for Psychophysiological Research, Washington, DC.

33. Larson, C. L., **Huggins, A. A.**, Parisi, E. A., Hajcak, G., & Miskovic, V. (2019, September). *High resolution imaging of fear generalization and the avoidance of threat*. Symposium presentation at the annual meeting of the Society for Psychophysiological Research, Washington, DC.

34. **Huggins, A. A.,** Belleau, E. L., Miskovich, T. A., Pedersen, W. S., & Larson, C. L. (2018, April). *Moderating effects of harm avoidance on resting state functional connectivity of the anterior insula.* Oral presentation at 20th annual research symposium hosted by UWM Association of Graduate Students in Psychology, Milwaukee, WI.

35. Shankman, S. A., Sarapas, C., Gorka, S. M., Campbell, M. L., Katz, A. C., Liu, H., Lieberman, L., DeLizza, A. A., Hodges, A. M., & **Huggins, A. A.** (2014, September). Family study of reward and threat sensitivity in internalizing psychopathology. In S. Morris (Chair), *The NIMH Research Domain Criteria initiative: Overview and exemplars.* Symposium conducted at 28th annual meeting of the Society for Research in Psychopathology, Evanston, IL.

Honors & Awards

2021	Society of Biological Psychiatry Travel Fellowship, Predoctoral Scholar
2019 – 2020	Distinguished Dissertation Fellowship, UWM
2018	Graduate Student Travel Award, UWM
2016	Department of Psychology Summer Graduate Research Fellowship, UWM
2016 – 2017	Distinguished Graduate Student Fellowship, UWM
2015 – 2017	Chancellor's Graduate Student Award, UWM
2013	Magna cum laude, USC
2013	Renaissance Scholar, USC
2012	Phi Beta Kappa Honor Society, USC
2009 – 2013	Dean's Scholar Award, USC

Grants Submitted

Acute Neurobehavioral Indicators of Fear Dysregulation as Predictors of Chronic Posttraumatic Distress
National Institute of Mental Health (NIMH)
F31 Ruth L. Kirschstein NRSA Individual Predoctoral Fellowship
Role: PI Sponsor: Christine Larson, Ph.D.
Impact Score: 30 Percentile: 20 (not funded)

Skills

Neuroimaging analysis	functional magnetic resonance imaging (fMRI; task-based, resting state); 7 Tesla MRI; generalized psychophysiological interactions (gPPI); volumetrics
Psychophysiology	EMG startle; heart rate variability; ERPs; EEG asymmetry; eye-tracking
Software	AFNI; CONN Toolbox; Freesurfer; BrainVision Analyzer; CardioEdit/CardioBatch; AcqKnowledge; E-Prime; Experiment Builder
Hardware	Biopac (EMG, skin conductance, shock); Biosemi EEG; Psychlab shock system; Eyelink 1000
Diagnostic assessment	Clinician-Administered PTSD Scale for DSM-5 (CAPS-5); Yale-Brown Obsessive Compulsive Scale (Y-BOCS); Y-BOCS for Neurotic Excoriation; Structured Clinical Interview for DSM-5 (SCID-5); MINI International Neuropsychiatric Interview
Clinical intervention	Behavioral Activation (BA), CBT-Social Anxiety, CBT-Eating Disorders, Exposure and Response Prevention (ExRP), Prolonged Exposure (PE), Unified Protocol for Transdiagnostic Treatment of Emotional Disorders

Teaching

2021	**Action Potential Advising Program**, Mentor, Simply Neuroscience (online)
2020	**Neuropsychology Summer Seminar**, Guest Lecturer, UWM *Topic:* Neuro-Oncology
2019	**First-Year Clinical Practicum**, Guest Lecturer, UWM *Topic:* Intelligence and Achievement Testing
2018 – 2019	**Cases in Clinical Neuropsychology**, Graduate Assistant, UWM
2016	**Personality**, Teaching Assistant, UWM
2016	**Child Psychology**, Teaching Assistant, UWM
2016	**Future Success Workshop for High School Students,** Mentor, UWM

Professional Memberships

Organization for Human Brain Mapping
Psi Chi
Society for Psychophysiological Research
Society for a Science of Clinical Psychology

Editorial Service

Ad hoc Reviewer for *American Journal of Psychiatry, Biological Psychiatry, Neurobiology of Stress, Psychophysiology*