NeuroImage: Clinical 2 (2013) 782–789

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Distinctive neural responses to pain stimuli during induced sadness in patients with somatoform pain disorder: An fMRI study

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ARTICLE INFO

Article history:
Received 5 March 2013
Received in revised form 25 May 2013
Accepted 3 June 2013
Available online 12 June 2013

Keywords:
Pain
Sadness
Somatoform pain disorder
fMRI
Insula
Parahippocampus

ABSTRACT

Pain is a multidimensional phenomenon. Patients with somatoform pain disorder suffer from long-lasting pain, with the pathology being closely associated with cognitive–emotional components. Differences between these patients and controls in cerebral responses to pain stimuli have been reported. However, to our knowledge, no studies of somatoform pain disorder have evaluated altered pain-related brain activation as modulated by emotional dysregulation. We examined the distinct neural mechanism that is engaged in response to two different pain intensities in a sad emotional condition, performing functional magnetic resonance imaging (fMRI) on a group of 11 somatoform pain patients and an age-matched control group. Our results showed that the ratio for low-pain intensity ratings between the sad and neutral conditions in patients was higher than in controls. They also showed significant increased activation in the anterior/posterior insula in the low pain sadness condition. Furthermore, there was specific functional connectivity between the anterior insula and the parahippocampus in patients during presentation of low-pain stimuli in the sad context. These findings suggest that a negative emotional context such as sadness contributes to dysfunctional pain processing in somatoform pain disorder. Greater sensitivity to low levels of pain in an emotional context of sadness might be an important aspect of the psychopathology of somatoform pain disorder.

1. Introduction

Pain has many physiological as well as psychological aspects. Clinical and experimental studies have elucidated the sensory-discriminative and the emotional–affective dimensions of pain (Price, 2002), and have revealed that both dimensions are influenced by various emotional elements aroused by psychological stimuli, including such states as fear, anxiety, and sadness. For example, greater subjective pain intensities have been reported during a state of sadness (Lehoux and Abbott, 2011; Loggia et al., 2008). Various studies have explored brain mechanisms underlying emotional modulation of pain in healthy subjects (Apkarian et al., 2005; Berna et al., 2010; Peyron et al., 2000). We have used functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) to show that sadness can enhance subjective pain perception and pain-related brain activity, including that of the anterior cingulate cortex (ACC), during pain processing in healthy volunteers (Yoshino et al., 2010; Yoshino et al., 2012).

Somatoform pain disorder is defined as the occurrence of one or more physical complaints for which appropriate medical evaluation reveals no explanatory physical pathology or pathophysiologic mechanism, or when such a pathology is present, the physical complaints or resulting impairment are grossly in excess of what would be expected from the physical findings, according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (APA, 1994). This disorder diminishes quality of life and is associated with increased depression and anxiety (Williams et al., 2012). Various studies have examined the mechanisms underlying chronic pain states from the brain structural, neuroplastic, neurochemical, electrophysiological, hormonal, and cognitive–emotional abnormality viewpoints (Apkarian et al., 2005; de Greck et al., 2011; Fayed et al., 2012; May, 2008; McEwen and Kalia, 2010; Noll-Hussong et al., 2013; Otti et al., 2013; Seifert and Maihöfner, 2011). fMRI studies of somatoform pain disorder patients report differences between patients and controls in cerebral responses to pain stimuli (Gündel et al., 2008; Stoeter et al., 2007). For example, Gündel et al. (2008) investigated cerebral processing of noxious heat stimuli, and found pain-related hypoactivation of the ventromedial prefrontal/orbitofrontal cortex, along with hyperactivation of the parahippocampus, amygdala and anterior insula in the patient group. Stoeter et al. (2007) investigated

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2213-1582
http://dx.doi.org/10.1016/j.nicl.2013.06.001

cerebral activation induced by pin prick pain stimuli, and found greater activation of brain regions such as the thalamus, anterior insula, hippocampus, and prefrontal cortex in the patient group.

Emotion plays an important modulatory role in pain perception of somatoform pain disorder patients (Dimsdale and Dantzer, 2007), and it is well established that negative emotions increase pain sensitivity in patients with chronic pain disorders as compared to controls (Burns, 2006; Zautra et al., 2005). However, to our knowledge, there are no other fMRI studies on negative emotion-induced brain activity changes in response to pain stimuli in somatoform pain disorder. Pain sensitivity in such patients is significantly affected by negative emotion (Burns, 2006; Zautra et al., 2005), and elucidating the mechanisms underlying this relationship is of both theoretical and clinical importance. Our previous studies examined sadness in this context (Yoshino et al., 2010, 2012). Sadness is one of the basic human emotions and it is generally accepted that sadness occurs in response to an aversive experience (Ellsworth and Smith, 1988).

We used fMRI to investigate how sadness affects subjective pain and associated brain mechanisms in patients with somatoform pain disorder, who responded to both moderate and low pain intensities. We hypothesized that both subjective pain intensities and pain-related brain activations (as modulated by sadness) would be greater in patients with somatoform pain disorder as compared to healthy subjects. Considering the relationship between somatoform pain disorder and cognitive–emotional abnormalities, the expected altered brain processing should involve mainly the brain structures mediating the emotional–affective dimensions of pain, including the ACC, insula, amygdala, and hippocampus.

2. Methods

2.1. Participants

The participants were eleven patients with somatoform pain disorders (6 women, mean age = 40.9 ± 6.5 years), diagnosed according to the DSM-IV criteria, and eleven gender- and age-matched control subjects (6 women, mean age = 40.6 ± 6.1 years). All participants were right-handed Japanese. Patients were recruited from outpatient sources at the Hiroshima University Hospital. The Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1992) was used to confirm participants' diagnostic status. Any analgesic that would be expected to alter pain perception was discontinued 24 h prior to fMRI scanning. Control participants were recruited from non-clinical populations and were matched to patients according to age and gender. The control participants endorsed no chronic pain problems and had no history of psychiatric disorders. All participants gave their written informed consent before participation, according to a protocol approved by the ethics committee of Hiroshima University.

2.2. Clinical assessments

2.2.1. Pain characteristics

The Short-Form McGill Pain Questionnaire (SF-MPQ) was used to assess pain characteristics (Melzack, 1987). The SF-MPQ consists of 15 descriptors (11 sensory, 4 affective) which are rated on an intensity scale as follows: 0 = none, 1 = mild, 2 = moderate or 3 = severe. The SF-MPQ is based on the full-length version and has a high degree of internal consistency. The SF-MPQ also includes the Present Pain Intensity (PPI) index and a visual analog scale (VAS). The Pain Catastrophizing Scale (PCS) was also used (Sullivan et al., 1995). The PCS is a 13-item self-report inventory designed to assess the extent to which a person uses a catastrophic thinking approach in response to pain stimuli. Patients are instructed to reflect on a painful experience and to indicate the extent to which they thought about each statement using a 5-point Likert scale ranging from 0 ("not at all") to 4 ("all the time"). Total catastrophizing scores range from 0 to 52. The PCS has demonstrated high internal consistency (Cronbach's $\alpha = 0.91$) and high test-retest reliability over a 6-week period ($r = 0.75$).

2.2.2. Psychometric evaluation

The Beck Depression Inventory (BDI) was used to measure depression symptoms (Beck et al., 1961). The BDI, a widely used 21-item self-report measure of depressive symptom severity, has acceptable psychometric properties that have been reviewed elsewhere (Rabkin and Klein, 1987). The State-Trait-Anxiety Inventory (STAI) was also administered (Spielberger, 1983). This inventory includes two scales to differentiate anxiety related to a transitory or situational state (STAI-S), and trait anxiety (STAI-T) that is a more consistently stable characteristic of the individual, resembling a personality trait. The Short Form Health Survey (SF-36) is a 36-item questionnaire that assesses functional status and well-being. The SF-36 is comprised of the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The PCS has four subscales: (1) physical functioning, (2) role-physical factors in functioning, (3) bodily pain, and (4) general health. The MCS has an additional four subscales: (5) vitality, (6) social functioning, (7) role-emotional factors in functioning and (8) mental health. Each scale score ranges from 0 to 100, with 0 representing the poorest functioning and 100 representing optimal health. The Cronbach's alpha reliability estimates for the Japanese SF-36 range from 0.71 to 0.87 for the subscales, indicating good test–retest reliability (Fukuhara et al., 1998). The Japanese version of the National Adult Reading Test (NART), a reading test of 50 irregularly spelled Japanese words, was used as an assessment of intellectual functioning (Matsuoka et al., 2006; Nelson, 1982).

2.2.3. Experimental paradigm and stimuli

The experiment was a simple 2 × 2 block within-subject design with the variables of pain stimulation (moderate or low) and emotional context (sad or neutral). A schematic representation of the experimental design is shown in Fig. 1. Facial expressions were presented for 4 s. The same emotion was represented four times sequentially *via* different randomly selected faces. Pain stimuli were delivered while the facial stimuli were presented. The interval between the pain stimuli was randomized, with an average duration of 1 s between stimuli (0.8–1.2 s). The present experimental design was a simplification and modification of the design used in our previous studies (Yoshino et al., 2010, 2012). We used two emotional conditions (sad or neutral) instead of three and a block design instead of an event-related task design. Each block was composed of four facial pictures with the same emotional valence (sad or neutral), sixteen pain stimuli of the same intensity (moderate or low), a rating activity, and a rest period. Each block was 32 or 36 s in duration. The participants rated the average intensity of the pain stimuli at the end of each block using a Numerical Rating Scale (NRS) projected onto the same screen for 8 s. The whole paradigm comprised a sequence of 16 randomized blocks (four blocks for each condition), and the total experimental duration was about 9 min. The order of the experimental conditions was counterbalanced across participants to mitigate order effects.

An intraepidermal stimulation method (Inui and Kakigi, 2012; Inui et al., 2002) was used to induce minor pain at the superficial skin level. The original method was slightly modified to provide a higher selectivity for the activation of nociceptors. We used a stainless steel concentric bipolar needle electrode (Nihon Kohden, Tokyo, Japan) for intraepidermal stimulation. The anode was an outer ring 1.2 mm in diameter, and the cathode was an inner needle that protruded 0.1 mm from the outer ring. This needle electrode permitted the selective stimulation of cutaneous A-delta fibers. The electrical stimuli used were 50 Hz current constant double pulses of 0.5 ms in duration. The electrical stimuli were intended to evoke the feeling of receiving an injection. The needle electrode was exchanged for each participant. The constant current stimulator (SEN-2201; Nihon Kohden, Tokyo, Japan) was located outside the MRI