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Experiential, autonomic, and neural responses during threat anticipation vary as a function of threat intensity and neuroticism☆

Emily M. Drabant [a,b,*], Janice R. Kuo [a], Wiveka Ramel [a], Jens Blechert [a], Michael D. Edge [a], Jeff R. Cooper [d], Philippe R. Goldin [a], Ahmad R. Hariri [c], James J. Gross [a]

[a] Psychology Department, Stanford University, Stanford, CA, USA
[b] Neurosciences Program, School of Medicine, Stanford University, Stanford, CA, USA
[c] Department of Psychology and Neuroscience, Duke University, Durham, NC, USA
[d] Trinity College Institute of Neuroscience, Trinity College, Dublin, Ireland

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ABSTRACT

Anticipatory emotional responses play a crucial role in preparing individuals for impending challenges. They do this by triggering a coordinated set of changes in behavioral, autonomic, and neural response systems. In the present study, we examined the biobehavioral impact of varying levels of anticipatory anxiety, using a shock anticipation task in which unpredictable electric shocks were threatened and delivered to the wrist at variable intervals and intensities (safe, medium, strong). This permitted investigation of a dynamic range of anticipatory anxiety responses. In two studies, 95 and 51 healthy female participants, respectively, underwent this shock anticipation task while providing continuous ratings of anxiety experience and electrodermal responding (Study 1) and during fMRI BOLD neuroimaging (Study 2). Results indicated a step-wise pattern of responding in anxiety experience and electrodermal responses. Several brain regions showed robust responses to shock anticipation relative to safe trials, including the hypothalamus, periaqueductal gray, caudate, precentral gyrus, thalamus, insula, ventrolateral PFC, dorsomedial PFC, and ACC. A subset of these regions demonstrated a linear pattern of increased responding from safe to medium to strong trials, including the bilateral insula, ACC, and inferior frontal gyrus. These responses were modulated by individual differences in neuroticism, such that those high in neuroticism showed exaggerated anxiety experience across the entire task, and reduced brain activation from medium to strong trials in a subset of brain regions. These findings suggest that individual differences in neuroticism may influence sensitivity to anticipatory threat and provide new insights into the mechanism through which neuroticism may confer risk for developing anxiety disorders via dysregulated anticipatory responses.

Introduction

One of the principal goals of affective neuroscience is to delineate neurobiological responses to emotional challenges. Typically, this goal has been pursued in laboratory contexts by inducing emotion and then examining changes in subjective experience (Dimberg, 1987; Hubert and de Jong-Meyer, 1991; Magai et al., 2006), peripheral physiology (Sequeira et al., 2009; Vrana et al., 1988), and neural responses (Carretie et al., 2009; Hagemann et al., 2003). For instance, conditioning studies have explored manifestations of fear responses to aversive stimuli, and dozens of studies have demonstrated increased skin conductance and brain activation in response to electric shock, loud noise, and other aversive stimuli (e.g., Cheng et al., 2003, 2007; Dunsmoor et al., 2007; Fischer et al., 2002; Knight et al., 2004b; LaBar et al., 1998; Phelps et al., 2004; for review, see Sehlmeyer et al., 2009).

Although this work is of fundamental importance, one limitation has been the frequent confounding of emotional responses inherent in the psychological representation of the event with the cascade of responses that take place once the body is actually enduring a challenge. For example, the anticipatory anxiety that happens while one awaits a visit to the dentist is importantly distinguishable from the responses that occur once the drilling has begun. It is crucial to parse these two components and carefully examine the anticipatory period before the aversive assault because (1) much of our emotional life is spent in the anticipation of future events and (2) this window allows a purer examination of the impact of the emotional representation of a stressor in the absence of the responses to the stressor itself. Unfortunately, less is known about the anticipatory component of emotional responding than is known about the responses that occur once the demanding situation is actually

☆ This research was conducted at Stanford University.

* Corresponding author. Stanford University, Bldg 420, Room 424, Stanford, CA 94305, USA. Fax: +1 650 725 5699.
E-mail address: drabant@stanford.edu (E.M. Drabant).

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unfolding. Still less is known about the way that individual difference variables moderate these anticipatory responses.

While the vast majority of fear-conditioning studies have employed a strategy in which a cue is presented and then nearly immediately (e.g., less than 500 ms) followed by an aversive stimulus, a handful of neuroimaging studies in humans have employed a "trace" conditioning strategy in which the cue is followed by a waiting period (e.g., from 500 ms to 8 s) before the aversive stimulus is deployed (Buchel et al., 1999; Carter et al., 2006; Cheng et al., 2008, 2006; Knight et al., 2004a). Unfortunately, most of these paradigms have not analyzed the waiting period separately from the receipt of the shock, making it difficult to interpret which element (anticipation or receipt of shock) is driving the findings. The literature on pain anticipation has addressed anticipatory emotional responses more directly, often using longer anticipatory delay periods, and a variety of aversive stimuli to induce anticipatory responses. Early studies of anticipatory anxiety have typically examined anticipatory effects on autonomic responding. For example, anticipation of electric shock (Chua et al., 1999; Kopacz and Smith, 1971) and venipuncture (Geddes et al., 1993) have been shown to lead to increased skin conductance responses (SCRs), and potentiate protective reflexes such as the eyeblink startle reflex (Grillon et al., 1993, 1991; Vrana et al., 1988).

A seminal study by Ploghaus and colleagues was the first neuroimaging study to disentangle the anticipation and receipt of pain, and they found a separable network of regions invoked purely by emotional distress in the absence of external stimulation (Ploghaus et al., 1999). Subsequent studies have begun to elucidate the neural correlates of anticipatory anxiety using standard threat of shock tasks in which shocks were delivered (Chua et al., 1999; Schunck et al., 2008; Straube et al., 2009), or not (Kumari et al., 2007), as well as threat of heat stimuli (Wager et al., 2004), or upsetting images (Nitschke et al., 2006; Waugh et al., 2008). These studies typically show increased activation in bilateral insula, anterior cingulate cortex (ACC), dorsomedial prefrontal cortex (dmPFC), and ventrolateral prefrontal cortex (vlPFC) (Mee et al., 2006). These brain regions have been associated with representing visceral body states and conscious feelings related to interoceptive processes (insula), integrating contextual cues and sensory information (ACC), self-referential processing (dmPFC), and representing the affective stimulus value and expectation of negative outcomes (vlPFC). Only one relatively small study ($N = 16$) has examined the relationship between varying levels of shock intensity and anticipatory responses in the brain (Straube et al., 2009), with findings that suggest that anticipatory processes are not "all or nothing" but are instead modulated by the intensity of the anticipated threat.

There is considerable individual-related variation in anticipatory anxiety. One particularly important individual difference dimension for understanding variation in negative emotional responses is neuroticism. Compared to individuals low in neuroticism, individuals high in neuroticism are more prone to anxiety and negative affect, respond to environmental stressors more negatively (Costa and McCrae, 1980), and are particularly concerned with averting possible threats (Zelenski and Larsen, 1999). Moreover, neuroticism has been associated with an avoidant coping style (Bolger, 1990; McCrae and Costa, 1986; Parkes, 1986) and increased levels of suppression (Gross and John, 2003). Neuroimaging studies have focused on the impact of neuroticism on responses during exposure to aversive images and faces and have found exaggerated neural responses (Canli, 2004; Canli et al., 2001; Carroll et al., 2007; Haas et al., 2007) in the left middle temporal gyrus, middle frontal gyrus, and insula. The autonomic literature, however, has been mixed, with some studies showing increased electrodermal responding to aversive images (Norris et al., 2007) and others showing decreased responding (De Pascalis et al., 2007). It is less clear whether neuroticism affects anticipatory responding before the stimulus actually occurs. Only one study to date has used fMRI to examine neuroticism in response to threat of noxious stimuli (Kumari et al., 2007), finding that neuroticism was negatively correlated with a number of prefrontal and parietal regions during threat greater than safe conditions in a brief task in which shocks were not delivered. Given that neuroticism has been identified as a risk factor for anxiety disorders, many of which are characterized by chronic worry and anxiety about the future (Barlow, 2002; Bienvenu and Stein, 2003), neuroticism may modulate anticipatory anxiety even in healthy individuals.

The goal of the present study was to investigate how anticipation of varying levels of shock intensity impacts anxiety experience, autonomic responding, and neural activity. To address this goal, we employed a task in which a long anticipatory cue period (7–11 s) allowed for robust responses to be generated. To create maximal levels of anxiety with minimal levels of habituation, three layers of unpredictability were embedded into the shock trials: event (whether the shock will occur or not), temporal (when will it occur), and intensity (how strong will it be) unpredictability. These levels of unpredictability have been shown to potentiate emotional reactivity (D'Amato and Gumenik, 1960; Monat et al., 1972), autonomic (Geer and Maisel, 1972), and neural responding (Carlsson et al., 2006). Multiple levels of shock intensity permitted investigation of a dynamic range of responses. In order to disentangle anticipatory anxiety from shock response, the anticipatory period was analyzed separately from the receipt of shock. A relatively large number of trials were employed to enhance power to detect effects, and a large sample of healthy women was employed to permit investigation of individual differences in neuroticism without confounding effects of gender or previous history of psychopathology. Multiple output channels were investigated to better elucidate the richness of anticipatory emotional responses.

Based on the extant literature on anticipatory anxiety, we hypothesized that as shock intensity increased, anticipatory anxiety would result in stepwise increases in (1) anxiety experience, (2) electrodermal responding, and (3) neural activity in brain regions including the insula, anterior cingulate, thalamus, and prefrontal cortex (but not in the amygdala). Based on studies showing exaggerated reactivity during negative stimulus presentation due to neuroticism, we further hypothesized that individuals high in neuroticism would show increases in anticipatory responding before stimulus presentation. Specifically, we expected greater increases in anxiety, electrodermal responding, and brain activity in the middle temporal gyrus, frontal gyrus and insula relative to those low in neuroticism.

Study 1: experiential and autonomic responses to shock anticipation

In Study 1, we devised a shock anticipation task that involved anticipating electric shocks to the wrist in three different intensity levels: safe (no shock), medium shock, and strong shock. To increase anxiety and prevent habituation, three layers of uncertainty were embedded into the shock trials: event, temporal, and intensity uncertainty. The task was administered in a sample large enough to examine the potential effect of neuroticism. We sought to examine the effects of shock anticipation on anxiety experience and electrodermal responses and to test whether neuroticism moderated these responses.

Methods

Participants

All potential participants were screened using an interview based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID for DSM-IV) (First et al., 1995). Eligible participants were healthy females who did not meet criteria for any psychiatric disorder within the past year, or for lifetime posttraumatic stress, bipolar, obsessive–compulsive, or psychotic disorders, and were not currently taking psychotropic medications.