The Threatened Brain

The human brain's distinct reactions to distant dangers and nearby threats may be deregulated in anxiety disorders.

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The world is a dangerous place. Every day we face a variety of threats, from careening automobiles to stock market downturns. Arguably, one of the most important functions of the brain and nervous system is to evaluate threats in the environment and then coordinate appropriate behavioral responses to avoid or mitigate harm.

Imminent threats and remote threats produce different behavioral responses, and many animal studies suggest that the brain systems that organize defensive behaviors differ accordingly[1]. On page 1079 of this issue, Mobbs and colleagues make an important advance by showing that different neural circuits in the human brain are engaged by distal and proximal threats, and that activation of these brain areas correlates with the subjective experience of fear elicited by the threat[2]. By pinpointing these specific brain circuits, we may gain a better understanding of the neural mechanisms underlying pathological fear, such as chronic anxiety and panic disorders.

To assess responses to threat in humans, Mobbs and colleagues developed a computerized virtual maze in which subjects are chased and potentially captured by an "intelligent" predator. During the task, which was conducted during high-resolution functional magnetic resonance imaging (fMRI) of cerebral blood flow (which reflects neuronal activity), subjects manipulated a keyboard in an attempt to evade the predator. Although the virtual predator appeared quite innocuous (it was a small red circle), it could cause pain (low- or high-intensity electric shock to the hand) if escape was unsuccessful. Brain activation in response to the predatory threat was assessed relative to yoked trials in which subjects mimicked the trajectories of former chases, but without a predator or the threat of an electric shock. Before each trial, subjects were warned of the contingency (low, high, or no shock). Hence, neural responses evoked by the anticipation of pain could be assessed at various levels of threat imminence not only before the chase, but also during the chase when the predator was either distant from or close to the subject.

How does brain activity vary as a function of the proximity of a virtual predator and the severity of pain it inflicts? When subjects were warned that the chase was set to commence, blood oxygenation level-dependent (BOLD) responses (as determined by fMRI) increased in frontal cortical regions, including the anterior cingulate cortex, orbitofrontal cortex, and ventromedial prefrontal cortex. This may reflect threat detection and subsequent action planning to navigate the forthcoming chase. Once the chase commenced (independent of high- or low-shock trials), BOLD signals increased in the cerebellum and periaqueductal gray. Activation of the latter region is notable, as it is implicated in organizing defensive responses in animals to natural and artificial predators[3,4]. Surprisingly, this phase of the session was associated with decreased activity in the amygdala and ventromedial prefrontal cortex. The decrease in amygdala activity is not expected, insofar as cues that predict threat and unpredictable threats activate the amygdala[5,6].

However, activity in these brain regions varied considerably according to the proximity of the virtual predator and the shock magnitude associated with the predator on a given trial. When the predator was remote, blood flow increased in the ventromedial prefrontal cortex and lateral amygdala. This effect was more robust when the predator predicted a mild shock. In contrast, close proximity of a predator shifted the BOLD signal from these areas to the central amygdala and periaqueductal gray, and this was most pronounced when the predator predicted an intense shock. Hence, the prefrontal cortex and lateral amygdala were strongly activated when the level of threat was low, and this activation shifted to the central amygdala and periaqueductal gray when the threat level was high.

The shift in neural activity from the forebrain to the midbrain may reflect increases in fear as the predator approaches. In support of this view, Mobbs *et al.* also showed that BOLD signals in the periaqueductal gray and the nearby dorsal raphe nucleus were highly correlated with the degree to which subjects feared the predator and how confident they were that they could escape. In animals, similar variations in fear define the topography of behavior along a "predatory imminence continuum"[7]. According to this view, the prefrontal cortex and lateral amygdala may coordinate behavior (such as avoidance) in the face of a distal threat, whereas the central amygdala and periaqueductal gray may coordinate defensive responses (such as freezing) when

threat is imminent[8]. Forebrain systems engaged by a remote predator may even inhibit midbrain defense systems to promote escape behavior. Indeed, when escape fails and capture becomes inevitable (when control is lost), prefrontal inhibition of amygdala activity[9] and midbrain defense circuits may be released to shift behavior into a defensive mode[10]. Although Mobbs *et al.* show that subjects were motivated to escape the virtual predator, it would be of interest to know whether the brain activation patterns they observed predicted fear responses (such as sweating or tachycardia) during the task.

The majority of fMRI studies investigating the neural substrates of aversive emotions—including fear—have used tasks in which the imminence of the threat does not vary, or varies in a way that would elude detection in a neuroimaging study[11]. For example, many studies have used Pavlovian fear conditioning procedures, in which a conditioned stimulus is paired with an aversive event (shock, loud noise, or a fear-evoking image). In this situation, the imminence of the aversive outcome does not vary, at least in a spatial domain, when the conditioned stimulus is presented. Although imminence might vary during the conditioned stimulus as the unconditioned stimulus approaches in time, modern fMRI techniques cannot resolve brain activity during the short conditioned stimuli (2 to 4 s) typically used in these experiments. Nonetheless, these approaches have identified brain responses to stimuli that predict aversive outcomes, and activation of the amygdala also figures prominently in this response[12–15].

What do the findings tell us about human anxiety and panic? As the imminence of a threat increases, the successive activation of neural circuits in the forebrain and midbrain may yield qualitative changes in the subjective experience of fear: Activation of the prefrontal cortex by distal, unpredictable threats might foster anxiety, whereas activation of the periaqueductal gray by proximal threats that predict pain may fuel panic. Dysfunction in these circuits is therefore likely to yield a variety of chronic anxiety disorders[16–18]. Indeed, decoupling of the midbrain periaqueductal gray from cortical-amygdaloid regulation may contribute to panic disorder, which is characterized by intense somatic and autonomic fear responses to stimuli or situations that pose no immediate threat. Mobbs and colleagues have now set the stage for future efforts to explore this intriguing possibility in patients with anxiety disorders.

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