Anticipation and the Neural Response to Threat

Nathaniel G. Harnett, Kimberly H. Wood, Muriah D. Wheelock, Amy J. Knight and David C. Knight

Abstract An important function of emotion is that it allows one to respond more effectively to threats in our environment. The response to threat is an important aspect of emotional behavior given the direct biological impact it has on survival. More specifically, survival is dependent upon the ability to avoid, escape, or defend against a threat once it is encountered. Anticipatory processes supported by neural circuitry that includes the prefrontal cortex and amygdala are critical for the expression and regulation of the emotional response. Further, these anticipatory processes appear to regulate the response to the threat itself. Healthy emotional function is characterized by anticipatory processes that diminish the emotional response to threat. In contrast, emotional dysfunction is characterized by anticipatory processes that lead to an exaggerated threat response. Thus, anticipatory mechanisms play an important role in both healthy and dysfunctional emotional behavior.

Keywords Anticipation · Conditioning · Fear · Emotion · Threat · Regulation

A valuable function of emotion is that it motivates effective responses to important events in our environment. For example, fear motivates defensive responses

N.G. Harnett · K.H. Wood · M.D. Wheelock · D.C. Knight (✉)
Department of Psychology, University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: knightdc@uab.edu

N.G. Harnett
e-mail: nharnett@uab.edu

K.H. Wood
e-mail: khwood@uab.edu

M.D. Wheelock
e-mail: mwheel@uab.edu

A.J. Knight
Department of Physical Medicine and Rehabilitation, University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: ajk@uab.edu

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(e.g., fight or flight) and promotes rapid associative learning of warning cues and the threats they predict, which is critical for survival. More specifically, the knowledge that a threat is imminent allows one to execute preparatory behaviors in anticipation of the impending threat. Thus, survival is promoted when threats can be anticipated and effectively managed. However, maladaptive anticipatory and threat-elicited responses appear to be linked to anxiety and stress-related disorders. A key goal, then, in the study of emotion is to understand the relationship between the anticipatory response and the response to the threat itself. Specifically, understanding how anticipatory functions influence threat-evoked behavior is important for understanding emotion learning, expression, and regulation processes that mediate anxiety and stress-related disorders.

1 Anticipatory Response

Pavlovian fear conditioning is a procedure that is frequently used to investigate emotion learning, memory, expression, and regulation processes [1–5]. During Pavlovian fear conditioning, an originally innocuous warning cue (i.e., a conditioned stimulus; CS) is typically paired with an innately aversive threat (i.e., an unconditioned stimulus; UCS) that produces a reflexive unconditioned response (UCR). Repeated pairing of the warning cue (CS) and threat (UCS) then elicits an anticipatory response (i.e., a conditioned response; CR) in anticipation of the threat. Thus, CR expression during Pavlovian conditioning reflects anticipation of the forthcoming threat. Skin conductance response (SCR), a measure of sweat gland activity that reflects sympathetic activation of the autonomic nervous system (ANS), is often used as an index of the peripheral emotional response in human fear conditioning research [6–9]. An anticipatory SCR (i.e., the CR) to the CS (i.e., the warning cue) occurs when one has learned the CS-UCS (i.e., cue-threat) contingency and serves as an objective measure of associative learning. Previous Pavlovian fear conditioning research has demonstrated that anticipation of threat initiates preparatory responses that promote behavioral and physiological reactions that minimize harm [10–14]. For example, conditioned hypoalgesia (decreased sensitivity to painful stimuli) develops during fear conditioning, reducing the pain produced by noxious stimuli [12, 15]. A similar process appears to diminish the ANS response to the threat itself during fear conditioning [16–20]

2 Threat-Elicited Response

In contrast to the anticipatory response (CR), the response (UCR) elicited by an aversive threat (UCS) is typically considered an innate and automatic reaction that does not require learning. However, learning-related changes in the response to

threat itself frequently develop during conditioning [10, 17, 20–25]. Specifically, the predictability of threat (UCS) modulates the magnitude of the threat-elicited response such that a diminished response is produced by predictable threat (UCS that follows a CS) compared to unpredictable threat (UCS presented alone). Thus, there is a conditioned reduction in the response to predictable versus unpredictable threat (conditioned UCR diminution) [16, 19, 23, 25, 26]. These findings are consistent with learning theory, which states:

1. Learning occurs when there is a discrepancy between expectations and outcomes.
2. The CS gains discriminatory control over the UCR to the UCS.
3. The UCR is diminished by predictable compared to unpredictable threat [5, 27, 28].

Thus, an enhanced anticipatory response to the warning versus safety cue demonstrates that the cue-threat association has been learned.

The anticipatory response (the CR to the CS+) appears to be essential for the diminution of the response to the threat itself (UCS). Specifically, conditioned diminution of the response to threat develops when the threat follows the warning cue (CS+), but not when the threat follows the safety cue (CS−) or when the threat is presented alone [16, 18, 19, 23, 25, 26]. Further, as the magnitude of the anticipatory response increases, the magnitude of the response to predictable threat decreases [23, 25]. However, a similar relationship is not observed when the threat is unpredictable. That is, the anticipatory response does not vary with the response to threat itself when threat unexpectedly follows a learned safety cue [23, 25]. These findings suggest that an anticipatory response specific to the warning cue is necessary for conditioned diminution of the response to threat.

3 Neural Substrates of Anticipatory and Threat-Elicited Responses

A neural network that includes the amygdala and prefrontal cortex (PFC) supports anticipatory processes and appears to regulate the emotional response to threat. The amygdala is a critical component of the neural circuit that mediates fear learning and expression of conditioned fear [2, 7, 15, 17, 29–34]. The amygdala receives information about the warning cue and the threat (CS and UCS), forms the cue-threat association, and projects to other brain regions (such as the periaqueductal gray, hypothalamus, and ventral tegmental area) to control the peripheral expression of emotion [15, 32, 35]. The conditioned emotional response mediated by the amygdala appears to be regulated by projections from the PFC [1, 36]. This PFC-amygdala circuitry is critical for the expression and regulation of conditioned changes in the peripheral emotional response. Further, the PFC and amygdala

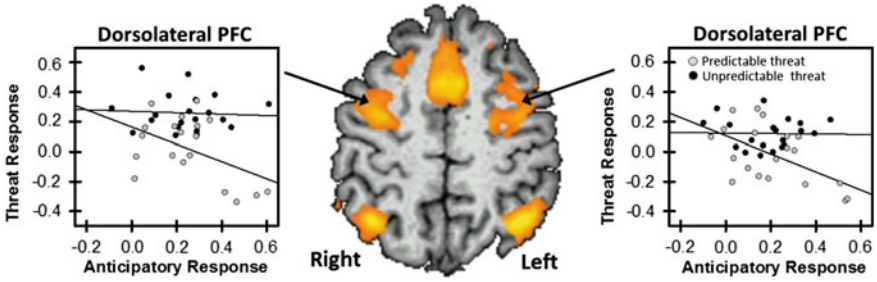

Fig. 1 Relationship between anticipatory and threat-related brain activity. Anticipatory activity was inversely related to threat-related activity on predictable trials within dorsolateral prefrontal cortex (PFC). In contrast, anticipatory activity did not modulate the response to unpredictable threat. These findings suggest that anticipatory activity inhibits threat-related activity within the dorsolateral PFC

appear to support processes that mediate the modulatory effect the anticipatory response (CR) has on the response to threat itself (UCR).

The amygdala and dorsal regions of the PFC (dorsomedial and dorsolateral PFC) show increased anticipatory activity to the warning cue (CR to the CS+) during fear conditioning [7, 30, 31, 37–40]. These same brain regions show diminished responses to predictable compared to unpredictable threat during fear conditioning [17, 24, 25, 41], which closely mirrors the behavioral response to threat itself [17, 21–23, 41]. Further, the dorsolateral PFC demonstrates an inverse relationship between anticipatory activity to the warning cue and the response to the threat (Fig. 1), such that as anticipatory activity increases, threat-evoked activity decreases [24, 25]. The anticipatory activity within the dorsolateral PFC appears to be particularly important for regulating threat-related activity within other brain regions such as the ventromedial PFC and the amygdala [25]. Further, our prior work demonstrates greater dorsolateral PFC connectivity to the dorsomedial PFC, ventromedial PFC, and amygdala during predictable compared to unpredictable threat [42]. Thus, anticipatory dorsolateral PFC activity appears to regulate threat-related responses, and may support healthy emotion regulation (Fig. 2).

Threat predictability and controllability appear to interact to influence the neural response to threat. Specifically, ventromedial PFC and hippocampal activity varies with the predictability and controllability of threats [43]. Activity within these brain regions is diminished when threats are both predictable and controllable. In contrast, ventromedial PFC and hippocampal activity is enhanced when threats are unpredictable and/or uncontrollable. Further, the stress-ameliorating effects observed when one has control over a threat appear to be mediated by the ventromedial PFC [44] and hippocampus [45]. For example, a prior encounter with a controllable threat modifies the ventromedial PFC function that regulates amygdala activity and controls the emotional response elicited by future threats [46–49]. These findings suggest that the ability to predict and control threat has an important impact on ventromedial PFC and hippocampal function. Given that the

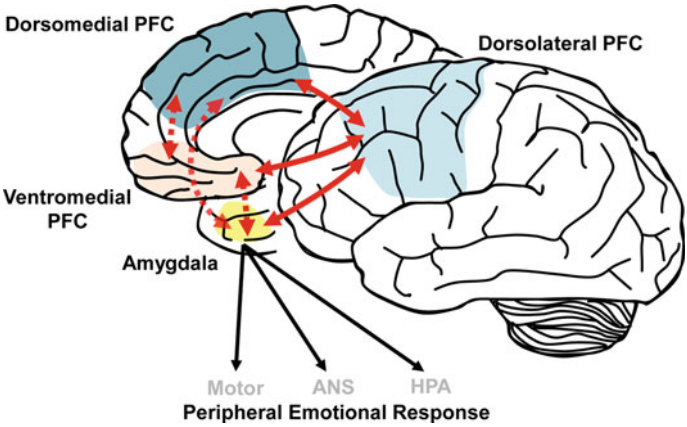

Fig. 2 Neural circuit hypothesized to regulate the emotional response to threat. Anticipatory dorsolateral PFC activity regulates threat-elicited activity within the PFC and amygdala (*solid lines*). Connectivity between other regions of the PFC and amygdala (*dotted lines*) also appears to influence emotion expression. In turn, the amygdala controls learning-related changes in the peripheral emotional response. *PFC* prefrontal cortex; *ANS* autonomic nervous system; *HPA* hypothalamic-pituitary-adrenal axis

ventromedial PFC and hippocampus are important components of the neural circuit that regulates emotion [45–47, 50–54], these brain structures may support processes that mediate the stress resilience that develops when one can control an imminent threat.

4 Understanding Internalizing Disorders

Neural circuitry that supports the cue-threat association may be important for understanding internalizing disorders. For example, individuals with anxiety and stress-related disorders display greater amygdala activity to warning cues compared to healthy controls [55–57]. Further, anxious individuals tend to show greater anticipatory activity to both warning and safety cues compared to healthy individuals [58]. This hyperarousal to warning cues persists even once the cue-threat contingency changes [54, 59, 60]. Thus, enhanced anticipatory activity observed in patient populations may fail to regulate the response to actual threats within the environment. Specifically, individuals with anxiety and stress-related disorders may show enhanced brain (amygdala) activity to predictable threat instead of the diminished response typically observed in healthy individuals. The enhanced threat-elicited response may be mediated, in part, by disruption of functional connectivity of the PFC-amygdala network. In turn, hyperactivity within this neural circuitry may mediate the hyperarousal associated with anxiety and stress-related disorders.

Disruption of PFC-amygdala circuitry may mediate the emotional disinhibition that characterizes many anxiety and stress-related disorders. For example, the hyperarousal associated with anxiety and stress may be due to insufficient top-down regulatory control. In fact, anxiety and stress disorders are often associated with hypoactivation of the ventromedial PFC [50, 54, 61, 62]. In turn, ventromedial PFC hypoactivation may lead to hyperactivation of the amygdala [50, 54, 63–65]. Thus, dysfunction of the PFC-amygdala circuit may mediate key symptoms of anxiety and stress-related disorders [52, 66–68]. Prior work from our laboratory indicates anticipatory processes regulate the emotional response to threat [20, 23, 25]. Thus, anticipatory processes that typically support healthy regulatory functions may instead disrupt emotion regulation and increase susceptibility to stress and anxiety.

5 Conclusion

Anticipation of threat is an important process that facilitates the healthy regulation of the emotional response to threat. Associative learning of the cue-threat relationship supports anticipatory processes that mediate the conditioned diminution of the response to threat. Conditioned diminution of the emotional response to threat appears to be mediated by a PFC-amygdala network. Anticipatory processes supported by the dorsolateral PFC regulate the dorsomedial PFC, ventromedial PFC, and amygdala response to threat. The ability to predict and control threats is a critical aspect of emotional resilience [43, 69–73]. Evidence suggests that the ventromedial PFC and hippocampus play an important role in the emotion regulation process [51, 52, 68, 74–76]. Thus, these brain regions appear to mediate functions that are important for stress resilience. Therefore, dysfunction of the PFC-amygdala network may result in maladaptive anticipatory processes that disrupt emotion regulation in the face of threat, and may be responsible for the emotional dysfunction associated with anxiety and stress-related disorders.

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