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Research Article

A Pontine Region is a Neural Correlate of the Human Affective Processing Network

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ABSTRACT

The in vivo neural activity of the pons during the perception of affective stimuli has not been studied despite the strong implications of its role in affective processing. To examine the activity of the pons during the viewing of affective stimuli, and to verify its functional and structural connectivity with other affective neural correlates, a multimodal magnetic resonance imaging methodology was employed in this study. We observed the in vivo activity of the pons when viewing affective stimuli. Furthermore, small-world connectivity indicated that the functional connectivity (FC) between the pons and the cortico-limbic affective regions was meaningful, with the coefficient λ being positively associated with self-reported emotional reactivity. The FC between the pons and the cortico-limbic-striatal areas was related to self-reported negative affect. Corroborating this finding was the observation that the tract passing through the pons and the left hippocampus was negatively related to self-reported positive affect and positively correlated with emotional reactivity. Our findings support the framework that the pons works conjunctively with the distributed cortico-limbic-striatal systems in shaping individuals' affective states and reactivity. Our work paves the path for future research on the contribution of the pons to the precipitation and maintenance of affective disorders.

1. Introduction

According to the literature, serotonin plays a crucial role in affective processing (Ren et al., 2013) as well as in regulating the biological rhythms of sleep, mood, and appetite (Monti and Jantos, 2008, Monti, 2011). Affective disorders induced by brain stem damage may be related to an altered neurotransmitter balance (Hurley et al., 2010). According to recent meta-analytic reviews, the serotonin transporter promoter variant has been found to be implicated in depression (Karg et al., 2011; Sharpley et al., 2014; Artigas, 2015). Additionally, serotonin transporter binding potential in the vicinity of the pons was reduced in people with bipolar disorders (Cannon et al., 2007). The basis pontis, however, is a crucial correlate in patients with pathological laughing and crying (PLC) episodes (Lee et al., 2003; Arif et al., 2005; Parvizi et al., 2009). The above pieces of clinical evidence indicate that the pons could be an important affective processing node. However, the current literature on the human affective processing network focuses largely on cortico-limbic correlates (Shah et al., 2012) and their inter-connectivity. These correlates include the limbic system, orbital, medial and lateral prefrontal cortex (PFC) (Price and Drevets, 2010). In vivo activity of the pons during affective perception has never been reported.

This study fills an important gap in the literature on the activity of the pons and its involvement in the perception of affective stimuli. To provide independent yet complementary information (Touroutoglou et al., 2014) on the role of the pons in affective processing, a multimodal approach was employed in this study to confirm the functional and structural connectivity between the pons and other correlates. We hypothesized that the viewing of affective stimuli would be associated

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with significant blood-oxygen-level-dependent (BOLD) signals at the pons because of the role of serotonergic neurons in affective processing. The observed significant activation of the pons was followed by a series of structural and functional connectivity studies. First, we verified the meaning of the connectivity between the seed region in the pons (the region of the pons showing significant activation while viewing affective stimuli) and the cortico-limbic affective processing network using the small-world (SW) connectivity method for data collected from the diffusion tensor imaging (DTI) scanning paradigm. The small-world network is characterized by regions highly connected to adjacent regions combined with fewer steps of information transfer from one region to another. This optimal wiring enables rapid and efficient information transfer with minimized connectivity cost. After confirming the significance of the SW connectivity, we investigated the functional and structural connectivity of the seed region and other cortical limbic regions using resting-state functional imaging data and the tractography built upon by DTI data. Given the lack of any previous literature on the connectivity of the pons and other affective processing correlates, we tested the null hypothesis of no significant functional and structural connectivity between the pons and the cortico-limbic affective correlates. Last but not least, to understand the meaningful role played by the activated pons region in affective processing, we examined whether the structural and functional connectivity between the pons and the other affective correlates was positively correlated with the following: 1. the affect states, measured by the Chinese Affect Scale (CAS) (Hamid and Cheng, 1996) and 2. emotional reactivity, measured by the Emotional Reactivity Scale (ERS) (Nock et al., 2008). To control for reward sensitivity to facial emotions, we used the international affective stimuli instead (Lang et al., 2008).

2. Materials and Methods

2.1. Participants

This study was approved by the Human Research Ethics Committee for Non-Clinical Faculties of The University of Hong Kong. We recruited 40 female Chinese participants for this study. Only women were invited to participate in this study to control for any gender-related confounding variance. All of them had finished at least a high school education (over 12 years of education). They all had normal or corrected-to-normal vision. They did not suffer from amblyopia (Freiburg Vision Test) (Bach, 2007) or color blindness/weakness (Yu et al., 2013). They had average intellectual abilities as estimated by the Test of Nonverbal Intelligence, 3rd edition (TONI-3) (Brown et al., 1997). They all presented with a normal mood as measured by the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) (See STable 1 in the Supplementary document for demographic information on these participants.) None of them had any history of traumatic brain injury/medical conditions/psychiatric disorders or was on any medications that could affect brain activity and functioning. All participants gave written informed consent for a protocol approved by the ethics committee of The University of Hong Kong. There was no significant mood change as measured by the affect grid (Russell et al., 1989) between pre- and post-scanning.

2.2. Task and Procedure

2.2.1. Stimuli

The experimental stimuli were 96 pictures involving human images selected from the International Affective Picture System (IAPS) (Lang et al., 2008). Among these 96 pictures, there were equal numbers of positive, neutral and negative pictures (32 pictures each). Their valence and arousal ratings (both original ratings and participants' ratings) are listed in STable 2 in the Supplementary materials. Analyses of the participant ratings showed that the valence of positive pictures was higher than the valence of neutral pictures ($t(39) = 17.737$, $p < 0.001$), and the valence of neutral pictures was higher than the valence of negative pictures ($t(39) = 17.063$, $p < 0.001$). Furthermore, the arousal of both positive ($t(39) = 11.092$, $p < 0.001$) and negative ($t(39) = 6.923$, $p < 0.001$) pictures was higher than for neutral pictures, while there was no significant difference in arousal between positive and negative pictures ($t(39) = 1.736$, $p = 0.086$).

The control stimuli were the mask images generated from the 96 IAPS pictures. A Matlab (The Mathworks, Inc.) program script was employed to scramble the pixels in these 96 pictures. These control stimuli matched the experimental stimuli in terms of illumination and hue.

To confirm if the participants were actually viewing the affective stimuli during scanning, a recognition procedure was performed after scanning. Each participant was required to identify the 96 target affective pictures among 96 foils (i.e., new IAPS pictures that also consist of 32 positive, 32 neutral and 32 negative pictures) (See STable 3 in the Supplementary document for percentage accuracy of classifying the IAPS pictures.).

2.2.2. Emotion-Processing Task (EPT)

This task was modified from the task paradigm developed by Lee et al. (2012). Each participant performed 2 runs of the task (for the task paradigm, see Fig. 1). Each run consisted of 6 meaningful picture blocks (i.e., positive, negative and neutral blocks) and 6 mask image blocks (i.e., masked positive, negative and neutral blocks). Each meaningful picture block consisted of eight trials of picture presentation (3.5 s) of the same type of emotion followed by a blank screen (0.25 s). Within each run, the mask image blocks were similar to the meaningful picture blocks except that the pictures presented were scrambled masks of the corresponding meaningful pictures. The mask image blocks were presented interleaved with the meaningful picture blocks. A meaningful picture block was separated from its mask image block in each run. This separation was designed to reduce the affective reactions in a block elicited by perceiving the similar brightness and colors presented in close proximity. The order of blocks was randomized for each participant and was balanced across participants. Participants were asked to passively view the pictures without any overt responses. A rest (approximately 30 s) was given between runs. Cortical activation while performing on the EPT was largely consistent with previous findings, confirming the validity of the paradigm (see STable 4 and STable 5 in the Supplementary materials).

2.2.3. Procedure

Before entering the scanner, participants were required to complete questionnaires regarding their demographic information and affective status. They were then administered 10 trials of the EPT task as practice. The stimuli used in these practice trials were different from the stimuli used in the experimental task. During resting-state scanning, the participants were instructed to lie quietly and keep their eyes open without falling asleep. During task-based scanning, the visual stimuli presentations were delivered by functional magnetic resonance imaging visual stimulus system (SA-9900, Shenzhen Sinorad Medical Electronics, http://www.sinorad.com). The participant viewed the visual stimuli from a mirror mounted on the head coil. To confirm that the participants were paying attention to the affective stimuli during scanning, they were administered a recognition trial (i.e., the old-new classification task), where the 96 experimental stimuli were mixed with 96 foils immediately post-scanning. The participants had to differentiate the targets from the foils. Afterwards, they were asked to rate the valence and arousal of the experimental and control stimuli on a 75-point scale (for valence rating: 1 = very negative, 75 = very positive; for arousal rating: 1 = totally calm, 75 = extremely excited). The affect grid was administered again to confirm that the participants' pleasure and arousal states had not changed between pre- and post-scanning.