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Functional connectivity of the frontoparietal network predicts cognitive modulation of pain

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ABSTRACT

The experience of pain can be significantly influenced by expectancy (predictive cues). This ability to modulate pain has the potential to affect therapeutic analgesia substantially and constitutes a foundation for nonpharmacological pain relief. In this study, we investigated (1) brain regions involved in visual cue modulation of pain during anticipation of pain, pain administration, and pain rating; and (2) the association between pretest resting state functional connectivity and the magnitude of cue effects on pain ratings. We found that after cue conditioning, visual cues can significantly modulate subjective pain ratings. Functional magnetic resonance imaging results suggested that brain regions pertaining to the frontoparietal network (prefrontal and parietal cortex) and a pain/emotion modulatory region (rostral anterior cingulate cortex) are involved in cue modulation during both pain anticipation and administration stage. Most interestingly, we found that pretest resting state functional connectivity between the frontoparietal network (as identified by independent component analysis) and the rostral anterior cingulate cortex/medial prefrontal cortex was positively associated with cue effects on pain rating changes. We believe that these findings will shed new light on our understanding of variable cue/expectancy effects across individuals and how the intrinsic connectivity of the brain may influence expectancy-induced modulation of pain.

1. Introduction

The experience of pain can be significantly influenced by our expectations [1,23,30,42]. Previous studies have demonstrated that positive expectancy (anticipating low-intensity pain) can significantly reduce pain, whereas negative expectancy (anticipating high-intensity pain) can significantly increase the painful experience. Paired with expectancy-induced changes in subjective pain ratings, there are widespread changes in the brain during the anticipation and experience of painful stimuli. Nevertheless, the capacity to modulate pain in response to expectancy varies substantially across individuals [54,61], which may reflect a crucial difference in the ability to recruit endogenous analgesia and protect our bodies from long-term exposure to pain. Despite the large impact of expectancy cues on pain modulation, the underlying mechanism remains unclear.

Previous investigators have hypothesized that 2 specific brain networks may be crucial for the modulatory effect of expectancy cues [1]: (1) the frontoparietal control network involved in attention and cognitive control [11] and (2) the limbic network involved in emotion modulation [38]. However, the role of these 2 networks for cognitive modulation of pain, and its relation to the individual variability of cue effects, is still unknown.

In recent years, the spontaneous low-frequency fluctuations in brain activity observed during rest have drawn the attention of neuroimaging investigators [6,19,44]. Investigators believe that the slow-frequency fluctuations may provide information about the intrinsic functional organization of the brain. Accumulating evidence suggests that resting state functional connectivity may be relevant for the understanding of human cognition and behavior [29,51,56,57,59]. For example, it has been shown that resting state scans can be used to predict inhibition responses [51], reading competency [29], and memory performance [56,57] across individuals. These results indicate that functional synchrony within a specific brain network during rest may influence subsequent behavioral responses that engage regions within that same network.

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Thus, using a modified cue model [1,23,30,40,47] in a relatively large cohort of subjects (n = 46), we combined task-related functional magnetic resonance imaging (fMRI) data with pretest resting state fMRI data to investigate (1) the brain networks involved in cue modulation of pain and (2) how pretest intrinsic resting state functional connectivity may influence subsequent pain modulation. Specifically, we first investigated the brain activations during task-related cue modulation using a paradigm including periods of pain anticipation, pain application, and subjective pain ratings. Then, we explored the association between the pretest resting state functional connectivity and the amplitude of the cue effects, using a data-driven data analysis: independent component analysis (ICA).

Based on previous ICA analyses, 3 networks were identified as networks of interest in the present study. These networks, the sensory motor, executive control, and right frontoparietal control networks [2,7,15,18,49], have reliably been observed in previous ICA studies. These 3 particular networks were chosen because of their association with perception–somesthesis–pain [49], and in particular, the frontoparietal network was chosen because it has been implicated in cue modulation effects [1].

2. Experimental procedures

2.1. Subjects

Forty-eight right-handed healthy volunteers (29 female), ages 21 to 33 years (mean 26.4 ± 3.6 SD) participated in the study. The Institutional Review Board at Massachusetts General Hospital approved the study, and all subjects gave written informed consent.

2.2. Thermal pain stimulation

Thermal pain stimuli were delivered to the skin of the right volar forearm using a TSA-2001 Thermal Sensory Analyzer with a 3 × 3 cm probe (Medoc Advanced Medical Systems, RimatYishai, Israel). All stimuli were initiated from a baseline temperature of 32°C and increased to a target temperature. Each stimulus was presented for 12 seconds, including 2.5 seconds to ramp up to the target temperature and 2.5 seconds to ramp down to baseline. After each stimulus, subjects rated their pain according to the Gracely Sensory scale [20].

2.3. Experimental procedure

At the beginning of the study, subjects were told that the aim of the experiment was to investigate the brain's response to different levels of thermal pain. Subjects were then familiarized with the visual presentation paradigm, including a prestimulus cue, a pain stimulus symbol, and a poststimulus rating scale. In addition, subjects were told that the prestimulus cue (text saying either "HIGH" or "LOW") would indicate the level of the subsequent pain stimulus.

All subjects who participated in the study also participated in an unrelated behavioral study to investigate the acute analgesic effect of different treatments (real and sham acupuncture treatment, and placebo pill).In that study, an ascending series of heat stimuli (starting at 38°C and increasing in increments of 1°C) was applied to both arms in the first session. The baseline temperature for the ascending series (32°C) was systemically increased to target temperatures to obtain subjective pain tolerance levels or to a maximum of 52°C. Temperatures that elicited subjective intensity ratings in the low pain range (approximately 5 on the 0 to 20 Sensory Box scale) and high pain range (approximately 15 on the 0 to 20 Sensory Box scale) were selected for each subject and used in the treatment study as well as the present MRI study. The 2 studies were separated by at least 2 weeks. Thus, at the time of this MRI study on cue effects, subjects were familiar with the pain rating scales and heat pain administration. Immediately before the fMRI scan, a brief pain sensitivity test was performed to further confirm the subjective high and low temperatures applied in this study, and adjustments were made where needed.

During fMRI scanning, after resting state fMRI data collection, 3 different series of pseudorandomized pain sequences were applied on the right distal forearm. Subjects were instructed to focus on a small black fixation cross in the center of the screen in front of them. The first scan was a contextual learning scan; subjects were presented with a prestimulus cue indicating (without deception) whether they would be administered a low or high pain stimulus. The duration of the cue was 2 seconds, and the time before onset of the pain stimulus varied among 4, 6, 8, and 10 seconds. The duration of the pain stimulus was always 12 seconds, and the intensity of the stimulus for this first sequence always corresponded to the prestimulus cue. After a delay of 4, 6, or 8 seconds, the Sensory Box scale was displayed on the screen for 8 seconds, and subjects rated the intensity of their subjective pain by moving a cursor along the scale. The interval between the end of the rating task and onset of the next stimulus cue ranged from 8 to 14 seconds, with an average of 12 seconds (Fig. 1A). In total, this learning sequence included 4 low and 4 high pain stimuli.

The initial contextual learning and conditioning scan was followed by 2 test scans in which the low cue was sometimes followed by the high pain stimulus (HP) (the LC condition), representing a condition in which subjects were expected to report less pain in response to a suggested low stimulus, and sometimes followed by the low pain stimulus. Both test scans included 9 stimuli, where 3 of the stimuli were cued as high pain and 6 were cued as low pain. After all high pain cues, a high pain stimulus was delivered (the HC condition). However, after 3 of the 6 low cues, a high pain stimulus was delivered (the LC condition) instead of a low pain stimulus. The order of stimuli was jittered. All other

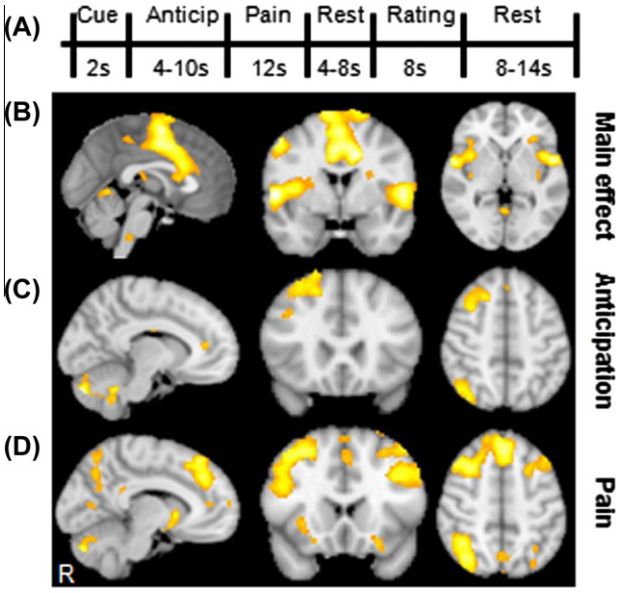

Fig. 1. Experimental paradigm and corresponding bold responses. (A) Each experimental heat pain trial included a cue (indicating either high or low pain), an anticipation period (black crosshair), a painful stimulus (red crosshair), a resting period (black crosshair), a pain rating scale (0 to 20), and an interstimulus interval (black crosshair). (B) The brain networks associated with experience of pain (contrast: high pain [HP] > low pain [LP]) across 3 functional runs. (C) Brain regions involved in the effects of predictive cue modulation during anticipation of pain (low-cue high pain [LC] > high-cue high pain [HC]). (D) Brain regions involved in cue modulation effects during pain administration (LC > HC).