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The Waiting Game: How Studying Anticipatory Processing Can Provide New Insight into the Neural Circuit of Dysfunction in Anxiety Disorders

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Anticipation of upcoming aversive or threatening events is a highly adaptive psychological process. During anticipation, individuals consider the current environment and prior memories to initiate cognitive and motor processes. Anticipation of aversive stimuli has been studied in a number of neuroimaging paradigms, and results have shown that anticipation results in increased activation in a network of brain regions. This network includes emotion reactivity regions—the amygdala and insula, which signal threat and arousal—and emotion regulation regions—the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex, which signal action and cognitive control. Balance between emotion reactivity regions and emotion regulation regions is necessary for the successful preparation for an upcoming aversive event. Anticipation can also be maladaptive, such as in anxiety disorders, and understanding anticipatory anxiety can provide new insight into dysfunction in the neural circuit in anxiety disorders. Patients with anxiety disorders may engage anticipatory processes to neutral or mildly aversive stimuli. When patients with anxiety disorders anticipate aversive stimuli, they have greater activation of emotion reactivity regions and less activity of emotion regulation regions, relative to controls. Among patients with anxiety disorders, patients who have greater activation of emotion regulation regions typically experience fewer symptoms. Individuals with social phobia typically experience extreme anticipatory anxiety prior to social situations; anticipatory anxiety has been studied using speech anticipation paradigms. In patients with social phobia, relative to controls, anticipation of social stimuli is associated with increased activity of emotion reactivity regions, and less activity of emotion regulation regions in patients with social phobia, relative to controls. Studying anticipation of social stimuli in patients with social phobia may lead to greater understanding of the pathophysiology of social phobia and help to identify new targets for treatment and prevention.

Keywords: *Anxiety, anticipation, fear, amygdala, dorsal anterior cingulate, dorsolateral prefrontal cortex, insula, social phobia*

Anticipation of Aversive Events

An upcoming aversive event, such as a having a thesis committee meeting, giving a scientific talk, or taking a test triggers anticipation of that event. Anticipation is often adaptive; during the anticipation of an event, mental and physical preparation takes place. Anticipation of aversive stimuli promotes survival in a changing environment[1]. Anticipation of aversive events can be broken down into a number of overlapping processes (see **Figure 1**): A.) orienting and threat detection;[2] B.) memory recall and evaluation;[3] and C.) motor preparation and cognitive control[4]. During anticipation of emotional stimuli, physiologic reactivity is heightened, suggesting emotional arousal[5,6]. Anticipatory processes may modify behavior, and avoid, prepare for, or alter the aversive event. Cognitive processes, such as reappraisal, distraction, or emotion suppression, may also reduce anxiety and allow for mental preparation for the aversive event. Better understanding of the neural processes of anticipation of aversive stimuli may provide insight into these adaptive responses

Anticipation of aversive events is mediated by emotion reactivity and emotion regulation brain regions. During anticipation of aversive events, common emotion reactivity regions activated include the amygdala[2,4,7–11] and the insula[2,4,8–17], and common emotion regulation regions activated include the dorsolateral prefrontal cortex (dlPFC)[1,4,9,10,13,14,17] and the dorsal anterior cingulate cortex (dACC)[1,2,4,11–13,15,16] (see **Figure 2**). The amygdala detects and attends to aver-

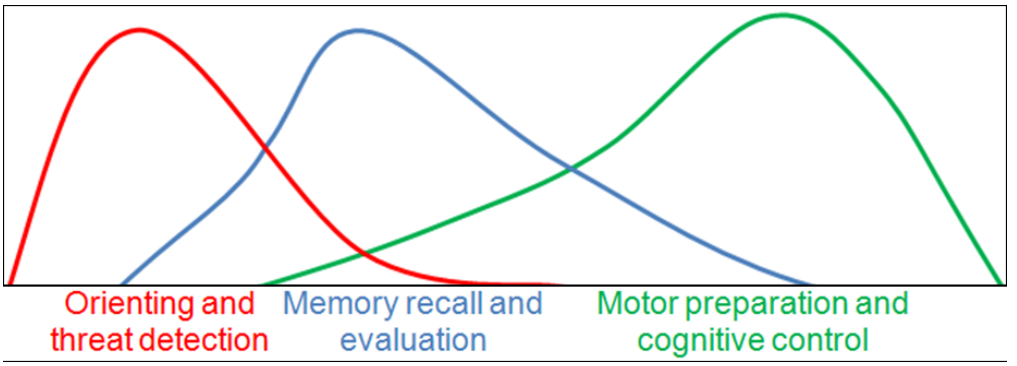

Figure 1: *Phases of anticipatory processing.* Anticipation of aversive events involves several distinct, yet overlapping processes, including orienting and threat detection, memory recall and evaluation, and motor preparation and cognitive control.

sive stimuli,[18,19] activates fear responses,[18] and engages emotional memory[20]. The insula detects and responds to emotional, interoceptive, and autonomic responses,[21] and may represent internal feelings of anticipatory anxiety[9], and amygdala-insula structural connections[22] may play an important role in anticipatory processing. During anticipation of aversive stimuli, emotion regulation regions have a dual role – initiating behavioral and cognitive responses and regulating activation in emotion reactivity regions. The dACC integrates cognitive, motor, and affective processes, and plans future behavioral or emotional responses.[21,23] During anticipation, the dACC may be particularly important in integrating emotional responses and cognitive processes.[21] The dlPFC also engages emotional working memory[24] and exerts cognitive control over emotional responses[25,26]. The dACC and dlPFC are reciprocally connected,[27,28] and dACC projections to the amygdala[29–31] and insula[32,33] may regulate emotion reactivity.

During anticipation of aversive events, cognitive control processes may regulate emotional responses. Cognitive control processes may be implicit (engaged spontaneously) or explicit (instructed); common cognitive control processes include reappraisal, reality checking, and even the use of a placebo, in studies examining response to pain. Cognitive control processes commonly activate the prefrontal cortex, including the dACC and dlPFC[34,35] and suppress activation in emotion reactivity regions, including the amygdala and insula[36]. More frequent use of cognitive reappraisal strategies is related to larger dACC volume[37]. Placebo analgesics are associated with increased activation in the dlPFC and reduced activation in the insula; the magnitude of the placebo effect correlates with the degree of change of neural response in the dlPFC and insula.[36] Individuals who use reappraisal more often during daily life have less amygdala activity during anticipation of aversive stimuli,[25] suggesting that individuals who are more practiced at reappraisal may more effectively suppress emotion reactivity responses. Importantly, during anticipation of negative stimuli, functional connectivity between dACC and left amygdala is increased,[28,30] suggesting that anticipation is a key time for emotion regulation and preparation. Cognitive control strategies may regulate emotional responses[38] and may be adaptive during anticipation of aversive stimuli.

Anticipation of Aversive Events in Anxiety Disorders

In patients with anxiety disorders, anticipation can be maladaptive. Patients often have heightened feelings of anticipation, which can lead to fear, helplessness, and feelings of uncontrollable future threat.[39] Heightened anticipation of aversive stimuli may result in symptoms of excessive worry and avoidance of otherwise safe situations. Greater anticipatory anxiety, and not severity or frequency of symptoms,[40] is related to more avoidance behavior, one of the most detrimental features of anxiety disorders[41]. Patients with anxiety disorders may also display inappropriate anticipation, resulting in anticipation of both phobic stimuli and of relatively minor events[24,42,43]. Patients with anxiety disorders have increased attention bias to threat[44] and are more likely to interpret neutral events as negative[45], both of which may result in increased anticipation. Anxiety disorders are also characterized by ineffective emotion regulation,[46] which may result in withdrawal or avoidance behaviors, rather than the more adaptive anticipation - cognitive control and approach behaviors. Differences in anticipatory processing are likely related to two mechanisms – increased threat detection and less effective emotion regulation.

In support of these hypotheses, patients with anxiety disorders also have increased amygdala[11,24,43] and insula[42,43,47,48] activation during anticipation of aversive stimuli. Most studies have also found less activation of emotion regulation regions during anticipation, including the dorsal anterior cingulate cortex (dACC)[43] and dorsolateral prefrontal cortex (dlPFC)[43,47,48] activation; however, results are not

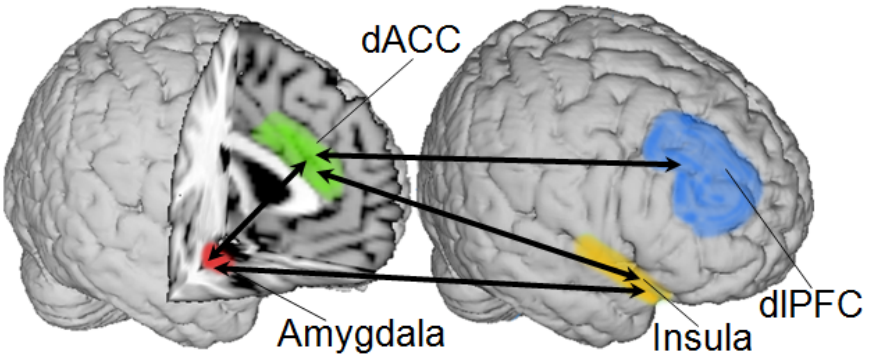

Figure 2: *Neural network of anticipation.* Regions of the brain activated during anticipation of aversive stimuli include the amygdala, insula, dorsal anterior cingulate cortex (dACC), and dorsolateral prefrontal cortex (dlPFC). Connectivity between emotion reactivity regions (amygdala and insula) and emotion regulation regions (dlPFC and dACC) has been observed.

consistent, and a few studies have found increased dACC[42] and dlPFC[24] activation during anticipation of aversive stimuli. Prefrontal cortex regions that are close in anatomic position, may have distinct functions and engage separate processes,[49] and our understanding of the function of prefrontal cortex regions is evolving over time (for example, see [50] and [51]). Further study is needed to determine the precise location and function of changes in prefrontal cortex activity in anxiety disorders. Unlike healthy controls,[25] when patients with social phobia engage cognitive control mechanisms during anticipation of aversive stimuli, they do not show increased activation of prefrontal cortex regulation regions[52].

Patients with anxiety disorders who are better able to engage emotion regulation regions during anticipation of aversive stimuli may have higher functioning, fewer symptoms, and better response to treatment. For example, greater dlPFC activation during anticipation of negative images is associated with fewer PTSD symptoms and better executive functioning.[47] In patients with generalized anxiety disorder, greater dACC activation during anticipation, was associated with greater reduction in anxiety and depression symptoms following treatment.[11] In summary, in patients with anxiety, greater activity of emotion regulation regions during anticipation of aversive events is associated with higher functioning and better treatment response.

Individuals with high trait anxiety are at high risk for developing anxiety disorders, and have increased attention bias to threat[53]. High trait anxious individuals show similar patterns of anticipation of aversive stimuli, including increased activation of the amygdala,[54] insula,[14,48] and dlPFC[14]. Degree of trait anxiety was positively associated with activation in the amygdala and insula during anticipation of aversive stimuli,[9] and high trait anxiety is associated with increased connectivity between the insula and emotion regulation regions, including the dlPFC and dACC.[14] In individuals with high trait anxiety, greater activation of emotion regulation regions and greater coupling between emotion regulation regions and emotion reactivity regions may compensate for heightened emotion reactivity in anxiety. Greater activation of emotion regulation regions during anticipation may protect high trait anxious people from engaging in withdraw or avoidance behavior, and may "protect" against development of anxiety disorders; however, this has not been explicitly tested.

Focus on Anticipation of Aversive Social Stimuli in Social Phobia

Social phobia is defined as the fear or avoidance of one or more performance or social evaluative situations, especially those in which an individual is exposed to social evaluation or scrutiny by others. Symptoms of social phobia are often most prominent during the anticipation of social situations and is accompanied by heightened physiological arousal,[24,55] anticipatory anxiety,[24,55] and negative self-beliefs[56,57]. Understanding the neurobiology of anticipation of social situations has the potential to advance our understanding of the pathophysiology of social phobia.

Anticipation of aversive social stimuli in social phobia has typically been measured using a speech anticipation task, which reflects some of the common triggers of social phobia – fear of social evaluation. Subjects are given several minutes to prepare a speech on a given topic, and then they deliver the speech to a group of experimenters or in front of a video camera. Anticipation of public speaking increases state anxiety,[24,55] negative affect,[55] and physiological arousal[24,55]. During speech anticipation, degree of social anxiety is correlated with increased negative self-beliefs,[56] self-reported anticipatory anxiety,[56,57] and physiologic arousal[56,57]. During anticipation of giving a speech, activa-

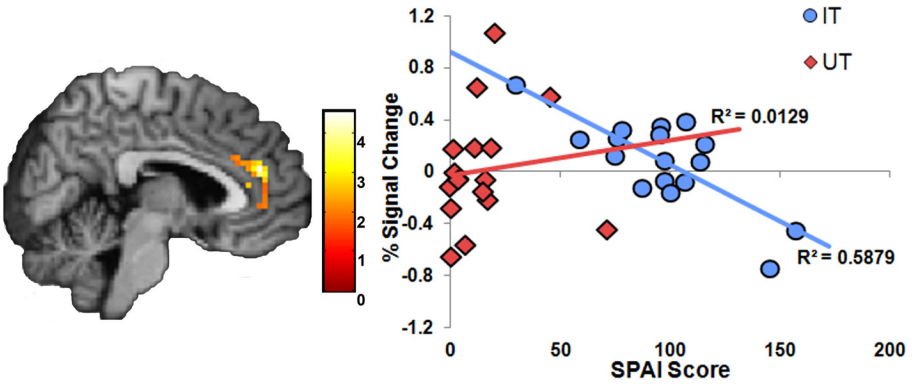

Figure 3: *Increased activation in the rostral anterior cingulate in subjects with fewer social anxiety symptoms.* During anticipation of fear faces, greater anterior cingulate activation in the inhibited temperament group (IT) was associated with fewer social anxiety symptoms (R2 = 0.59), but not in the uninhibited temperament group, (UT; R2 = 0.01).

tion is increased in regions associated with anticipation of aversive stimuli, including in the amygdala[24,43] and insula[43], and decreased in the dACC and dlPFC[43], in patients with social phobia, compared with controls. While studies of anticipation of "protect" against development of anxiety disorders; however, this has not been explicitly tested.

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Social phobia has two subtypes: generalized and non-generalized. Generalized social phobia includes multiple social fears; non-generalized social anxiety disorder is confined to a single social fear (usually public speaking), is less disabling, and is rarely brought to medical attention[58]. Generalized social phobia is highly impairing and can result in fear of interacting with other people,[58] dropping out of school,[58] losing a job,[58] and psychiatric comorbidities, including other anxiety disorders and depression[59]. While studying the anticipation of public speaking is important in understanding non-generalized social anxiety disorder, giving talks in front of large groups of people can often be avoided. In generalized social anxiety disorder, encounters with unfamiliar individuals on a day-to-day basis cause impairment and anxiety, and cannot be avoided. Therefore, studying differences in brain activation to more common social stimuli, such as novel faces, is important in understanding the neural basis of generalized social phobia and to prevent and treat this disorder. One way to understand the pathophysiology of generalized social phobia might be to examine brain function during the anticipation of mildly aversive social stimuli.

One study by our lab (Clauss & Blackford, in preparation) has examined the neural correlates of anticipation of fear faces. To study social anxiety disorder, we study a high-risk group, individuals with an inhibited temperament. Inhibited temperament is associated with a 7-fold increased odds of developing social phobia.[60] In individuals with an inhibited temperament, anticipation of fear faces is associated with greater activation in the dlPFC and dACC, relative to those with an uninhibited temperament. In the inhibited

temperament group, dACC activation was negatively correlated with social phobia symptoms, as measured by the Social Phobia and Anxiety Inventory[61] (see **Figure 3**). The uninhibited group showed no significant change in activation from baseline during anticipation of faces, suggesting that an upcoming mild social stimulus evokes anticipatory activity in the inhibited temperament group only; additionally, there was no relationship between dACC activation and symptoms in the uninhibited temperament group (see **Figure 3**). These results suggest that anticipation of a mildly aversive social stimulus may be a unique probe for social anxiety symptoms.

Implications for Treatment

Anticipation of aversive stimuli is a key process in anxiety disorders and should be targeted in treatment of the disorders.[4] Neural responses during anticipation of aversive stimuli have been shown to be sensitive to treatment effects. Anxiolytic medications, including selective serotonin reuptake inhibitors and pregabalin, decrease insula and amygdala activity during anticipation.[62,63] Additionally, non-pharmacologic treatments are effective in modulating activity of emotion reactivity and regulation regions. In patients with social anxiety disorder[52], engaging in emotion regulation strategies during anticipation reduced insula and amygdala activity and increased ACC activity during anticipation and perception of aversive stimuli; in healthy controls, emotion regulation strategies also increased activity in the dlPFC and individual differences in emotion regulation were negatively correlated with amygdala activity during anticipation[25]. Greater pre-treatment anterior cingulate activation during anticipation in patients with generalized anxiety disorder was associated with better treatment response, suggesting that individuals who engage emotion regulation areas more at baseline may be more responsive to treatment.[11] Therapies that engage emotion regulation regions during aversive anticipation may be effective treatments for anxiety disorders.

Summary

Anticipation is a key psychological process and is highly adaptive by allowing individuals to avoid or modify upcoming aversive events. A network of brain regions is activated during anticipation of aversive stimuli, including the amygdala, insula, dorsal anterior cingulate cortex, and dorsolateral prefrontal cortex. In individuals with anxiety disorders, this network is disrupted; typically, activation of emotion reactivity regions is higher and activation of emotion regulation regions is lower. Anticipation of public speaking has been studied extensively in social phobia, but anticipation of more mild aversive social stimuli, such as single fear faces, has only been studied in a high-risk group. Considering the disability associated with generalized social phobia, which includes fear of daily social interactions, anticipation of more mild aversive social stimuli should be investigated and targeted for treatment. Enhanced activity of emotion regulation regions is associated with compensatory activity in high-risk, but high-functioning individuals, better outcomes, and better treatment response, suggesting that emotion regulation regions may be an important target for treatment of anxiety disorders.

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