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Original Reports

The Lateral Prefrontal Cortex Mediates the Hyperalgesic Effects of Negative Cognitions in Chronic Pain Patients

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Abstract: Although high levels of negative affect and cognitions have been associated with greater pain sensitivity in chronic pain conditions, the neural mechanisms mediating the hyperalgesic effect of psychological factors in patients with pain disorders are largely unknown. In this cross-sectional study, we hypothesized that 1) catastrophizing modulates brain responses to pain anticipation and 2) anticipatory brain activity mediates the hyperalgesic effect of different levels of catastrophizing in fibromyalgia (FM) patients. Using functional magnetic resonance imaging, we scanned the brains of 31 FM patients exposed to visual cues anticipating the onset of moderately intense deep-tissue pain stimuli. Our results indicated the existence of a negative association between catastrophizing and pain-anticipatory brain activity, including in the right lateral prefrontal cortex. A bootstrapped mediation analysis revealed that pain-anticipatory activity in the lateral prefrontal cortex mediates the association between catastrophizing and pain sensitivity. These findings highlight the role of the lateral prefrontal cortex in the pathophysiology of FM-related hyperalgesia and suggest that deficits in the recruitment of pain-inhibitory brain circuitry during pain-anticipatory periods may play an important contributory role in the association between various degrees of widespread hyperalgesia in FM and levels of catastrophizing, a well-validated measure of negative cognitions and psychological distress.

***Perspective:** This article highlights the presence of alterations in pain-anticipatory brain activity in FM. These findings provide the rationale for the development of psychological or neurofeedback-based techniques aimed at modifying patients' negative affect and cognitions toward pain.*

***Key words:** Fibromyalgia, catastrophizing, negative affect, functional magnetic resonance imaging, psychophysics.*

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Fibromyalgia (FM) is a chronic common disorder characterized by persistent, widespread pain and myofascial tenderness. It is a primary cause of disability and one of the most challenging-to-treat rheumatologic conditions.[41] The diversity of symptoms reported by FM patients is consistent with the view that FM is a pervasive nervous system disorder involving a complex interaction of biopsychosocial mechanisms. Although recent evidence of small-fiber neuropathy suggests that peripheral alterations contribute to the pathophysiology of FM in a subset of patients,[26,45] it is well established that negative cognitive and affective factors play a prominent role in maintaining pain and disability in this and other pain disorders.[6] In fact, FM is characterized by a strong association with psychiatric comorbidities, including anxiety and depression, and has been considered an affective spectrum disorder.[16] Catastrophizing is a pain-specific psychosocial construct composed of cognitive and emotional processes such as helplessness, pessimism, rumination about pain-related symptoms, and magnification of pain complaints. Although catastrophizing positively correlates with general measures of negative affect such as depressive symptoms, anxiety, or neuroticism, it also shows a unique and specific influence on pain-related outcomes.[6] Several brain imaging studies have found that greater catastrophizing in FM patients, compared to healthy controls, was associated with enhanced pain-evoked activation in dorsolateral and medial prefrontal and dorsal anterior cingulate cortices.[12] However, the brain mechanisms mediating the hyperalgesic effect of catastrophizing are unknown.

In addition to catastrophizing and hyperalgesia, FM patients also demonstrate lower brain reactivity to pain-anticipatory cues (as well as to relief-anticipatory cues) than healthy individuals.[21] This observation, which we argued may be in part the result of the alterations in dopaminergic[53,54] and/or GABAergic[10] neurotransmission that have been documented in these patients, adds to a growing literature supporting reduced responsiveness of FM patients to a variety of experimental manipulations.[19,44,54]

The pain experience can be dramatically shaped by anticipatory processes, and the brain state preceding a painful stimulation has been shown to predict responses to experimental,[2,31] as well as clinical, pain.[23] Thus, in the present study, we used functional magnetic resonance imaging (fMRI) and mediation analyses in a cohort of patients with FM and a wide range of catastrophizing scores to test the hypotheses that 1) individual levels of catastrophizing modulate brain responses to pain anticipation in FM and 2) anticipatory brain activity mediates the hyperalgesic effect of higher catastrophizing.

Methods

Subjects

One hundred four FM patients (n = 13 male) were initially screened by phone for probable eligibility to participate in this experiment at the Brigham and Women's Hospital Pain Management Center and Martinos Center for Biomedical Imaging at Massachusetts General Hospital in Boston, Massachusetts. Patients were screened and enrolled over a 16-month period between September 2010 and December 2011. Of the 104 patients initially contacted, 53 (n = 7 male) signed a consent form and were invited for a screening visit; the others were either not interested (n = 18) or ineligible (most commonly due to claustrophobia, being on opioids, or having peripheral neuropathy) (n = 22) or had scheduling conflicts (n = 11). Of the subjects who were invited to the screening visit, 5 were determined to be ineligible and excluded at the behavioral session (for implanted metal, leg edema, or neuropathy) and 4 subsequently dropped out. Of the remaining 44 (n = 6 male) who proceeded to the scan visit, only 31 (n = 4 male) had complete and analyzable data for the purposes of the present study. Thus, 13 subjects did not successfully complete the fMRI scanning noted below because of inability to tolerate pain procedures (n = 5), scanner time constraints (n = 4), and scanner/equipment failure (n = 4).

Average age (mean ± standard deviation) was 44.0 ± 11.9, symptom duration was 12.5 ± 12.2 years, and current clinical pain intensity was 34.3 ± 25.2 (out of 100). For additional details on the patients' clinical and demographic characteristics, please refer to our previous publication.[21] Enrolled patients were diagnosed with FM (as confirmed by physician and medical records) and also met the recently proposed Wolfe et al criteria,[52] which require the presence of widespread pain and endorsement of multiple somatic and cognitive symptoms. Exclusion criteria included younger than age 18 years; history of claustrophobia; neurologic disorders, including peripheral neuropathy; history of significant head injury; serious cardiovascular disease; current use of opioids; implanted medical or metallic objects; and pregnancy. Although these criteria led to a sizable number of excluded subjects following initial screening, the criteria were either necessary (eg, claustrophobia for MRI evaluation) or did not significantly compromise the generalizability of our study sample, as, for example, recent prospective studies and reviews point to a lack of evidence for the effectiveness of long-term opioid therapy in patients with FM, and consequently very few FM patients are on chronic opioids.[29] All participants in the study provided written informed consent in accordance with the hospitals' institutional review boards. This was an exploratory study designed to power a larger clinical trial.

Study Overview

After a training visit, which was used to familiarize subjects with the stimuli and rating procedures, subjects participated in a brain imaging visit on a separate date. At the beginning of the visit, the intensity of stimulation needed to achieve a pain intensity rating of ~50 out of 100 was assessed (for more details, see[21]). During a functional imaging scan run, the subjects' brain activity was investigated using blood oxygen level–dependent fMRI while they underwent 3 separate tonic (ie, 46–74 sec)