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Neural activity to threat in ventromedial prefrontal cortex correlates with individual differences in anxiety and reward processing

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ABSTRACT

Emotion studies show that ventromedial prefrontal cortex (vmPFC) plays a critical role in negative affect evaluation. Here we investigated two questions: Does the neural sensitivity to threat of bodily harm in vmPFC alter as anxiety levels increase? If the neural sensitivity to threat in vmPFC reflects a kind of general emotional processing, does it predict reward processing? To address these questions, we first recorded participants' selfreported anxiety. In an investigation of neural responses in vmPFC (Session 1), we measured brain activity (fMRI) associated with the anticipation of threat, using a sphere based ROI approach. In a behavioral experiment (Session 2), participants' reward processing efficiency was evaluated when they performed a visual discrimination task in which they had the opportunity to earn cash rewards. We found that across participants, there were tightly coupled associations between signal changes in the vmPFC and self-reported state anxiety. Specifically, participants who showed more activation in vmPFC to threat also exhibited greater behavioral efficiency in reward processing. Path analysis revealed a closely interconnected network of vmPFC (cortical) and VS (ventral striatum, subcortical) which predicted reward processing. Therefore, in addition to negative affect evaluation, neural sensitivity in vmPFC correlated with both anxiety and reward-related metrics. These results support an emerging model in which the vmPFC functions to defend the organism from acute stress and facilitate reward processes.

1. Introduction

At a basic level, behavioral options are linked to either positive or negative outcomes. Such that, behavior could be understood in terms of two general classes of motivation processes. In line with this, Knorkski (1967) proposed that exteroceptive reflexes are either protective (e.g., withdraw from, or rejection of noxious agents) or preservative (e.g., ingestion, copulation, nurtures of progeny). This speculation has further been developed into two opponent aversive and attractive motivational systems (Dickinson and Dearing, 1979; Hu, 2016; Lang, 2010). Threat and reward are described as something that an animal will work to avoid or achieve, respectively, and both are the two essential cases that determine one's adaptive actions. Although the existence of an interrelationship between negative and positive processes (e.g., threat and reward) is intuitively appealing, few empirical data exist to characterize the corresponding behavioral and brain mechanism.

So far, negative and positive processes (e.g., threat and reward)

have been investigated largely in an independent manner. It is reported that negative emotion generally impairs performance across a diverse set of cognitive tasks, including visual processing and execution function (Dolcos and McCarthy, 2006; Erthal et al., 2005; Hartikainen et al., 2000, but see Hu et al., 2012; Hu et al., 2015), while monetary reward facilitates perceptual processing and boosts cognitive performance (Anderson et al., 2011; Engelmann and Pessoa, 2007; Hu, 2018; Hu et al., 2018a, 2018b; Shen and Chun, 2011). Scientists have started to explore the interrelationship between threat and reward. For instance, it has been suggested that under conditions (e.g., tonic aversive events), negative emotion recruits reward processing to help direct behavior toward homeostatic equilibrium (Grossberg, 1984; Solomon and Corbit, 1974), which is in line with emotion regulation in nature (Eisenberger et al., 2003; Motzkin et al., 2015; Phelps et al., 2004). Further, Kim et al. (2006) showed that successful avoiding an aversive outcome in fact recruited the same neural circuitry as that elicited by a reward itself. As such, the authors suggested that avoiding an aversive outcome

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is in itself a reward (Kim et al., 2006). Consistently, it has been demonstrated that threat and reward simultaneously improved cognitive performance (Hu et al., 2013), and threat and reward increased the signal communication between cortical and subcortical regions (Kinnison et al., 2012). It has now been documented that some brain regions recruited in the experience of stress and threat were also involved in the experience of reward, including ventral medial prefrontal cortex (vmPFC), dorsal medial prefrontal cortex (dmPFC), amygdala, anterior cingulate cortex (ACC), and thalamus (Aarts et al., 2011; Chandrasekhar et al., 2008; Choi et al., 2012; Mobbs et al., 2010; Padmala and Pessoa, 2011; Savine and Braver, 2010). In the present study, we explored whether vmPFC involvement in negative processing predicts positive processing.

As a core region of the emotional brain, vmPFC (sometimes, also referred to as medial orbitofrontal cortex) has been extensively implicated in both negative affect and reward process (Hiser and Koenigs, 2017; Manohar and Husain, 2016; Myers-Schulz and Koenigs, 2012). It has been reported that vmPFC plays a special role in linking emotional appraisals with automatic responses (Damasio et al., 1996). For instance, vmPFC lesion patients showed an abnormally emotional event processing, and exhibited an inability to activate somatic states at the most basic level (Damasio et al., 1990). A PET study showed that resting regional cerebral blood flow within vmPFC positively correlated with individuals' negative affect ratings (Zald et al., 2002). Consistently, it was reported that vmPFC activation coupled with the expression of fear learning (Phelps et al., 2004). Yet, a recent meta-analysis of fMRI studies indicated that vmPFC was deactivated during fear conditioning (Fullana et al., 2016). On the other hand, fMRI studies have linked vmPFC activity with reward processing, and a representation of value in a wide variety of decision-making paradigms (Levy and Glimcher, 2012; Liu et al., 2011). In line with this, patients with vmPFC damage showed a severe defect in value-based decision making tasks (Barrash et al., 2000; Eslinger and Damasio, 1985). Although there is converging evidence that vmPFC plays an important role in either negative or positive process, there is less understanding of the vmPFC as a potential coordinator of adaptive behaviors, such as threat and reward processing. Here we investigate two questions: Does the neural sensitivity to threat of bodily harm in vmPFC alter as anxiety levels increase? If the neural sensitivity to threat in vmPFC reflects a kind of general emotional processing (e.g., arousal and salience), does it predict reward processing (Eysenck and Calvo, 1992; Eysenck et al., 2007)?

To begin to test our formulation empirically, we designed a set of experiments aimed at effectively capturing the relations between threat, reward and individual differences. Anxiety was considered as it has been shown that brain activity in vmPFC correlates with individual differences in ratings of negative affect (Zald et al., 2002). Importantly, it is thought that individual difference in anxiety influences the recruitment of vmPFC in response to threat-related distraction, and one prominent perspective highlights the role of vmPFC as a crucial neural mechanism that may be defective in certain mood and anxiety disorders (Myers-Schulz and Koenigs, 2012). vmPFC activation was assessed by having participants anticipate a mild electrical shock to the fingers of one hand, while undergo functional magnetic resonance imaging (fMRI). The central goal of the present study was to examine the mechanism of threat processing in the brain, and for the first time, whether the neural sensitivity of vmPFC to anticipated threat predicts reward processing efficiency (Eysenck and Calvo, 1992; Eysenck et al., 2007). Current literature demonstrated that rostral anterior cingulate cortex (rACC) is involved in emotional processing (Bush et al., 2000; Eisenberger and Lieberman, 2004) and, in particular, emotion monitoring (Eisenberger et al., 2003; Goldin et al., 2008; Sawamoto et al., 2000), while ventral striatum (VS) exhibited strong functional connectivity with vmPFC during reward processing (Cauda et al., 2011; LeDoux, 2003; Quirk et al., 2003; Rudebeck et al., 2013). Accordingly, these two important regions were considered in the analysis, as well.

2. Methods and procedure

Parts of the data, not including the analysis described here, have been published in our previous report (Hu et al., 2013). Thirty-one undergraduate and graduate students were recruited from the University of Maryland, College Park (age 17–34; 19 males). All participants had self-reported normal or corrected-to-normal vision and intact color vision and all were naïve to the purpose of the study. All individuals were screened for psychiatric disorders and excluded on meeting criteria for any major psychiatric diagnoses. Five subjects were excluded from further analysis due to initially pilot settings. The study was approved by the university's Institutional Review Board, and all participants provided written informed consent before participating in the study. All were paid immediately after the experiment.

The present study consisted of three parts: scale measures, fMRI scanning, and a behavioral experiment. They were separate, and scale scores were recorded at the start of the study. Then we followed it with two sessions: Session 1 (fMRI study), and then Session 2 (behavioral study). Between each session, there was a short break. All three were completed on the same day.

2.1. Anxiety scale

To achieve a more comprehensive understanding of the relationship between negative and positive processes, we deliberately introduced a self-report anxiety measurement in the present study. All participants completed the State-Trait Anxiety Inventory (STAI) at the beginning of the study (Spielberger et al., 1970). The State-Trait Anxiety Inventory (STAI) is reported to be reliable and valid and has been used extensively in research and clinical practice. Trait anxiety was measured using the sub- Trait Inventory (20 items), while state anxiety was assessed using the sub- State Inventory (also 20 items).

2.2. Session 1: Threat processing

This session was to investigate the mechanism of the threat processing in the brain, with a focus on the neural sensitivity to threat in vmPFC. We scanned participants using fMRI while they passively view colored squares (no response was required). The general method was introduced in our previous report (Hu et al., 2013). During the threat conditioning (Fig. 1A), each trial started with a fixation display (1 s) and was followed by a colored (yellow or green, Fig. 1B) square (0.8 s). The trial finally ended with a blank display (jittered 2-6 s, mean: 3 s). Before the start of the session, participants were explicitly informed that they would possibly receive a mild electric shock when one of the colored squares appeared (e.g., yellow [CS+] and green [CS-]; counterbalanced across participants), but the probability (25%) was not informed to the participants. They were told that the mild electrical shock would cause pain but would not cause injury. The US was 0.5 s in duration and was delivered after 0.3 s from the onset of the CS+ stimulus and hence co-terminated with it. The threat conditioning run included 40 trials (half neutral and half threat). It started and ended with a 20 s blank display to provide an adequate baseline signal for the fMRI analysis. Shocks were administered with an electrical stimulator (Coulbourn Instruments, PA, USA) on the fourth ("ring") and fifth ("pinky") fingers of the non-dominant (left in all cases) hand.

MR data were collected using a 3 T Siemens TRIO scanner (Siemens Medical Systems, Erlangen, Germany) with a 32-channel head coil (without parallel imaging). The scanning session began with a high-resolution MPRAGE anatomical scan (TR = 1900 ms, TE = 2.32 ms, TI = 900 ms, 0.9 mm isotropic voxels). Subsequent functional run, 96 EPI volumes, was acquired with a TR of 2500 and TE of 25 ms. Each volume consisted of 44 oblique slices with a thickness of 3 mm and an in-plane resolution of 3×3 mm (192 mm field of view).

If vmPFC plays a special role in the integration of emotional and cognitive processes (Simpson et al., 2001), it should be relevant to

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