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Functional connectivity across multi-frequency bands in patients with tension-type headache: a resting-state fMRI retrospective study

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Abstract

Objectives Tension-type headache (TTH) is the most common nervous system disorder worldwide. This study aimed to examine abnormal network-level brain functional connectivity (FC) alterations in patients with TTH across multi-frequency bands.

Methods The study enrolled 63 subjects, comprising 32 patients with TTH and 31 healthy controls (HC). According to our team's previous research, the brain regions with abnormal ReHo in the conventional frequency band (0.01–0.08 Hz) and the slow-5 band (0.01–0.027 Hz) were chosen as seed regions of interest (ROIs). Subsequently, the FC between ROIs and the entire brain analysis across various frequency bands was calculated to evaluate network-level alterations, and differences between the TTH and HC were analyzed. Pearson's correlation analysis was conducted to assess the relationship between significantly altered FC values in two frequency bands and visual analog score (VAS) in TTH patients.

Results In the slow-5 band (0.01–0.027 Hz), FC between right medial superior frontal gyrus and right medial temporal pole/right inferior temporal gyrus as well as right middle frontal gyrus and left supramarginal gyrus of TTH patients exhibited significantly higher, compared to the HC group, while FC between right middle frontal gyrus and right lateral occipital cortex reduced. For the correlation results, there was no correlation between abnormal brain regions of FC and VAS score.

Conclusions Changes in FC within brain regions associated with TTH are linked to pain processing. And the altered FC in TTH patients were frequency dependent. These initial observations could enhance our understanding of TTH's pathophysiological mechanism and offer insights for its future diagnosis and treatment.

Keywords Tension-type headache, Resting-state functional MRI, Functional connectivity, Frequency band specificity

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Introduction

Tension type headache (TTH) is the most common nervous system disorder in the whole world [1, 2], often perceived as a "normal" headache, leading to infrequent medical consultation [3]. In the Global Burden of Diseases, Injuries, and Risk Factors Study 2016, TTH ranks sixth globally in incidence and third in prevalence [4], and it can occur in each age group [5]. TTH usually leads to anxiety, depression, sleep disorder, fibromyalgia, masseter pain and other symptoms [6–9], which not only reduces the quality of patients' daily lives, but also brings huge economic burden to the society. Research shows that TTH have decreased work efficiency, resulting in absenteeism rate of three times that of migraine [10]. Although the TTH has a wide impact, scientists have paid insufficient attention and allocated less resources [11, 12]. Since the early twenty-first century, the pathogenesis is still unclear due to the lack of relevant studies.

Resting state functional magnetic resonance imaging (RS-fMRI) using blood oxygen level-dependent signals reflects intrinsic abnormalities and reveals more basic brain function alterations [13, 14]. In conventional analyses of RS-fMRI data, regional homogeneity (ReHo) is functional indicator reflecting local brain areas, and the correlation of signal fluctuations between distinct brain regions is calculated as an index of 'functional connectivity (FC)' to reveal networks of brain regions that have highly synchronous activity [15]. FC can reflect the communication strength of anatomic separated brain functional regions [16–18]. Oscillating waves in a specific low frequency range (usually defined as 0.01–0.08 Hz, i.e., the conventional frequency oscillation) have been shown to be associated with a variety of neural processes [19–21]. Therefore, most RS-fMRI studies focus on the conventional frequency band (0.01–0.08 Hz), but it has been reported that the conventional frequency band can also be subdivided into slow-4 band (0.027–0.073 Hz) and slow-5 band (0.01–0.027 Hz) [20, 22, 23]. In the previous research results of our team [24], TTH showed that the ReHo increases in the right medial superior frontal gyrus in conventional frequency band and in the right medial superior frontal gyrus and right middle frontal gyrus in slow-5 band. In the process of pain processing, the frontal lobe is participated in the descending pain modulatory system by regulating the cortical and subcortical injury pathways [25], serving as a key panel point in networks participated in nociceptive handling and pain regulation [26]. Accordingly, abnormal activity of local brain regions in the frontal lobe may improve the pain perception and regulation ability of TTH patients [27].

The FC analysis method based on regions of interest (ROIs) is to select significant ROIs through previous relevant studies and analyze the correlation between ROI and the time series of other brain regions in order to find out whether there are other regions closely related to ROIs, which represents the existence of some potential cooperative activities between them. This method is extensively utilized in pain diseases research, including conditions like migraine [28–30], cluster headache [31, 32], phantom limb pain [33], fibromyalgia [34], irritable bowel syndrome [35], and burning mouth syndrome [36], due to its high sensitivity, straightforward operation and ease of result interpretation. The altered FC may indicate the internal pathophysiological alterations of different brain diseases. Anatomically related different brain regions are most probably remained functionally related as well [37]. With the help of linear time correlation, the seed-based connectivity analysis using Rs-fMRI data can determine that two spatially independent regions are functionally connected. This type of data, to some extent, makes it possible to analyze and understand the occurrence and development of brain diseases [38]. However, the research on TTH by FC is relatively limited, which has limited our comprehension of the mechanism. Using the abnormal ReHo brain regions as ROIs, we can determine the FC between ROIs and other brain regions, and obtained more accurate results. In present study, we adopted the ROI-based FC analysis method and selected the abnormal ReHo brain regions in the conventional frequency band and slow-5 frequency band in our previous research as ROIs. We hypothesized that, in the resting state, TTH patients may exhibit altered FC between ROIs and the whole brain across different frequency bands, potentially correlating with clinical symptoms.

Materials and methods

Subjects

From May 2018 to July 2019, 38 TTH patients were recruited at the Department of Neurology of the Affiliated Hospital of Shandong Second Medical University according to the inclusion and exclusion criteria. During the interview, demographic data such as age, sex, education level were gathered, while pain severity and relief were assessed using Visual Analogue Scale (VAS) scores. All subjects were Han Chinese, aged from 18 to 60 years old, and right-handed. The inclusion criteria were: (1) adherence to the International Classification of Headache Disorders 3rd Edition, beta version criteria (ICHD-3 beta) [39], more stringent criteria were adopted in this study, that is, the pain must be meeting the five characteristics of compression, mild to moderate, bilateral, no nausea and vomiting, and no aggravation of daily activities; (2) no history of neurological and psychiatric diseases; (3) TTH patients with first consultation; (4) no history of drug abuse; (5) no contraindication for MRI examination. Exclusion criteria were: (1) presence of other headache or chronic pain disorders; (2) previous computed tomography or MRI scans found intracranial organic lesions; (3) female pregnancy or menstruation; (4) patients with previous history of craniocerebral trauma and surgery; (5) have long-term chronic disease history, such as coronary heart disease, diabetes, hypertension and so on. According to the diagnosis of neurologists and radiologists, the scanning of TTH patients was performed during between attacks (interictally) and ≥ 24 h after the last episode. At the same time, 38 healthy controls (HC) without any headache history were recruited from the health examination persons in our hospital. The Affiliated Hospital of Shandong Second Medical University Committee on Human Research approved this study. All participants signed a written informed consent.

MRI acquisition

All participants were scanned with 3.0-T MRI scanning system (Signa HDxt, GE Medical Systems, Waukesha, WI, USA). Every subject was required to close eyes and as far as possible to remain as still and relaxed as possible during the scanning, but not to sleep or think. The scan would be terminated immediately when the subjects had any discomfort.

The whole scanning process was as follows: (1) all subjects underwent T1-weighted imaging (T1WI), T2WI, and T2-FLAIR sequence scans, which were reviewed by two experienced radiologists to rule out organic brain lesions; (2) Rs-fMRI data were acquired using an echo-planar imaging sequence: repetition time = 2,000 ms, echo time = 30 ms, flip angle = 90°, slice thickness = 4.0 mm, matrix = 64 × 64, field of view = 240 × 240 mm^2, number of slices = 32, total volume = 200, the session lasted 400 s; (3) three-dimensional high-resolution T1WI anatomical images were obtained using the spoiled gradient recalled acquisition, TR = 7.8 ms, TE = 3.0 ms, flip angle = 15o, slice thickness = 1.0 mm, FOV = 256 × 256 mm^2, matrix = 256 × 256, number of slices = 188, the session lasted 250 s (Fig. 1).

Data preprocessing

The raw resting-state functional MRI data were pretreatment using the volume-based analyses pipeline in the CONN platform toolbox version 20.b [40] (http://web.conn-toolbox.org/home), operating on MATLAB R2019b (MathWorks, Natick, MA, USA). The data processing steps included: (1) slice-timing correction, (2) realignment and unwarp, (3) center to (0, 0, 0) coordinates, (4) outlier detection using ART-based identification for scrubbing, (5) indirect segmentation and normalization to MNI space, and (6) smoothing. The 10 points of initial time were removed to achieve MRI signal equilibrium and to ensure that subjects were accustomed to the scanner noise. We selected conservative scrubbing parameters for functional outlier detection, using the 95th percentile of normative sample, with a global-signal z-value threshold of 3 and a subject-motion threshold of 0.5 mm. Spatial smoothing was performed according to an 8-mm full-width at half-maximum Gaussian kernel. Any participants whose head motion shifted by

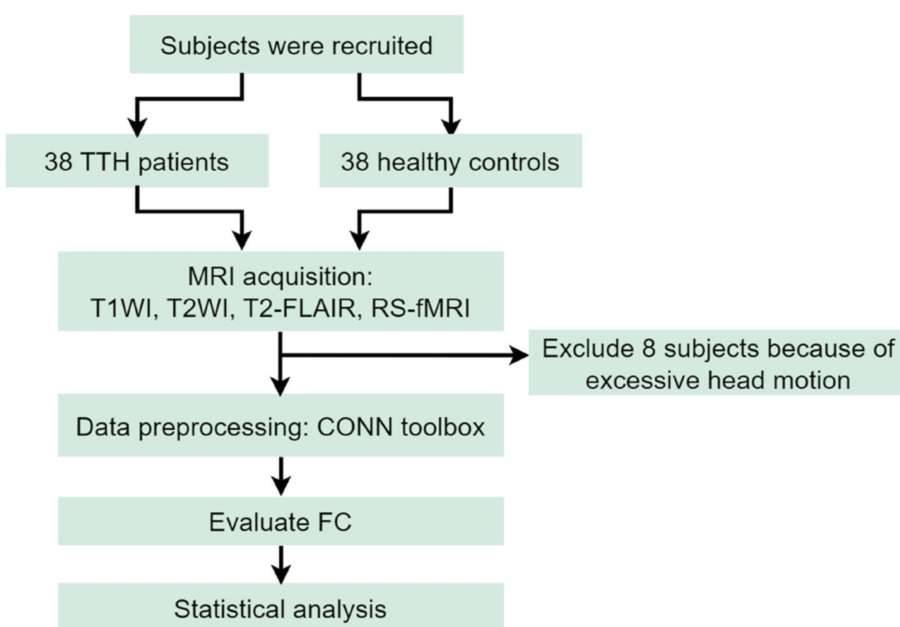

Fig. 1 Study flowchart

more than 3.0 mm of maximum translation in any axis and rotated by 3° were excluded, resulting in the removal of eight participants (seven from the HC group and one from the TTH group) from further analysis by this criterion. Then a series of denoising methods was processed to reduce the influence of physiological signal variation. The process involved removing volumes with displacement above the 95th percentile, regressing out of the 10 principal components derived from 5 white matter and 5 composition of cerebrospinal fluid, and regressing out of 24 head motion parameters, including linear and rotational indicators, as well as their time derivatives and squared values.

Functional connectivity

FC was assessed using the seed-based connectivity method via the CONN platform toolbox version 20.b [40]. Based on our previous findings [23], five clusters were exhibited significant, as follows: (1) cluster 1 (peak MNI coordination: x = 9, y = 48, z = 24) located in the right medial superior frontal gyrus (SFG) within the conventional frequency band, (2) cluster 2 (peak MNI coordination: x = 9, y = 45, z = 30) located in the right medial SFG in the slow-5 band, (3) cluster 3 (peak MNI coordination: x = 36, y = 57, z = 24) located in the right middle frontal gyrus (MFG) in the slow-5 band, (4) cluster 4 (peak MNI coordination: x = 48, y = 33, z = 36) located in the right MFG in the slow-5 band, (5) cluster 5 (peak MNI coordination: x = 39, y = 12, z = 51) located in the right MFG in the slow-5 band. We specified the spherical cluster with the peak coordinates of the above five clusters as the center and the radius of 10 mm as the seed areas. The band-pass filter was applied using both a conventional frequency band (0.01–0.08 Hz) and slow-5 band (0.01–0.027 Hz). For the seed-to-voxel FC analysis, we only selected cluster 1 as ROI 1 in the conventional frequency band and cluster 2, 3, 4 and 5 sequentially as ROI 2, 3, 4, 5 in the slow-5 band.

Statistical analysis

A two-sample *t*-test was conducted using the CONN version 20.b [40] to compare FC differences between TTH and HC in brain imaging analysis. Age, gender, years of education were regressed out in the statistical analysis. The Gaussian Random Field theory was utilized for multiple comparison correction. We applied a significance threshold of $p < 0.05$ at the cluster level with the false discovery rate (FDR), $p < 0.001$ uncorrected at the voxel level. Finally, we analyzed the correlation between brain regions with significant FC and VAS scores of TTH group using Pearson correlation analyses in all the two frequency bands with SPSS statistical software version 23.0, $p < 0.05$ was supposed meaningful.

Results

Demographic characteristics

The demographic feature of the two groups of subjects is shown in Table 1. Seven subjects in the HC group and one in the TTH group were removed due to overactive head movement, while five subjects in the TTH group were removed because they were over age. Therefore, 31 subjects in the HC group and 32 subjects in the TTH group were finally bring into our study. There was no statistically significant divergence in age, gender, and education level between two groups.

Seed-based functional connectivity analysis in different frequency bands

In the conventional frequency band (0.01–0.08 Hz), no brain regions showed significant differences between the TTH and HC groups.

In the slow-5 band (0.01–0.027 Hz), differences in FC between TTH patients and HC after adjusting for age are shown in Table 2 and Fig. 2. There were two clusters showing significant FC increase in TTH group compared with HC group, specifically finding: (1) the right medial SFG and right temporal pole (TP), right inferior temporal gyrus (ITG) (see Fig. 2A); (2) the right MFG and left supramarginal gyrus (SMG) (see Fig. 2C). Only one cluster emerged that the FC between the right MFG and right lateral occipital cortex was markedly decreased in TTH group as compared with HC group (see Fig. 2B). Yet, we contrasted the spatial distribution pattern of brain regions about age regression to ascertain whether or not age has an impact (see Table 3 and Figs. 3, 4 and 5 for details).

Correlation analyses

For the TTH patients, there were no significant correlation between the strengths of these functional connections and VAS scores in the slow-5 band (0.01–0.027 Hz) (see Table 4).

Table 1 Demographic characteristics of all subjects

	TTH ($n = 32$)	HC ($n = 31$)	*p*-Value
Age (years)	42.27 ± 12.26	36.87 ± 10.01	0.059
Sex			0.641
Male	13 (41%)	14 (45%)	
Female	19 (59%)	17 (55%)	
Education	10.24 ± 3.28	11.03 ± 2.77	0.202
VAS score	4.84 ± 1.25	–	–

TTH tension-type headache, *HC* healthy controls, *VAS* visual analog scale

Table 2 The FC difference in slow-5 frequency band between TTH and HC

ROIs	Coordinate (x, y, z)	Cluster size (voxels)	Brain region	Voxels in specific region	Peak *t*-value
ROI 2 (R medial SFG)	+34, +10, −40	162	R temporal pole	61	5.68
			R inferior temporal gyrus	7	
ROI 3 (R MFG)	+26, −82, +06	123	R lateral occipital cortex	41	−4.69
ROI 4 (R MFG)	−52, −40, +50	116	L supramarginal gyrus	110	4.80

FC functional connectivity, *TTH* tension-type headache, *HC* healthy controls, *ROI* region of interest, *SFG* superior frontal gyrus, *MFG* middle frontal gyrus, *R* right, *L* left

Discussion

Maina interpretation

In this study, based on our team's previous research findings, we selected the ReHo abnormal brain regions with of TTH patients in multi-frequency bands as ROIs, and used the FC method between ROIs and the whole brain to explore the abnormal connection pattern in TTH patients in the conventional frequency band (0.01–0.08 Hz) and slow-5 band (0.01–0.027 Hz). Our results showed that the FC of several brain regions exhibited significant differences only in the slow-5 band (0.01–0.027 Hz) in TTH patients compared with HC, which indicate that the altered FC of TTH is frequency dependent. Additionally, our study also found no correlation between the altered FC of brain regains and VAS scores in TTH patients in the slow-5 band (0.01–0.027 Hz).

Neurological diseases remain the main killer worldwide [41, 42]. The TP is a joint multisensory region, which also processes visual, odor and auditory information [43], but its role in pain processing is still unclear. It has been reported that it can affect the emotional tone of short-term memory allocation related to pain [44]. Moulton et al. [43] reported that TP showed FC enhancement in brain areas related to pain processing in migraine patients during attack, and had extensive white matter associations with the pulvinar nucleus, which was a structure of posterior thalamus and associated with sensitization during migraine attack. Zeng et al. [45] found that abnormal FC between the TP and parahippocampal gyrus reflected the dysfunction of visceral monitoring in depression patients. The high frequency of depression is shown in TTH patients. Some studies found that under the influence of depression, patients with frequent headache were more likely to suffer from TTH [46]. Besides, Chen et al. found that the grey matter volume of TP increased in TTH patients [47]. In the current study, we detected that FC among the right medial SFG and right TP heightened in TTH patients, which may not only reflect that TP participates in the central sensitization mechanism of TTH, but also provide some evidence for the relationship between TTH and depression.

The ITG is related to spontaneous cognition and language fluency, and plays a critical role in the processing of visual stimuli [48, 49]. It is considered to be the final stage of the ventral cortical visual system [50]. As a component of pain transmission circuit [31], the functional alterations of ITG in cluster headache were considered as the action mode of hypothalamic deep brain stimulation [51]. In addition, ITG is considered to be a part of default mode network (DMN) [52], and has been certificated to be connected to worsening pain [53]. It is reported that DMN regulates cognitive process, affects reaction behavior to stress experience, and promotes coping strategies to promote adaptation [54]. Previous Rs-fMRI studies had shown that DMN functional connections were disrupted in pain situations, indicating the existence of adverse reactions of the brain to repeated stress and pain [32]. The voxel based morphological study showed that the gray matter volume of the right ITG decreased in TTH [55]. Our study showed that the FC of the right SFG and the right ITG was increased, which may have a certain impact on the pain degree of TTH patients and play a role in the process of pain transition to chronicity, which may also confirm that the ITG is involved in the limbic pain regulatory network to some extent.

The lateral occipital cortex is involved not only in visual processing, but also in the cognitive assessment of pain [56] and in abnormal emotional processing and self-focus [57]. Reduction of occipital cortical gray matter volume in chronic pain has been reported in previous studies [58]. Chen et al. [47] demonstrated the gray matter volume of lateral occipital cortex increased in TTH. Khan et al. [59] reported that the FC between medial prefrontal cortex and anterior cingulate cortex, occipital cortex enhanced in burning mouth syndrome. The medial prefrontal lobe is a constituent of limbic system, and the occipital lobe may receive potential impulses from neurons in the limbic system and participate in emotional regulation. Many studies have shown that the lateral occipital cortex is dysfunctional in cluster headache [31, 60]. Our study showed that the FC between right MFG and right lateral occipital cortex was weakened. which may not only lead to the impairment of the cognitive assessment of pain, but also aggravate the negative emotions (such as anxiety and depression) often associated with TTH. Nevertheless, cross-sectional data do not

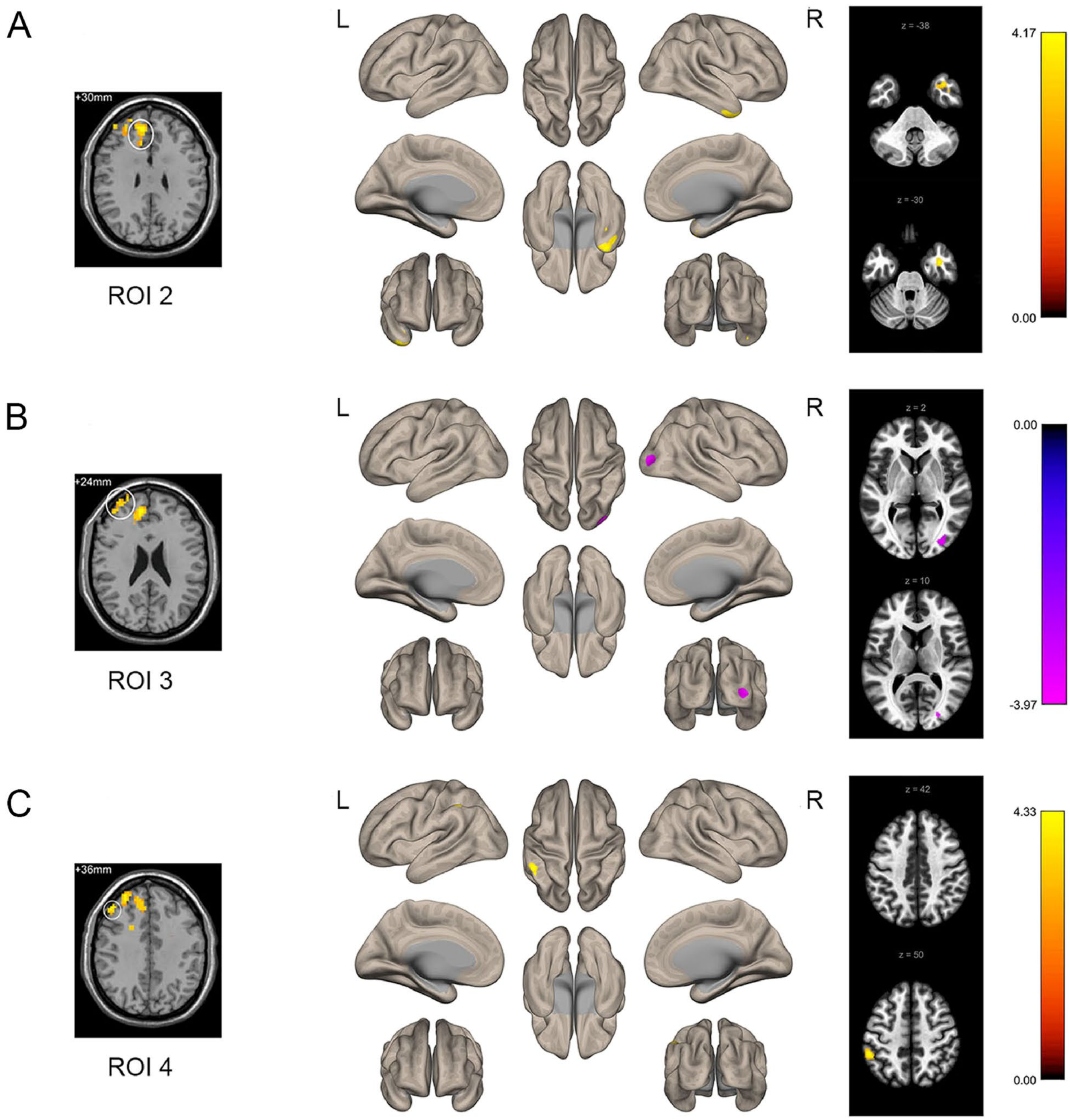

Fig. 2 The altered FC with TTH in the slow-5 band. Tension-type headache showed altered FC in the slow-5 band (0.01–0.027 Hz) compared with healthy control. **A** Enhanced FC between R medial SFG and R temporal pole/right inferior temporal gyrus. **B** Reduced FC between R MFG and R lateral occipital cortex. **C** Enhanced FC between R MFG and L supramarginal gyrus. FC, functional connectivity; SFG, superior frontal gyrus; MFG, middle frontal gyrus; R, right; L, left

establish the cause relationship between TTH and negative emotions. A longitudinal study has shown that pain and emotional factors may have a bidirectional effect on the burden of chronic TTH [61]. However, the specific functional alterations of occipital lobe in TTH still need further study.

The impairment of SMG is manifested by impaired sensitivity to memory related expectations or cognitive control of these violations, especially when the subject has strong prior expectations of new stimuli [62]. It has been reported that the left SMG is not only related to the regulation of cognition, but also a brain region that

Table 3 The FC difference in slow-5 frequency band between TTH and HC (without age regressed)

ROIs	Coordinate (x, y, z)	Cluster size (voxels)	Brain region	Voxels in specific region	Peak *t*-value
ROI 2 (R medial SFG)	+34, +10, −40	178	R temporal pole	71	6.00
			R inferior temporal gyrus	4	
ROI 3 (R MFG)	+26, −82, +06	128	R lateral occipital cortex	36	−4.71
ROI 4 (R MFG)	–	–	–	–	–

FC functional connectivity, *TTH* tension-type headache, *HC* healthy controls, *ROI* region of interest, *SFG* superior frontal gyrus, *MFG* middle frontal gyrus, *R* right, *L* left

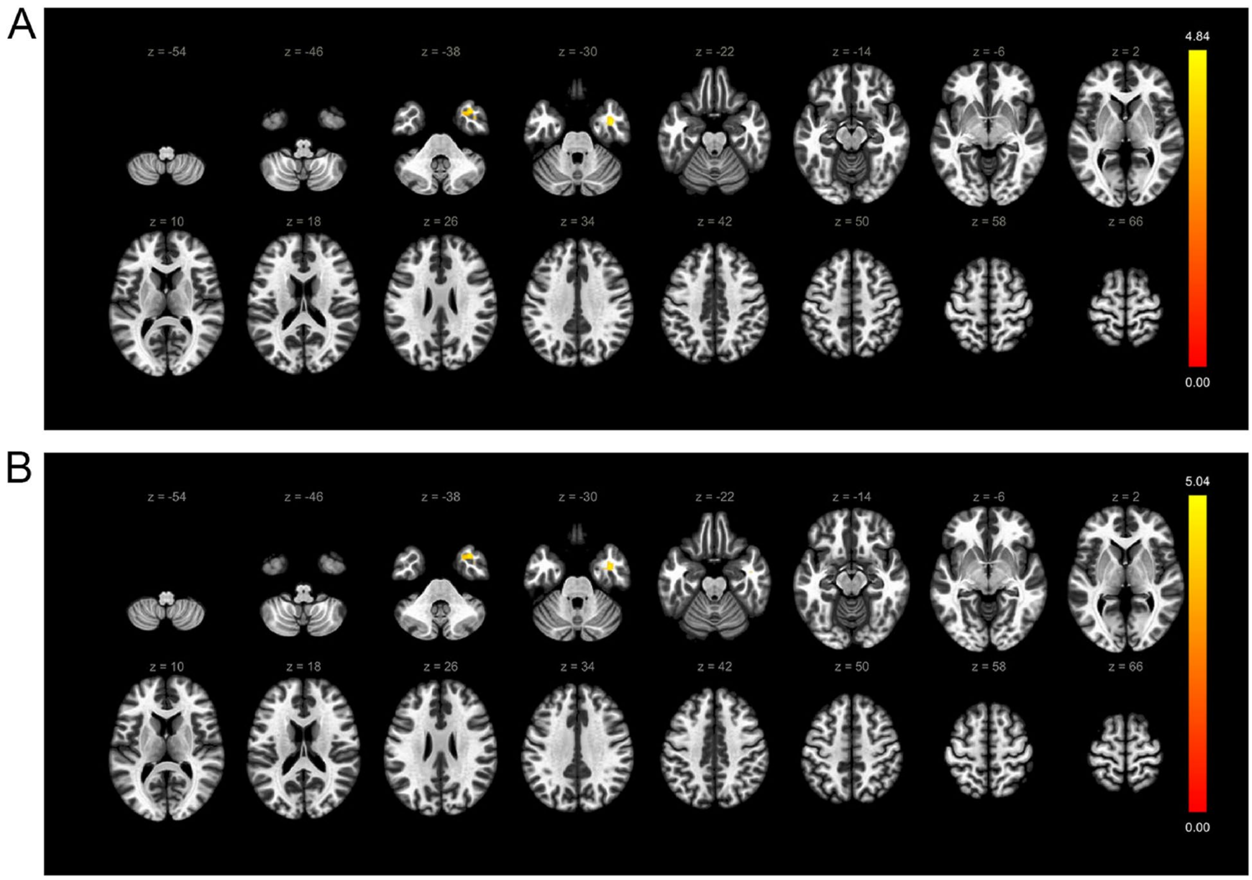

Fig. 3 The impact of age regression with increased FC between R medial SFG and R temporal pole/right inferior temporal gyrus. Patterns of results that age is regressed (**A**) and patterns of results that age is not regressed (**B**) with the increased functional connectivity between right medial superior frontal gyrus and right temporal pole/right inferior temporal gyrus in the slow-5 frequency band (0.01–0.027 Hz)

specifically processes negative emotions [63]. Chen et al. [47] showed the gray matter volume of the SFG increased in TTH. Our results demonstrated the FC between right MFG and left SMG in TTH patients was heightened. This enhanced connectivity might reflect a long-term compensation mechanism, where damaged neurons need increased connectivity to generate the same signal. Demographic according to data display that anxiety, depression and sleep disorders are more widespread in TTH people than in the general population without headache [64–66], and this phenomenon may have an impact on the functional activities of SMG.

The effect of age on resting-state brain function has been extensively studied, and age-related changes have been reported in many investigations [67, 68], therefore we also compared the results before and after age regression to account for the possible effect of age. Interestingly, the FC between the right MFG and the left SMG were no longer abnormal without age regression. SMG is related to cognition and negative emotions, while pain is

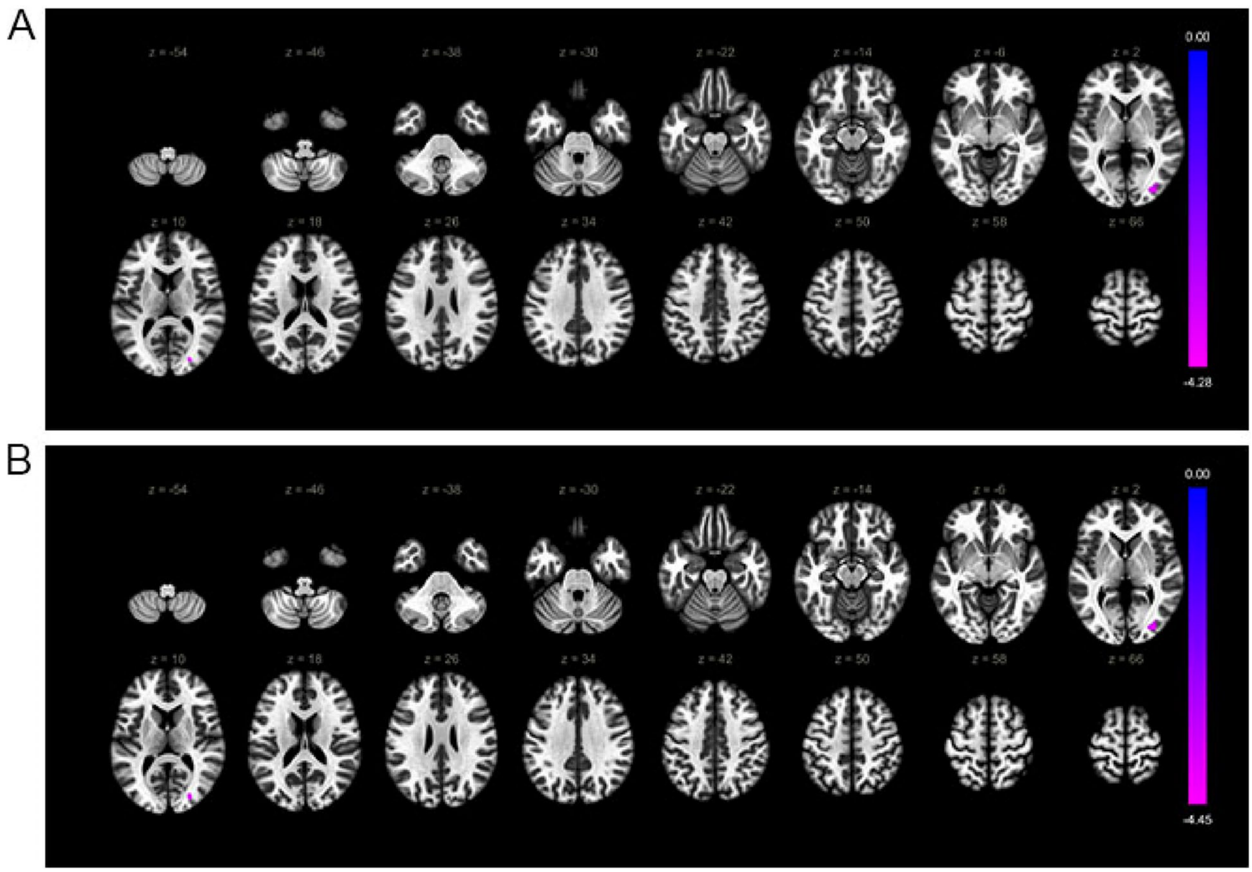

Fig. 4 The impact of age regression with decreased FC between R MFG and R lateral occipital cortex. Patterns of results that age is regressed (**A**) and patterns of results that age is not regressed (**B**) with the decreased functional connectivity between right middle frontal gyrus and right lateral occipital cortex in the slow-5 frequency band (0.01–0.027 Hz)

easily impacted on perception and cognition [69], hence the impact of age on TTH is understandable. TTH prevalence is more variable than the relationship between migraine and age [70]. The prevalence of TTH peaked between the age of 30–39 and then declined slightly [71]. In our study, the TTH group was slightly older outweigh the HC group. The age range of the subjects we collected is relatively smaller, so more researches will be demanded to develop this verdict to the entire age range.

The most important finding of this study is that the slow-5 band has better reliability for measuring abnormal FC alterations of TTH. Earlier studies have evidenced that the different frequency bands had different sensitivities to vary brain diseases. For instance, Han et al. [72] found that the slow-5 band was more susceptible to detecting anomalous spontaneous brain activity in mild cognitive dysfunction, while Meylakh et al. [73] considered that the hypothalamus and periaqueductal grey revealed greater power in the slow-4 band in the phase immediately prior to migraine. Our team's research results showed that the slow-5 band was superior to the conventional band and the slow-4 band in detecting abnormal ReHo and FC of TTH. The study showed that the brain regions of TTH patients did not exhibit significant FC alterations in the conventional frequency band, which is an important negative finding. The absence of FC changes in the conventional frequency band also provides some rationale for why the slow-5 band differences are notable. However, whether or not this kind of band specific fluctuations could be used for the diagnosis of TTH remains to be further studied.

Limitations

Our research has several potential limitations. First, the capacity of sample was too limited to fully summarize the results of the study, and large-scale clinical validation would be still needed. Second, our study was limited to a heterogeneous population of TTH patients. Due to the small number of cases, no distinction was made between episodic and chronic TTH. Third, the FC analysis method has inherent limitations in anatomical connection and the direction of

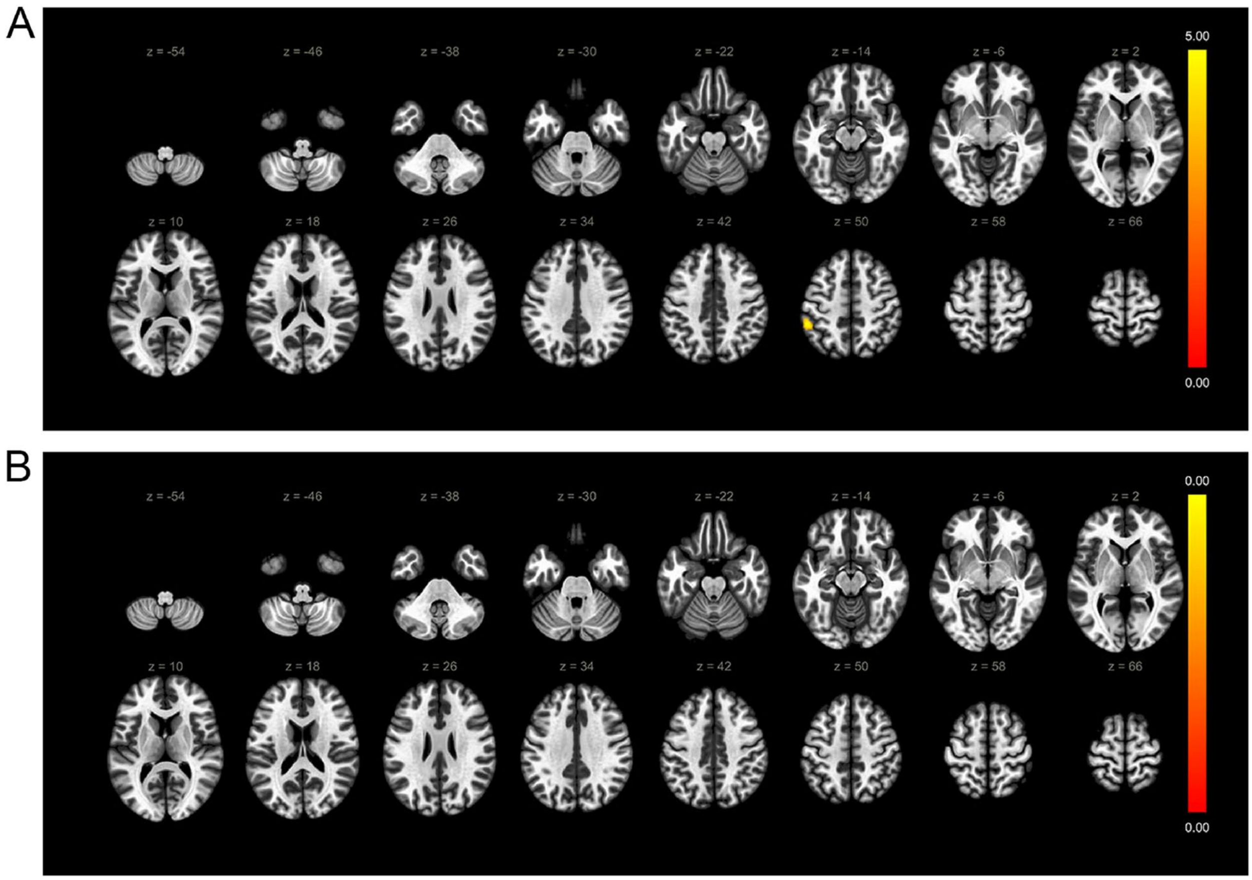

Fig. 5 The impact of age regression with increased FC between R MFG and L supramarginal gyrus. Patterns of results that age is regressed (**A**) and patterns of results that age is not regressed (**B**) with the increased functional connectivity between right middle frontal gyrus and left supramarginal gyrus in the slow-5 frequency band (0.01–0.027 Hz)

Table 4 Correlation between FC values and VAS scores in the slow-5 frequency band

Brain region		VAS scores
Right temporal pole/ inferior temporal gyrus	Pearson correlation (*r*)	0.119
	Significance (*p*)	0.509
Right lateral occipital cortex	Pearson correlation (*r*)	0.030
	Significance (*p*)	0.868
Left supramarginal gyrus	Pearson correlation (*r*)	0.257
	Significance (*p*)	0.149

information flow from one region to another. Fourth, the anxiety and depression status of the patient needs further evaluation [74]. Fifth, whether there is an effect of age on the brain function of TTH. These problems will be solved in the subsequent studies.

Conclusions

In TTH patients, FC abnormalities between the right SFG and right TP and ITG are associated with pain management, while FC changes between the right MFG and right lateral occipital cortex, as well as left SMG, are associated with negative emotions such as anxiety and depression. However, these abnormalities are frequency dependent and only occur in the slow-5 frequency band. These findings will deepen our understanding of the pathophysiological mechanisms of TTH to a certain extent, and may provide some references for future research.

Abbreviations

TTH	Tension type headache
RS-fMRI	Resting state functional magnetic resonance imaging
ReHo	Regional homogeneity
FC	Functional connection
ROIs	Regions of interest
VAS	Visual Analogue Scale
ICHD-3	International Classification of Headache Disorders 3rd Edition
HC	Healthy controls
T1WI	T1-weighted imaging
TR	Repetition time
TE	Echo time
FOV	Field of view
SFG	Superior frontal gyrus
MFG	Middle frontal gyrus
FDR	False discovery rate
TP	Temporal pole

ITG Inferior temporal gyrus
SMG Supramarginal gyrus
DMN Default mode network

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Clinical trial
N/A.

Authors' contributions
YZ and SXZ designed the study. QYX and SXZ collected the case data. JLW analyzed the data. JLW, TL, and HJS prepared the manuscript. All authors read and approved the final manuscript.

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Data availability
Data are available on https://www.jianguoyun.com/p/DYYxdz0QuaiFChiSod8FIAA.

Declarations

Ethics approval and consent to participate
This study has been approved by the Ethics Committee of the Affiliated Hospital of Shandong Second Medical University, exempting the subject's informed consent (approval number: 2024YX118). Our study adhered to the Declaration of Helsinki.

Consent for publication
Patients write inform content for publication.

Competing interests
The authors declare no competing interests.

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