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·Original Article·

# Regional homogeneity abnormalities in patients with tension-type headache: a resting-state fMRI study

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## ABSTRACT

Tension-type headache (TTH) is the most prevalent type of primary headache. Many studies have shown that the pathogenesis of primary headache is associated with fine structural or functional changes. However, these studies were mainly based on migraine. The present study aimed to investigate whether TTH patients show functional disturbances compared with healthy subjects. We used resting-state functional magnetic resonance imaging (fMRI) and regional homogeneity (ReHo) analysis to identify changes in the local synchronization of spontaneous activity in patients with TTH. Ten patients with TTH and 10 age-, gender-, and education-matched healthy controls participated in the study. After demographic and clinical characteristics were acquired, a 3.0-T MRI system was used to obtain resting-state fMRIs. Compared with healthy controls, the TTH group exhibited significantly lower ReHo values in the bilateral caudate nucleus, the precuneus, the putamen, the left middle frontal gyrus, and the superior frontal gyrus. There was no correlation between mean ReHo values in TTH patients and duration of TTH, number of attacks, duration of daily attacks, Visual Analogue Scale score, or Headache Impact Test-6 score. These results suggest that TTH patients exhibit reduced synchronization of neuronal activity in multiple regions involved in the integration and processing of pain signals.

**Keywords:** tension-type headache; resting-state fMRI; ReHo; basal ganglia

## INTRODUCTION

Headache is one of the most common symptoms encountered in general practice, and tension-type headache (TTH) is the most prevalent type of primary headache[1]. The prevalence of TTH differs by country but the current estimated global percentages of the adult population with an active TTH is 42%[2]. Similar to migraine, most sufferers of TTH are young adults[3, 4]. Although patients with episodic TTH require no special treatment[1], the overall social burden of TTH is greater than that of migraine according to a recent global burden study[2]. Unlike migraine, however, there have been no significant treatment advances for chronic TTH in the past few decades, probably due to the limited understanding of its pathophysiology compared with that of migraine[5].

According to the International Headache Classification (ICHD-II)[6], primary headache is not accompanied by responsibility nidus. However, a recent voxel-based morphometry study comparing 20 chronic TTH patients with

20 healthy controls found reduced gray-matter volumes in the dorsal rostral and ventral pons, the perigenual anterior cingulate cortex (ACC), the middle ACC, and other areas involved in pain processing[7]. Thus, chronic TTH patients may have reduced gray matter in pain processing areas as a consequence of frequent pain[7]. But this research did not study the brain function of TTH patients.

Resting-state fMRI refers to the use of blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI) to study spontaneous brain activity in individuals performing no specific task. Regional homogeneity (ReHo) is a resting-state data analysis method using the Kendall's coefficient of concordance to measure regional synchronizations of temporal changes in BOLD activity in a voxel-wise manner[8]. This method has been used widely in neurological and psychiatric studies[9-11] to compare local circuit activity patterns between healthy participants and patients. And the test-retest reliability for ReHo has been tested[12]. In the field of primary headache, Yu *et al.*[9] reported that migraine patients without aura have significantly lower ReHo values in the right rostral anterior cingulate cortex, prefrontal cortex, orbitofrontal cortex, and supplementary motor area than healthy controls. To our knowledge, however, there is no ReHo study of TTH patients.

Therefore, this study examined whether the synchrony of regional brain activity in patients with TTH differs from that in healthy controls and if so, whether the changes in ReHo are associated with the processing of pain.

## PARTICIPANTS AND METHODS

### Participants

Ten patients meeting the Second Edition of the International Headache Classification (ICHD-II)[6] for TTH were recruited at the outpatient clinic of West China Hospital between September 2011 and April 2012. All patients were diagnosed by at least two neurologists. Ten healthy volunteers with no history of headache and matched for sex ratio (1:1), mean age, and years of education were also recruited. The inclusion criteria of all participants were (1) Han ethnicity (the predominant ethnic group in China), (2) 18−60 years of age, (3) right-handed, (4) no history of cognitive dysfunction, and (5) first came to the clinic seeking medical help for TTH. Exclusion criteria were (1) taking analgesics or other drugs that could potentially affect neurological function within two weeks of resting-state fMRI scanning, (2) known history of hypertension, diabetes, anxiety, depression, other systemic disease, chronic pain disorders, serious neurological disorders, or psychiatric disorders, (3) suffering from other types of headache, (4) intracranial lesions in previous MRI or CT scans, or (5) headache attack within 24 h after fMRI scanning. The study protocol was approved by the Institutional Review Board of West China Hospital, Sichuan University, according to the updated version of the Declaration of Helsinki. All patients and controls gave informed consent prior to participation.

### MRI Data Acquisition

A 3.0-T MRI scanning system (Siemens Trio Tim, Erlangen, Germany) was used to acquire all MRI data. Participants were secured in the scanner with the head cushioned by plastic foam pads to minimize movement and with two appropriately-sized earplugs to minimize noise exposure. The participant was instructed to remain still and relaxed, with eyes closed but without pondering or sleeping. The scanning was terminated if the participant complained of any discomfort. The scanning sequences were as follows: (1) T1-weighted image sequence using repetition time (TR) 2 000 ms, echo time (TE) 20 ms, slice thickness 3 mm, slice interval 1 mm, field of vision (FOV) 16 × 16 cm², matrix 320 × 224, 2 NEX; (2) three-dimensional T1-weighted image sequence using the spoiled gradient recalled acquisition, TR 1 900 ms, TE 3.4 ms, flip angle 12°, slice thickness 1 mm, FOV 24 × 24 cm², matrix 512 × 512, voxel size 0.47 × 0.47 × 1.00 $mm^3$, and (3) resting-state fMRI using echo planar imaging, TR 2 000 ms, TE 30 ms, voxel size 3.75 × 3.75 × 5 $mm^3$, flip angle 90°, slice thickness 5 mm, matrix 64 × 64, FOV 24 × 24 $cm^2$; the scan lasted 6 min and 180 images were obtained. The scanning for all participants was performed by two independent board-certified neuroradiologists blinded to groups.

### Image Preprocessing

Image preprocessing was conducted using Statistical Parametric Mapping software (SPM8, Welcome Department of Imaging Neuroscience, London, UK). Briefly, the fMRI images were corrected for the acquisition delay between slices and head motion. Participants would be

excluded if the maximum head displacement in x, y, or z exceeded 3 mm, or the angular motion was >3°. None of the participants were excluded due to excessive movement. We also evaluated the group differences in translation and rotation of head motion according to the following formula[13]:

$$\text{Head motion/rotation} = \frac{1}{L-1}\sum_{i=2}^{L}\sqrt{|x_i - x_{i-1}|^2 + |y_i - y_{i-1}|^2 + |z_i - z_{i-1}|^2}$$

where $L$ is the length of the time series, $x_i$, $y_i$ and $z_i$ are translations/rotations at the i$^{th}$ time point in the x, y, and z directions. The results revealed no significant differences between the two groups in head motion and rotation (two sample $t$ test, $t$ = 0.1890, $P$ = 0.8524 for translational motion and $t$ = 1.0351, $P$ = 0.3151 for rotational motion). After correction for acquisition delay and head motion, the fMRI images were normalized to the standard SPM8 echo-planar imaging template and resampled at 3 × 3 × 3 mm. Several sources of spurious variance along with temporal derivatives were removed from the data by linear regression, including the six parameters obtained by rigid body correction of head motion, and signals from cerebrospinal fluid (CSF) and white matter (WM) were averaged. The WM and CSF masks were obtained using REST software. The linear trend was removed from the resulting fMRI time series data, which were then band-pass filtered (0.01−0.08 Hz) to reduce low-frequency drift and physiological high-frequency respiratory and cardiac noise.

### ReHo Calculation

ReHo analysis was performed automatically using REST software (http://www.resting-fmri.sourceforge.net)[14]. Individual ReHo maps were generated by calculating the Kendall's coefficient of concordance (KCC) of the time series of a given voxel relative to its nearest neighbors (26 voxels). The formula for calculating the KCC was as used in a previous study[15]. To reduce the influence of individual variations in the KCC, ReHo maps were normalized prior to group analyses by dividing the KCC for each voxel by the average KCC across the whole brain[16]. In addition, we found no significant difference of mean ReHo value between the TTH and control groups ($t$ = 0.6031, $P$ = 0.5549).

The two-sample $t$ test implemented in SPSS 16.0 software was used to compare the demographic variables between groups. $P$ <0.05 indicated a significant difference. Statistical differences in ReHo between the healthy control and TTH groups were calculated using SPM8 software with age, gender, and the mean gray matter volume across the whole brain and frame-wise displacement (FD) as the confounding variables[17]. The FD was computed as:

$$FD = |x_{i-1} - x_i| + |y_{i-1} - y_i| + |z_{i-1} - z_i| + 50 \cdot \frac{\pi}{180}\left(|\alpha_{i-1} - \alpha_i| + |\beta_{i-1} - \beta_i| + |\gamma_{i-1} - \gamma_i|\right)$$

where $x$, $y$, $z$ are the translational displacement, $\alpha$, $\beta$, $\gamma$ are the rotation displacement, and 50 mm is the assumed radius of the head. Before statistical analysis, the resulting ReHo maps were spatially smoothed with a Gaussian kernel of 8 × 8 × 8 mm$^3$ full-width at half-maximum to minimize differences in the functional anatomy of the brain across participants. We used the AlphaSim program to perform multiple comparison correction with a statistical significance level set at $P$ <0.05 (with a combined threshold of $P$ <0.005 and a minimum continuous voxel cluster of 46).

The regions showing significant between-group differences were extracted as regions of interest (ROIs), then Pearson correlation analysis was performed to measure the relationship in patient group between the mean ReHo values of these ROIs and the duration of TTH, number of attacks, duration of daily attacks, Visual Analogue Scale (VAS) score and Headache Impact Test (HIT-6) score. $P$ <0.05 (Bonferroni correction, corrected) was used to determine significant correlations.

## RESULTS

### Demographic and Clinical Characteristics

The demographic characteristics of the control and primary TTH groups are shown in Table 1. This total cohort included 10 males and 10 females, mean age 32.3 ± 9.3 years (range, 23–57), with 13.3 ± 3.9 years of formal education (range, 6–19), and a mean Montreal Cognitive Assessment (MoCA) score of 27.4 ± 2.4 points (range, 22–30). There were no significant differences in demographic variables between groups. The clinical characteristics of the TTH patients are summarized in Table 2.

### Group Differences in ReHo

Compared with the healthy controls, the TTH group exhibited significantly lower ReHo values in the bilateral caudate nucleus (CAU), the precuneus (PCUN), the putamen (PUT), the left middle frontal gyrus (MFG), and

**Table 1. Basic demographic characteristics of patient and control groups**

| | TTH patients (*n* = 10) | Healthy controls (*n* = 10) | *P*-value |
|---|---|---|---|
| Handedness (right/left) | 10/0 | 10/0 | 1.000 |
| Sex (M/F) | 5/5 | 5/5 | 1.000 |
| Age (mean ± SD, years) | 33.7 ± 10.8 | 30.9 ± 7.9 | 0.516 |
| Education (mean ± SD, years) | 11.7 ± 4.0 | 14.9 ± 3.3 | 0.066 |
| MoCA (mean ± SD) | 26.9 ± 2.2 | 28.2 ± 1.9 | 0.181 |

MoCA, Montreal Cognitive Assessment.

**Table 2. Clinical characteristics of TTH patients (*n* = 10)**

| | Minimum | Maximum | Mean ± SD |
|---|---|---|---|
| Duration of TTH (years) | 2.0 | 24.0 | 5.1 ± 6.8 |
| Number of attacks (days per month) | 2 | 30 | 14.2 ± 10.4 |
| Duration of daily attack (hours) | 0.5 | 24 | 4.9 ± 6.9 |
| VAS score (0–100) | 30 | 70 | 50.0 ± 12.5 |
| HIT-6 | 46 | 69 | 58.6 ± 6.5 |

VAS: visual analogue scale; HIT-6, Headache Impact Test.

**Table 3. Brain areas with a lower ReHo value in TTH patients than controls**

| Brain area | Number of voxels | MNI coordinates | | | *T*-value |
|---|---|---|---|---|---|
| | | X | Y | Z | |
| Left CAU | 111 | -3 | 9 | -3 | -3.864 |
| Right CAU | 100 | 3 | 9 | -3 | -2.964 |
| Left MFG | 107 | -21 | 30 | 51 | -3.303 |
| Left SFG | 135 | -18 | 18 | 69 | -3.317 |
| Left PCUN | 154 | -15 | -51 | 24 | -3.594 |
| Right PCUN | 93 | 15 | -48 | 21 | -3.140 |
| Left PUT | 70 | -21 | 6 | 6 | -2.643 |
| Right PUT | 115 | 24 | 0 | 6 | -2.560 |

CAU: caudate nucleus; MFG: middle frontal gyrus; PCUN: precuneus; PUT: putamen; SFG: superior frontal gyrus. All $P$ <0.005 for cluster size 46 (AlphaSim correction).

the superior frontal gyrus (SFG) (Table 3, Fig. 1). Eight ROIs were defined for correlation analysis. No significant correlations were found between any regional ReHo values and the duration of the TTH, number of attacks, duration of daily attack, VAS score, or HIT-6 score ($P$ >0.05, Bonferroni correction, corrected, Table 4).

## DISCUSSION

TTH is experienced on occasion by almost half of the world's adult population[2]. According to ICHD-II[6], patients with TTH do not exhibit structural brain abnormalities on routine MRI scans. In our study, however, ReHo analysis of the resting-state fMRI showed significantly lower ReHo

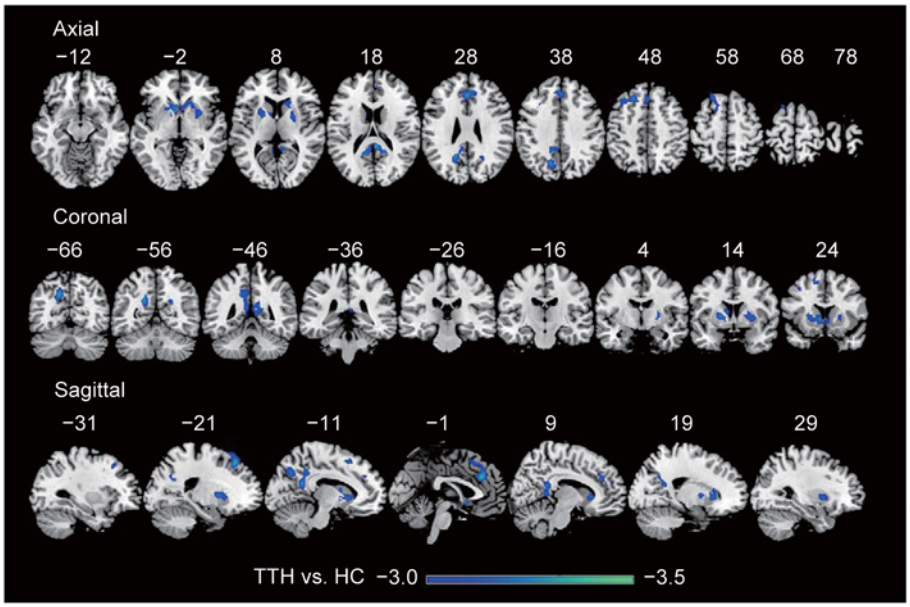


**Fig. 1. Statistical differences in ReHo between controls and TTH patients. Brain regions in blue had decreased ReHo values in TTH patients relative to the HC group (two-tailed two-sample t test; color bar, *T* value of group analysis).**

**Table 4. Association between brain regions showing significant differences in ReHo value between TTH and HC and clinical variables using Pearson correlation analysis**

| Brain regions | Correlation values | | | | |
|---|---|---|---|---|---|
| | Duration of TTH | Number of attacks | Duration of daily attack | VAS score | HIT-6 |
| Left CAU | *r*=0.581 | *r*=-0.714 | *r*=-0.509 | *r*=0.362 | *r*=0.107 |
| | P=0.078 | *P*=0.020 | *P*=0.133 | *P*=0.304 | *P*=0.768 |
| Right CAU | *r*=0.450 | *r*=-0.390 | *r*=-0.548 | *r*=0.496 | *r*=0.342 |
| | *P*=0.193 | *P*=0.265 | *P*=0.101 | *P*=0.145 | *P*=0.334 |
| Left MFG | *r*=-0.028 | *r*=0.195 | *r*=-0.412 | *r*=0.632 | *r*=0.237 |
| | *P*=0.940 | *P*=0.589 | *P*=0.237 | *P*=0.050 | *P*=0.510 |
| Left PCUN | *r*=0.477 | *r*=0.042 | *r*=-0.274 | *r*=0.695 | *r*=0.634 |
| | *P*=0.163 | *P*=0.908 | *P*=0.443 | *P*=0.025 | *P*=0.049 |
| Right PCUN | *r*=0.556 | *r*=0.177 | *r*=-0.211 | *r*=0.661 | *r*=0.608 |
| | *P*=0.095 | *P*=0.625 | *P*=0.559 | *P*=0.037 | *P*=0.062 |
| Left PUT | *r*=0.229 | *r*=0.153 | *r*=-0.281 | *r*=0.627 | *r*=0.525 |
| | *P*=0.525 | *P*=0.674 | *P*=0.431 | *P*=0.053 | *P*=0.119 |
| Right PUT | *r*=0.204 | *r*=0.197 | *r*=-0.326 | *r*=0.748 | *r*=0.694 |
| | *P*=0.573 | *P*=0.586 | *P*=0.359 | *P*=0.013 | *P*=0.026 |
| Left SFG | *r*=-0.293 | *r*=0.711 | *r*=-0.105 | *r*=0.512 | *r*=0.481 |
| | *P*=0.412 | *P*=0.021 | *P*=0.773 | *P*=0.130 | *P*=0.159 |

*r*, Pearson correlation coefficient; CAU, caudate nucleus; HIT-6, Headache Impact Test; MFG, middle frontal gyrus; PCUN, precuneus; PUT, putamen; SFG, superior frontal gyrus; VAS, visual analogue scale.

values in the bilateral CAU, PCUN, PUT, left MFG, and SFG than in controls. ReHo analysis, first proposed by Zang and colleagues[15], has been used to measure the synchronization or time-series similarity of neighboring voxels and is considered an indirect measure of local neuronal activity[15]. ReHo anomalies may indirectly suggest changes in the synchronization of neuronal activity. To the best of our knowledge, this was the first ReHo study of resting-state fMRI in TTH patients and demonstrated aberrantly low regional synchrony in specific brain areas. Therefore, we speculate that in the bilateral CAU, PCUN, PUT, left MFG, and SFG the synchronization of neuronal activity in TTH patients is significantly reduced.

The CAU and PUT are major components of the basal ganglia which are important sites of brain plasticity[18]. In addition to their classical roles in action selection, motor control, and habit learning, the basal ganglia also regulate pain sensation, analgesic responses, and pain signal transmission[19, 20]. Indeed, the basal ganglia–thalamic–cortical loop integrates many aspects of pain[21]. That is, the basal ganglia not only receive pain signals from the direct and indirect pain pathways, but also receive inputs *via* the cortex and subcortical areas which constitute the basal ganglia–thalamic–cortical loops. These cortical and subcortical areas include anterior cingulate cortex, dorsolateral prefrontal cortex and orbitofrontal cortex, parietal lobe, insula and hippocampus[21]. Due to these extensive connections, abnormalities in pain processing within the basal ganglia may have adverse effects on other brain areas. We have also found functional abnormality in the basal ganglia in headache. An fMRI study by Maleki *et al*.[22] showed that patients with progressive episodes of migraine exhibit reduced activity in the CAU, PAL, and PUT compared with patients with migraine episodes that did not progress. In TTH patients, the lower ReHo values compared with controls in the bilateral CAU and PUT may be associated with pain processing.

The MFG and SFG may modulate cortical and subcortical nociceptive pathways[23]. Many studies have shown functional changes in frontal lobe in pain disorders[24,25]. In a recent voxel-based morphometric study, Absinta *et al*.[24] reported that cluster headache patients have significantly reduced grey matter volumes in the right thalamus, head of the right CAU, and the bilateral MFG than controls, and that the decreased volume in the left MFG is significantly correlated with disease duration. Lutz *et al*.[25] also reported that fibromyalgia patients have a significantly higher fractional anisotropy value in the frontal cortex than healthy controls in a diffusion tensor imaging study. As a pain disorder, patients with TTH may also have frontal lobe functional abnormalities like other pain disorders.

The PCUN integrates sensation, cognition, and other higher activities into a sense of self-awareness[26]. Goffaux *et al*.[27] examined 16 healthy individuals and found that pain sensitivity is closely related to pain-evoked responses in the contralateral PCUN. Patients with TTH may show alterations in pain sensitivity as the disease progresses[5], possibly reflecting plasticity in these circuits. However, it remains unknown whether these changes in PCUN activity and pain sensitivity contribute to TTH or if TTH alters the ReHo in the PCUN.

The central limitation of this study is that it was preliminary and our results were limited to a small sample size ($n$ = 10 per group) with heterogeneous etiology, which may affect the statistical analysis and comprehensive interpretation of the results. Further studies with more patients with homogeneous etiology are needed. Second, the patients and controls only received one scanning session and were monitored for only 24 h thereafter. Establishing a causal relationship between the ReHo abnormalities and the clinical features of TTH requires further studies.

## CONCLUSIONS

The present study using resting-state fMRI revealed less synchronization of neuronal activity individually in multiple regions involved in the integration and processing of pain signals in TTH patients: the bilateral CAU, PCUN, PUT, left MFG, and SFG. These abnormalities suggest functional alterations. However, whether these functional changes contribute to TTH requires further study.

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