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

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## ARTICLE INFO

## 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.

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## 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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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
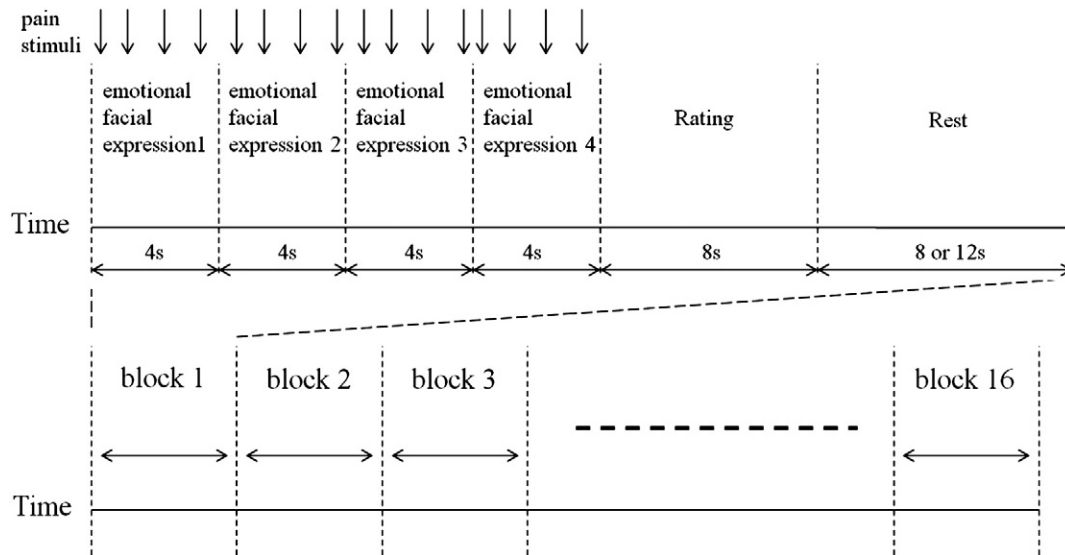
**Fig. 1.** Schematic representation of the experimental design. Facial expressions were presented for 4 s. The same emotion was represented 4 times sequentially in different faces randomly selected. Pain stimuli were delivered while the facial stimuli were presented. The interval between the pain stimuli was randomized, with an average of 1 s. Immediately after the pain stimuli, participants were instructed to rate their average level of pain across the 8 s using a numeric rating scale (NRS) ranging from 0 (no pain at all) to 10 (worst imaginable pain). They pushed the button to stop the bar moving between 0 and 10 to rate the intensity of their pain perception.

room, and the electrode was connected to the stimulator *via* a magnet-compatible extension cable. We established the stimulus current intensities for moderate pain (1.3 mA) and low pain (0.35 mA) based on our previous studies (Yoshino et al., 2010, 2012) and a preliminary experiment conducted before the present study. We stimulated the left forearm of each participant. The insertion of the needle electrode caused no bleeding or visible damage to the skin of any participant.

We used pictures of faces as emotional stimuli of the type that have been employed in previous functional neuroimaging studies that examined neural responses to emotional stimuli (Doallo et al., 2012; Groenewold et al., 2012; Whalen et al., 2013). We used sad and neutral facial expressions to induce different emotional contexts while the participants were exposed to the pain-inducing stimuli. Eight sad or eight neutral facial expressions displayed by eight different Japanese individuals (4 females and 4 males) were taken from a standardized series of stimuli (Kamachi et al., 2001) and were presented for 4 s each per facial image. During fMRI recording, participants were instructed to imagine how the person depicted in each image felt when the image appeared on the screen. An MR-compatible back projection screen (Silent Vision SV-6011; Avotec, USA) was used to present the facial stimuli.

### 2.2.4. Behavioral data analysis

Subjective pain intensity ratings were analyzed using 3-way repeated measures ANOVAs performed using SPSS version 16.0, with group (patients or controls) as a between-subjects factor, and pain (moderate or low) and emotional context (sad or neutral) as within-subjects factors. We examined the pain intensity rating ratios between the sad and neutral contexts in order to contrast the strength of pain perception in the sad emotional context condition with the neutral condition, based on a previous study (Murray and Arnott, 1993). The ratio was analyzed using 2-way repeated measures ANOVAs, with group (patients or controls) as a between-subjects factor and pain (moderate or low) as a within-subjects factor. These data were also examined using post-hoc tests performed using SPSS version 16.0.

### 2.2.5. fMRI acquisition

The fMRI procedure was performed using a Magnex Eclipse 1.5 T Power Drive 250 (Siemens, Munich, Germany). A time course series of 366 scans was acquired using T2*-weighted, gradient echo, echo planar

imaging (EPI) sequences. Each volume consisted of 28 slices, with a slice thickness of 4 mm with no gap, and covered the entire cerebral and cerebellar cortices. The time interval between two successive acquisitions of the same image (TR) was 3000 ms, the echo time (TE) was 46 ms, and the flip angle was 90°. The field of view (FOV) was 256 mm, and the matrix size was 64 × 64, giving voxel dimensions of 4 mm × 4 mm × 4 mm. Scan acquisition was synchronized to the onset of each trial. After functional scanning, structural scans were acquired using a T1-weighted gradient echo pulse sequence (TR =2160 ms; TE = 3.93 ms; flip angle = 15°; FOV = 256 mm; voxel dimensions of 1 mm × 1 mm × 1 mm) to facilitate localization.

### 2.2.6. fMRI analysis

Image processing and statistical analyses were carried out using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, London, UK). The first three volumes of each fMRI run were discarded because the MRI signal was unsteady. Each set of functional volumes was realigned to the first volume. A slice timing correction was performed on the model slice to correct for the sequential sampling of the brain in the slice direction. Volumes were spatially normalized to a standard template based upon the Montreal Neurological Institute (MNI) reference brain, and finally smoothed using an 8-mm FWHM Gaussian kernel.

For the statistical analysis, subject-specific t-contrast images were calculated for the pain effects using the general linear model (first level analysis). For each participant the preprocessed data were assigned to the following four conditions in the model specification: High pain during sad facial images, low pain during sad facial images, high pain during neutral facial images, and low pain during neutral facial images. These contrasts were entered into the second level analysis. Using group analysis according to a random effects model, we conducted repeated measures 3-way ANOVAs as implemented in SPM8 with group (patients or controls) as a between-subjects factor and pain (moderate or low) and emotional context (sad or neutral) as within-subjects factors. BDI, STAI-S, and STAI-T scores were used as covariates to control for individual differences in depressive and anxiety states, in consideration of the modulatory effects of depression and anxiety on pain sensitivity. The spatial coordinates provided by SPM8, which are in MNI brain space, were converted to

spatial coordinates of the Anatomical Automatic Labeling (AAL) atlas using the MarsBar SPM Toolbox. Peak voxel parameter estimates from interactions were examined using post-hoc Bonferroni multiple comparisons performed in SPSS version 16.0.

We conducted a psychophysiological interaction (PPI) analysis (Friston et al., 1997) to examine interactions between brain regions in relation to the experimental paradigm. This approach can capture the way in which activity in one brain region modulates activity in another region by specifically assessing responses to the active task relative to an informative baseline. To undertake PPI analysis a design matrix is established, which typically contains three columns of variables as follows: (1) a psychological variable that reflects the experimental paradigm, (2) a time series variable representing the time course of the source region; here, the source region was a 6-mm sphere with a center defined by the peak coordinate of the foregoing analysis, and (3) a variable that represents the interaction between (1) and (2). The regression coefficient for the interaction term provides a measure of PPI. In the present context, a significant effect for PPI means that the correlation (or covariance) between the source and the sink region during an emotional pain condition is significantly different from that during another emotional condition. In this regard, PPI analysis assesses differences in functional connectivity between the regions of interest. To perform PPI analyses, the first eigenvariate time series of the 6-mm sphere activated according to the previous analyses was extracted. The effect of the interaction term was then studied using the contrast [1 0 0], where the first column represents the interaction term. The extracted individual images were then taken to the second level to perform a random effects analysis, using a one-sample t-test.

The statistical threshold for all the imaging analyses described above was set at an uncorrected $p$ value of 0.001 and at a minimum cluster size of 20 voxels, based on previous pain related fMRI studies (Ochsner et al., 2006; Yoshino et al., 2010).

Finally, we examined the correlations between the brain regions involved in modulating low pain levels within the context of sadness and the sadness-specific low-pain rating scores of patients. We also analyzed the correlations between the brain regions involved in modulating low pain levels within the context of sadness and BDI or STAI scores for all participants, and examined whether sadness-induced pain perception changes were correlated with individual differences in depressed mood or anxiety state. A correlation analysis was performed for the brain areas for which there was a significant interaction effect in the 3-way ANOVAs (the anterior/posterior insula and the hippocampus) as regions of interest (ROIs).

## 3. Results

### 3.1. Participant characteristics

Detailed demographic and clinical characteristics of the participants are presented in Tables 1 and 2. The clinical pain in the patient group was located in the head ($n = 4$), mouth ($n = 4$), chest ($n = 2$), or abdomen ($n = 1$). Patients felt more depressive and anxious prior to the study than did controls and reported more impairment in their daily activities. No significant differences in NART performance (intelligence levels) between the groups were observed.

### 3.2. Behavioral results

Participants reported different pain intensities across the emotional context conditions (Table 3). A 3-way ANOVA revealed a significant main effect of emotional context, $F (1, 20) = 7.69$, $p < 0.05$; pain intensities in the sad emotional context condition were significantly higher than in the neutral condition. No significant differences in subjective pain perception between the groups were observed.

**Table 1**
Demographic and psychometric variables of patients and controls.

|  | Patients (n = 11) | Controls (n = 11) | $T_{score}$ |
|---|---|---|---|
| *[Demographic variables]* |  |  |  |
| Age | 40.9 ± 6.5 | 40.6 ± 6.1 | 0.1[ns] |
| Female/male | 6/5 | 6/5 | 0.0[ns] |
| Pain duration (months) | 91.0 ± 85.7 | – | – |
| Rating of clinical pain (NRS) | 7.6 ± 1.7/10 | – | – |
| Psychiatric diagnosis |  |  |  |
|  Pain disorder | 11/11 | – | – |
|  Current major depressive episode | 0/11 | – | – |
|  Major depression in history | 5/11 | – | – |
|  Generalized anxiety disorder | 3/11 | – | – |
|  Other psychiatric disorders | 0/11 | – | – |
|  |  |  |  |
| *[Psychometric variables]* |  |  |  |
| BDI | 15.9 ± 11.1 | 4.0 ± 4.9 | 3.2[**] |
| STAI |  |  |  |
|  State | 55.3 ± 11.3 | 37.8 ± 8.6 | 4.1[**] |
|  Trait | 55.8 ± 11.9 | 41.4 ± 10.7 | 3.0[**] |
| SF-36 |  |  |  |
|  Physical functioning | 84.5 ± 13.7 | 97.3 ± 3.4 | −3.0[*] |
|  Role physical | 45.5 ± 48.5 | 84.1 ± 23.1 | −2.4[*] |
|  Bodily pain | 39.5 ± 28.0 | 92.7 ± 13.4 | −5.7[***] |
|  General health | 33.7 ± 23.9 | 75.2 ± 14.9 | −4.9[***] |
|  Vitality | 38.2 ± 28.6 | 59.5 ± 12.7 | −2.3[*] |
|  Social functioning | 63.6 ± 21.3 | 94.3 ± 11.7 | −4.2[***] |
|  Role emotional | 54.5 ± 45.4 | 81.8 ± 34.6 | −1.6[ns] |
|  Mental health | 35.3 ± 20.1 | 52.0 ± 10.3 | −2.5[*] |
| NART | 110.1 ± 6.7 | 112.9 ± 4.3 | −1.2[ns] |
| SF-MPQ |  |  |  |
|  Sensory | 12.5 ± 8.2 | – | – |
|  Affective | 3.3 ± 2.5 | – | – |
| PCS | 35.5 ± 9.1 | – | – |

ns = not significant.
NRS = numeric rating scale; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; SF-36 = Short Form-36; NART = National Adult Reading Test; SF-MPQ = Short Form of the McGill Pain Questionnaire; PCS = Pain Catastrophizing Scale.
  [*] $P_{two-sided} < 0.05$ (two sample t-test).
 [**] $P_{two-sided} < 0.01$ (two sample t-test).
[***] $P_{two-sided} < 0.001$ (two sample t-test).

Regarding the ratio for pain intensity ratings between the sad and neutral conditions, a 2-way ANOVA revealed a significant interaction between group and pain, $F (1, 20) = 4.96$, $p < 0.05$. Bonferroni post-hoc tests showed that the ratio for low pain levels between the sad

**Table 2**
Patients' characteristics.

| No | Medical diagnosis | Medications |
|---|---|---|
| 1 | Somatoform pain disorder Generalized anxiety disorder Major depression in history | Tryptanol 75 mg, sulpiride 150 mg, loxoprofen 180 mg |
| 2 | Somatoform pain disorder Major depression in history | Tryptanol 75 mg, clonazepam 1.5 mg |
| 3 | Somatoform pain disorder | Mirtazapine 45 mg, pregabalin 75 mg, loxoprofen 180 mg, eperison 100 mg |
| 4 | Somatoform pain disorder | Nortriptyline 50 mg, clonazepam 0.5 mg, tizanidine 3 mg |
| 5 | Somatoform pain disorder | Tryptanol 75 mg |
| 6 | Somatoform pain disorder | Duloxetine 40 mg, tizanidine 3 mg |
| 7 | Somatoform pain disorder | Amoxapine 25 mg |
| 8 | Somatoform pain disorder Major depression in history | Tryptanol 25 mg, trazodone 25 mg Loxoprofen 180 mg |
| 9 | Somatoform pain disorder Generalized anxiety disorder | Duloxetine 20 mg, quetiapine 25 mg, clonazepam 0.5 mg, sodium valproate 400 mg |
| 10 | Somatoform pain disorder Generalized anxiety disorder Major depression in history | Nortriptyline 150 mg, tizanidine 3 mg |
| 11 | Somatoform pain disorder Major depression in history | Tryptanol 50 mg, trazodone 50 mg, carbamazepine 200 mg, clonazepam 1 mg, eletriptan 20 mg |

and neutral conditions in patients was higher than the ratio for moderate pain levels in patients and for low pain levels in controls ($p < 0.05$).

### 3.3. fMRI data

#### 3.3.1. Brain regions involved in pain perception (main effect of 'pain')

Significant changes in signal intensity were detected in a number of brain regions related to pain perception (Table 4), including the ACC, insula, thalamus, second somatosensory area (SII), and prefrontal cortex.

#### 3.3.2. Differences in cerebral pain processing between groups (interaction of 'group' × 'pain' × 'emotion')

To test differences in pain-related activation between patients and controls during presentation of pain stimuli, we looked at brain activation as reflected in the interaction of 'group' × 'pain' × 'emotion' (Fig. 2A–C). There was significant activation in the anterior insula, posterior insula, and hippocampus.

### 3.4. Post-hoc comparisons between groups

#### 3.4.1. Anterior insula

Activation during the low pain sad and high pain neutral conditions was significantly greater in patients than in controls ($p < 0.05$). Activation during the low pain in neutral condition was significantly greater in controls than in patients ($p < 0.05$).

#### 3.4.2. Posterior insula

Activation during the low pain sad condition was significantly greater in patients than in controls ($p < 0.01$). Activation during the low pain neutral condition was significantly greater in controls than in patients ($p < 0.01$).

#### 3.4.3. Hippocampus

Activation during the high pain neutral condition was significantly greater in patients than in controls ($p < 0.01$). Activation during the low pain neutral condition was significantly greater in controls than in patients ($p < 0.001$).

### 3.5. Psychophysiological interaction (PPI) analysis

The above whole-brain ANOVAs revealed that blood oxygenation level-dependent (BOLD) responses for the anterior/posterior insula during the presentation of low-pain stimuli were larger for the sad condition than for the neutral condition in patients. PPI analyses were performed to assess possible functional connectivity differences between patients and controls in the anterior insula [6-mm sphere centered x = 28, y = 22, z = −16], with other areas focusing

primarily on the low pain sad emotional context condition, given that many studies suggest that the anterior insula is associated with the affective dimension of pain (Craig, 2002; Gu et al., 2013; Yuan et al., 2013). Considering behavioral and fMRI data results, we examined brain region connectivity for the low pain sadness condition.

The PPI analysis for the sad-specific low pain component ((low pain with sad facial images) − (low pain with neutral facial images)) revealed that anterior insula activity was accompanied by increased functional interaction with the right parahippocampus [x = 24, y = −10, z = −26; z-score 4.28, cluster extent 30] (Fig. 2D), to a greater extent in patients than in controls.

### 3.6. Correlation analysis

Sadness-specific lower pain level rating scores were positively correlated with sadness-specific activation during low-pain stimuli in the anterior insula ($r = 0.71$, $p = 0.019$). This finding emerged in the patient group. No regions showed negative correlations with pain rating scores.

No ROIs showed positive or negative correlations between sadness-specific activation during low-pain stimuli and BDI or STAI scores.

## 4. Discussion

In comparison to the matched controls, we demonstrated that the ratio for low-pain intensity ratings between the sad and neutral conditions in patients was higher than in controls. At the same time, the patients also showed stronger anterior/posterior insula activation induced by sadness-context low-pain stimuli. In patients, we found more effective connections between the parahippocampus and anterior insula during the presentation of low-pain stimuli in the sad context. This is the first fMRI study that has compared somatoform pain disorder patients with controls, in order to examine the relationship between pain perception and sad emotional context.
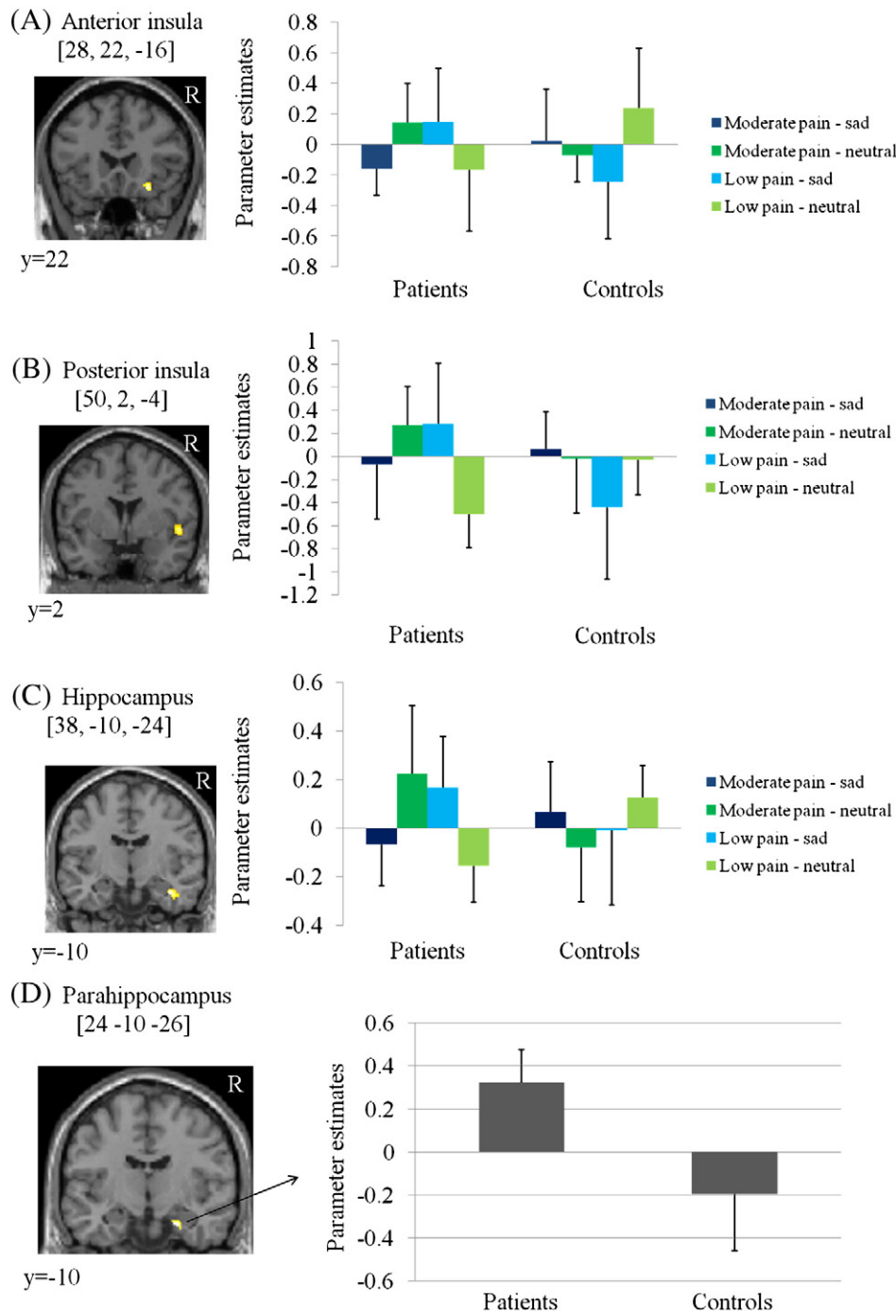
### 4.1. Subjective pain intensities

We examined changes in perceived pain intensity as influenced by sadness, using the same stimuli across sad and neutral conditions. Subjective pain intensities in the sad context were significantly greater than the subjective pain intensities in the neutral context, for both patient and control groups. The finding that sadness subjectively increased pain replicates the findings of our previous studies (Yoshino et al., 2010, 2012). However, we did not find significant differences in pain threshold between the groups. A behavioral study also reported this pain-amplifying effect for sadness both in participants with and without chronic pain, but there was no difference between the groups (van Middendorp et al., 2010). No between group differences in terms of physical pain stimulus intensity have been reported across many other fMRI studies (Baliki et al., 2006; Gündel et al., 2008; Kirsch et al., 2005; Stoeter et al., 2007).

In the present study, there was a significant difference between groups in the ratio between sad and neutral contexts for low-pain stimuli. Previous studies have identified greater pain responses associated with negative emotions in patients with chronic pain disorder than among controls (Burns, 2006; Zautra et al., 2005). Furthermore, it has also been reported that low-pain stimuli are experienced as more aversive by these patients (Morris et al., 1995). Our results suggest that patients with somatoform pain disorder may be more susceptible to the perception of low-pain stimuli in a sad emotional context, as compared to a neutral context.

### 4.2. Insula

Insula activation has been observed during a majority of imaging studies involving pain stimuli (Apkarian et al., 2005). Various studies have demonstrated that negative emotional states enhance pain-

**Table 3**
Pain ratings by the differences of facial images.

|  | Patients (Mean ± SD) | Controls (Mean ± SD) |
|---|---|---|
| Sad |  |  |
| Moderate pain | 4.2 ± 0.8 | 4.3 ± 0.9 |
| Low pain | 1.1 ± 0.7 | 0.8 ± 0.5 |
| Neutral |  |  |
| Moderate pain | 4.0 ± 0.8 | 4.2 ± 0.7 |
| Low pain | 0.6 ± 0.3 | 0.7 ± 0.3 |
| Sad/neutral |  |  |
| Moderate pain | 1.1 ± 0.3 | 1.0 ± 0.1 |
| Low pain | 1.9 ± 0.6 ♦ | 1.2 ± 0.7 |

SD, standard deviation.

*Statistically significant difference between emotions (p < 0.05).

♦Significant interaction between group and emotion (p < 0.05). Bonferroni's post hoc tests showed that the ratio between sad and neutral on low pain in patients was more highly rated than moderate pain in patients and low pain in controls (p < 0.05).

Fig. 2. BOLD-signal differences between patients with somatoform pain disorder and controls. A–C; Group × pain × emotion interactions in the insula and the hippocampus are shown (3-way-ANOVA; BDI, STAI-S, and STAI-T scores as covariates). In patients, stronger activations were found in the moderate pain neutral and low pain sad conditions. In controls, stronger activation was found in the moderate pain sad condition. D; The graph shows the parameter estimate of the peak coordinate as the difference of connectivity strength for low-pain stimuli in the sad condition. Anterior insula activity covaried more strongly with activity in the parahippocampus in patients.

related activity in the insula (Lutz et al., 2012; Terasawa et al., 2013). The present study found that activation of the anterior/posterior insula during low-pain stimuli in a sad emotional context was stronger in somatoform pain disorder patients than in controls. Previous studies also reported stronger activation of the insula for pain stimuli in patients with somatoform pain disorder as compared to controls (Gündel et al., 2008; Stoeter et al., 2007). We suggest that a vulnerability to pain perception modulated by emotional dysregulation, as well as pain perception itself, is one of the important pathophysiological factors underlying somatoform pain disorder.

Peyron et al. (2000) found that insula activation is positively correlated with pain ratings. The present study also found that anterior insula activation associated with sad-context low-pain stimuli is related to subjective ratings of such stimuli provided by patients. We suggest that the anterior insula activations we observed reflected the subjective pain ratings that we obtained.

These findings suggest the possibility that sadness is associated with more increased sensitivity to pain perception in patients with somatoform pain disorder as compared to controls, and that the insula is involved in this process.

### 4.3. Hippocampus and parahippocampus

Reports of pain-related responses in the hippocampus have been contradictory, but various studies have reported that the hippocampus is involved in the processing of pain stimuli (Apkarian et al., 2005; Peyron et al., 2000). The hippocampus plays a critical role in supporting the influence of context on memory encoding, storage, behavior, and the retrieval of pleasant or aversive stimuli (Rudy, 2009). Some evidence suggests that hyperalgesia induced by negative emotional states is associated with activation in the hippocampus (Berna et al., 2010; Ploghaus et al., 2001). Patients with somatoform pain disorder show altered hippocampal activation in response to pain stimuli, in comparison with controls (Gündel et al., 2008; Stoeter et al., 2007). Studies also indicate that the hippocampus is connected with pain-related brain regions such as the insula, and that hippocampus activity can enhance pain perception (Kong et al., 2008; Ploghaus et al., 2001). The present study found strong hippocampus activation in patients for low pain stimuli in a sad emotional context. We speculate that a similar mechanism may also underlie sadness-induced pain perception.

We conducted a PPI analysis to examine brain regions in relation to the insula during sadness-specific low-pain perception. Anterior insula activity was accompanied by increased functional interaction involving the parahippocampus, to a greater extent in patients than in controls. The parahippocampus plays a central role in recollection, sending information from the hippocampus to the association areas (Diederen et al., 2010). Previous studies have demonstrated effective connectivity between the parahippocampus and anterior insula in healthy controls (Ploner et al., 2011; Tanaka et al., 2008). It has been reported that stronger intensity of pain stimuli in a negative emotional context is associated with neural activity in the anterior insula, mediated by the parahippocampus (Ploner et al., 2011). Patients with somatoform pain disorder show an altered activation pattern in the parahippocampus in response to pain stimuli, in comparison to controls (Gündel et al., 2008; Stoeter et al., 2007). We therefore assume that an increased functional connectivity between the anterior insula and parahippocampus may be a distinctive feature of somatoform pain disorder in a sad emotional context. The present behavioral results suggest that the subjective experience of pain appears to be exacerbated by negative emotional states for such patients. They may perceive even relatively low pain levels as more intense during sadness, with conditioning possibly playing a role in this process. However, this interpretation may be premature, and further study is needed to elucidate the relationship between pathophysiology in somatoform pain disorder and the parahippocampus.

We also hypothesized that ACC activation would differ across patients with somatoform pain disorder and healthy controls. Although there was a main effect of pain level on ACC activity, there were no group differences, consistent with previous studies (Gündel et al., 2008; Stoeter et al., 2007). Gündel et al. (2008) described a negative correlation between intensity of patients' clinical pain and the experimental pain stimuli in terms of ACC activation, and they have explained this limited activation of the ACC in response to experimental pain in terms of increased neuronal baseline activity due to the experience of chronic pain. There is a clear need for continued research to elucidate the role of the ACC in somatoform pain disorder.

The present study has several limitations. First, the small sample size limits the robustness of our findings. Second, the display duration for the facial images (4 s) was longer than that used in previous studies (Doallo et al., 2012; Whalen et al., 2013). We must therefore consider the possibility that any context-induced emotional effects might have been attenuated via habituation. Third, a higher level of anxiety and depression in patients may influence the fMRI data. Previous studies have shown that somatoform patients have significantly higher depression or anxiety scores (Gündel et al., 2008; Stoeter et al., 2007). We analyzed a 3-way ANOVA using BDI, STAI-S, and STAI-T scores as covariates, and

**Table 4**
Main effect of pain.

| Brain regions | L/R | x/y/z | z-score | Cluster extent |
|---|---|---|---|---|
| ACC (BA 32) | R | 8/34/24 | 3.32 | 43 |
| ACC (BA 24) | R | 6/20/30 | 3.75 | 124 |
| ACC (BA 24) | L | −8/6/32 | 4.17 | 152 |
| Insula | R | 42/0/−4 | 3.40 | 24 |
| Insula | L | −40/−8/−6 | 4.22 | 50 |
| Thalamus | R | 6/−4/12 | 4.07 | 227 |
| Thalamus | L | −8/−4/14 | 5.21 | 259 |
| Superior frontal gyrus (BA9) | L | −18/54/26 | 3.96 | 65 |
| Middle frontal gyrus (BA8) | L | −34/24/48 | 4.58 | 118 |
| Inferior frontal gyrus (BA45) | L | −56/8/8 | 5.63 | 392 |
| Caudate | L | −16/14/8 | 3.69 | 21 |
| S1 (BA2) | L | −66/−24/34 | 4.12 | 78 |
| S2 (BA40) | R | 60/−24/20 | 5.82 | 468 |
| S2 (BA40) | L | −60/−24/20 | 4.94 | 347 |
| SMA (BA6) | L | −2/12/58 | 5.72 | 435 |
| M1 (BA4) | R | 50/2/44 | 3.99 | 114 |
| M1 (BA4) | L | −38/−8/62 | 4.23 | 65 |
| Middle temporal gyrus | L | −56/−62/6 | 3.99 | 58 |
| Superior temporal gyrus | L | −56/4/10 | 5.63 | 81 |

Brain regions stated in MNI coordinates with activation maxima of experimentally induced p, thresholded at uncorrected p < 0.001. Minimum activation cluster size is 20 voxel.
ACC, anterior cingulate cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SMA, supplementary motor area; M1, primary motor cortex.

adjusted the fMRI data accordingly. Furthermore, no brain regions showed correlations between sadness-specific activation for low-pain stimuli and BDI or STAI scores across the participants. These results mean that the effects of depression and anxiety were probably limited in the present study, but nevertheless we cannot rule out such effects. Fourth, an uncertainty may remain in our experimental paradigm regarding the extent to which we adequately distinguished between pain and emotion. It has been reported that pain itself is a specific emotion (Craig, 2003), and pain and emotion show much overlap in terms of psychological and brain functional aspects although they are not necessary the same. Finally, our exclusion criteria did not include all treatments that might influence the patients' pain perception, such as antidepressants, although it included opioids, and a 24 h analgesic-free observation period prior to the fMRI was not generally fully effective. It has been reported that antidepressants have an analgesic effect in somatoform pain disorder (Luo et al., 2009) and such drugs produce clear changes in brain activity (Wiech and Tracey, 2009). We therefore cannot rule out all treatment effects on the brain activity that we observed in this study. However, it is not clear whether antidepressants influence antinociceptive effects in acute pain (Schreiber et al., 2009). Furthermore, any analgesic effects may be related to specific antidepressant effects (Luo et al., 2009). We believe that such treatment effects probably play a minor role in our findings, given that we adjusted our fMRI data to control for the presence of depressive states as described above.

In summary, our results provide evidence that patients with somatoform pain disorder tend to show slightly higher pain sensitivities to low pain stimuli in contexts of sadness. The insula, hippocampus, and parahippocampus show altered activity under such conditions. These results provide some insight into sadness-induced distinctive changes in neural pain-related activity within the context of somatoform pain disorder, with interactions between brain activity and emotional context potentially playing an important role in the pathophysiology of this disorder.

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