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Research paper

Threat visibility modulates the defensive brain circuit underlying fear and anxiety

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HIGHLIGHTS

- We used human fMRI and a novel computer-based task to study the effects of visual threat uncertainty on brain activity.
- Lack of visual threat information increased activity in hippocampus, ventromedial prefrontal cortex and amygdala (regions involved in anxiety).
- Presence of visual threat information increased activity in periaqueductal gray (involved in fear).
- High trait-anxiety participants anticipated hippocampal activation when visual threat information was not provided.

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ABSTRACT

Recent theories distinguish anxiety from fear in the brain. Anxiety is associated with activation in ventromedial prefrontal cortex and hippocampus, while fear is associated with activation in periaqueductal gray, with amygdala involved in processing aspects of both emotional responses. These theories propose that the amount of information available about threat determines which of the two defensive responses is elicited, with fear and anxiety associated with well-defined and uncertain threats respectively. However, a direct test of this hypothesis is lacking. Here we provide such a test using fMRI to record participants' brain activity while they performed a computer-based task which required to press a button to move an artificial agent to a target position while an artificial predator chased the agent. In one condition (associated with fear) the predator was visible, while in another condition (associated with anxiety) the predator was invisible. Ventromedial prefrontal cortex, hippocampus, and amygdala showed increased activity when the predator was invisible compared to visible, while the opposite effect was observed in periaqueductal gray. We also observed that participants with high but not low trait-anxiety showed an hippocampal activation with invisible threat at an earlier time stage during the trial. These findings help clarify the neural mechanisms that underlie different defensive emotions and shed light on how these mechanisms may contribute to exaggerated anxiety.

1. Introduction

Complex organisms are equipped with a vast repertoire of defensive responses that have evolved to adapt to a considerable variety of aversive conditions. Research investigating the neural substrates underlying defensive behavior suggests that defensive responses are supported by a brain circuit extending from ventromedial prefrontal cortex (vmPFC), hippocampus and amygdala to periaqueductal gray (PAG; [11,23]). Central to this brain system is the amygdala, a region involved in learning and coordinating conditioned responses [8,10] and regulated by bidirectional connections with vmPFC [31]. The key role of hippocampus in defensive behavior is supported by several findings [1,2,17,33] such as the evidence that anxiolytic effects of benzodiazepines are mediated by an impact on hippocampus [2]. Another important region of the defensive network is PAG which plays a central role in guiding freezing and fight/flight reactions [12,15,26,27].

Although the areas comprising the brain's defensive network appear well-established, it remains unclear how activation in these areas is modulated by different aversive contexts. Contemporary theories propose that evolution has favored the differentiation of two kinds of defensive responses that can be traced back to fear and anxiety, each recruiting distinct neural regions. Fear has been

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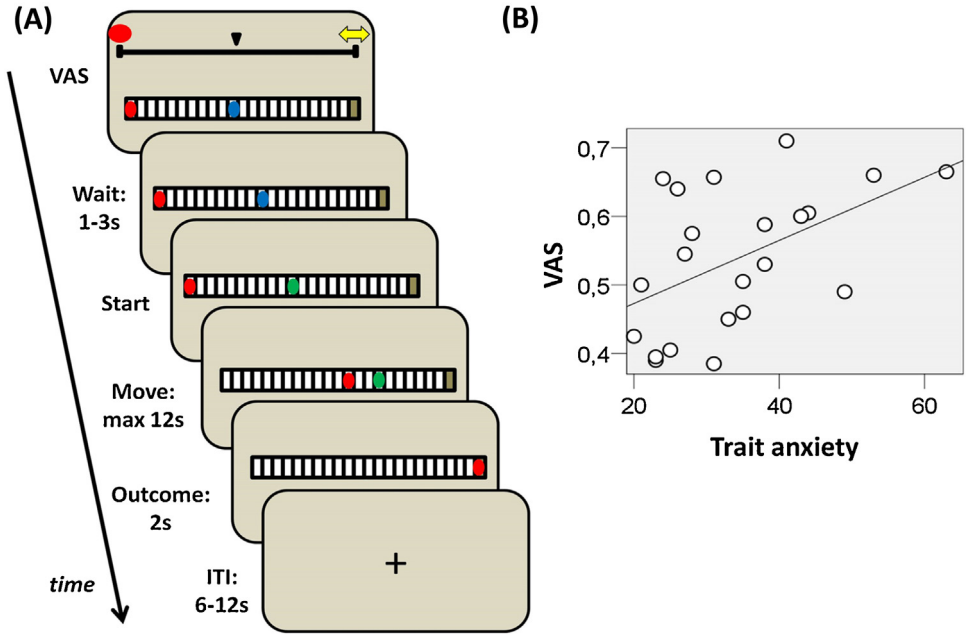

Fig. 1. (A) Task description. Participants started each trial by indicating on a VAS scale their expectancy of being captured by the artificial predator in the next trial. At the same time, participants were informed about the condition (HID or VIS) of the next trial by a panel displayed on the bottom of the screen reproducing the condition. After, a rectangular path was displayed together with a blue ball representing the agent positioned in the middle of the path plus, in VIS trials only (presented in the example shown in this figure), a red ball representing a predator appearing on the left extreme side of the path. After 1–3 s, the blue ball turned green and participants had to press a button and keep it pressed to move the green ball/agent toward the target position represented by a gray square at the far right side of the path. At the same time, the red ball/predator moved closer to the agent. On 50% of trials capture occurred (50% of the time at target position, as in the example, 50% along the path), while on 50% of trials the agent reached the target without being caught and a safety signal (two yellow horizontal arrows) was displayed upon the target. (B) Relationship between trait-anxiety and average VAS score indicating the subjective probability of being captured by the predator ($r(22) = 0.498$, $p = 0.018$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

associated with activation in PAG, and anxiety with activation in hippocampus and vmPFC, with the amygdala involved in processing aspects of both emotional responses [9,11,23,28,29]. The level of uncertainty regarding danger is thought to be one of the key dimensions that elicit either of the two defensive responses, with fear and anxiety being evoked by well-defined and undetermined threats respectively [9,17,19,25,32]. Threat uncertainty is affected by the amount of visual information, an aspect important in several ecological circumstances. For instance, the night prevents viewing a predator, inducing a response different from that exhibited in the daylight [18]. However a direct investigation of the impact of threat uncertainty, and more specifically of threat visibility, on activity in the defensive brain system is lacking.

In order to study the impact of uncertainty on the defensive brain network, we used a paradigm which manipulated visual information about threat. We used functional magnetic resonance imaging (fMRI) to record the neural response of healthy individuals while they performed a computer-based task (Fig. 1A) in which they had to press a button to move an artificial agent, displayed on the screen, to a target position, while an artificial predator was chasing the agent. In a condition associated with low threat uncertainty, visual feedback on the predator position was provided throughout the trial (visible threat: VIS), while in another condition, associated with high threat uncertainty, visual feedback on the predator's position was not provided (hidden threat: HID). On half of the trials the agent reached the target without being caught and on the other half the predator captured the agent and a loud scream noise was delivered as punishment. Consistent with recent proposals [9,11,23], we predicted that VIS compared to HID would activate PAG, which guides fight/flight reactions associated with fear, whereas HID compared to VIS would activate vmPFC and hippocampus which are thought to underlie the cognitive processes characterizing anxiety. We also predicted the involvement of the amygdala, although given its role in both fear and anxiety responses, we did not have a priori hypotheses regarding this region [11,23].

We were also interested in investigating the relationship between individual differences in emotional responding and the function of the defensive brain circuit. To address this, we studied the impact of trait-anxiety [36] on neural response to HID compared to VIS. It has been suggested that a key difference between anxious and non-anxious individuals is that the former tend to anticipate in time an anxiety response to danger [22]. Based on this, we predicted that, in high trait-anxiety but not in low trait-anxiety individuals, the neural response in hippocampus and vmPFC for HID compared to VIS would emerge at an earlier time point during the trial, reflecting an anticipated anxiety reaction in high trait-anxiety participants.

2. Methods

2.1. Participants

Twenty-six healthy right-handed adults participated in the experiment. After pre-processing of fMRI data, 4 participants were excluded from further analyses due to excessive movement in the scanner (translation > 6 mm along one of the three axes during realignment of images to the mean). Thus, the sample used in the statistical analyses included 22 participants (11 females, aged 19–42, mean age 25, SD = 6). Participants were recruited through the MRC Cognition and Brain Sciences Unit's research participation system. All participants had normal or corrected-to-normal vision. None had history of head injury, a diagnosis of any neurological or psychiatric condition, or was currently on medication affecting the central nervous system. The study was approved by the Cam-