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Do patients with fibromyalgia show abnormal neural responses to the observation of pain in others?

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ABSTRACT

Chronic widespread pain is a hallmark of fibromyalgia (FM). Previous neuroimaging studies have reported that the pain neuro-matrix in patients with FM showed augmented activation in response to actual pain. However, the effect of observing pain in others among patients with FM remains poorly understood. Both healthy female control subjects ($n = 24$) and female patients with FM ($n = 23$) underwent functional magnetic resonance imaging while observing a series of color pictures depicting others' hands and feet being injured, and a matched set of control pictures that did not show any painful events. Compared with healthy subjects, patients with FM showed a smaller neural response to pain-related versus neutral stimuli in several neural regions, including the thalamus, anterior cingulate cortex, dorsolateral prefrontal cortex, pre- and post-central gyrus, and supplementary motor area. In contrast to augmented pain processing in response to actual experimental pain, patients with FM did not show an enhanced pain response but generally showed lesser activation in cortical regions known to play a role in processing of pain. These hemodynamic alterations observed in patients with FM suggest that patients with chronic pain may empathize less with others in pain, possibly in order to lessen arousal and aversive self-oriented emotions.

1. Introduction

Among various chronic pain syndromes, fibromyalgia (FM) is characterized by widespread musculoskeletal pain accompanied by fatigue, waking unrefreshed, and cognitive symptoms (Wolfe et al., 2010). Functional neuroimaging studies have begun to provide insight into the central mechanisms associated with abnormal perception of pain in FM. Two early functional magnetic resonance imaging (fMRI) studies using painful blunt pressure suggested augmented pain processing in patients with FM, compared to healthy participants. When pressure was applied, greater activation was observed in several pain-related regions of the brain, including the somatosensory cortex, inferior parietal lobule, superior temporal gyrus, and insula, in patients with FM (Giesecke et al., 2004; Gracely et al., 2002). This augmented central pain processing has consistently been observed in different pain modalities and experimental paradigms (Burgmer et al., 2009; Cook et al., 2004). Further studies have revealed that pain-related brain activity is modulated by factors associated with pain modulation, such as hypnosis (Derbyshire et al., 2009), fear of pain, or pain catastrophizing (Gracely et al., 2004). For example, Gracely et al. (2004) reported an

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association between pain catastrophizing and activation of the dorsolateral prefrontal cortex, dorsal anterior cingulate cortex (ACC), medial prefrontal cortex, and motor areas.

However, to the best of our knowledge, because previous studies of patients with FM have exclusively investigated the effect of actual pain, the effect of observing others in pain remains poorly understood. In addition to the simple perception of another person's pain, understanding the feelings, thoughts, and behavioral reactions of other conspecifics has a survival value in terms of protecting the observer or delivering care to others. In this context, the observation of others in pain is also referred to as empathy for pain (Benuzzi et al., 2009; Botvinick et al., 2005; Jackson et al., 2005; Singer et al., 2004). Two recent meta-analyses confirmed that the sight of pain activates regions of the brain associated with the processing of one's own pain, including the thalamus, insula, medial/anterior cingulate, and somatosensory cortices (Keysers et al., 2010; Lamm et al., 2011). Further studies have revealed that empathy for pain in others also modulates components of brain activity generated in the primary (SI) and secondary (SII) somatosensory regions (Akitsuki and Decety, 2009; Cheng et al., 2007; Gu and Han, 2007; Jackson et al., 2006). Notably, vicariously instigated activation in the pain matrix is not necessarily specific to the emotional experience of pain but may be related to other processes, such as negative stimulus evaluation, attention to noxious stimuli, somatic monitoring, and selection of appropriate skeletomuscular defensive movements (Decety, 2010; Yamada and Decety, 2009).

Based on the aforementioned fMRI studies of FM, we hypothesized that the overall pattern of regional brain activity associated with observation of pictures depicting painful events would be similar to that associated with the experience of actual somatic pain in patients with FM. A previous study reported that healthy subjects showed increased activity in brain regions involved in pain processing when observing painful events (Ogino et al., 2007). However, we also hypothesized that patients with FM would show different patterns of brain activity in the ACC during observation of pictures depicting painful events. The ACC has been implicated in affective motor responses to observed pain (Morrison et al., 2007) and anticipation of pain (Porro et al., 2003). In effect, in studies of FM using pain modulation paradigms such as hypnosis, the ACC is the most commonly reported region displaying abnormal neural activity (Derbyshire et al., 2009; Wik et al., 1999) and catastrophizing (Gracely et al., 2004).

2. Subjects and methods

2.1. Participants

Twenty three right-handed female participants with fibromyalgia (38.0 ± 7.3 years of age) were recruited from the rheumatology clinics of four university hospitals and one general hospital. All patients had undergone examination by experienced rheumatologists and met the diagnostic criteria for FM as defined by the American College of Rheumatology (Wolfe et al., 1990). To exclude the effects of the menstrual cycle on cognitive functions, all patients completed their tests between four days following the cessation of menstrual flow and seven days prior to the onset of flow. All patients were on stable doses of medication and were instructed not to take any medication on the test day.

Twenty four right-handed, healthy female participants (37.3 ± 8.1 years of age) were recruited for this study using internet advertisements and via patient social networks. None of the control subjects took psychoactive medication, and none had a current psychiatric diagnosis. Exclusion criteria for all subjects included: (a) a history of head injury or other neurological condition, (b) a history of a medical condition associated with cognitive dysfunction, and (c) a history of substance abuse. The study protocol was approved by the Institutional Review Board at Kyungpook National University Hospital (No. 74005-1703). After receiving a detailed explanation of the study design and potential risks, all participants agreed to participate in our fMRI study and provided written informed consent.

2.2. Clinical measures

The Korean Fibromyalgia Impact Questionnaire (KFIQ) (Bae and Lee, 2004), a self-report measure comprising 10 subscales and including 20 items originally developed for FM, was used for measurement of the *Current severity of fibromyalgia* (Burckhardt et al., 1991). Tender points were surveyed using a single manual application of pressure measuring 4 kg/cm^2 at 18 specific tender point sites; the number of points reported by the subject as tender was used as a proxy for severity. The Korean version of the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI), each consisting of 21 self-report items scored from 0 to 63, was used for measurement of the *Current level of depression and anxiety* (Lee and Song, 1991; Yook and Kim, 1997). The Korean version of the Brief Fatigue Inventory (BFI-K) was used for measurement of the *Current levels of fatigue* (Yun et al., 2005, 2008).

2.3. Measurement of pain threshold according to thumbnail pressure

Prior to performance of the fMRI experiment, pain threshold was assessed using a method described previously by Geisser et al., 2008. Pain stimuli were applied to the left thumbnail for five minutes using a hard rubber probe measuring 1 cm^2. The initial pressure applied through the rubber probe was 0.5 kg/cm^2, which was then increased gradually by 0.5 kg/cm^2 at 30 s intervals to either the maximal tolerable level or 4.5 kg/cm^2. Levels of pain stimulation ranged from level 1 (0.5 kg/cm^2) to level 9 (4.5 kg/cm^2). At each level, subjects were instructed to choose the word that best described the severity of applied pain from the Verbal–Visual Analogue Scale (VAS), which was adapted from the Gracely Box SL pain scale (Gracely and Kwilosz, 1988). The first time they answered "painful," the given level of pain stimulation was regarded as their pain threshold.

2.4. Stimuli and scanning method

A total of 96 color pictures depicting others' hands and feet being injured, and a matched set of 96 ontrol pictures that did not show any painful events, which had been developed and validated by Jackson et al. (2005, 2006) were used in this paradigm (Fig. 1). The paradigm design of this study was described in a previous study (Moriguchi et al., 2007). Participants took part in one fMRI session. The session consisted of 26 blocks. Participants were instructed to view and evaluate pictures showing right hands or feet in painful situations as a task condition (12 blocks) and right hands or feet in a neutral situation as a control condition (12 blocks). Baseline trials showed a fixed cross at the middle and end of the session (2 blocks). Each task or control block consisted of eight trials showing eight pain-related or neutral pictures. Pain-related or neutral pictures were randomly assigned according to the painfulness (pictures showing low, medium, and high levels of pain; only for pain-related pictures) and the body part (hands or feet). In each trial, each picture was shown for 2.0 s, followed for 2.0 s by a modified version of the Wong-Baker FACES Pain Rating Scale, consisting of four faces (1, 2, 3, and 4 for no, mild, moderate, and severe pain) (Wong et al., 2001). The subjects were asked how painful the situation was for the depicted person. Selected scores from 1 to 4