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Controllability modulates the neural response to predictable but not unpredictable threat in humans

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ABSTRACT

Stress resilience is mediated, in part, by our ability to predict and control threats within our environment. Therefore, determining the neural mechanisms that regulate the emotional response to predictable and controllable threats may provide important new insight into the processes that mediate resilience to emotional dysfunction and guide the future development of interventions for anxiety disorders. To better understand the effect of predictability and controllability on threat-related brain activity in humans, two groups of healthy volunteers participated in a yoked Pavlovian fear conditioning study during functional magnetic resonance imaging (fMRI). Threat predictability was manipulated by presenting an aversive unconditioned stimulus (UCS) that was either preceded by a conditioned stimulus (i.e., predictable) or by presenting the UCS alone (i.e., unpredictable). Similar to animal model research that has employed yoked fear conditioning procedures, one group (controllable condition; CC), but not the other group (uncontrollable condition; UC) was able to terminate the UCS. The fMRI signal response within the dorsolateral prefrontal cortex (PFC), dorsomedial PFC, ventromedial PFC, and posterior cingulate was diminished during predictable compared to unpredictable threat (i.e., UCS). In addition, threat-related activity within the ventromedial PFC and bilateral hippocampus was diminished only to threats that were both predictable and controllable. These findings provide insight into how threat predictability and controllability affects the activity of brain regions (i.e., ventromedial PFC and hippocampus) involved in emotion regulation, and may have important implications for better understanding neural processes that mediate emotional resilience to stress.

Introduction

Resilience to stress is mediated, in part, by our ability to predict and control threats in our surroundings. For example, chronic exposure to unpredictable and uncontrollable threat is an important trigger in the development of anxiety-related disorders (Chorpita & Barlow, 1998; Foa et al., 1992; Maier & Seligman, 1976). Therefore, determining the impact of threat predictability and controllability on brain regions that regulate the emotional response is necessary for a better understanding of the factors that promote resilience to emotional dysfunction. Prior human neuroimaging work has examined threat predictability (Dunsmoor et al., 2008; Knight et al., 2010; Wood et al., 2012, 2013) and controllability (Kerr et al., 2012; Salomons et al., 2004, 2007; Wiech et al., 2006) independently; however, important questions regarding how threat predictability and threat controllability interact within the human brain remain unanswered. Thus, there is a critical gap in our understanding of the impact that predictability and controllability have on the neural response to threat in humans. Determining the neural response to predictable and controllable threat may provide important new insights into processes that mediate resilience to emotional dysfunction and guide the development of future interventions for anxiety disorders.

Although the predictability and controllability of aversive events have been previously studied, most prior work has only focused on one of these two factors (i.e., predictability or controllability) (Dunsmoor et al., 2008; Kerr et al., 2012; Salomons et al., 2004, 2007; Wiech et al., 2006; Wood et al., 2012, 2013). For example, prior investigations of controllability have generally not included unpredictable stimulus presentations that were both controllable and uncontrollable (Kerr et al., 2012; Salomons et al., 2004, 2007; Wiech et al., 2006). Thus, research that compares both predictability and controllability is necessary for a complete understanding of these processes and how they interact. Further, predictability and controllability have often been tightly linked in prior work on this topic (Foa et al., 1992; Maier

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& Seligman, 1976; Mineka & Kihlstrom, 1978; Mineka & Hendersen, 1985). For example, the termination of a controllable threat can be predicted, whereas the termination of an uncontrollable threat cannot be predicted (Amat et al., 1998, 2008; Baratta et al., 2007, 2008; Rozeske et al., 2011). However, threat predictability can be operationalized in terms of whether or not a warning signal precedes the threat, which would permit a more independent assessment of controllability (i.e., controllable vs. uncontrollable threat) and predictability (i.e., presentations of both predictable and unpredictable threat) as well as the interaction of these processes.

Human anxiety disorders are characterized by emotional behavior that resembles Pavlovian conditioned fear responses (Davis et al., 2009; Grillon, 2002; Nitschke et al., 2006, 2009). Therefore, fear conditioning has become a popular paradigm for the study of emotion expression and regulation. The conditioned response (CR) is often the primary focus of conditioning studies, and there are a number of interesting issues related to the impact controllability has on the CR. However, the response to the threat itself is of utmost biological relevance (Domjan, 2005), and recent work from our lab has demonstrated important emotion and learning-related differences in threat-elicited brain and behavioral responses (Dunsmoor et al., 2008; Knight et al., 2010, 2011; Wood et al., 2012, 2013, 2014). Therefore, determining the neural processes that mediate the influence predictability and controllability have on the threat-elicited response is vital to understanding emotional behavior.

The prefrontal cortex (PFC), hippocampus, and amygdala are important components of the neural circuit that mediates expression and regulation of the conditioned emotional response (Davis, 1992; Fanselow, 1994; Hartley & Phelps, 2010). In particular, the ventromedial PFC (vmPFC) and hippocampus support learning-related processes that appear to inhibit conditioned and unconditioned fear expression in humans (Milad et al., 2007, 2009; Rauch et al., 2006; Schiller et al., 2013; Wood et al., 2012). Further, animal model studies indicate that the vmPFC and hippocampus mediate stress resilience to predictable and controllable threats (Amat et al., 1998; Baratta et al., 2007, 2008; Franklin et al., 2012; Russo et al., 2012). Therefore, the vmPFC and hippocampus may support processes that regulate the emotional response to predictable and controllable threat in humans.

Research using functional magnetic resonance imaging (fMRI) and psychophysiological recording often employ within-subject designs to account for inter-subject differences and reduce error variance. However, within-subject designs can introduce confounds (e.g., carry-over effects) and interfere with the interpretation of the results. For example, confounds related to habituation and/or prior associative learning prevent assessing control using a within-subject design in separate scanning sessions, or separate blocks in the same scanning session, because participants must have control in the first session to match for threat duration in the second session. In contrast, a yoked Pavlovian fear conditioning paradigm, similar to prior animal model research (Amat et al., 1998, 2008; Baratta et al., 2008, 2009; Maier & Seligman, 1976; Maier, 1986; Maier & Watkins, 2010; Rozeske et al., 2011), can be used to investigate the effect that threat predictability and controllability have on human brain activity while limiting confounds related to habituation and prior conditioning. Yoked conditioning studies typically consist of one group that has the ability to control (i.e., terminate) the threat and a second group that is "yoked" to the first group, and thus receives the same stimuli, but cannot control the threat. Finally, yoked conditioning paradigms ensure that the order, onset, duration, and intensity of stimuli are consistent across groups that receive varying degrees of predictable and controllable threat (i.e., between-subject design).

Prior human neuroimaging studies that have employed a within-subject design to investigate controllability have typically given participants control on some trials, but not on other trials (Kerr et al., 2012; Wiech et al., 2006). Thus, these manipulations do not simply compare control vs. no control but also control vs. loss of control. The distinction between not having control vs. losing control may seem subtle, but is an important issue in the learned helplessness literature (Maier & Seligman, 1976). Other human neuroimaging studies have primarily focused on the perception of control, instead of actual behavioral control over a threat (Salomons et al., 2004, 2007). Each of these studies are valuable contributions to the field; however, the current study focused on important questions specifically related to controllable vs. uncontrollable threat.

The present study investigated the effect of predictability and controllability on the threat-elicited neurophysiological response to better understand the underlying processes that support emotional resilience. In addition, this study includes psychophysiological, cognitive, and self-assessment measures to identify relationships that may influence stress resilience. Similar to prior animal model research, this study employed a yoked Pavlovian conditioning procedure to assess threat-elicited brain activity to predictable-controllable, predictable-uncontrollable, unpredictable-controllable, and unpredictable-uncontrollable presentations of threat. Given that the PFC and hippocampus support emotion regulation, we hypothesized that predictability and controllability would modulate the amplitude of the threat-elicited response within these brain areas. Although previous research has demonstrated greater activity within the vmPFC and hippocampus during the anticipation of threat (Kerr et al., 2012; Milad et al., 2007), our prior work has demonstrated that anticipatory and threat-related activity are inversely related (Wood et al., 2012). Thus, we expected diminished PFC and hippocampal activity to predictable and controllable threats.

Materials and methods

Experimental design

Volunteers participated in a differential fear conditioning procedure during fMRI that consisted of yoked pairs of subjects. To examine the effect of threat controllability, one group received a controllable unconditioned stimulus (UCS) (controllable condition; CC) and the second group received an uncontrollable UCS (uncontrollable condition; UC). CC participants had the ability to terminate the UCS, whereas UC participants could not terminate the UCS. Instead, the timing, duration, and order of stimuli presented to each CC participant were recorded and used to determine stimulus presentation for their yoked match in the UC group. In this way, CC participants controlled the duration of the UCS for their matched counterpart in the UC group. Threat predictability was assessed by comparing presentations of the unconditioned stimulus (UCS; threat) that was paired with the conditioned stimulus (i.e., CS + UCS) to presentations of the UCS alone.

Participants

A total of fifty-four (27 CC and 27 UC) healthy right-handed volunteers participated in this study [28 female, 26 male; age = 23.39 ± 0.77 years (mean ± SEM); range = 18–38 years]. Participants in the two groups were matched on gender, ethnicity, age, and level of education (Table 1). There were no significant differences between the two

Table 1
Demographics and group characteristics.

Measures	Controllable Condition	Uncontrollable Condition	t	p
Male/female	13/14	13/14		
Age	23.37 ± 1.10	23.41 ± 1.11	−0.03	0.97
Range	18-38	18-38		
Education (years)	14.89 ± 0.49	15.26 ± 0.59	−0.68	0.50
Range	12-22	12-21		
State anxiety	33.30 ± 1.47	35.30 ± 1.49	−1.05	0.30
Trait anxiety	36.93 ± 1.71	38.63 ± 1.23	−0.81	0.42

There were no differences in gender, age, education, or anxiety level between the groups.