ORIGINAL ARTICLE

Altered Neural Correlates of Emotion Associated Pain Processing in Persistent Somatoform Pain Disorder: An fMRI Study.

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■ **Abstract:** Patients with persistent somatoform pain disorder (PSPD) suffer from long-term pain and emotional conflicts. Recently, accumulating evidence indicated that emotion has a significant role in pain perception of somatoform pain disorder. To further understand the association between emotion and pain-related brain activities, functional activities of patients with PSPD fulfilling ICD-10 criteria and healthy controls were assessed using functional magnetic resonance imaging technology, while participants viewed a series of positive, neutral, or negative pictures with or without pinprick pain stimulation. Results showed that patients with PSPD had altered brain activities in the parietal gyrus, temporal gyrus, posterior cingulate cortex, prefrontal cortex, and parahippocampus in response to pinprick pain stimuli during different emotions compared with the healthy control group. Moreover, patients with PSPD consistently showed hyperactivities in the prefrontal, the fusiform gyrus and the insula in response to negative stimuli under pinprick pain vs. non-pain condition. The current findings provide some insights into the underlying relationship between emotion and pain-related brain activity in patients with PSPD, which is of both theoretical and clinical importance. ■

Key Words: functional magnetic resonance imaging, persistent somatoform pain disorder, emotion, pain

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INTRODUCTION

Persistent somatoform pain disorder (PSPD) is a type of somatoform disorder with medically unexplained

somatic symptoms.[1–4] According to International Statistical Classification of Diseases, 10th Revision (ICD-10: F45.4) (also taking Diagnostic and Statistical Manual of Mental Disorders, Fourth and Fifth Edition (DSM-IV and DSM-V) as references), patients with PSPD suffer from long-term pain (commonly lasts for more than 6 months), with no somatic lesions explaining the persistent pain complaint from the patient. Pain in patients is generally flexible in multiple parts, and it is most commonly felt in the head and back. Pain in the limbs, waist, and chest has also been reported. The patients may also have emotional conflicts or psychosocial problems, such as increased depression and anxiety, impaired social functions,[5] and decreased quality of life.[6,7]

Several studies have revealed that emotion is significantly associated with pain in patients with somatoform pain disorder.[8,9] Emotional response and regulation were evidenced to influence both the perceptual and affective dimensions of pain.[10] Various emotional elements aroused by affective stimuli, including such states as sadness, fear, and anxiety, can influence pain-related brain activation. For example, negative emotions (eg, anger, hopelessness, frustration, irritability, and sadness) augment pain sensitivity and pain-evoked brain activity in patients with chronic pain disorders in comparison with the controls.[11–14] Moreover, subjective pain intensities are greater during a state of sadness.[15,16] Therefore, greater sensitivity to pain stimuli in the negative emotional context of sadness might be involved with the psychopathology of somatoform pain disorder. By contrast, positive emotions such as listening to pleasant music or viewing pictures of a romantic partner, which can activate brain reward circuitry, reduce pain or pain analgesia.[17–20]

These regions mainly include the emotional brain circuitry comprising the prefrontal cortex (PFC), amygdala, hippocampus, ACC, and ventromedial striatum, which are associated with intergrating and processing emotional information and generating emotional behaviors. Accumulating studies have focused on the brain mechanisms underlying emotional modulation of pain in healthy subjects and patients with clinical pain condition.[21–23] Many methods are used to study the mechanism of PSPD, including brain imaging and neuropsychology. However, a systematic recognized conclusion is still lacking, which reflects the complexity of this disease. Neuroimaging techniques have been of considerable help to visualize brain areas that become activated during timing tasks. Functional magnetic resonance imaging (fMRI) has been applied in studies on patients with somatoform pain disorder reporting differences between patients and controls in cerebral responses to pain stimuli.[24,25]

A voxel-based morphometric study suggested that patients with pain disorder show gray matter loss in pain-processing structures such as prefrontal, cingulate and insula cortex.[26] Changes in frontal limbic cerebral structure are also found in patients suffering from chronic fibromyalgia and chronic tension-type headache.[27] Previous functional imaging research showed hypoactivated ventromedial prefrontal/orbitofrontal cortex and hyperactivated parahippocampus, amygdala, and anterior insula in patients under noxious heat stimuli.[24] Similarly, greater activation of brain regions, including the thalamus, anterior insula, hippocampus, and prefrontal cortex, was found in the patient group than in the control group under pinprick pain stimuli.[25] The emotion-related cerebral region is involved in the pain disorder. Yoshino et al.[28] found more effective functional connectivity between the parahippocampus and the anterior insula cortex during processing low-pain stimuli in the sad context.

However, no other detailed fMRI studies have been conducted on different emotion-induced brain activity changes in response to pinprick pain stimuli in patients with PSPD and healthy controls. In this study, Patients with PSPD and aged-, gender-, education-matched healthy controls were required to view various types of emotional pictures with or without pinprick pain during MRI scanning. We analyzed activity of brain regions in patients with PSPD during different emotional contexts. We hypothesized that different emotions exert various influences on pain-related activation of brain regions in patients with PSPD, especially on the prefrontal–temporal–limbic circuit and emotional brain circuitry.

METHODS

Patients and Controls

We recruited twelve inpatients or outpatients with PSPD according to the diagnostic criteria of the International Classification of Diseases (ICD 10:F45.4) from the Tongji Hospital Affiliated with Tongji University, Shanghai, China. (gender: 5 females, 7 males; age: 18 to 65 years, mean: 45.83 SD: 14.95; righthanded; education level: 12 to 18, mean: 2.9, SD: 3.1) (Table 1). The duration of illness was more than 6 months, and chronic pain was not caused by organic diseases or

Table 1. Clinical Data of Patients and Controls

	Female/Male	Age Range	VAS_total score	SAS_total score	SDS_total score
Patients (n = 12)	5/7	45.83 (SD 14.95)	5.83 (SD 11.68)	45.54 (SD 1.85)	47.39 (SD 2.11)
Controls (n = 10)	4/6	35.2 (SD 10.78)	0	35.89 (SD 3.137)	37.26 (SD 2.92)

SAS = Zung Self-Rating Anxiety Scale; VAS = Visual Analog Scale; SDS = Zung Self-Rating Depression Scale.

obvious psychological factors. In addition, we recruited ten healthy controls with age, gender, and education level matched (gender: 4 females, 6 males; age: 18 to 65 years, mean 35.2 ± 10.78; right-handed; education level: 12 to 18, mean 16.6 ± 2.9) (Table 1). All the patients and controls were of Chinese Han origin.

Exclusion criteria included neurological illness, severe physical disease, organic brain disorder, pregnancy, and use of opioid or cocaine medication. Pain characteristics of all patients with PSPD were self-assessed with the guidance of a professional psychologist using the following psychological assessment scales (Table 1):

Visual Analog Scale (VAS), a self-assessment scale on pain feeling by indicating a position along a line between 2 endpoints;

Zung Self-Rating Anxiety Scale (SAS), a 20-item self-report assessment to evaluate anxiety levels, with each item being scored from 1 to 4. The total scores are divided into 4 ranges: 20 to 44 = normal, 45 to 59 = mild, 60 to 74 = severe, and 75 to 80 = extreme[29];

Zung Self-Rating Depression Scale (SDS), a 20-item self-report assessment to measure depression levels, with each question being scored on a scale of 1 to 4. The scores fall into 4 levels: 20 to 44 = normal, 45 to 59 = mild, 60 to 69 = moderate, and > 70 = severe[30,31];

The reliability and validity of Chinese version SAS and SDS have been confirmed by previous studies[32,33];

Short Form (36) health survey (SF-36), a 36-item self-report on personal health condition; and

Medical Outcomes Study Pain Measures, a self-report including 7 items on pain experience within the last 4 weeks.

All these scales are widely used and validated.[34,35] This study was approved by the Ethics Committee Board of Tongji Hospital. Before inclusion into the study, informed consent was obtained from all subjects.

Experimental Design

The individual pain threshold was assessed before fMRI scanning (Table 2). Percutaneous nerve electrical stimulation method (potassium ion penetration-induced pain) was used to induce pain. Sanyinjiao acupoint of the lower medial leg was used for electrical acupuncture. An EP601C pain threshold detector was applied for detection in clinical trials. The actual pain and stress scores were assessed by a questionnaire using VAS before and after the fMRI examinations. Data were analyzed using SPSS 19.0 statistical software (IBM Corp., Armonk, NY, USA). Statistics of the psychophysiological parameters of each group were assessed with one-way repeated-measures ANOVA and compared against each other with 2-sample Mann–Whitney U-test to investigate differences between the patient and control groups.

Table 2. Pain Threshold of Patients with Persistent Somatoform Pain Disorder (PSPD) and Healthy Controls

	HC M (25%/75%)	PSPD M (25%/75%)	P-value
Pain threshold	1.35 (0.80/1.85)	0.75 (0.67/1.11)	0.035

Emotional pictures selected from international affective picture system (IAPS) were used as emotional stimuli. IAPS pictures have good international applicability. However, considering that certain differences exist between Eastern and Western cultures, and the affectional expression of Chinese people is not strong, the selected IAPS pictures were more familiar with daily life and in line with regular emotions. The participants were prompted to rate each image according to the valence (positive/negative/neutral) they felt on a 9-point scale after the test. The scores generally met the valence rating in the IAPS. According to the valence and arousal ratings, the positive image: valence score ≥7; neutral: valence score 4 to 6; negative: valence score < 4.

A schematic representation of the experimental design is shown in Figure 1.

Task 1 included 7 blocks, and it was applied in the following sequence: positive-neutral-negative-neutral-positive-neutral-negative. Each block contained 6 pictures, and each picture was presented for 5 seconds. Each block was followed by a rest period of 30 seconds (shown as "+"). The paradigms lasted for 7 minutes

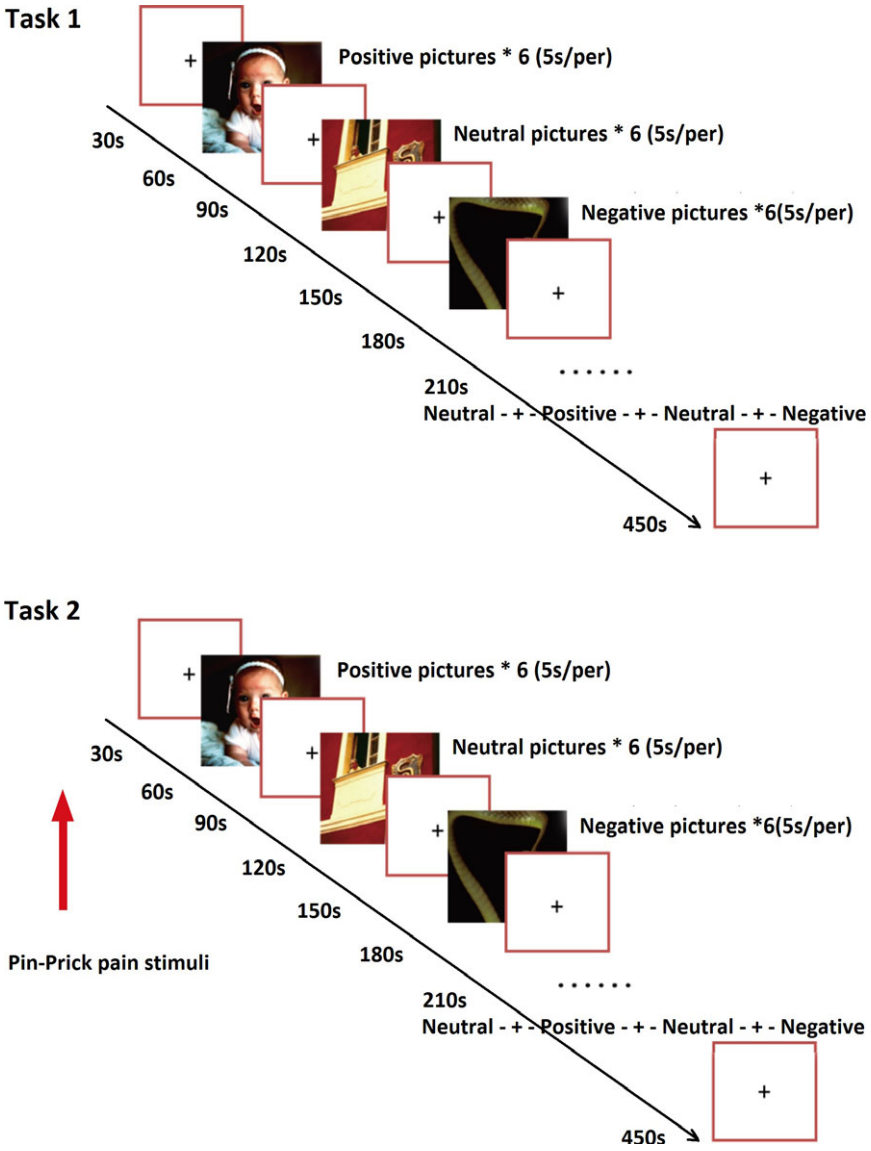

Figure 1. Schematic of the experimental design.

30 seconds. Task 2 was administrated to the participants following the "task 1" in the pinprick pain condition. In the pain condition, pinprick pain stimulation (2-fold of pain threshold) was applied through the pain threshold detector, and the participants continued to view the pictures. The scanning time was 7 minutes 30 seconds. The pictures were projected on a 1.0 m × 0.8 m screen on the food side of the subjects. The subjects lying inside the scanner watched the pictures through a plane mirror in the sight of 5 cm. During fMRI scanning, the pictures were presented through E-Prime procedure. The E-Prime is the abbreviation of Experimenter's Prime (best), a psychology experiment platform, which is a set of experimental generation systems for computerized behavior research.

fMRI Acquisition and Analysis

Functional neuroimaging was performed using Siemens MRI Trio 3.0T from the Department of Physics, East China Normal University. An echo-planar imaging (EPI)-based gradient echo sequence was used. Each volume consisted of 32 slices, with a slice thickness of 5 mm with no gap, covering the entire cerebral and cerebellar cortices. The time interval between 2 successive acquisitions of the same image (TR) was 2000 ms. The echo time (TE) was 25 ms, and the flip angle was 90°. The field of view (FOV) was 240 mm, and the matrix size was 64 × 64. Scan acquisition was synchronized to the onset of each trial. After functional scanning, structural scans were acquired using a 3DT1

Table 3. Group difference maps of activation by negative pictures between patients and controls (without pinprick pain)

Activation by Negative Pictures		Left			Right		
Patients vs. Controls	Regions	Coordinates x/y/z	Cluster Size	Max *t* Score	Coordinates x/y/z	Cluster Size	Max *t* Score
Controls > Patients	Precentral Gyrus (BA 4)	−45/−9/42	52	4.51	63/−9/36	29	3.57
	Precentral Gyrus (BA 4)	−48/−6/51		3.83			
	Precentral Gyrus (BA 6)				63/−3/30		3.24
	Superior Temporal Gyrus (BA 22)	−60/−48/12	25	4.18			
	Superior Parietal Lobe (BA 7)	−30/−57/54	18	4.11			
	Fusiform Gyrus (BA 19)	−27/−78/−12	27	3.65			
	Precentral Gyrus (BA 44)	−54/12/6	15	3.51			
Patients > Controls	Subgenual Anterior Cingulate Cortex	−9/42/−6	31	4.04			
	Subgenual Anterior Cingulate Cortex (BA 32)				12/45/−6	14	3.52
	Subgenual Anterior Cingulate Cortex (BA 32)				0/51/−6		3.10
	Middle Temporal Gyrus (BA 39)	−48/−66/15	13	3.63			
	Insula (BA 22)				48/−21/0	11	3.87
	Superior Temporal Gyrus (BA 13)				48/−48/15	10	3.36

Negative–Baseline, $P < 0.005$ (uncorrected), cluster size > 10 voxels.

Spin Echo (SE) sequence (TR = 1900 ms; TE = 3.43 ms; flip angle = 9°; FOV = 256 mm; matrix size = 256 × 256; slices = 1 mm × 160 slices) for about 5 minutes to facilitate localization.

Slice timing and head movement corrections were conducted. The images were then spatially normalized to the EPI standard template of Montreal Neurological Institute (resampling voxel size = 3 mm × 3 mm × 3 mm) and smoothed using an 8 mm full width at half-maximum Gaussian kernel.

Image preprocessing and statistical analysis were carried out using Statistical Parametric Mapping (SPM8) software (http://www.fil.ion.ucl.ac.uk). The within-subject and between-subject effects were separately tested using 1-sample and 2-sample *t*-test, and the statistical threshold of correlation maps was set to $P < 0.005$ (uncorrected), with a cluster size > 10 voxels to concentrate cluster extension.

RESULTS

Altered Brain Activations by Different Emotional Pictures With and Without Pain Stimulus in PSPD

It revealed that patients with PSPD showed increased brain activities in the subgenual anterior cingulate cortex (sgACC), the left middle temporal gyrus (MTG), the right insula and the right superior temporal gyrus (STG) in response to negative pictures without pain stimulation compared with healthy controls. There were other brain areas such as bilateral precentral gyrus (PCG), the left STG, the left superior parietal lobe (SPL), the left fusiform gyrus and the left PCG where patients with PSPD showed decreased activation compared with controls (Table 3). While viewing of positive stimuli, patients with PSPD demonstrated hyperactivations in the left poscentral gyurs and the bilateral insula and hypoactivations in the left SPL and the right precunues under non-pain condition compared to healthy controls (Table 4).

Under the pinprick pain condition, compared with the healthy controls, patients with PSPD showed hyperactivations associated with emotionally positive pictures mainly in the right PCG, the left inferior semilunar lobe, the right dorsolateral prefrontal cortex (dlPFC), the left ventral lateral prefrontal cortex (vlPFC), the right putamen, the right thalamus, and the right cerebellar tonsil compared with healthy controls (Table 5, Figure 2). Pinprick pain induced diminished activities in the bilateral insular, left STG, left fusiform gyrus, bilateral posterior cingulate cortex (PCC), right parahippocampus, and left lingual gyrus in the PSPD patient group during neutral picture-induced emotion compared with those in the healthy controls. Meanwhile, regions activated by pinprick pain stimuli during negative emotions in the right STG, bilateral MTG, left fusiform gyrus, right PCC, right middle frontal lobe (MFL), left caudate body, right mammillary body, left uvula, left culmen, and bilateral cerebellar tonsil were stronger in the patients with PSPD, unlike those in the controls. Moreover, activation in the left PCG and right thalamus was greater in patients with PSPD during pinprick pain stimulation under negative emotions than that under positive ones.

Differences in Cerebral Pain Processing Between Groups

The group difference maps of activation by negative pictures with and without pain stimulation in patients

Table 4. Group Difference Maps of Activation by Positive Pictures between Patients and Controls (Without Pinprick Pain)

		Left			Right		
Activation by Positive Pictures	Regions	Coordinates x/y/z	Cluster Size	Max t	Coordinates x/y/z	Cluster Size	Max t
Controls > Patients	Superior parietal lobe (BA 7)	−30/−54/51	14	3.93	6/−66/48	19	3.69
	Precuneus (BA 7)				9/−60/42		3.03
Patients > Controls	Postcentral gyrus (BA 7)	−15/−48/69	18	3.79	48/−6/−6	51	4.19
	Insula (BA 13)				57/2/−6		4.15
					54/18/0		4.1
	Insula (BA 13)	−33/24/3	16	3.51			
	Insula (BA 13)	−42/3/6	16	3.33			
	Insula (BA 13)				42/6/−15	18	3.79

Positive–Baseline, $P < 0.005$ (uncorrected), cluster size > 10 voxels.

Table 5. Group Difference Maps of Activation by Different Emotional Pictures Between Patients and Controls (With Pinprick Pain)

		Left			Right		
	Regions	Coordinates x/y/z	Cluster Size	Max *t* Score	Coordinates x/y/z	Cluster Size	Max *t* Score
Neutral Controls > Patients	Posterior Cingulate Cortex (BA 31)	−9/−24/42	37	3.96			
	Posterior Cingulate Cortex (BA 24)				6/−12/39	12	3.21
	Parahippocampus (BA 28)				27/−18/−12	43	3.57
	Insula (BA 13)	−42/−18/18	34	3.88	42/0/6	18	3.48
	Insula (BA 13)				42/0/15		3.07
	Superior Temporal Gyrus (BA 13)	−48/−18/6		3.33			
	Superior Temporal Gyrus (BA 22)	−48/0/−9	10	3.47			
	Fusiform Gyrus (BA 19)	−27/−81/−12	22	3.4			
	Lingual Gyrus (BA 18)	−21/−75/−3		3.26			
Neutral Patients > Controls			N.S.			N.S.	
Positive Controls > Patients			N.S.			N.S.	
Positive Patients > Controls	Inferior Semilunar Lobe	−6/−72/−39	52	4.42			
	Inferior Semilunar Lobe	−30/−72/−39	18	3.88			
	Cerebellar Tonsil				27/−66/−39	11	4.11
	Putamen				24/15/−9	12	3.69
	Ventral Lateral Prefrontal Cortex (BA 47)	−33/30/−12	10	3.63			
	Dorsolateral Prefrontal Cortex (BA 8)				39/24/45	33	3.52
	Precentral Gyrus (BA 9)				42/18/33		3.26
	Thalamus				9/−3/21	10	3.28
Negative Controls > Patients			N.S.			N.S.	
Negative Patients > Controls	Uvula	−9/−72/−36	164	4.84			
	Cerebellar Tonsil	−24/−57/−36		3.82	33/−45/−36	11	4.11
	Middle Temporal Gyrus (BA 39)	−45/−63/15	22	3.91	48/−63/24	23	3.83
	Culmen	−45/−57/−30		3.77			
	Posterior Cingulate Cortex (BA 31)				24/−36/24	18	3.83
	Middle Frontal Lobe (BA 6)				51/15/48	12	3.43
	Mammillary Body				3/−9/−9	11	3.53
	Fusiform Gyrus (BA 37)	−45/−42/−9	13	3.81			
	Caudate Body	−15/−6/27	25	3.46			
	Caudate Body	−24/−12/27		3.18			
	Superior Temporal Gyrus (BA 39)				48/−51/12	27	3.37
	Superior Temporal Gyrus (BA 13)				48/−48/21		3.28

$P < 0.005$ (uncorrected), cluster size > 10 voxels.

showed that the patients had diminished activation in MFG with pinprick pain stimuli. However, in the control group with negative emotions, pinprick pain induced diminished evocations in the left fusiform gyrus, left PCC, bilateral dlPFC, right inferior frontal gyrus, right MFC, right parahippocampus, right medial globus pallidus, right amygdala and right lingual gyrus, left uvula, declive, and cerebellar tonsil. When directly

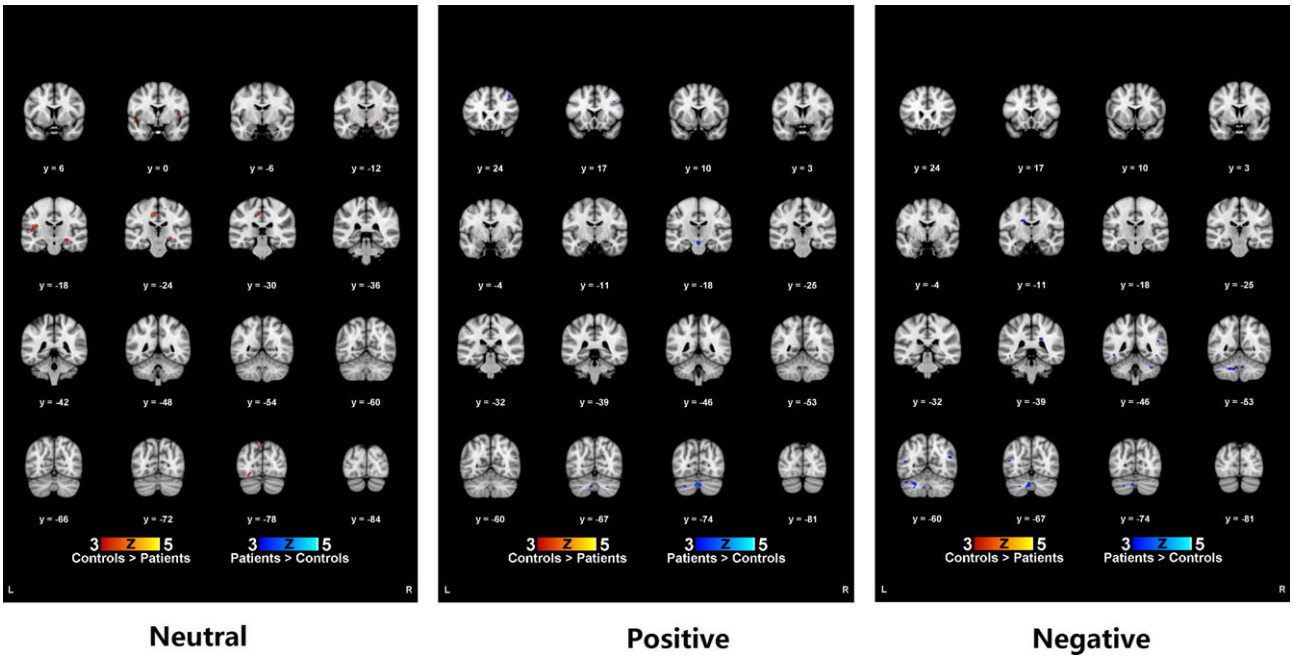

Figure 2. Group difference maps of activation by pinprick pain stimuli in different emotional conditions. Patients with persistent somatoform pain disorder vs. healthy controls ($P < 0.005$, uncorrected).

comparing with healthy controls, we found that patients with PSPD exhibited hyper-activation mainly in the left fusiform gyrus, the bilateral dlPFC, the left vlPFC, medial prefrontal cortex (mPFC), the PCG, and the right insula during viewing of negative pictures for the contrast of pinprick pain versus no pinprick pain stimuli. However, we did not observe any decreased activations in patients with PSPD. As for positive pictures, compared with healthy controls, patients with PSPD almost did not show enhanced or decreased brain activations (except for the right SPL) with pinprick pain versus no pinprick pain stimuli compared with healthy controls. For neutral pictures, patients with PSPD demonstrated increased activation in the mPFC but decreased activations in the right dlPFC, left MFG, right inferior parietal lobe (IPL), left cuneus, ACC and PCC compared with healthy controls (See supplementary Table 1). Thus, we speculated that the patients with PSPD were inconsistent with the controls on emotion perception.

DISCUSSION

The present fMRI analysis revealed that the cerebral activations induced by emotion and pain in the patients with PSPD were mainly distributed within the areas corresponding to the emotional response and lateral nociceptive systems as the PFC and parietal cortex, cingulate cortex, insula, postcentral/precentral gyrus, and temporal gyrus. In addition, our group difference maps (patients vs. controls) showed increased activities mainly in the bilateral dlPFC, mPFC, the vlPFC, the MFG, the SFG, the left fusiform gyrus, the right PCG, the right insula, the bilateral cerebellar tonsil in patients in response to pinprick pain vs. non-pinprick pain stimulation during processing of negative emotion. However, patients with PSPD showed diminished activations in the dlPFC, the MFG, the ACC, the PCC, the cuneus, and the mPFC in response to pinprick pain vs. non-pinprick pain stimuli under neutral emotion state compared with healthy controls. As for positive emotion, patients almost showed no significant alterations in brain activations compared with healthy controls. Our results indicated that patients with PSPD differentially demonstrated neural dysfunction associated with different emotional processing under pinprick pain stimuli and the different emotional states might influence the pain related brain activities in patients. Thus, during psychological treatments of patients with PSPD, we propose that psychologists should consider that positive emotion and easy conditions may help patients with PSPD relieve pain.

Patients with PSPD have a lower quality of life with pain, depression, and anxiety compared with the general population.[36] Pain can vary widely in different psychological states among people and within the

individual.[37] The emotional state can enormously influence pain. Several studies demonstrated that a negative emotional state increases pain, whereas a positive state relieves pain.[38] For example, the analgesic effect of the opioid agonist remifentanil with a clinical dose can be completely reversed by a negative expectation,[39] whereas the expectation of pain relief is an important component of placebo analgesia.[40] Patients with somatoform pain disorders show enhanced pain sensitivity,[5] and negative emotional context, such as sadness, increases pain sensitivity in somatoform pain disorders, thereby contributing to the psychopathology of this disorder.[28] In line with previous studies, our results demonstrated that emotion was significantly associated with the pathogenesis of PSPD. In the current results, pinprick pain-related activation of brain regions were enhanced under negative emotional condition in patients with PSPD. As expected, these brain regions in patients were not altered under positive emotional condition. Enhanced care and keeping patients in a relatively positive emotional state may promote the treatment efficacy of patients with PSPD.

In terms of different emotional responses, Paradiso et al. found that subjects in the process of positive emotions activated the medial frontal cortex, dorsolateral frontal cortex, and orbital cortex compared with the negative emotions. By contrast, the negative emotions activated the amygdala, visual cortex, and cerebellum relative to the positive condition.[41] In the present study, we also found different activation of PFC, which was previously demonstrated to play an important role in moderating social behavior,[42–46] such as inhibiting emotional responses,[47] and it is involved with pain-related emotion-based decision-making deficits in humans[48] and animals.[49–52] Our results showed that in neutral condition, patients with PSPD showed decreased PFC activation compared with healthy controls. However, the PFC regions were more activated in the patients during negative emotion and pinprick pain stimulation than that in the healthy controls. Additionally, the activities of PFC in the patients were less changeable during emotional changes, unlike those in the controls. A recent study showed that pain-related hyperactivity in the amygdala induces the deactivation of the mPFC, which is closely interconnected with the emotional brain center amygdala.[49] Another study comparing patients with controls found a noxious heat stimulation-related hypoactive state of the ventromedial prefrontal/orbitofrontal cortex (BA 10/11) and a hyperactive state of the parahippocampal gyrus, amygdala, and anterior insula in patients with somatoform pain disorder.[24] We also found that supramarginal gyrus was altered in patients with PSPD under pain vs. non-pain condition during processing negative emotion. In line to our finding, previous imaging studies reported that emotional pictures also produce sizable clusters in the right inferior and superior parietal lobules.[53] Positively valenced stimuli have been found to induce activation in the right IPL, PCC, and mPFC.[54,55] The inferior parietal lobe/gyrus is involved in the perception of emotions in facial stimuli and interpretation of sensory information.[56] Moreover, the STG is involved in the perception of emotions in facial stimuli. Beauregard[57] demonstrated that the right anterior temporal lobe is activated in response to negative images. It can also be activated by thread-related or emotional states in patients with generalized anxiety disorders.[58] In line with these findings, the current data indicated that negative emotion-induced stronger activation in the right STG and left MTG in PSPD patients with and without pinprick pain stimuli compared with the controls. Our results may indicate the relation between STG/MTG with pinprick pain during negative emotion in patients with PSPD.

Furthermore, fMRI analysis also indicated that the insula, which is reportedly associated with the affective dimension of pain,[59] was also more evoked by pinprick pain stimulation in the controls during neutral emotion, but it was inhibited by pinprick pain stimulation in the patients during positive emotion. Previous studies also reported stronger activation of the insula for pain stimuli in patients with somatoform pain disorder vs. controls,[24,25] and negative emotional states enhance pain-related activity in the insula.[21,60,61] In line with these previous findings, our study found that patients with PSPD demonstrated hyperactivation in the insula in response to pain in negative emotion compared to healthy controls. In addition, we also observed altered activations in the occipital lobe (including fusiform gyrus and middle occipital lobe), the PCG, the precunues, the ACC, the PCC and the cerebellum in patients in response to negative and neutral stimuli. Among them, the occipital lobe may be involved in emotion processing.[62] Additionally, neuroimaging studies evaluating the effects of emotional states on pain processing also found that a number of brain regions, but most consistently the ACC, show altered pain-evoked cortical activation in negative emotional states produced by looking at emotional faces, listening to unpleasant music, or smelling unpleasant odors.

Our research had some limitations because of the small sample size. Moreover, the race of the participants and patient states differed from those in previous reports. In addition, the unknown potential variations in brain dynamics among different individuals and patients or some neglect mechanisms may have influenced our findings. Thus, more accurate evaluations of the illness severity and individual social psychological factors, as well as their relation to different activated brain regions, are needed for further investigations.

In summary, our data provided evidence that different cerebral (prefrontal–temporal–limbic circuit) activation patterns exist in patients with PSPD. Patients with PSPD tend to show hyper brain activities in this prefrontal-limbic circuit compared with controls in response to pinprick pain stimulation during negative emotional conditions. These results provide some insight into emotional changes influencing pinprick pain-related activity in patients with PSPD, suggesting the potential role of emotion in the pain processing and pathophysiology of PSPD.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Group Difference Maps of Activation by Different Emotional Pictures Between Patients and Controls (With Pinprick Pain versus Without Pinprick Pain).

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