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Anxiety sensitivity and the anticipation of predictable and unpredictable threat: Evidence from the startle response and event-related potentials

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ABSTRACT

There is growing evidence that heightened sensitivity to unpredictable threat is a core mechanism of dysfunction in anxiety disorders. However, it is unclear whether anxiety sensitivity is also associated with sensitivity to unpredictable threat. In the present study, 131 participants completed the Anxiety Sensitivity Index-3, which includes physical concerns (PC), social concerns (SC), and cognitive concerns (CC) subscales, and a predictable vs. unpredictable threat-of-shock task. Startle eyeblink and ERP responses (N100, P300) to the acoustic startle probes were measured during the task. PC and CC were associated with heightened and attenuated, respectively, startle for the unpredictable (but not predictable) condition. CC were also associated with attenuated probe N100 for the unpredictable condition only, and PC were associated with increased P300 suppression across the predictable and unpredictable conditions. This study provides novel evidence that the different anxiety sensitivity dimensions demonstrate unique relationships with the RDoC domains "acute" and "potential" threat.

1. Introduction

Anxiety sensitivity (AS) is the fear of anxiety-related sensations due to their perceived physical, psychological, or social consequences (Reiss & McNally, 1985). AS was originally conceptualized as an individual difference factor that contributed to the etiology and maintenance of panic disorder (PD) (McNally, 2002). Indeed, research has shown that AS is elevated in first-degree relatives of probands with PD relative to healthy controls (Van Beek & Griez, 2003) and prospectively predicts panic attacks (Maller & Reiss, 1992; Schmidt, Lerew, & Jackson, 1999), panic symptoms (Cox, Taylor, Clara, Roberts, & Enns, 2008), and panic response to a CO_2 challenge (Bernstein, Zvolensky, & Schmidt, 2009; Blechert, Wilhelm, Meuret, Wilhelm, & Roth, 2013). However, AS has also been linked to several other psychopathological behaviors and conditions (Deacon & Abramowitz, 2006; Taylor, Koch, Woody, & McLean, 1996), including alcohol use (Allan, Albanese, Norr, Zvolensky, & Schmidt, 2015; Schmidt, Buckner, & Keough, 2007), depression (Allan, Capron, et al., 2014; Viana & Rabian, 2009), generalized anxiety disorder (GAD; Allan, Macatee, et al., 2014), and suicide (Capron, Cougle, Ribeiro, Joiner, & Schmidt, 2012; Medley, Capron, Korte, & Schmidt, 2013). Thus, AS has more recently been considered a transdiagnostic factor of psychopathology (Boswell et al., 2013).

The National Institute of Mental Health's Research Domain Criteria (RDoC) initiative seeks to identify biobehavioral dimensions that are common across several disorders and then relate those dimensions to specific biological processes (Insel et al., 2010; Sanislow et al., 2010). AS is an ideal construct to examine using the RDoC approach given its dimensional nature (Asmundson, Weeks, Carleton, Thibodeau, & Fetzner, 2011; Broman-Fulks et al., 2008, 2010), genetic correlates (Taylor et al., 2008; Waszczuk et al., 2013), high heritability (Stein et al., 1999), and the aforementioned relationship with multiple psychopathologies (Deacon & Abramowitz, 2006; Taylor et al., 1996). In terms of physiological correlates, greater AS has been associated with a heightened baseline startle eyeblink electromyography (EMG) response (McMillan et al., 2012), decreased baseline startle habituation (Campbell et al., 2014), and heightened startle response in anticipation of interoceptive threat (Melzig et al., 2008).

Affective responses to threat, however, are not uniform. Predictability is an important feature of threat that has been suggested

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to impact defense system activation and differentiate the states of fear and anxiety (Barlow, 2000; Grillon et al., 2004; Hamm & Weike, 2005). Fear is associated with predictable threat and a more immediate fight, flight, or immobilization response. Conversely, anxiety is elicited when perceived threat is less certain (or present) and requires a sustained state of vigilance and defensive preparedness. The distinction between fear and anxiety has been well supported by animal (Davis, 1998), psychophysiological (Grillon et al., 2004; Nelson & Shankman, 2011), and pharmacological studies (Grillon et al., 2006), and is represented by separate Negative Valence System constructs ("acute" and "potential" threat, respectively) in the RDoC matrix (NIMH, 2011). Several anxiety disorders (e.g., PD, PTSD) have been associated with an increased startle response in anticipation of unpredictable threat, although the role of predictable threat has been mixed (Grillon et al., 2008, 2009; Shankman et al., 2013). Similarly, high AS has been associated with a preference for predictable relative to unpredictable CO_2 administration (Lejuez et al., 2000). However, no study has examined whether AS is associated with the startle response in anticipation of unpredictable vs. predictable threat. This is the first aim of the present study.

High levels of AS have also been associated with increased attention toward threatening stimuli (Hunt et al., 2006; Keogh et al., 2001; Lees et al., 2005). Importantly, this relationship can be examined in the context of startle methods, as the startle probe elicits event-related potential (ERP) measures of early sensory and attentional processing. Specifically, the startle probe elicited N100 is a negative deflection in the ERP signal that is maximal around frontocentral sites and occurs 100 ms after the onset of the startle probe. The probe N100 reflects early perceptual processing of auditory stimuli and is enhanced when participants are instructed to attend to the startle probe while viewing unpleasant relative to pleasant or neutral pictures (Cuthbert et al., 1998). In addition to the probe N100, the startle probe P300 is a positive deflection of the ERP signal that is maximal at centroparietal sites and occurs approximately 300 ms after the onset of the startle probe (Putnam & Roth, 1990; Roth, Dorato, & Kopell, 1984; Sugawara, Sadeghpour, Traversay, & Ornitz, 1994). The probe P300 reflects attention toward the startle probe and is reduced when viewing emotional relative to neutral pictures due to increased attention to emotional foreground stimuli (leaving less attention allocated to the probe itself) (Bradley, Codispoti, & Lang, 2006; Cuthbert, Schupp, Bradley, McManis, & Lang, 1998; Schupp, Cuthbert, Bradley, Birbaumer, & Lang, 1997). Importantly, the startle probe N100 and P300 responses do not reflect the same attentional processes and behave differently: the N100 and P300 are potentiated and reduced, respectively, in the context of threat. Thus, examining the association between AS and startle allow for the examination of both EMG and ERP responses during the same task.

In a recent investigation, Nelson et al. (in press) examined the psychometric properties of the probe N100 and P300 responses during a no, predictable, and unpredictable threat-of-shock (NPU-threat) task. The NPU-threat task contains three distinct within-subjects conditions during which participants anticipate no threat (no aversive stimulus is delivered), predictable threat (aversive stimulus is signaled by short duration cue), or unpredictable threat (aversive stimulus is not signaled). Results indicated that the probe N100 was enhanced in the unpredictable (but not predictable) condition even though participants were not specifically instructed to attend to the startle probe. These data suggest that the anticipation of unpredictable electric shock, relative to unpleasant pictures, may more readily prime early cortical processing of sensory input. In contrast, the probe P300 was attenuated during both the predictable and unpredictable conditions. In addition, the probe N100 and P300 were not correlated across threat conditions, indicating they were measuring separate attentional processes. Collectively, these results suggest that the anticipation of unpredictable threat enhances early perceptual processing and the anticipation of threat in general (irrespective of predictability) increases attention during the threatening conditions of the NPU-threat task. However, no study has examined individual differences in these ERP responses.

Utilizing data from Nelson et al. (in press), the current study examined the association between AS and startle EMG and ERP responses in anticipation of predictable and unpredictable threat. Specifically, 131 undergraduates completed the NPU-threat task and the startle eyeblink EMG response and electroencephalography (EEG) were recorded during the different threat conditions. Self-reported anxiety was also assessed at the end of the task. The current study focused on continuous variation in AS in a college student sample to (1) minimize the contribution of severe psychopathology that is more prevalent in clinical populations and (2) limit the possibility of a restricted range of AS scores in a clinical sample. Moreover, AS was not examined using a taxometric approach (Bernstein et al., 2007), because we did not expect to have a significant number of participants in the "high-risk" group to adequately examine AS as a dichotomous construct. We hypothesized that AS would be associated with increased startle EMG, probe N100, and self-reported anxiety and decreased probe P300 in anticipation of unpredictable (but not predictable) threat.

AS was originally conceptualized as a unitary construct measured with the Anxiety Sensitivity Index (ASI) (Reiss et al., 1986). However, since its inception there have been multiple revisions to the ASI and increased recognition that AS is multifaceted. In the present study, participants completed the ASI-3 (Taylor et al., 2007), the most recent version of the ASI, which consists of three factor analytically derived subscales: physical concerns (PC), cognitive concerns (CC), and social concerns (SC). The discriminant validity of these dimensions has been supported by a number of investigations that have examined the ASI-3 subscales in relation to anxiety and depression symptoms. Specifically, research has indicated that ASI-3 PC has been most consistently associated with panic, CC with depression and worry, and SC with social anxiety (Allan, Capron, et al., 2014; Kemper et al., 2012; Olthuis et al., 2014; Wheaton et al., 2012). We did not have specific hypotheses regarding which AS subscales would be associated with responding during the NPU-threat task. However, given that the aversive stimulus used in the task was a physical danger (electric shock), we hypothesized that the association between AS and these measures would be particularly strong for the PC subscale.

Finally, the ASI-3 CC subscale has been strongly associated with depression (Olthuis et al., 2014; Taylor et al., 1996). Therefore, to determine the unique association between ASI-3 CC and the anticipation of predictable and unpredictable threat, participants also completed a self-report measure of depression, and additional analyses were conducted with this measure included as a covariate. We hypothesized that the relationship between AS (and, in particular, the ASI-3 CC subscale) and startle EMG, probe ERPs, and self-reported anxiety would be independent of depression.

2. Method

2.1. Participants

The sample included 131 introduction to psychology students from the University of Illinois-Chicago who participated for course credit. Exclusion criteria were an inability to read or write English, history of head trauma with a loss of consciousness, or being left-handed (as confirmed by the Edinburgh Handedness Inventory; range of laterality quotient: +10 to +100; Oldfield, 1971). The sample was college-aged (M = 19.36, SD = 2.02), 64.9% female, and