ORIGINAL RESEARCH

Abnormal Degree Centrality in Zoster-Associated Pain with or Without Psychiatric Comorbidities: A Resting-State Functional MRI Study

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Purpose: Zoster-associated pain (ZAP) is frequently concomitant with psychiatric comorbidities. However, the underlying neuropathological mechanisms of ZAP with psychiatric comorbidities remain poorly understood.

Patients and Methods: Rest-stating functional MRI (rs-fMRI) data from 41 ZAP patients without anxiety or depression (noA/D-ZAP), 11 ZAP patients with anxiety or depression (A/D-ZAP) and 29 healthy controls (HCs) were acquired. Degree centrality (DC) based on rs-fMRI was used to explore the node changes in the brain functional network in these subjects. Moreover, correlations and receiver operating characteristic curve analysis were performed.

Results: One-way analysis of variance revealed abnormal DC values in the right middle frontal gyrus (MFG) and bilateral precuneus among the three groups. Compared with HCs, A/D-ZAP showed increased DC values in the bilateral pons, while noA/D-ZAP showed increased DC values in the right pons, left brainstem and rectal gyrus and decreased DC values in the right cingulate gyrus and bilateral precuneus. A/D-ZAP showed increased DC values in the left MFG and precentral gyrus (PG) compared with noA/D-ZAP. The DC value of the left pons in A/D-ZAP was positively correlated with the self-rating anxiety scale score. Areas under the curve of DC values in the left PG and MFG for distinguishing A/D-ZAP from the noA/D-ZAP group were 0.907 and 1.000, respectively.

Conclusion: This study revealed the node differences in the brain functional network of ZAP patients with or without psychiatric comorbidities. In particular, abnormal DC values of the left MFG and PG may play an important role in the neuropathologic mechanism of the disease.

Keywords: functional MRI, degree centrality, zoster-associated pain, anxiety, depression

Introduction

Herpes zoster (HZ) occurs when the varicella-zoster virus during the latent state is reactivated in the dorsal root or cranial nerve ganglia. HZ causes pain known as zoster-associated pain (ZAP), including acute pain and postherpetic neuralgia (PNH).[1] The risk of HZ and its comorbidities increases markedly with age.[2] The aging of the population increases the incidence of HZ worldwide.[3] The incidence of HZ ranges from 2.9 to 5.8 per 1000 person-years in individuals aged ≥50 years in mainland China.[4] ZAP is a stubborn peripheral neuropathic pain, and the occurrence of anxiety or depression in patients with ZAP is associated with acute and chronic pain following the onset of HZ.[5,6] As previous studies have concluded, patients with pain are at increased risk of anxiety or depression.[7–9] In addition, the findings from animal studies have demonstrated that animals with varicella zoster virus infection and nerve injury demonstrated an anxiety-like

pattern of ambulation.[10] However, much more remains unknown about how brain changes occur in ZAP patients with psychiatric comorbidities, such as anxiety or depression.

To date, a number of studies have explored the functional changes in the brain in various types of pain with psychiatric comorbidities by using resting-state functional MRI (rs-fMRI). Patients with back pain showed significantly increased hemodynamic activity in the subgenual anterior cingulate cortex (ACC) after improvement of pain and depression symptoms, and it positively correlated with sad valence ratings.[11] The degree centrality (DC) values of the bilateral inferior occipital gyrus, bilateral calcarine fissure, and left paracentral lobule decreased in persistent somatoform pain disorder patients, and abnormal DC values of those brain regions were negatively correlated with self-rating anxiety scale (SAS) and self-rating depression scale (SDS) scores.[12] Zhang et al constructed a rat model of neuropathic pain and found that after anxiety and depression-like behaviors manifested, rats exhibited increased amplitude of low frequency fluctuation (ALFF) values in the left somatosensory and medial prefrontal cortex (PFC) and increased DC values in the right motor cortex, as well as changes associated with alterations in emotion.[13] Trigeminal neuralgia patients exhibited enhanced resting-state functional connectivity (FC) between the right amygdala and right PFC, and the strength of FC was associated with anxiety and depression.[14] Li et al found that FC between the periaqueductal gray (PAG) and primary somatosensory cortex (SI) was negatively correlated with the depression inventory and that the effect of the depression inventory on the pain index was mediated by PAG-SI FC in PHN patients.[15] These findings support that the brain has complex functional alterations to process anxiety and depression triggered by pain. However, previous studies only used correlation analysis to find the correlations between abnormal brain imaging features and anxiety or depression scales but did not directly compare brain imaging features in pain patients with or without psychiatric comorbidities. Furthermore, the pathophysiological mechanism of ZAP with psychiatric comorbidities such as anxiety and depression was not well elucidated in the published literature.

The DC based on rs-fMRI can reflect the importance of the node in the brain functional network by calculating the number of functional connections of a single node to others within the network at the voxel level.[13,16] The presence of higher DC values indicates a greater density of functional connections within the node. This provides a metric indicating the brain functional network "hub" properties. An altered DC value indicates abnormal functional properties of node, suggesting disorganized function of the corresponding brain region. As a result of the development of imaging techniques and analytical methods, DC has been widely used in brain network research, providing new insights into the neuropathological mechanism of many diseases, such as various pain and depression.[12,13,17–20] Consequently, in this study, combined with psychological scale assessment, we used the DC analysis method based on graph theory of rs-fMRI to explore the changes in brain network node properties in ZAP patients with psychiatric comorbidities. Moreover, the correlations between DC values of the brain regions with significant differences and clinical characteristics were also assessed.

Materials and Methods
Participants

The participants of this study consisted of 51 right-handed ZAP patients who were treated in the Pain Department of the Affiliated Hospital of Southwest Medical University and 29 right-handed healthy controls (HCs) from 2018 to 2021. This study included 11 ZAP patients with anxiety or depression (A/D-ZAP) and self-rating depression scale (SDS) scores >0.5 or self-rating anxiety scale (SAS) scores >50 and 40 ZAP patients without anxiety or depression (noA/D-ZAP) and SDS scores ≤0.5 or SAS scores ≤50.[21] A total of 29 HCs who were gender- and age-matched with patients were recruited. All HCs were free from pain and had no history of any major psychiatric illnesses. All participants were between 40 and 80 years of age and free from neurological illnesses, brain structural abnormalities, or alcohol or drug abuse. Participants who presented remarkable cerebral infractions or had maximal head movement or displacement >2.5 mm or head rotation >2.5° in any direction were excluded. All procedures used in the present study were approved by the Medical Research Ethics Committee of the Affiliated Hospital of Southwest Medical University. The written informed consent was obtained from each participant and the study was performed in accordance with the Declaration of Helsinki.

Demographic Data and Clinical Assessment

The sex, age and illness duration of all participants were collected. All ZAP patients were asked to evaluate the intensity of spontaneous pain using the visual analogue scale (VAS) before the MRI scan. The sensory and affective aspects of pain were measured by the short-form McGill Pain Questionnaire (SF-MPQ). Additionally, anxiety and depression symptoms were evaluated in all participants using the SAS and SDS.

Image Acquisition

All imaging data were acquired using Philips Achieva 3.0 T MRI scanner with a standard eight-channel head coil, including T1-weighted 3D high-resolution brain structural images and rs-fMRI. During the scanning process, participants were directed to rest, close their eyes, breathe calmly, and try not to carry out any thinking movement and physical activity. The head of the subject was fixed with foam cushions to reduce head translation and rotation during the scanning process, and earplugs were worn for the subject to reduce noise. The scan was started after the subject was familiar with the environment.

T1-weighted 3D high-resolution brain structural images: The T_1-FFE sequence was used for sagittal high-resolution three-dimensional structure imaging. The scanning parameters were as follows: repetition time (TR)=8 ms, echo time (TE)=4 ms, field of view (FOV)=256×256, flip angle (FA)=7°, voxel size=1 mm×1 mm × 1 mm, slice thickness=1.0 mm, and a total of 160 sagittal slices.

Rs-fMRI: Echo planar imaging (EPI) sequence was used for axial scanning. Scanning parameters: TR=2000 ms, TE=30 ms, matrix 64×64, FOV=240×240×152, FA=90°, voxel size=3.75 mm×3.75 mm×4 mm, slice thickness=4.0 mm, slice gap =0 mm, axial scanning 38 layers, scanning time of 9 min 6 s and a total of 270 time points.

Data Postprocessing

The DPARSFA toolbox (http://www.rfmri.org/content/dparsf) was used to preprocess the original data through the MATLAB 2017a platform. The main steps are as follows: (1) the first 10 volumes were removed; (2) slice timing; (3) realignment was performed to correct head motion; (4) registration of the structural image to functional image; (5) normalization into the MNI space; (6) covariables regressed; (7) removal of linear trends; (8) bandpass filtering performed on the time series of each voxel.

DC Analysis

The calculation of the DC value was performed using RestPlus software (http://www.restfmri.net). Each voxel is a node, and the functional connection between any two voxels is an edge. The whole-brain FC matrix was constructed using the Pearson correlation coefficient between any two voxels. To conform to the normal Gaussian distribution, the voxel DC value of each subject was converted into *Z* scores, and spatial smoothing was performed to obtain a standardized DC map for statistical analysis.

Statistical Analysis

Demographic and clinical data were analyzed using statistical software (SPSS 17.0) (https://www.ibm.com/spss). The ages of the three groups were compared by performing one-way analysis of variance (ANOVA). The χ^2 test was used for the comparison of sex. The group differences in illness duration, VAS score, SF-MPQ score, SDS score and SAS score between patient groups were detected using a two-sample *t* test. *P*<0.05 was considered statistically significant.

The SPM12 toolbox (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) was used to perform one-way ANOVA on the standardized DC maps among the three groups, with age and sex as covariates. The statistical threshold was set as uncorrected P<0.005 and cluster size ≥15 voxels. Post hoc analysis using two-tailed two-sample t tests was performed to explore the differences in DC values between groups. For the results obtained by two-tailed two-sample t tests, we adopted AlphaSim correction, and the threshold of statistical significance was set at voxel-level P<0.01 and cluster-level P<0.05. Age and sex were included in these tests as covariates.

The brain regions with significant differences between A/D-ZAP group or noA/D-ZAP group and HCs were used as ROIs, and the DC values of these ROIs were extracted. Pearson correlation analysis was used to explore the correlations between the DC values of the above ROIs and the clinical characteristics (VAS score, SF-MPQ score, SDS score and SAS score) of the patients in the A/D-ZAP group and the noA/D-ZAP group, respectively. Receiver operating characteristic (ROC) curve combined with the area under the curve (AUC), 95% confidence interval (CI), sensitivity and specificity were used to evaluate the identification performance of DC for distinguishing A/D-ZAP from the noA/D-ZAP group.

Result
Demographic and Clinical Features
A total of 80 participants were included in this study, including 11 A/D-ZAP patients (7 males, mean age: 56.91 years), 40 noA/D-ZAP patients (23 males, mean age: 62.12 years) and 29 HCs (15 males, mean age: 58.62 years). The demographic and clinical details are listed in Table 1. There were no significant differences in age (F = 2.451, P = 0.093) and sex ($\chi2$ = 0.504, P = 0.777) among the three groups. No significant differences were noted in illness duration (t = 0.675, P = 0.503), VAS score (t = −0.030, P = 0.976), SF-MPQ-sensory score (t = −0.195, P = 0.846) or SF-MPQ-affective (t = −0.079, P =0.938) score in the patient groups. The A/D-ZAP group exhibited higher SDS scores (t= −7.079, P < 0.001) and SAS scores (t= −6.177, P < 0.001) than the noA/D-ZAP group.

Group Differences in DC Values
One-way ANOVA revealed abnormal DC values in the right middle frontal gyrus (MFG) and bilateral precuneus among the three groups (uncorrected, P<0.005) (Figure 1a, Table 2). A/D-ZAP showed increased DC values in the left MFG and left precentral gyrus (PG) compared with noA/D-ZAP (AlphaSim correction, voxel-level P<0.01, cluster-level P<0.05, cluster size≥18 voxels) (Figure 1b, Table 2). Compared with HCs, A/D-ZAP patients showed increased DC in the bilateral pons (AlphaSim correction, voxel-level P<0.01, cluster-level P<0.05, cluster size≥19 voxels) (Figure 1c, Table 2). Compared with the HCs, noA/D-ZAP patients showed increased DC values in the right pons, left brainstem and left rectal gyrus and decreased DC values in the right anterior cingulate, right cingulate gyrus and bilateral precuneus (AlphaSim correction, voxel-level P<0.01, cluster-level P<0.05, cluster size≥19 voxels). (Figure 1d, Table 2).

**Table 1** Demographic and Clinical Characteristics of the Participants

Clinical information	A/D-ZAP	noA/D-ZAP	HCs	χ2/t/F	P value
	n=11	n=40	n=29		
Age (year)	56.91±10.67	62.12±8.06	58.62±7.69	F=2.451	P=0.093
Sex (males/females)	7/4	23/17	15/14	χ2=0.504	P=0.777
Illness duration of ZAP (month)	40.55±36.98	88.65±234.03	-	t=0.675	P=0.503
VAS	7.00±0.77	6.99±1.31	-	t=−0.030	P=0.976
SF-MPQ					
SF-MPQ-Sensory	10.91±3.53	10.58±5.34	-	t=−0.195	P=0.846
SF-MPQ-Affective	7.18±3.74	7.05±5.19	-	t=−0.079	P=0.938
SDS	0.53±0.09	0.36±0.06	-	t=−7.079	P<0.001
SAS	48.91±7.71	36.16±5.55	-	t=−6.177	P<0.001

Notes: -, no available data; Data presented as the mean ± SD or number.
Abbreviations: ZAP, zoster-associated pain; A/D-ZAP, zoster-associated pain with anxiety or depression; noA/D-ZAP, zoster-associated pain without anxiety or depression; HCs, healthy controls; VAS, visual analogue scale; SF-MPQ, short-form McGill pain questionnaire; SDS, self-rating depression scale; SAS, self-rating anxiety scale.
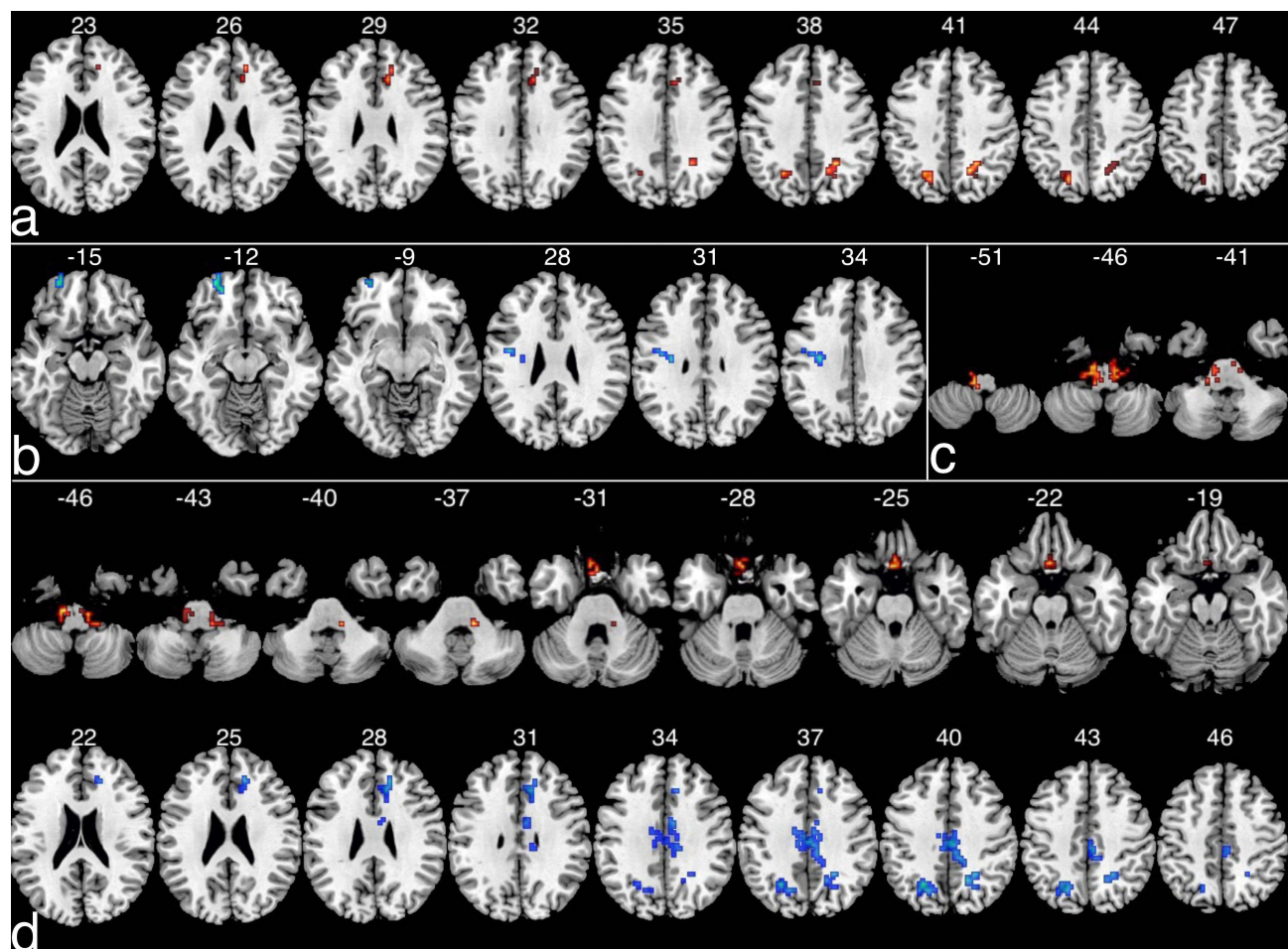
Figure 1 Regions showing DC value alterations among the three groups. Red indicates the brain region with an increased DC value, and blue indicates the brain region with a decreased DC value. (**a**) The brain regions with different DC values include the right MFG and bilateral precuneus among the three groups (P<0.005, uncorrected). (**b**) Compared with noA/D-ZAP, A/D-ZAP showed increased DC values in the left MFG and left PG (voxel-level P<0.01, cluster-level P<0.05, AlphaSim-corrected). (**c**) Compared with HCs, A/D-ZAP patients showed increased DC values in the bilateral pons (voxel-level P<0.01, cluster-level P<0.05, AlphaSim-corrected). (**d**) Compared with HCs, the noA/D-ZAP group showed significantly increased DC values in the right pons, left brainstem and left rectal gyrus and significantly decreased DC values in the right anterior cingulate, right cingulate gyrus and bilateral precuneus (voxel-level P<0.01, cluster-level P<0.05, AlphaSim-corrected).

Abbreviations: DC, degree centrality; A/D-ZAP, Zoster-associated pain with anxiety or depression; noA/D-ZAP, zoster-associated pain without anxiety or depression; HCs, healthy controls; MFG, middle frontal gyrus; PG, precentral gyrus.

Correlations Between Clinical Features and Abnormal DC Values

The DC value of the left pons was positively correlated with the SAS score in A/D-ZAP (r = 0.627, P = 0.039) (Figure 2A). Nevertheless, no correlations between DC values in other brain regions and clinical characteristics were found in the A/D-ZAP or noA/D-ZAP.

Table 2 Regions Showing DC Value Alterations Among the Three Groups

Cerebral areas	Cluster size	Peak MNI Coordinates/mm			t value
		X	Y	Z	
A/D-ZAP_noA/D-ZAP_HCs					
Right MFG	15	15	39	27	9.6919
Left precuneus	18	−24	−60	39	12.3827
Right precuneus	21	24	−51	36	12.5941

(*Continued*)

Table 2 (Continued).

Cerebral areas	Cluster size	Peak MNI Coordinates/mm			t value
		X	**Y**	**Z**	
A/D-ZAP_noA/D-ZAP					
Left PG	21	−30	−15	33	−3.614
Left MFG	18	−24	51	−12	−3.7195
A/D-ZAP_HCs					
Left pons	41	−12	−24	−45	4.122
Right pons	22	9	−24	−45	4.2659
noA/D-ZAP_HCs					
Right pons	20	12	−36	−36	3.3257
Left brainstem	22	−9	−24	−45	3.9968
Left rectal gyrus	24	−6	18	−30	3.7129
Right anterior cingulate	23	15	36	27	−4.2363
Right cingulate gyrus	72	6	−24	39	−4.7035
Left precuneus	34	−24	−60	39	−5.1903
Right precuneus	22	24	−51	36	−4.4021

Abbreviations: DC, degree centrality; MNI, Montreal Neurological Institute; A/D-ZAP, zoster-associated pain with anxiety or depression; noA/D-ZAP, zoster-associated pain without anxiety or depression; HCs, healthy controls; MFG, middle frontal gyrus; PG, precentral gyrus.

ROC Curve Analysis Between the A/D-ZAP Group and the noA/D-ZAP Group

As shown in (Figure 2B), the AUC value of the DC value in the left PG was 0.907 (CI: 0.827–0.927), and the AUC value of the DC value in the left MFG was 1.000 (CI: 1.000–1.000) for distinguishing the A/D-ZAP from the noA/D-ZAP group.
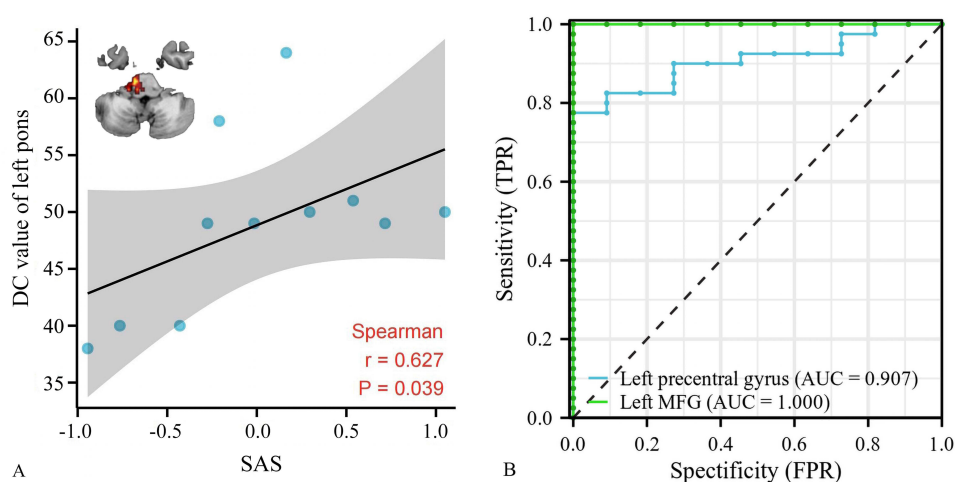
Figure 2 The results of correlation analysis and ROC analysis. (**A**) The DC value of the left pons was positively correlated with the SAS score of A/D-ZAP. (P<0.05). (**B**) ROC analysis of the DC values of the left precentral gyrus and left MFG for the prediction of A/D-ZAP.
Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; DC, degree centrality; SAS, self-rating anxiety scale; A/D-ZAP, Zoster-associated pain with anxiety or depression; noA/D-ZAP, zoster-associated pain without anxiety or depression; MFG, middle frontal gyrus.

Discussion

This study used the DC analysis method based on rs-fMRI to explore the changes in brain network nodes in ZAP patients with psychiatric comorbidities. The present study identified several abnormal brain regions involved in pain modulation and the sensory aspects of pain. Specifically, higher DC values were discovered in the left MFG and left PG of A/D-ZAP patients compared with noA/D-ZAP patients. Moreover, higher DC values were discovered in the bilateral pons of A/D-ZAP patients compared with HCs, and the DC value of the left pons showed a positive correlation with the SAS score. In addition, noA/D-ZAP patients demonstrated higher DC values in the right pons, left brainstem and left rectal gyrus and lower DC values in the right anterior cingulate, right cingulate gyrus and bilateral precuneus compared with the HCs. ROC analysis suggested that the changes of DC values in the left PG and the MFG had significant predictive value for ZAP with anxiety or depression patients. The abnormalities of the brain network in the above cerebral regions may constitute an important neuropathologic basis for the development and maintenance of ZAP with psychiatric comorbidities.

Our findings suggest that the changes in the left MFG and left PG were associated with symptoms of anxiety or depression in ZAP patients. The MFG is one of the components of the PFC and correlated with sensory and emotional processing. The functional activity of the PFC is regulated by serotonin and norepinephrine,[22,23] and the disturbances of these two neurotransmitter systems is associated with the occurrence of anxiety and depression.[24,25] Previous literature recognized that the activity in PFC is abnormal for patients with anxiety or depression symptoms, which is consistent with our study.[26–30] Furthermore, Peng et al revealed that decreased white matter fractional anisotropy of the left MFG was improved in patients with treatment-resistant depression after repeated transcranial magnetic stimulation (r-TMS), and the degree of improvement was correlated with the degree of depressive symptom relief, indicating that the white matter integrity of the MFG is related to the severity of depression.[31] Moreover, the medial PFC transmits signals to the PAG for inhibition of pain and could induce pain chronification.[32] In addition, the orbitofrontal cortex (OFC) is part of the PFC and receives projections from the mediodorsal nucleus of the thalamus. Structural or functional abnormalities of the orbitofrontal OFC have been found in depression and anxiety populations.[33] Xue et al found that resting-state FC between the right subfield of the medial OFC and the precuneus was associated with anxiety.[34] Many studies suggest that in depression and anxiety populations, the lateral OFC is overactive, while the medial OFC is less active.[35,36] These findings collectively indicate that PFC plays a pivotal role in the persistence of pain and the occurrence of psychiatric comorbidities in ZAP patients.

The PG is the motor center. Stimulation such as rTMS of the primary motor cortex can produce an analgesic effect.[37] Zheng et al holds that the primary motor cortex can regulate the sensation and negative emotions of neuropathic pain, which can relieve pain.[38] The patients with anxiety showed decreased FC between the right PG and right amygdala.[39] Generalized anxiety disorder patients showed lower ALFF and regional homogeneity (ReHo) in the right PG.[40] Major depressive disorder (MDD) patients showed decreased ReHo in the left PG.[41] There was a significant reduction in ReHo and ALFF of the bilateral PG in MDD patients with somatic symptoms compared with pure MDD.[42] These results seem to suggest that decreased activity in the PG is associated with the somatic symptoms of depression.

The brainstem provides relay nuclei for ascending and descending signals and is an important brain region for processing pain sensation.[43] Current studies have found that the paracarpal nucleus (PB) and PAG of the brainstem are closely related to the regulation of pain. The PB transmits pain-related information from the spinal cord to the central amygdala, and the amygdala also sends pain-inhibiting signals to the PB.[44,45] Buhle et al found that physical pain can activate the PAG.[46] The stimulation of the PAG projecting to the rostral ventromedial medulla contributes to descending pain inhibition.[47] In addition, the brainstem contains serotonergic, dopaminergic and noradrenergic nuclei, and all of these neurotransmitters contribute to the regulation of emotion.[48]

It has been reported that limbic regions of the pain matrix, such as the cingulate cortex, encode emotional aspects of pain perception.[49,50] The ACC can interact with the PAG to activate the descending opioidergic pain inhibitory pathway.[47] The study by Cao et al indicated that PHN deactivated the cingulate cortex.[51] The ACC and its associated neural projections are involved in the production of anxiety caused by chronic pain. Postsynaptic long-term potentiation (post-LTP) and presynaptic long-term potentiation (pre-LTP) occur in the ACC. Post-LTP is related to chronic pain, while

pre-LTP is considered to be related to anxiety triggered by chronic pain, and inhibition of pre-LTP can produce anxiolytic and analgesic effects.[52,53]

The precuneus is involved in the episodic memory function of the human brain and is part of the DMN. The DMN plays an important role in the occurrence of mood disorders. Abnormal function of the DMN is often observed in patients with chronic pain, suggesting that sensory monitoring may be impaired in these patients.[54,55] Li et al performed a resting-state FC analysis that revealed that PHN patients had weak FC between the thalamus and the PCC and precuneus.[15] Zhu et al observed that compared with healthy controls, patients with major depression had lower FC in the posterior cingulate cortex and precuneus that was negatively correlated with the overgeneral autobiographical memory score.[56] Combined with this finding, it was found that the sensory monitoring function of ZAP patients with negative memory was impaired.

It is reasonable to speculate that functional changes in specific brain regions in ZAP patients with psychiatric comorbidities may alter the levels of neurotransmitters in those regions. The physical and mental suffering of ZAP patients with anxiety or depression is severe. Pain is at increased risk of anxiety or depression, and in turn, anxiety disorders and depression can also increase the risk of pain.[7–9] Improving the anxiety or depression state of ZAP patients is helpful to improve the therapeutic effect of physiological diseases. Our findings may provide a theoretical basis for therapeutic strategies to alleviate psychiatric comorbidities in patients with ZAP.

Our study has several limitations that should be considered. First, the number of D/A-ZAP samples in this study was not sufficient, and the sample number among the three groups was not matched, which may affect the credibility and generalizability of the results. In addition, although age was included in the analysis as a covariate to exclude the effect of age on the results, the impact of this kind of pain in aging was not investigated because of the small sample size. Second, to maintain the stability of the patient's condition, the use of analgesics in patients was not controlled in the study, so the effect of drugs on the nervous system cannot be ruled out. Third, this study is a cross-sectional study and did not draw causal conclusions between these findings and ZAP with psychiatric comorbidities. In the future, a longitudinal design with larger sample studies should be considered to monitor the activity changes from ZAP to ZAP with psychiatric comorbidities.

Conclusion

This study used the DC analysis method based on rs-fMRI to reveal the node differences in the brain functional network in ZAP patients with or without psychiatric comorbidities. In particular, our study found increased DC values of the left MFG and left PG in ZAP patients with psychiatric comorbidities, which indicates that abnormal DC values of the left MFG and left PG play an important role in the neuropathological mechanism in ZAP patients with psychiatric comorbidities.

Acknowledgments

Disclosure

The authors declare no conflicts-of-interest in relation to this work.

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