The medial thalamus plays an important role in the cognitive and emotional modulation of orofacial pain: a functional magnetic resonance imaging-based study

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Abstract

Background The thalamus plays a critical role in the perception of orofacial pain. We investigated the neural mechanisms of orofacial pain by exploring the intrinsic functional alterations of the thalamus and assessing the changes in functional connectivity (FC) between the thalamic subregions with significant functional alterations and other brain regions in orofacial pain using the seed-based FC approach.

Methods The study comprised 49 participants in the orofacial pain group and 49 healthy controls. Orofacial pain was caused by orthodontic separators. The resting-state functional magnetic resonance imaging data of the two groups were analyzed to obtain the fractional amplitude of low-frequency fluctuations (fALFFs) of the thalamus, and the thalamic subregions with significant fALFF abnormalities were used as seeds for FC analysis. Student's t-tests were used to perform comparisons. Pearson's correlation analysis was performed using SPM software.

Results Forty-four participants with orofacial pain (mean age, 21.0±0.9 years; 24 women) and 49 age- and sex-matched healthy controls (mean age, 21.0±2.6 years; 27 women) were finally included. Compared with the control group, the orofacial pain group demonstrated (1) increased function in the dorsal thalamus and decreased function in the medial thalamus; (2) decreased FC between the medial thalamus and 12 brain regions ($p<0.05$, family-wise error corrected, voxel>100); and (3) potential positive and negative correlations between the medial thalamus-seeded FC and visual analog scale score changes ($p<0.05$, AlphaSim corrected).

Conclusions The findings show that the medial and dorsal thalamus play important roles in orofacial pain perception and that the medial thalamus likely plays an important role in the cognitive and emotional modulation of orofacial pain.

Background

Orofacial pain, an ache localized in the oral and facial regions [1], is a symptom of a variety of diseases, such as pulpitis, periodontitis, and temporomandibular joint disorder (TMD) [2]. It is a common condition; studies in Brazil [3] and Hong Kong [4] found that over 40% of the population had experienced orofacial pain. Because of the complexity of the affected regions, orofacial pain can have a deleterious effect on the patients' daily functions (including eating, drinking, and speaking) and can seriously affect various social functions and the quality of life [5, 6].

It is well known that the trigeminal nerve contains most sensory nerve fibers innervating orofacial tissues and is important for orofacial pain perception. Once stimulated, the peripheral nerves transmit nociceptive information to the central nervous system. The trigeminal primary afferent projects the information to second-order neurons located in the trigeminal brainstem sensory nuclear complex through the trigeminal ganglion. The trigeminal nucleus sends the information in the ventroposterior nucleus of the thalamus, and the thalamus relays it to the cortex [7].

In the abovementioned pathways, the thalamus is a key node. It serves as a global hub, connected with the entire cortex, relaying sensory information to the cortex and mediating the transmission of cortico-cortical information [8, 9]. Moreover, it is important in both nociceptive transmission and pain modulation[10, 11]. Furthermore, the thalamus can be divided into several subregions anatomically and functionally as a heterogeneous structure [12, 13]. Although it is well documented that it plays a critical role in orofacial pain perception, there is limited imaging evidence of how the thalamus and its subregions contribute to orofacial pain perception.

Functional magnetic resonance imaging (fMRI) is used to measure neural activity by detecting spontaneous blood oxygen level–dependent fluctuations [14]. In recent years, fMRI has been used to study the neural mechanism of orofacial pain (including TMD, trigeminal neuralgia, and orthodontic pain), and the authors identified some significant abnormalities in brain functions and functional connectivity (FC) [15-17]. However, no fMRI studies have focused on the functional and FC changes of the thalamus in orofacial pain.

Therefore, we created a model of orofacial pain by placing orthodontic elastic separators to the teeth and explored the intrinsic functional alterations of the thalamus in orofacial pain. We used the seed-based FC approach to analyze resting-state fMRI (rfMRI) data to assess the changes in FC between the thalamic subregions that showed significant functional alterations and other brain regions.

Methods

Subjects

Participants included individuals with orofacial pain and age- and sex-matched healthy controls. All participants were recruited after meeting the following inclusion criteria: right-handed adults; bachelor degree or above; no serious malocclusion, temporomandibular joint disease, or other diseases causing orofacial pain; no history of drug or alcohol abuse; no history of neurological disorders; and no contraindications for MRI, including cardiac pacemakers and other metallic implants.

Study Design

Orofacial pain is caused by placement of orthodontic elastic separators to the mesial sides of the left lower first molar in the orofacial pain group [2]. rfMRI was performed after 24 h because orofacial pain peaks at 24 h after placement of the separator [18]. The healthy controls underwent rfMRI scan without separators. A 100-mm visual analog scale (VAS, ranging from 0 to 100) and the Symptom Checklist-90-Revision (SCL-90-R) were used for degree of discomfort measurement and psychological evaluation, respectively, both before the elastic separator placement and before the scan. Patients experiencing greater discomfort tend to have higher VAS scores. The elastic separators were removed after the scan.

MRI Data Acquisition

All participants underwent rfMRI. Imaging was performed with a Siemens 3.0-T MRI system (Trio; Siemens, Erlangen, Germany). During data acquisition, all participants were instructed to rest with their eyes closed, not asleep, and not to move their heads or think of anything in particular. Each participant's head was fixed with foam pads to minimize head motion. The fMRI scan parameters were as follows: repetition time (ms)/echo time (ms), 2,000/30; flip angle, 90°; field of view, 240×240 mm^2; matrix size, 64×64; voxel size, 3.75×3.75×5 mm^3; and section thickness, 5 mm; 205 volumes were obtained.

Image Processing and Data Analysis

MRI data analysis was performed using software (SPM8, Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/software/spm8). For image preprocessing, the initial 10 volumes were discarded to obtain a steady state of the resting condition. Thus, we analyzed the remaining 195 volumes. Head translation movement of the participants who were finally included was <2.5 mm and the rotation was <2.5°[19]. Nuisance signal, including white matter and cerebrospinal fluid signal, and 24-parameter motion correction were regressed out. The linear regression model with motion "spike" as a separate regressor was used for temporal scrubbing. We defined the motion "spike" as the time point with a high framewise displacement (>1). Next, all brain image volumes were registered to the standard space, which is defined by the Montreal Neurological Institute. Moreover, a Gaussian kernel of 4-mm full-width half-maximum was used to smooth the normalized functional images.

Fractional Amplitude of Low-frequency Fluctuations Analyses

The REST (http://www.restfmri.net/forum, version 1.8) software was used to calculate the fractional amplitude of low-frequency fluctuations (fALFF) of the thalamus. We transformed the time series of the whole-thalamus signal into a frequency domain power spectrum after preprocessing. Subsequently, we performed the root-mean-square calculation on the power spectrum at the range of 0.01–0.1 Hz, and the ALFF value was obtained. The fALFF value was computed as a ratio of the sum of the amplitudes of the entire low-frequency band (0.01–0.1 Hz) to that of the whole detected frequency range. Finally, the fALFF value of each voxel was divided by the whole-thalamus mean fALFF value in order to normalize all subject data for standardization. The fALFF was compared using a two-sample t-test.

Seed-based FC Analyses

As we report below, significant fALFF abnormalities in the orofacial pain group were demonstrated in two thalamic subregions, the medial and dorsal thalamus, and these two subregions were chosen as seeds

for seed-based FC analysis by using REST.

We averaged the rfMRI time series of voxels in each seed to extract the reference time series for each seed. A correlation analysis was performed to analyze the association between each seed region with that of other voxels across the rest of the brain to generate FC maps [20]. Fisher's r-to-z transformation was used to convert the distribution of the correlation coefficients (r) into a normal distribution. Linear regression analyses of the confounding factors of age and sex were performed in the statistical analyses. A one-sample t test provided mean group z-score statistical maps of thalamic FC in both the orofacial pain and control groups ($p<0.05$, family-wise error [FWE] correction). A two-sample t test model was performed to assess the differences between the two groups ($p<0.05$, FWE correction). Automated Anatomical Labeling atlas (https://www.oxcns.org/aal.html) was used to determine the anatomical boundaries of areas that showed significant changes in FC to the medial thalamus or the dorsal thalamus.

Statistical Analyses

Statistical analyses were performed using SPSS software (version 20.0; SPSS, Chicago, III). The paired t test was used to compare the VAS and SCL-90-R scores before the elastic separator placement and before the scan. We performed two-tailed Pearson's correlation analysis using SPM software to determine whether the FC was associated with pain intensity changes and anxiety ($p<0.05$, AlphaSim correction).

Results

Patients' Demographics

Forty-nine individuals with orofacial pain and 49 age- and sex-matched healthy controls were enrolled. We excluded five participants with orofacial pain who had excessive head movement of >2.5 mm or 2.5° during imaging. Thus, 44 participants in the orofacial pain group (mean age, 21.0±0.9 years; 24 women) and 49 healthy controls (mean age, 21.0±2.6 years; 27 women) were included in the analysis. There were no significant differences in the age distribution or the sex ratio between the two groups ($p>0.05$).

In the orofacial pain group, the VAS score before the scan was significantly increased compared with that before the elastic separator placement (23.0±20.7 vs. 13.7 ±16.4, $p=0.01$). The mean S-scores of the SCL-90-R before the elastic separator placement and before the scan were 27.7±11.0 and 29.3±10.5, respectively, with no statistically significant difference ($p=0.206$; Table 1).

Table 1. Pain intensity and psychological evaluation of the participants with orofacial pain.

	Before elastic separator placement	Before scan	p-value
VAS (mean±SD)	13.7±16.4	23.0±20.7	0.010
SCL-90-R (mean±SD)	27.7±11.0	29.3±10.5	0.206

VAS, visual analog scale; SD, standard deviation; SCL-90-R, Symptom Checklist-90-Revision.

Values are presented as means±standard deviations.

fALFF Differences and Seed-based FC

First, we examined the differences between the two groups in the whole-thalamus fALFF. The results showed that the fALFF of the medial thalamus was significantly reduced, and that of the dorsal thalamus was significantly increased compared with those of the control group (Fig. 1).

Next, we examined the FC between the two seeds and the remaining brain regions. Compared with the control group, the seed-based FC analysis of the medial thalamus seed region showed decreased FC to 12 brain regions: the left cerebellum, bilateral anterior cingulate cortex (ACC), right parahippocampal gyrus, bilateral middle frontal gyrus, bilateral superior frontal gyrus, right inferior frontal gyrus, right middle temporal gyrus, right insula, and left thalamus ($p<0.05$, FWE corrected, voxel>100; Fig. 2). However, we did not find altered FC between the dorsal thalamus and any of the brain regions.

Correlation Analyses

The participants in the orofacial pain group demonstrated a positive correlation between the medial thalamus-seeded FC and the VAS score changes in the right ACC and posterior cingulate cortex (PCC), and a negative correlation in the left cerebellum (Fig. 3).

Discussion

The current study indicates that thalamic internal function alters in individuals with orofacial pain. The FC of the medial thalamus significantly differed between the groups. This study provided evidence of the key role of the thalamus in the mechanism of orofacial pain and may shed light on the different roles of the thalamic subregions in orofacial pain perception.

The thalamus is considered to be a critical region in pain transmission and modulation [21]. Over the past decade, functional and structural changes were found in the thalamus in patients with orofacial pain [16, 22]. Previous studies suggested that the thalamus can be divided into several subregions in different ways [23]. For example, the thalamo-cortical pathways can be segregated into lateral and medial

pathways, which are mainly involved in sensory discrimination and pain perception, respectively [24]. In addition, a previous study provided classification for the thalamic nuclei: sensorimotor group, limbic group, and sensorimotor/limbic bridging nuclei [25]. This is similar to our findings: we found different functional activities in different thalamic subregions, that is, decreased fALFF in the medial thalamus and increased fALFF in the dorsal thalamus in participants with orofacial pain. Thus, we speculate that the medial and dorsal thalamus may play important roles in orofacial pain perception.

Although increased fALFF was observed in the dorsal thalamus, we did not observe any FC changes between the dorsal thalamus and other brain regions in participants with orofacial pain. The dorsal thalamus might work as “bridging nuclei” or be associated with orofacial pain sensation considering the role of the lateral thalamus in sensory-discriminative function [24], although further research should be undertaken to investigate its exact role.

The medial thalamus demonstrated decreased fALFF, and we found a lower FC of the medial thalamus with some regions; interestingly, most of them belong to the prefrontal cortex (PFC) and temporal cortex. The PFC plays a critical role in a range of cognitive processes, including decision-making, working memory, and emotional regulation [26]. The temporal cortex is known to be associated with various cognitive functions, such as memory, auditory cognition, and semantics [27]. The medial temporal lobe includes the parahippocampal cortex, essential in recognition and source memory [28]. Thus, the reduced FC between the thalamus and the PFC may be associated with aberrant emotion regulation and cognition, and the reduced FC between the thalamus and the temporal cortex may be involved in recognition memory in orofacial pain.

Interestingly, the ACC, PFC, insula, temporal cortex, and parahippocampal gyrus are all components of the limbic system. Emotion, memories, and behavior emerge from the coordinated activities of regions connected by the limbic system [29]. Moreover, the ACC was reported to receive nociceptive information from the medial thalamus and contribute to the affective and motivational instead of sensory and discriminative aspects of pain [30]. In fact, both the ACC and insula have long been considered to be important for encoding the emotional aspects of pain [31]. Therefore, the medial thalamus is closely connected to the limbic system and plays a vital role in the cognitive and emotional modulation of orofacial pain.

Recently, the cerebellum was reported to be involved in pain perception [32]. A previous study demonstrated that the cerebellum might be associated with the activation of endogenous pain inhibitory mechanisms [33]. In our study, we found negative correlations between the VAS score changes and the medial thalamus-seeded FC in the left cerebellum, indicating that the cerebellum may be associated with pain intensity.

In the present study, the FC between the thalamus and other brain regions involved in acute nociceptive stimuli were not significantly different between the groups, which may be because of the fact that the separator-induced orofacial pain is a type of chronic pain, and the brain activity is confined to emotion-related networks in chronic pain [34].

Positive correlations were found between the VAS score changes and medial thalamus-seeded FC in the right ACC and PCC, suggesting that the orofacial pain intensity is associated with the FC between the medial thalamus and these brain regions, which may be associated with adaptation to orofacial pain. However, there were no significant FC changes between the medial thalamus and the PCC compared with the healthy controls. This finding should be further investigated.

This study had some limitations. First, the age range of our participants was narrow (19–23 years); hence, the results are only valid for the youth population and should not be generalized to a broader population. Second, the exploratory correlation analyses of pain intensity and seed-based FC changes were only corrected with the AlphaSim correction in this study; therefore, the correlation we observed should be treated with caution and worth further study as an a priori hypothesis.

Conclusions

Our study demonstrated alteration in the functional activity in thalamic subregions, suggesting that the medial and dorsal thalamus play important roles in orofacial pain perception and that the medial thalamus plays an important role in the cognitive and emotional modulation of orofacial pain. The possible central mechanism of orofacial pain is illustrated in Fig. 4. The analysis of intrinsic functional changes in orofacial pain by fMRI may be helpful to further understand the mechanism of this disorder and guide the effective treatment.

List Of Abbreviations

ACC, anterior cingulate cortex;

fALFF, fractional amplitude of low-frequency fluctuations;

FC, functional connectivity;

fMRI, functional magnetic resonance imaging;

FWE, family-wise error;

PCC, posterior cingulate cortex;

PFC, prefrontal cortex;

rfMRI, resting-state functional magnetic resonance imaging;

SCL-90-R, Symptom Checklist-90-Revision;

TMD, temporomandibular joint disorder;

VAS, visual analog scale.

Declarations

Ethics approval and consent to participate

This prospective study was approved by the Ethics Committee of the West China Stomatological Hospital of Sichuan University (Sichuan, China), and all participants provided written informed consent before enrollment. All procedures were in line with the tenets of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YJ: Conceptualization; Methodology; Data curation; Formal analysis; Writing - original draft; Writing - review & editing. **HY**: Conceptualization; Methodology; Data curation; Formal analysis; Writing - original draft; Writing - review & editing. **FZ**: Methodology; Data curation; Formal analysis; Writing - original draft; Writing - review & editing. **JW**: Conceptualization; Data curation; Formal analysis; Writing - original draft; Writing - review & editing. **H Liu:** Methodology; Data curation; Writing - original draft; Writing - review & editing. **XY**: Conceptualization; Data curation; Formal analysis; Writing - original draft; Writing - review & editing. **H Long**: Conceptualization; Methodology; Formal analysis; Writing - original draft; Writing - review & editing. **FL**: Methodology; Data curation; Formal analysis; Writing - original draft; Writing - review & editing. **QG**: Conceptualization; Methodology; Formal analysis; Writing - original draft; Writing - review & editing. **WL:** Conceptualization; Methodology; Formal analysis; Writing - original draft; Writing - review & editing. All authors gave their final approval and agree to be accountable for all aspects of the work.

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Figures

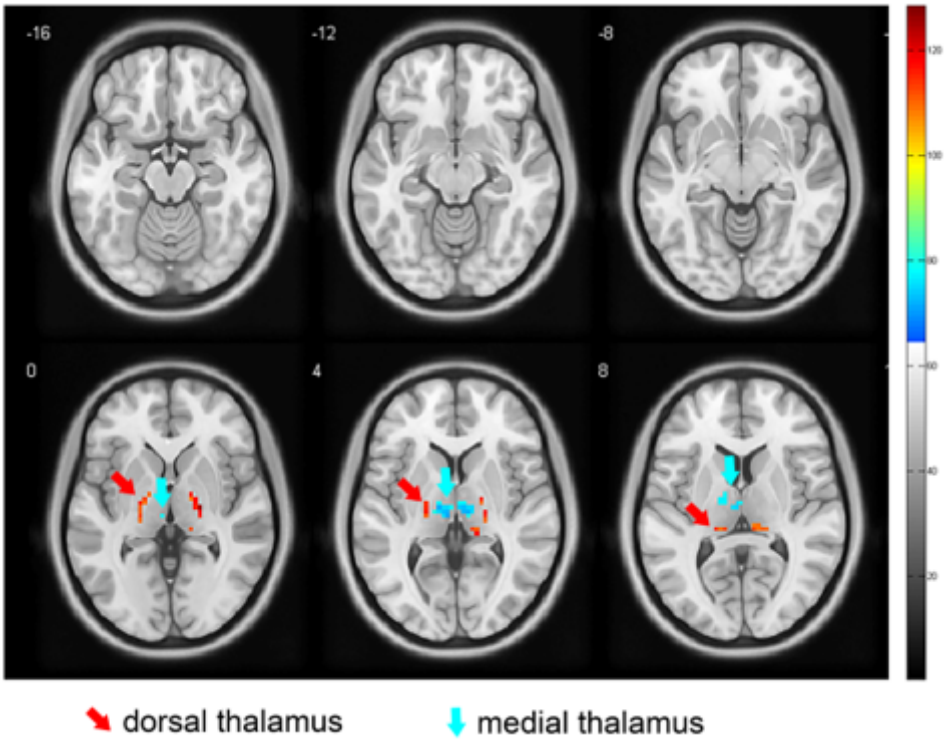

Figure 1

Images showing the results of the fALFF analysis. Compared with the controls, the orthodontic patients showed a decreased fALFF (blue) in the medial thalamus and increased fALFF (red) in the dorsal thalamus. fALFF, fractional amplitude of low frequency fluctuation.

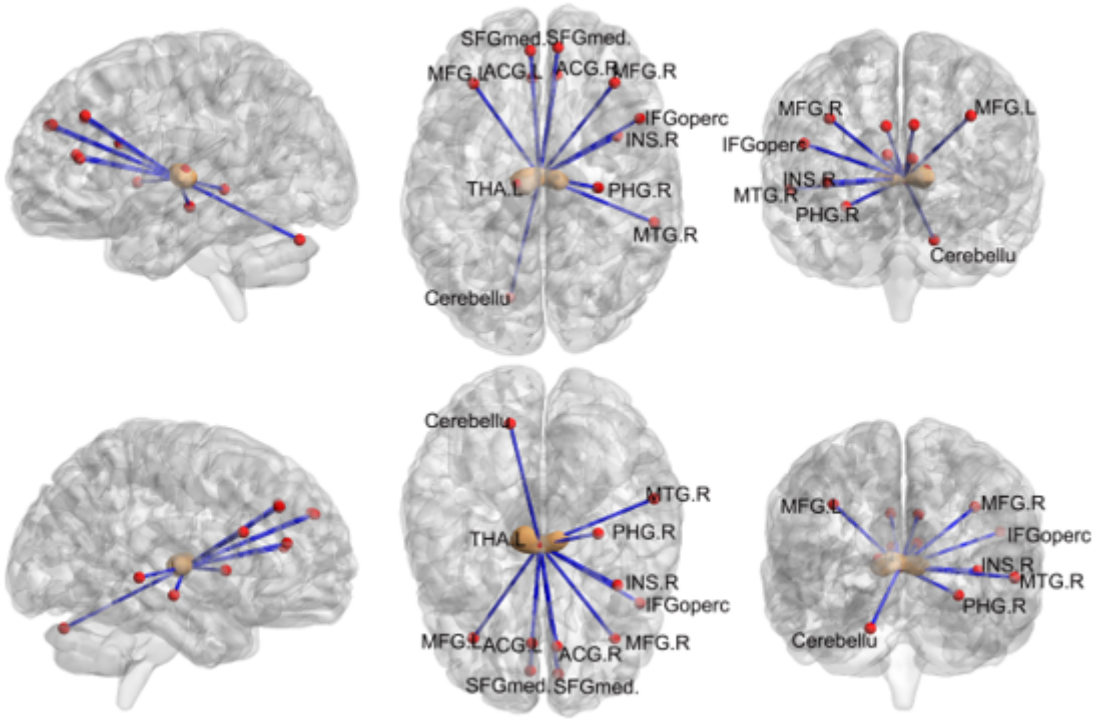

Figure 2

Thalamic functional connectivity in patients with orofacial pain compared with that in the control group. Patients exhibited significantly lower functional connectivity in clusters located in the left cerebellum, bilateral anterior cingulate cortices, right parahippocampal gyrus, bilateral middle frontal gyri, right inferior frontal gyrus, bilateral superior frontal gyri, right middle temporal gyrus, right insula, and the left thalamus ($p<0.05$, FWE corrected, voxel>100). ACG, anterior cingulate and paracingulate gyri; PHG, parahippocampal gyrus; MFG, middle frontal gyrus; SFGmed, superior frontal gyrus; MTG, middle temporal gyrus; INS, insula; IFGoperc, inferior frontal gyrus, opercular part; THA, thalamus; FWE, family-wise error.

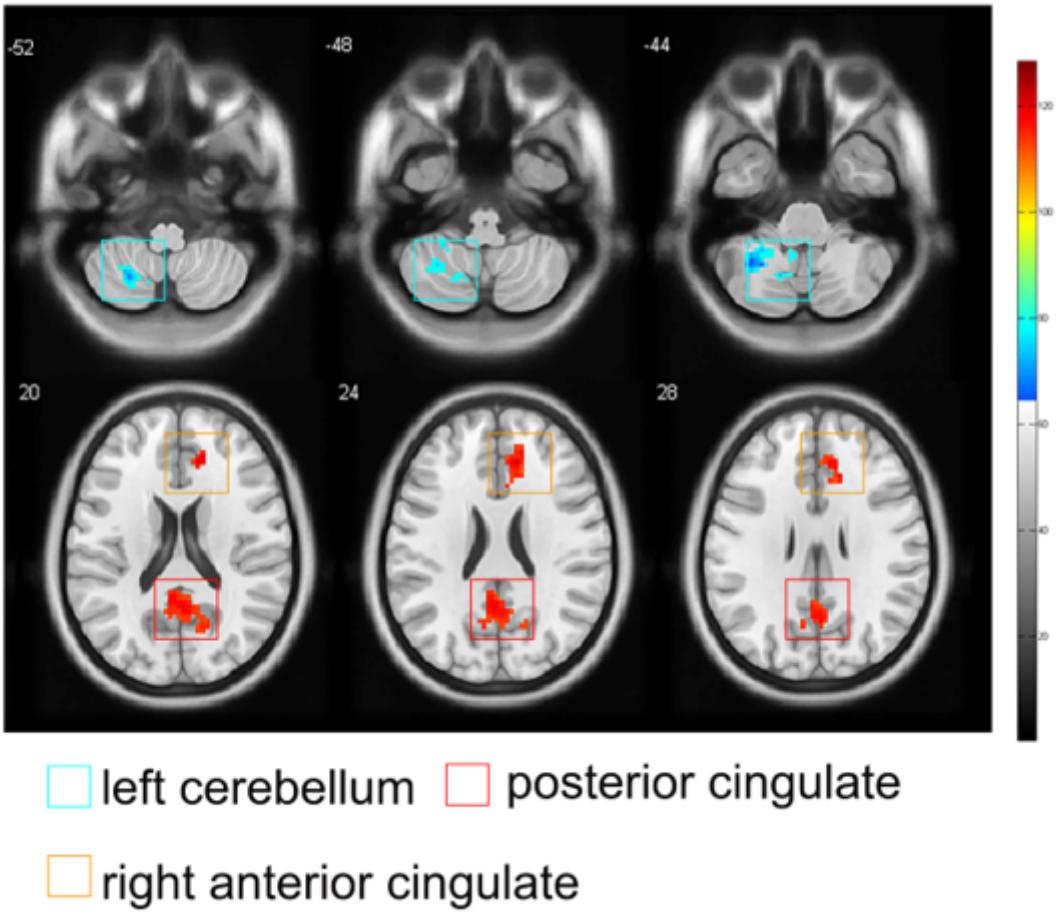

Figure 3

Results of the correlation analysis. The images show the correlations between the medial thalamus-seeded functional connectivity and the visual analog scale score changes in patients with orofacial pain. Red areas represent positive correlations (the posterior cingulated cortex and right anterior cingulated cortex), blue areas represent negative correlations (the left superior cerebellum), $p<0.05$, AlphaSim corrected.

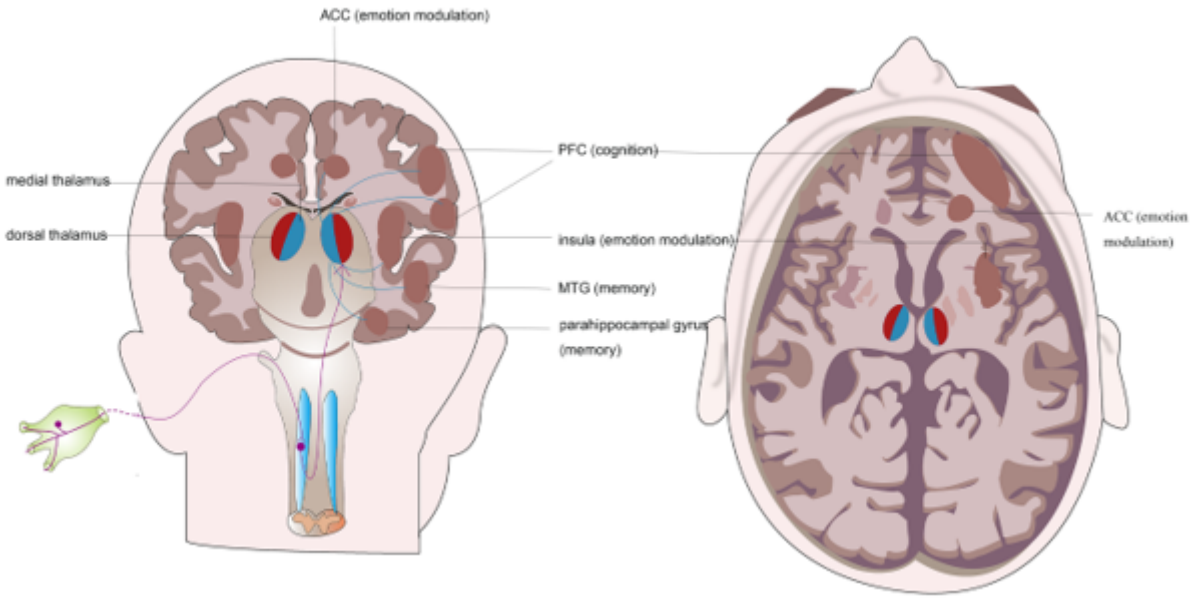

Figure 4

Image showing the possible central mechanism of orofacial pain. ACC, anterior cingulate cortex; PFC, prefrontal cortex; MTG, middle temporal gyrus.