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An Event-Related Potential Investigation of Fear Generalization and Intolerance of Uncertainty

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Fear generalization is a key process in the development and maintenance of anxiety disorders. Psychobiological investigations of fear generalization have predominantly focused on defensive system activation (e.g., startle reflex), and it is unclear whether aberrant attentional processing contributes to fear generalization. The late positive potential (LPP) is an event-related potential component that indexes sustained attention and elaborative processing of motivationally salient information, and is larger in response to arousing compared to nonarousing stimuli. In the present study 48 participants completed a fear generalization paradigm using electric shocks. The LPP and retrospective risk ratings of shock likelihood were measured in response to the conditioned stimulus (CS+) and multiple generalization stimuli (GS) that varied in perceptual similarity to the CS+. In addition, intolerance of uncertainty (IU) was examined in relation to fear generalization. The LPP was enhanced for the CS+ relative to the GS, but the GS did not differ from one another. Thus, overall the LPP did not reflect fear generalization. However, the LPP to the GS differed as a function of IU, such that high Prospective IU was associated with an *attenuated* LPP to the GS, and this was independent of trait anxiety. Risk ratings tracked fear generalization irrespective of IU. We discuss the potential influence of IU and attentional processing on fear generalization. Overall, the present study supports the LPP as a useful tool for examining individual differences in fear generalization.

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Fear conditioning is a form of associative learning that is central to many etiological accounts of anxiety disorders (Craske et al., 2009; Mineka & Zinbarg, 2006). Laboratory studies of fear conditioning often examine differential conditioning, during which two (or more) conditioned stimuli (CS) are presented, one paired with an aversive stimulus (i.e., CS+) and the other not paired (i.e., CS-). A meta-analysis of fear conditioning research in anxiety disorders indicated heightened fear responding to the CS+ *and* CS- (Lissek et al., 2005). These results are consistent with fear generalization, the process through which the fear response is extended to stimuli that resemble the CS+ (i.e., generalization stimuli: GS).

Psychobiological investigations of fear generalization have predominantly focused on defensive system activation using the startle reflex (Lissek et al., 2008). For example, Hajcak and colleagues (2009) developed a fear generalization paradigm in which the startle reflex was recorded while viewing a CS+ (a red rectangle that was followed by an electric shock) and multiple GS that varied in perceptual similarity to the CS+ (red rectangles with gradually different lengths from the CS+, which were never reinforced). The paradigm was designed to provide a rich representation of fearful responding to complex stimuli, similar to real-world scenarios where danger and safety cues share perceptual similarities (Lissek et

al.). In the Hajcak et al. study, the startle reflex was greatest during the CS+ and declined parametrically as the GS became less perceptually similar to the CS+, producing a fear generalization gradient (e.g., CS+ > GS ± 20% > GS ± 40%). Recently, Greenberg and colleagues (2013) used functional magnetic resonance imaging (fMRI) to explore this paradigm in healthy controls and found that insula activation tracked the fear generalization gradient. Taken together, research suggests that GS activate defensive system activation in proportion to their perceptual similarity to the CS+.

It is not yet clear how attentional processes might contribute to fear generalization. One possibility is that GS that are more similar to the CS+ might also demand increased attention (relative to less similar stimuli) as individuals attempt to discriminate threat cues from safety cues. The increased attention could then prompt greater demand for the mobilization of physiological resources, in case a defensive response needs to be mounted (Lang, Bradley, & Cuthbert, 1997). One way to test this hypothesis is through the use of event-related potentials (ERPs), which are particularly useful for understanding mechanisms of attention (Luck, Woodman, & Vogel, 2000). In particular, the late positive potential (LPP) is a sustained positive deflection of the ERP signal that begins as early as 200-ms after stimulus onset and persists throughout (and beyond) stimulus presentation, and is posited to index sustained attention and elaborative processing of motivationally salient visual information (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Hajcak & Olvet, 2008; Weinberg, Ferri, & Hajcak, 2013). Fear conditioning studies have confirmed that the LPP is increased for CS+ relative to CS- (Baas, Kenemans, Böcker, & Verbaten, 2002; Böcker, Baas, Kenemans, & Verbaten, 2004; Bublatzky & Schupp, 2011), suggesting that it may provide an objective measure of increased attentional processes important to fear discrimination. However, the LPP has not been used to examine the role of attention in fear generalization.

Additionally, fear generalization appears to play an important role in the etiology and maintenance of multiple anxiety disorders, and several studies have reported that trait anxiety is associated with greater startle reflex and skin conductance response during fear generalization (Dunsmoor, White, & LaBar, 2011; Gazendam, Kamphuis, & Kindt, 2013; Haddad, Pritchett, Lissek, & Lau, 2012; although see Torrents-Rodas et al., 2013). However, anxiety is not a monolithic construct and the recent Research Domain Criteria (RDoC) initiative has emphasized examining transdiagnostic constructs that cut across multiple disorders (Cuthbert & Insel, 2010; Sanislow et al., 2010). In the present study, we wished to examine specific anxiety-relevant transdiagnostic processes that might contribute to increased attention to safety cues that are perceptually similar to threat cues. In particular, it is possible that the *uncertainty* associated with determining whether a stimulus indicates threat (CS+) or safety (CS-) can impact attentional processing. If so, individuals who are highly averse to uncertainty may demonstrate aberrant processing of the GS. Intolerance of uncertainty (IU) is a cognitive bias that influences perceptions, interpretations, and responses to uncertain situations (Dugas, Buhr, & Ladouceur, 2004). IU has been associated with several anxiety disorders, including generalized anxiety disorder (GAD; Dugas, Gagnon, Ladouceur, & Freeston, 1998), obsessive-compulsive disorder (OCD; Tolin, Abramowitz, Brigidi, & Foa, 2003), and social anxiety disorder (SAD; Boelen & Reijntjes, 2009). Therefore, IU may be associated with fear discrimination/generalization via the uncertainty related to differentiating the CS+ and GS; however, no study has examined this relationship.

Factor analytic studies have indicated that IU is characterized by two related (but distinct) factors—Prospective IU and Inhibitory IU (Birrell, Meares, Wilkinson, & Freeston, 2011). Prospective IU characterizes "cognitive" concerns about uncertain future events, while Inhibitory IU represents "behavioral" inhibition and/or avoidance due to uncertainty (Carleton, Norton, & Asmundson, 2007). A growing number of studies have identified distinct relationships between Prospective and Inhibitory IU and psychobiological responding to uncertainty. For example, Inhibitory IU has been shown to be associated with decreased startle reflex (Nelson & Shankman, 2011) and increased insula activation (Shankman et al., 2014) while anticipating uncertain threat, whereas Prospective IU has been associated with decreased approach motivation (as indicated by a reduced frontal electroencephalography [EEG] asymmetry) while anticipating uncertain reward (Nelson, Shankman, & Proudfit, 2014). These results suggest that Prospective and Inhibitory IU may demonstrate disparate relationships with the processing of uncertainty, and we therefore separately examined their relationship with fear generalization.

In the present study, participants completed Hajcak, Castille, and colleagues' (2009) fear generalization paradigm while EEG was recorded. The LPP was examined in response to the CS+ and multiple GS that varied in perceptual similarity to the CS+. At the end of the task participants completed self-reported risk ratings (i.e., perceived shock likelihood) for the CS+ and GS. We also examined the association between Prospective and Inhibitory