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ORIGINAL RESEARCH

Aberrant Thalamic-Centered Functional Connectivity in Patients with Persistent Somatoform Pain Disorder

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Purpose: Recent task-based fMRI studies have shown that Persistent Somatoform Pain Disorder (PSPD) patients demonstrated aberrant activity in a wide range of brain regions associated with sensation, cognition and emotion. However, these specific task-based studies could not clearly uncover the alterations in the spontaneous brain networks that were associated with the general pain-related symptoms in PSPD.

Patients and Methods: In the present study, 13 PSPD patients and 23 matched healthy controls (HCs) were enrolled. Resting state and 3D structural imaging data were collected during magnetic resonance imaging (MRI) scans. Ninety regions of interest (ROIs) were selected from the automated anatomical labeling (AAL) template. The functional connectivity toolbox "CONN" was used to calculate the functional connectivity (FC) coefficients.

Results: Our results showed that PSPD patients exhibited increased FCs between the left thalamus and the right amygdala, the right hippocampus, and multiple sub-regions of the occipital lobe when compared to HCs. Correlation analysis revealed a negative correlation between the left thalamus-right amygdala FC and the level of anxiety in PSPD patients.

Conclusion: These findings suggest that the altered FC between thalamus and amygdala may be the neural mechanisms underlying the pain-related anxiety in PSPD.

Keywords: persistent somatoform pain disorder, functional magnetic resonance imaging, resting-state, functional connectivity

Introduction

Persistent somatoform pain disorder (PSPD), also called somatoform pain disorder or pain disorder, is known as a special type of somatoform disorders. It is characterized by the predominant complaint of persistent and distressing pain, which could not be sufficiently explained by a physiological process or a physical disorder (ICD-10, Version: 2016). Since the pathogenesis of this disease remains still unclear, there is nearly no effective treatment, which not only gravely affects the living conditions of the patients but also brings undue burdens to the medical system.[1] Therefore, it is compelling to investigate the underlying psychopathology of PSPD symptoms.

In the past years, with the rise of brain imaging research, the neurological mechanism of PSPD was gradually revealed. Structural magnetic resonance imaging researcher exhibited that cortical thickness of patients with chronic pain disorder was thinner than healthy controls, where were localized to regions that correspond to sensory and affective dimensions of pain processing, including the

left precentral, postcentral gyri, left inferior temporal sulcus, right middle frontal, inferior parietal gyri, and right anterior temporal pole.[2] During the cognitive task, patients with somatoform pain disorder have decreased prefrontal brain activation compared with healthy controls.[3] By using noxious or stress stimuli during the functional MRI (fMRI) scanning, researchers have found that patients with PSPD demonstrated dysfunctions in a variety of brain regions associated with sensation (such as the thalamus) and emotional processing (such as the insular cortex, the amygdala, the cingulate cortex, and the operculo-insular cortex).[4–7] However, these task-based studies could not clearly uncover the basic pathogenesis of PSPD, because the pain symptoms usually appear without the influence of real stimuli from the outside environment.

Researchers have shown increasing interest in spontaneous and low-frequency neural activities in PSPD patients using resting-state fMRI or electroencephalography (EEG). For instance, it was found that somatoform pain disorder patients exhibited higher regional homogeneity (ReHo) in the left precentral gyrus, the prefrontal cortex and default-mode network, but decreased ReHo in the bilateral primary somatosensory cortex, the posterior cerebellum, and the occipital lobe comparing with healthy controls.[8,9] Further, using independent component analysis to isolate intrinsic connectivity networks (ICNs) and to calculate the functional network connectivity (FNC) such as intra- and inter-ICNs, Zhao and his colleagues found altered FNCs between the sensorimotor network, the audio network, the visual network, the default-mode network, the executive control network, the salience network, the right-frontoparietal network, the left-frontoparietal network, and the cerebellum network in PSPD patients.[10] A resting-state EEG study revealed that somatoform pain disorder patients exhibited hyperexcitability resting-state cortical oscillations at the parietal region.[11] The evidence above suggests that PSPD patients manifest large-scale brain functional reorganization at different levels.

However, the whole-brain FC pattern of PSPD remains still largely unknown. Recently, researchers have recognized that brain regions are connected and that disturbances within whole-brain FC pattern could influence the onset, expression and course of diseases like Parkinson's disease, schizophrenia, depressive disorder, and anxiety disorders.[12–15] We believed that whole-brain FC pattern was altered in PSPD and this change would provide new evidence for exactly localizing the functionally abnormal brain areas. To confirm this hypothesis, the present study adopted 90 anatomically cerebrum regions from the automated anatomical labeling (AAL) template[16] as regions of interest (ROIs), and a seed-based FC analysis was used to explore the whole-brain FC pattern in PSPD patients and HCs. Through comparisons between groups, we anticipate that the altered FC mainly related to pain sensation, cognition, emotion and memory brain regions such as the thalamus, the somatosensory cortex, the prefrontal cortex, the amygdala and the hippocampus.

Materials and Methods
Ethics Statement
This study was approved by the local Ethics Committee of Tongji Hospital of Tongji University (No.141). All participants were informed of the experimental procedures and written informed consent was obtained from every participant prior to the experiment. All procedures were conducted in accordance with principles expressed in the Declaration of Helsinki and each of the participants was paid 500 (Chinese Yuan) for completing the experiment.

Participants
Thirteen PSPD patients were enrolled from May 2012 to May 2016 through the inpatient and outpatient service in Tongji Hospital of Tongji University, and 23 HCs were enrolled via advertisements posted in nearby communities. All the patients were diagnosed by one psychiatrist and they all met the following inclusion criteria: (1) diagnosis of PSPD according to the criteria of 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10): F45.4; (2) the duration of disease was longer than 6 months; (3) between the age of 18 and 65; (4) right-hand dominance, and exclusion criteria: (1) presence of pain symptoms due to severe somatic diseases; (2) presence of severe somatic diseases, such as cardiovascular disease, cerebrovascular disease, epilepsy; (3) presence of other mental disorders; (4) substance abuse; (5) current pregnancy.

Clinical Assessments
Multiple self-reported scales were used to assess the pain intensity and the emotional problems, including the Visual Analogue Scale (VAS), the Zung Self-Rating Anxiety Scale (SAS) and the Zung Self-Rating Depression Scale (SDS). The VAS is a one-dimensional method to measure the pain intensity by marking one score on the line where "0" stands for no pain and "10" for worst pain,

respectively.[17] The SAS, which contains 20 items, was applied to assess the anxiety severity.[18] Each response was rated on a 4-point scale, from "none of the time" to "most of the time". The Chinese version of SAS with acceptable reliability and validity was adopted in the present study.[19,20] In addition, the SDS was employed to assess the level of depression.[21] Twenty items reflect four groups of specific symptoms of depression: Psycho-emotional symptoms (like "I feel down-hearted and blue"), Somatic disorders (such as "I notice that I am losing weight"), Psychomotor disorders (eg, "I am restless and can't keep still") and Depressive mental disorder (eg "I am more irritable than usual"). The Chinese version of SDS with acceptable reliability and validity was used in the present study.[19,20]

MRI Data Acquisition

Functional neuroimaging data were acquired using a Siemens Trio 3.0 Tesla MRI scanner (Siemens, Erlangen, Germany) at the Shanghai Key Laboratory of Magnetic Resonance, East China Normal University. At the beginning of the fMRI scan, participants were instructed to keep their eyes closed, not to think of anything in particular and not to fall asleep. Foam pads were used to tightly fix the participant's head to reduce movement.[22] Rs-fMRI data were collected axially using an echo-planar imaging (EPI) sequence: echo time = 30 ms, repetition time = 2000 ms, flip angle =90°, field of view = 192 mm×192 mm, axial slices = 33, slice thickness = 4 mm, no gap, matrix = 64×64. T1-weighted images covering the entire brain were obtained in a sagittal orientation employing a magnetization-prepared rapid gradient echo sequence before each resting image. 240 fMRI image volumes and 192 T1 image volumes were collected for each participant.

fMRI Data Pre-Processing

Prior to analysis, the first 10 volumes of the fMRI data of each participant were discarded to allow for magnetization equilibrium.[9] The data were subsequently preprocessed and analyzed in the functional connectivity toolbox "CONN" v.16b (http://www.nitrc.org/projects/conn) running on Matlab R2014a and using the Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) default parameter choices. The pipeline procedures included functional slice timing correction, functional realignment and unwarping, functional center to (0,0,0) coordinates, structural center to (0,0,0) coordinates, structural segmentation & normalization, functional normalization, functional outlier detection (ART-based

scrubbing), and smoothing (8-mm FWHM Gaussian filter). Then, the toolbox step to a denoising procedure: the confounding effects such as the white matter, cerebrospinal fluid, realignment results, scrubbing results, and the rest were regressed out of the fMRI time series, and after that, the data were bandpass-filtered (0.01 to 0.08 Hz)[23] and linear detrended.

ROI Regions Selection

Regions of interest (ROIs) were selected from the automated anatomical labeling (AAL) template (www.fil.ion.ucl.ac.uk/spm/ext/), which was an atlas widely used for manual micro-anatomical parcellation of the single-subject MNI-space template brain.[24] The entire cerebrum was divided into 90 regions which were considered as seeds and nodes in the later FC analysis. The index, abbreviations, and MNI coordinate of the 90 cerebrum regions used in this study are shown in Supplementary information Table S1.

ROI-to-ROI FC Analysis

Regional mean blood oxygen-level-dependent (BOLD) time series was estimated by averaging the time series of all voxels at each ROI.[25,26] Bivariate correlation coefficient was used to measure the level of linear association of the BOLD time series between each pair of ROI:[27]

$$r = (x^t \cdot x)^{1/2} \cdot b \cdot (y^t \cdot y)^{1/2}$$

Before entering into a further statistical analysis, a Fisher's r-to-z transformation was applied in order to improve the normality assumptions of the general linear model.[27] To this end, we constructed a 90 × 90 matrix where each cell represented the FC between two brain regions. Then, multiple comparisons were adjusted by applying the correction of False discovery rate (p<0.05).

Correlation Analysis

To investigate the relationship between identified FCs and scores on the clinical assessments, we performed a Spearman's rank correlation analysis to determine the relationships between the z-scores of the identified FCs and the VAS scores/SAS scores/SDS scores/duration of illness by using SPSS 20.0 (IBM, USA).

Results
Participants' Characteristics

PSPD patients and HCs showed no significant difference in age and gender ratio. Table 1 presents the demographic

Table I Demographic and Clinical Data of Patients with PSPD

Group	PSPD (n=13) Mean±sd	HC (n=23) Mean±sd	t/x^2	p
Gender (male:female)	5:8	12:11	0.63	0.43[a]
Age(year)	46.0±14.33	46.0±12.73	−0.01	0.99[b]
Duration(year)	3.5±2.57	–		
VAS score	5.69±2.10	–		
SAS score	35.62±9.42	–		
SDS score	38.54±9.31	–		

Notes: [a]Chi-Square test. [b]Independent samples *t*-test
Abbreviations: VAS, visual analogue scale; SAS, self-rating anxiety scale; SDS, self-rating depression scale.

characteristics of all participants and scores of the clinical assessment in the PSPD patients.

FC Within Groups

The whole-cerebrum FC results of the PSPD and HC groups are presented in Figure 1A and B, respectively. On the whole, most of the strong functional connectivities (large z-scores) were found between inter-hemispheric symmetric regions (the node near the diagonal) such as between the left rectus and the right rectus, the left insula and the right insula, the left-anterior cingulate cortex and the right-anterior cingulate cortex, the left calcarine and the right calcarine. In addition, strong connectivities were observed between the anatomically adjacent brain areas such as the calcarine fissure, the cuneus, the lingual gyrus, the superolateral occipital gyrus, the medial occipital gyrus, the inferior occipital gyrus, and the fusiform gyrus.

Group Differences in FC Intensity

PSPD patients showed increased intensity of FCs between the left thalamus and the right amygdala, the left thalamus and the right hippocampus, the left thalamus and multiple sub-regions of the occipital lobe including bilateral calcarine fissure and surrounding cortex, bilateral lingual gyrus, bilateral fusiform gyrus, and left Inferior occipital gyrus ($p_{\text{FDR-corrected}} <0.05$). However, the intensity of FC was observed decreased between the left amygdala and the right putamen in the PSPD patients (Table 2 and Figure 2).

Relationship Between FC Intensity and Clinical Symptoms in PSPD Patients

A strong negative correlation (r = −0.61, p = 0.03) between the standardized intensity of the left thalamus–the right amygdala FC and the scores on the SAS (Figure 3) was observed. However, no any other significant correlations were found between the intensity of identified FCs and VAS scores, SDS scores or duration of illness.
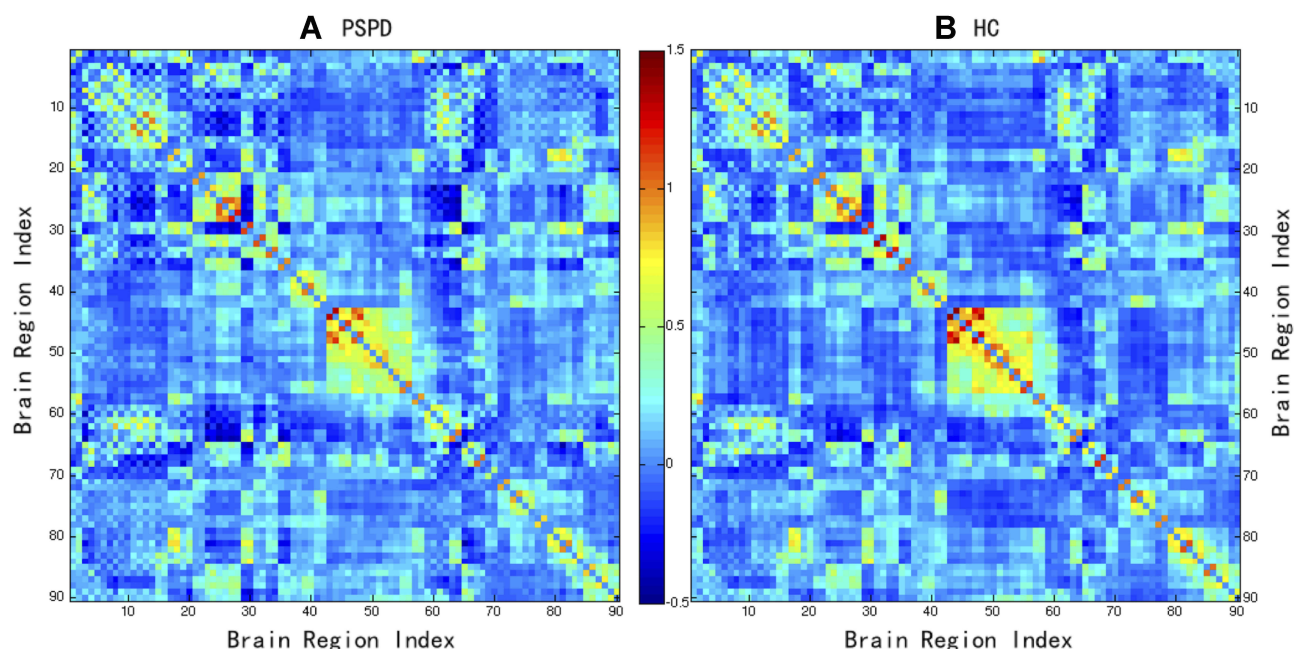

Figure I 90×90 FC matrix of PSPD patients and HCs. The number in the axis stand for the 90 AAL cerebrum regions. Red represents positive functional connectivity; the dark color indicates large z-score. Blue represents negative functional connectivity; the darker color indicates the smaller the z-score. (**A**) 90×90 FC matrix of PSPD patients; (**B**) 90×90 FC matrix of HCs.
Abbreviation: FC, functional connectivity.

Table 2 Group Difference in the Intensity of ORI-to-ORI FC Between Patients with PSPD and HCs

ORI-to-ORI		*F*	*p*$_{uncorrected}$	*p*$_{FDR}$
PSPD>HC				
THA.L (−11, −18, 8)-	HIP.R (29, −20, −10)	3.64	0.0009	0.0316
	AMYG.R (−23, −1, −17)	3.20	0.0029	0.0374
	CAL.L(−7, −79, 6)	3.01	0.0049	0.0485
	CAL.R(16, −73, 9)	3.06	0.0043	0.0478
	LING.L(−15, −78, −5)	3.30	0.0023	0.0374
	LING.R(16, −67, −4)	3.47	0.0014	0.0316
	IOG.L(−36, −78, −8)	3.23	0.0027	0.0374
	FFG.L(−31, −40, −20)	3.50	0.0013	0.0316
	FFG.R(34, −39, −20)	3.86	0.0005	0.0316
HC>PSPD				
AMYG.L (−23, −1, −17)-	PUT.R (28, 5, 3)	3.99	0.003	0.0296

Abbreviations: ROI, regions of interest; THA, thalamus; AMYG, amygdala; CAL, calcarine; FFG, fusiform; HIP, hippocampus; IOG, inferior occipital gyrus; LING, lingual gyrus; PUT, putamen; L, left; R, right.

Discussion

In this study, we investigated the functional connectivity across the whole cerebrum in PSPD patients using rs-fMRI. Similar to a newly study,[28] we found considerable functional connectivity altered in PSPD patients. By Degree centrality analysis and functional connectivity analysis, Liu et al found six functional hubs (the bilateral inferior occipital gyrus, bilateral calcarine fissure, left paracentral lobule) and multiple decreased FC values between these six regions. Differently, the present study only found one functional hub (the left thalamus) and exhibited a thalamic-centered whole-brain FC altered.

Increased Thalamic-Centered Functional Connectivity in PSPD Patients

Through a seed-based whole-cerebrum FC analysis, for the first time, we found an aberrant thalamic-centered FC pattern in PSPD patients. Consistent to our findings, previous animal studies found that a lesion made to the thalamic nuclei could help to alleviate the symptoms of neuropathic pain,[29,30] and previous human brain imaging studies revealed that the thalamus was one of the crucial brain areas which involved in the pain processing.[31–33] For instance, one task-related fMRI study on the somatoform pain disorder found that patients showed increased activation of thalamus under the stimulation of pin-prick pain and cognitive stress.[4] Nevertheless, other resting-state fMRI researches reported comparable levels of ReHo or FNC of the thalamus in PSPD patients, which was not in line with our findings.[8–10] This difference may be derived

from the diverse spatial scale of the statistical subjects and diverse statistical method of the correlation coefficient.

It is generally known that the thalamus is the destination of ascending sensory pathway where the sensory information is relayed to the cerebral cortex and limbic system via the thalamocortical radiations and the thalamus-limbic pathway, respectively.[34] Hence, the thalamus is regarded as the essential organ of the affective side of sensation, especially pain.[32] Previous studies have found that the thalamus showed greater spontaneous firing and excessive burst firing in patients with chronic pain.[35–37] In the animal models of peripheral neuropathic pain, thalamus also showed spontaneous hyperexcitability, evoked hyperactivities, expansion of receptive fields, and bursting firing.[38,39] It may be suggested that the persistent chronic pain and associated symptoms of PSPD were caused by spontaneous hyperexcitability or evoked hyperactivities in the thalamus, from which the spontaneous pain-related impulses transmitted to other brain regions such as the occipital lobe, the amygdala, the hippocampus via the thalamocortical radiations and the thalamus-limbic pathway.

In line with our findings, previous imaging studies have also reported altered FCs of the occipital areas in patients with chronic pain.[40–42] The altered FCs were found between the occipital areas and the anterior cingulate cortex, the medial prefrontal cortex, the inferior frontal gyrus, and the insula. The altered connectivity between thalamus and visual cortex might be related to the impaired visual attention functioning in chronic pain condition.[43,44] One of these studies also found that participants with chronic pain fixated significantly more
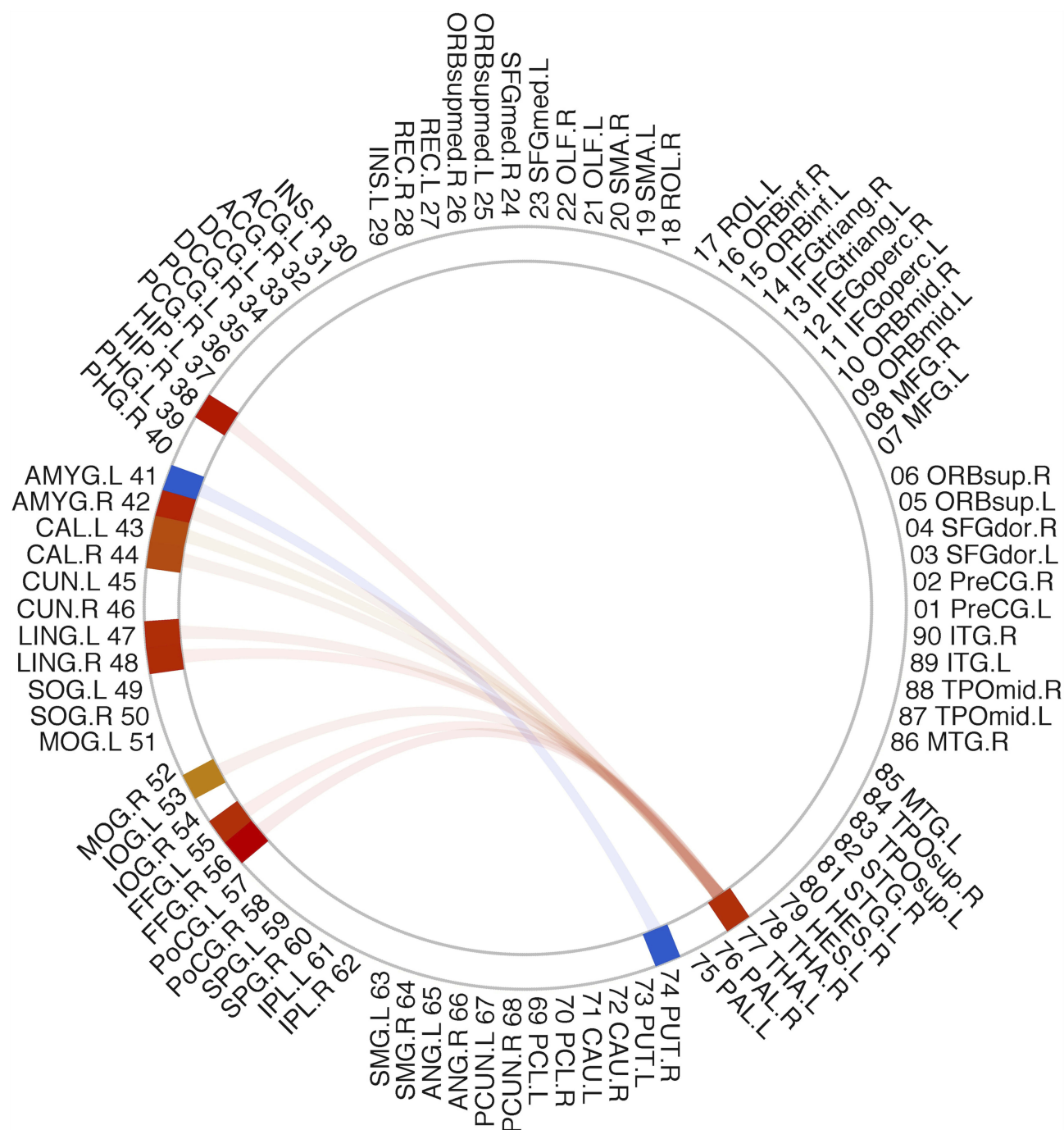
Figure 2 ORI-to-ORI FC z-score showing significant group difference between PSPD patients and HC. The number and abbreviation outside the circle stand for the 90 AAL cerebrum regions. The red line stands for increased FC and the blue line stands for decreased FC in PSPD patients compared to HCs.
Abbreviation: FC, functional connectivity.

frequently on pain words than pain-free participants, supporting the hypothesis that individuals with chronic pain displayed specific attentional biases toward pain-related stimuli.[43]

Additionally, studies have found altered FC between the hippocampus and multiple subareas of the cingulate cortex,[45–47] and between the amygdala and multiple subareas of the cingulate cortex[45,46,48] in chronic pain patients. Correspond with previous researches, the present study also showed altered FC between left thalamus and the hippocampus and the amygdala, and found a strong negative correlation between the altered left
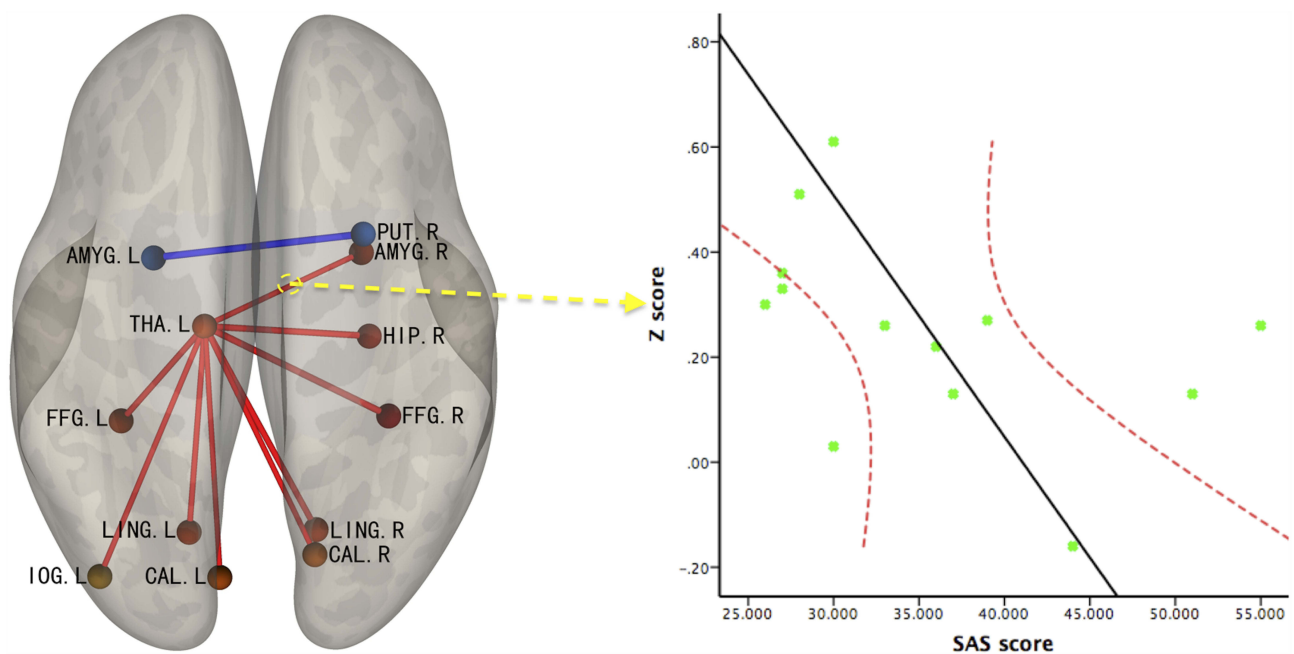
Figure 3 The result of correlation analysis between identified FCs and the score on the SAS.
Abbreviations: FC, functional connectivity; THA, thalamus; AMYG, amygdala; L, Left; R, Right; SAS, Self-Rating Anxiety Scale.

thalamus-right amygdala FC and the SAS scores. The amygdala and the hippocampus were related to the enhanced memory for pleasant and aversive stimuli.[49,50] While the thalamus-amygdala pathway was shown to be involved in the affective behaviors such as stress/anxiety.[34] We thus draw a relatively safe conclusion that the altered FC between thalamus and amygdala may be the neural mechanisms underlying the pain-related anxiety in PSPD.

Decreased Functional Connectivity in PSPD Patients

There was only one decreased FC that was found between the left amygdala and the right putamen in PSPD patients. As mentioned above, the amygdala was related to enhanced memory for pleasant and aversive stimuli.[49,50] The putamen was mainly to regulate movements,[51] and affect various kinds of learning.[52] And a recent review recruiting 266 cutaneous pain fMRI studies found that the left putamen is the brain area which was consistently activated under chronic pain condition.[53] A possible explanation for the decreased FC between the two brain regions might be derived from the potential neural alteration in the putamen associated with the impairments in learning of patients' past negative experience caused by pain, which subsequently leads to reduced connectivity and activities in the amygdala while processing negative emotional signals.

Limitation

There were still some limitations in the current study. Firstly, the simple size of PSPD patients was very small and the amount of subjects in the two groups is quite different. It is inevitable that there is somewhat bias in the present study, though the statistical results were FDR corrected. In reality, there are quite a small proportion of PSPD patients who are willing to see the psychiatrist or psychologist in the mental health hospitals. In addition, for ethical reasons, the PSPD patients did not suspend any of their medication during the fMRI scan. So the influence of drugs such as antidepressant and antianxiety drug, and especially sedatives and hypnotics cannot be excluded. For example, midazolam and zolpidem can increase fluctuation and synchrony of the resting brain BOLD signal.[54,55] These may restrict the relational explanatory capability of the present study in clinical.

Conclusion

In summary, the functional connectivity between the thalamus and other pain-related regions were altered in the PSPD patients, implying that the thalamus might play an important role in the psychopathological mechanism of PSPD. A strong negative correlation between the altered left thalamus-right amygdala FC and the SAS scores suggests that the altered FC may

be the neural mechanisms underlying the pain-related anxiety in PSPD. Finally, we hope that our findings will be helpful in improving the understanding of PSPD.

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Disclosure

The authors report no conflicts of interest in this work.

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