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Acupuncture modulates the abnormal brainstem activity in migraine without aura patients

Zhengjie Li[a,1], Fang Zeng[a,1], Tao Yin[a,1], Lei Lan[a], Nikos Makris[b,c], Kristen Jorgenson[b,c], Taipin Guo[a], Feng Wu[a], Yujie Gao[a], Mingkai Dong[a], Mailan Liu[d], Jie Yang[a], Ying Li[a], Qiyong Gong[e], Fanrong Liang[a,*], Jian Kong[b,c,*]

[a] The 3rd Teaching Hospital, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China
[b] Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, MA, USA
[c] Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA
[d] Acupuncture & Tuina School, Hunan University of Chinese Medicine, Changsha, Hunan, China
[e] Huaxi MR Research Center, West China Hospital of Sichuan University, Chengdu, Sichuan, China

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ABSTRACT

Migraine is a common neurological disease with a high prevalence and unsatisfactory treatment options. The specific pathophysiological mechanisms of migraine remain unclear, which restricts the development of effective treatments for this prevalent disorder. The aims of this study were to 1) compare the spontaneous brain activity differences between Migraine without Aura (MwoA) patients and healthy controls (HCs), using amplitude of low-frequency fluctuations (ALFF) calculation method, and 2) explore how an effective treatment (verum acupuncture) could modulate the ALFF of MwoA patients. One hundred MwoA patients and forty-six matched HCs were recruited. Patients were randomized to four weeks' verum acupuncture, sham acupuncture, and waiting list groups. Patients had resting state BOLD-fMRI scan before and after treatment, while HCs only had resting state BOLD-fMRI scan at baseline. Headache intensity, headache frequency, self-rating anxiety and self-rating depression were used for clinical efficacy evaluation. Compared with HCs, MwoA patients showed increased ALFF in posterior insula and putamen/caudate, and reduced ALFF in rostral ventromedial medulla (RVM)/trigeminocervical complex (TCC). After longitudinal verum acupuncture treatment, the decreased ALFF of the RVM/TCC was normalized in migraine patients. Verum acupuncture and sham acupuncture have different modulation effects on ALFF of RVM/TCC in migraine patients. Our results suggest that impairment of the homeostasis of the trigeminovascular nociceptive pathway is involved in the neural pathophysiology of migraines. Effective treatments, such as verum acupuncture, could help to restore this imbalance.

1. Introduction

Migraine is a common neurological disease with a high prevalence, a heavy social and economic burden (Stovner and Hagen, 2006), disabling effects (Leonardi et al., 2005) and unsatisfactory treatment options (Diener et al., 2015). About 64% of migraines are classified as Migraine without Aura type (MwoA) (Rasmussen and Olesen, 1992). However, the pathophysiological mechanisms of MwoA remain unclear, which restricts the development of effective treatments for this prevalent disorder.

Current models of migraine pathophysiology suggest that the disturbed homeostasis of the trigeminovascular nociceptive pathway, especially in the brainstem, is a key factor for susceptibility to migraine headaches. Specifically, sensory afferents from the head and neck either travel as trigeminal afferents through the trigeminal ganglion or as afferents from the greater occipital nerve through the cervical ganglion, and synapse on second-order neurons in the trigeminocervical complex (TCC) (DaSilva et al., 2002). In the brainstem, the descending modulation of the TCC nociceptive signals originate mainly from the periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM) (Akerman et al., 2011). The TCC/RVM (ascending input/descending modulation) imbalance hypothesis, based on animal models, is increasingly supported by human brain imaging studies in migraine patients (Weiller et al., 1995; Stankewitz and May, 2011; Stankewitz et al., 2011; Kröger and May, 2015). For instance, in a positron emission tomography study (Weiller et al., 1995), Weiller and colleagues found

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that only the cerebral blood flow increase in the brainstem (including PAG, RVM, etc.) was observed after an injection of sumatriptan, which induced complete relief from migraine attack. In another study, Stankewitz and colleagues (Stankewitz et al., 2011) compared the fMRI signal changes between migraine patients and controls during trigeminal nerve stimulation. The only difference between the two groups was detected in the lower brainstem (TCC area). These results suggest that an imbalance in activity between brainstem nuclei regulating antinociception and vascular control may play an important role in the pathogenesis of migraines.

Recently, resting state fMRI has drawn the attention of investigators. One method to characterize the resting state regional spontaneous neuronal activity is the amplitude of low frequency fluctuations (ALFF) calculation (Zang et al., 2007). As a reliable and reproducible data-driven approach measuring low frequency BOLD signals, ALFF can be defined as the total power within a certain frequency range, which reflects the intensity of regional spontaneous brain activity (Zou et al., 2009; Zuo et al., 2010). The alternations in ALFF have also been observed in several disorders including chronic pain (Xue et al., 2013; Qi et al., 2015; Wang et al., 2016), amnestic mild cognitive impairment (Han et al., 2011), schizophrenia (Hoptman et al., 2010) and hepatic encephalopathy (Qi et al., 2012).

In this study, we first compared the ALFF differences between MwoA patients and healthy controls (HCs), then explored how an effective treatment could modulate the ALFF of patients with migraine. We hypothesized that 1) MwoA patients had dysfunction in the ascending input/descending modulation system, especially in the brainstem regions, and 2) effective treatment might regulate the dysfunction of the ascending input/descending modulation system.

We chose acupuncture as an effective treatment in this study, as many studies have demonstrated that acupuncture treatments are effective and safe for migraine prophylaxis (Linde et al., 2005; Diener et al., 2006; Facco et al., 2008; Wang et al., 2011; Vickers and Linde, 2014; Wang et al., 2015). And verum acupuncture treatment is more effective in reducing headache intensity for MwoA patients, compared with sham acupuncture treatment (Li et al., 2012; Zhao et al., 2017); thus, this study focuses on how the ascending input and descending modulation system can be modified after an effective treatment (verum acupuncture treatment) and the different modulation effects between verum and sham acupuncture treatment.

2. Methods and materials

The experimental procedures are briefly described below. Please also see a previously published study for more details on the experimental procedure (Li et al., 2016). In this study, we investigated the ALFF difference between the migraineurs and controls as well as the modulation effect of repeated acupuncture treatments on ALFF.

2.1. Participants

2.1.1. Migraine without aura patients

MwoA patients were recruited at the outpatient department of the 3rd Teaching Hospital and the campus of Chengdu University of Traditional Chinese Medicine. Diagnosis of MwoA was based on the International Classification of Headache Disorders, 2nd Edition ICHD-II MwoA criteria (Headache Classification Subcommittee of the International Headache, 2004). Inclusion criteria required that all patients (1) were aged between 17 and 45 years old and were right-handed, (2) had not taken any prophylactic headache medicine nor had acupuncture treatment during the last three months, (3) had at least six months migraine duration, and (4) had at least once headache attack per month during the last three months. Patients were excluded if they (1) were alcohol or drug abusers, (2) were pregnant or lactating, (3) suffered from psychiatric, neurological, cardiovascular, respiratory, or renal illnesses, (4) suffered from any other chronic pain conditions or

had a history of head trauma with loss of consciousness, (5) had MRI contraindications, such as claustrophobia, and (6) had acupuncture contraindications, such as a bleeding tendency.

2.1.2. Healthy controls

Aged-matched, right-handed HCs were recruited for this study by advertisement. Each subject underwent a medical history evaluation, physical examination, hepatic and renal function tests, and routine analysis of blood, urine, and stool to exclude organic disease carriers. Individuals were excluded for any chronic pain conditions, abnormal test results, history of head trauma with loss of consciousness, or for pregnancy/lactation.

The study protocol was approved by the Ethics Committee of the 1st Teaching Hospital of Chengdu University of Traditional Chinese Medicine, and registered on www.clinicaltrial.gov (NCT01152632, June 27, 2010). Informed consent was obtained from all participants.

2.2. Study design

The total observation period for MwoA patients was eight weeks. After screening, all MwoA patients were randomized into five groups, including verum acupuncture groups 1, 2, and 3 (VA1, VA2, VA3), sham acupuncture group (SA), and waiting-list (WT) group. In this study, we included three verum acupuncture prescriptions to better represent different acupoint selection strategies (Li et al., 2012). Weeks 1 to 4 served as a baseline phase used to record baseline headache diaries. Weeks 5 to 8 served as an intervention phase, during which patients in treatment groups received either verum or sham acupuncture treatment. All patients continued recording headache diaries during this period. In addition, MRI scans were administered at the ends of the fourth and eighth weeks for migraine patients. All MwoA patients were migraine-free for at least 72 h at the time of the MRI scans. HCs received only the baseline MRI scans.

2.3. Interventions

The treatment for the acupuncture groups consisted of 20 sessions of acupuncture treatment with a duration of 30 min per session, each administered over a period of 4 weeks (5 sessions per week). No verum acupuncture nor sham acupuncture treatments were applied on HC and MwoA patients in the waiting-list group.

Acupoint and non-acupoint selections were similar to those in our previous RCT studies (Li et al., 2009; Li et al., 2012). Acupoints selected in VA1 were Yanglingquan (GB34), Qiuxu (GB40) and Waiguan (SJ5). VA2 acupoints were Xiyangguan (GB33), Diwuhui (GB42) and Sanyangluo (SJ8). VA3 acupoints were Zusanli (ST36), Chongyang (ST42) and Pianli (L16). SA acupoints included NAP1, NAP2 and NAP3.

Two licensed acupuncturists administered all acupuncture treatments. All acupoints and non-acupoints were punctured bilaterally. The needles were inserted perpendicularly at a penetration of 5 to 15 mm and were gently manipulated to achieve deqi sensation (a complex feeling including soreness, numbness, heaviness, distention or dull pain at the site of needle placement) in all treatment groups (Kong et al., 2007).

Patients agreed not to take any regular medications for the treatment of migraines for the duration of the study. In case of severe pain, ibuprofen (300 mg capsule with sustained release) was allowed as a rescue medication.

2.4. Outcome measures

Migraine intensity and frequency of migraine attacks were chosen as outcome measures to assess the clinical efficacy of acupuncture treatments. Headache intensity was evaluated with a 0–10 visual analogue scale (VAS), with 0 indicating no pain, and 10 indicating the worst pain imaginable. The frequency of migraine attacks is defined

as the number of migraines separated by pain free intervals of at least 48 h, and is based on patients' headache diaries according to the guidelines of the IHS for Clinical Trials in Migraine (Tfelt-Hansen et al., 2000). In addition, the self-rating anxiety scale (SAS) and the self-rating depression scale (SDS) were administered to assess the MwoA patients' anxiety and depression status (Seidel et al., 2009; Usai et al., 2009).

2.5. MRI data acquisition

MRI data was acquired with a 3.0T magnetic resonance scanner (Siemens 3.0T Trio Tim, Munich, Germany) with an 8-channel phase-array head coil at the West China Hospital MRI center. Subjects were asked to stay awake and to keep their heads still during the scan, with their eyes closed and ears plugged. Prior to the functional run, a high-resolution structural image for each subject was acquired using a three-dimensional MRI sequence with a voxel size of 1 mm^3 employing an axial fast spoiled gradient recalled sequence (TR = 1900 ms; TE = 2.26 ms; data matrix: 256×256; field of view: $256 \times 256 \text{ mm}^2$). The BOLD resting-state functional images were obtained with echo-planar imaging (30 contiguous slices with a slice thickness of 5 mm; TR = 2000 ms; TE = 30 ms; flip angle: 90°; field of view: $240 \times 240 \text{ mm}^2$; data matrix: 64×64; total volumes: 180).

2.6. Data analysis

2.6.1. Clinical data analysis

The clinical outcomes were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL). Within and between-group comparisons were performed using paired or unpaired *t*-tests or χ^2, as appropriate. The significance level used for the statistical analysis with 2-tailed testing was $P < 0.05$.

2.6.2. ALFF analysis

The fMRI data preprocessing was performed using Data Processing Assistant for Resting-State fMRI (DPARSF) software (available at: http://rfmri.org/DPARSF) in MATLAB (Mathworks, Inc., Natick, Massachusetts). The software is based on Statistical Parametric Mapping (SPM12) (http://www.fil.ion.ucl.ac.uk/spm) and a Resting-State fMRI Data Analysis Toolkit (http://www.restfmri.net) (Song et al., 2011).

2.6.2.1. Data processing. The first 10 volumes of functional data for each subject were discarded to allow for signal equilibration effects. The remaining volumes were slice timing corrected, within-subject spatially realigned, coregistered to the respective structural images for each subject, segmented. Then, white matter and CSF signals were regressed out (global signal not included (Saad et al., 2012)). To perform subject-level correction of head motion, the Friston 24-parameter model (6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items) (Friston et al., 1996; Yan et al., 2013) were used. Images were normalized by using structural image unified segmentation and then re-sampled to 3-mm cubic voxels. Subjects with head movements exceeding 2 mm on any axis or with head rotation > 2° were excluded. After smoothing with a 6 mm full-width at half maximum (FWHM) Gaussian kernel, the linear and quadric trends of the time courses were removed. Finally, imaging data were temporally filtered (band pass, 0.01–0.1 Hz) to remove the affects of very low-frequency drift and high-frequency noise (e.g., respiratory and cardiac rhythms).

Group analysis was performed with a random effect model using SPM12. We first compared the ALFF difference between MwoA patients and HCs using two sample *t*-tests. Then, we compared the changes of ALFF difference (post-treatment minus pre-treatment) between verum acupuncture groups (VA, VA1 + VA2 + VA3) and waiting-list group in factorial design module in SPM12. To explore the association between

the clinical outcomes and the ALFF, we also applied regression analyses between baseline ALFF and the corresponding migraine symptom (VAS). For all group analyses, age, gender, disease duration, SAS, and SDS were included as non-interest covariates. A threshold of a voxel-wise $P < 0.001$ uncorrected and $P < 0.05$ family wise error (FWE) correction at cluster level were applied for all analyses.

3. Results

150 MwoA patients were screened and 100 of them were recruited for this study. 46 age- and gender-matched healthy controls were recruited in this study, and 4 HCs were excluded due to excessive head movements (head movements exceeding 2 mm on any axis or head rotation > 2°). 88 patients participated in the first fMRI scan, and 81 patients participated in the second fMRI scan; 7 patients did not participate in the second fMRI scan due to scheduling conflicts (2 in VA1, 2 in VA2, 1 in VA3, and 2 in SA groups). Of the 81 patients who participated in the two fMRI scans, 9 patients were excluded from data analysis due to incomplete scans (lack of resting state fMRI or T1 anatomy; 3 in V1, 1 in V2, 2 in V3, 2 in SA, and 1 in WT), and 10 patients were excluded due to excessive head movements (head movements exceeding 2 mm on any axis or head rotation > 2°; 1 in V1, 3 in V2, 2 in V3, 2 in SA and 2 in WT).

3.1. Baseline characteristics

We found no statistical differences among VA1, VA2, VA3, SA and WT groups in age, gender, weight, height, duration of disease, headache intensity (VAS score), headache frequency, SAS and SDS (P > 0.05). We also found no statistical differences in age, gender, weight and height between all MwoA patients and healthy controls (P > 0.05) (Table 1).

3.2. Clinical outcomes

After acupuncture treatment, VA1, VA2, and VA3 groups showed significant improvement in VAS score (P < 0.05) (Table 2). VA1 and VA3 groups showed significant improvement in headache frequency (P < 0.05), while VA2 group showed a tendency to improve headache frequency (P = 0.111). SA showed insignificant improvement in VAS score and headache frequency (P > 0.05). However, insignificant differences were found in the changes of VAS score, changes in headache frequency, the SAS and SDS improvement (P > 0.05) (Table 3) among VA1, VA2, VA3 and SA groups, and there were no significant differences between VA (VA1 + VA2 + VA3) and SA groups, due to small sample size. We observed that VA showed significant therapeutic effects compared to the waiting-list group in VAS score and headache frequency improvement (P < 0.05) (Table 3).

3.3. ALFF results

3.3.1. MwoA patients vs. HCs

Compared with healthy controls, MwoA patients showed significant ALFF increases at the left posterior insula and left putamen/caudate, and ALFF decreases in the bilateral middle occipital cortex/cuneus and bilateral rostral ventromedial medulla (RVM)/trigeminocervical complex (TCC) (Fig. 1A and B, Table 4A). To explore the association between the ALFF value and baseline clinical outcomes, we extracted the ALFF value of the peak MNI coordinate (sphere, 2 mm radius) at each of the above regions, applied partial regressions with clinical variables (VAS and headache frequency), including age, gender, disease duration, SAS and SDS as non-interest variables. Partial regression showed that only ALFF value in RVM/TCC (x = − 3, y = − 33, z = 57, sphere, 2 mm radius) was negatively associated with VAS ($r = -0.426$, $p = 0.001$, significant after Bonferroni correction) (Fig. 1C).

Table 1
Baseline characteristics of MwoA patients (subjects completed two MRI scans with completed MRI data) in different groups and healthy controls.

HC, healthy controls; MwoA, migraine without aura; VA, verum acupuncture; SA, sham acupuncture group; SAS, self-rating anxiety scale; SDS, self-rating depression scale; WT, waiting-list. *, one-way ANOVA was applied for the comparisons among VA1, VA2, VA3, SA and WT groups; **, two-sample *t*-test was applied for the comparisons between HC and MwoA groups. A P value < 0.05 was considered statistically significant.

Characteristics	VA1, n = 11	VA2, n = 11	VA3, n = 13	SA, n = 11	WT, n = 16	P value*	HC, n = 42	MwoA, n = 62	P value**
Female n (%)	9 (81.8%)	8 (72.7%)	10 (77.2%)	9 (81.8%)	12 (77.5%)	0.979	34 (81.0%)	48 (77.4%)	0.808
Age (y)	21.73	21.18	21.00	21.18	21.38	0.889	21.21	21.29	0.771
Mean (95%CI)	(20.56; 22.89)	(19.69; 22.67)	(19.98; 22.02)	(20.52; 21.84)	(20.33; 22.42)		(20.93; 21.49)	(20.85; 21.73)	
Height (cm)	158.00	163.45	159.69	157.00	162.63	0.163	161.00	160.34	0.633
Mean (95%CI)	(153.65; 162.35)	(158.25; 168.67)	(155.35; 164.04)	(154.00; 160.00)	(157.60; 167.65)		(159.23; 162.77)	(158.40; 162.28)	
Weight (kg)	51.64	56.27	50.73	48.27	53.94	0.164	50.98	52.27	0.382
Mean (95%CI)	(47.22; 56.05)	(48.61; 63.93)	(47.94; 53.52)	(45.91; 50.64)	(48.58; 59.29)		(49.12; 52.84)	(50.19; 54.34)	
Duration (mo)	62.91	68.91	67.38	58.00	73.31	0.843	–	–	–
Mean (95%CI)	(43.91; 81.84)	(39.88; 97.93)	(45.44; 89.33)	(39.94; 76.06)	(53.15; 93.47)				
Headache intensity	5.45	5.32	5.69	5.18	5.66	0.765	–	–	–
Mean (95%CI)	(4.54; 6.37)	(4.68; 5.96)	(5.12; 6.26)	(4.19; 6.17)	(5.16; 6.15)				
Headache frequency	5.91	7.45	5.54	6.45	4.31	0.152	–	–	–
Mean (95%CI)	(3.88; 7.93)	(5.03; 9.88)	(3.35; 7.72)	(4.34; 8.57)	(2.91; 5.71)				
SAS score	45.05	45.27	46.75	45.68	46.81	0.980	–	–	–
Mean (95%CI)	(39.72; 50.37)	(39.71; 50.83)	(40.50; 53.00)	(40.35; 51.01)	(41.52; 52.11)				
SDS score	42.41	50.86	43.90	44.27	47.34	0.326	–	–	–
Mean (95%CI)	(34.55; 50.27)	(45.14; 56.59)	(36.43; 51.38)	(37.41; 51.14)	(42.48; 52.21)				

Table 2
Clinical outcomes at the baseline and end of the study in different groups.

VA, verum acupuncture (VA1 + VA2 + VA3); SA, sham acupuncture group; SAS, self-rating anxiety scale; SDS, self-rating depression scale; WT, waiting list. Paired-*t*-test was applied for comparisons in each group. A P value < 0.05 was considered statistically significant.

Outcome measures	VA1, n = 11	VA2, n = 11	VA3, n = 13	SA, n = 11	VA, n = 35	WT, n = 16
Headache intensity						
Mean (95%CI)						
Baseline	5.45	5.32	5.69	5.18	5.50	5.66
	(4.54; 6.37)	(4.68; 5.96)	(5.12; 6.26)	(4.19; 6.17)	(5.13; 5.87)	(5.16; 6.15)
End of treatment	3.18	3.73	3.15	4.04	3.34	5.72
	(2.24; 4.12)	(2.82; 4.63)	(2.31; 3.99)	(3.09; 5.00)	(2.87; 3.81)	(4.84; 6.59)
P value	0.003	0.002	0.000	0.158	0.000	0.861
Headache frequency						
Mean (95%CI)						
Baseline	5.91	7.45	5.54	6.45	6.26	4.31
	(3.88; 7.93)	(5.03; 9.88)	(3.35; 7.72)	(4.34; 8.57)	(5.08; 7.44)	(2.91; 5.71)
End of treatment	4.18	6.18	4.08	6.45	4.77	8.63
	(2.60; 5.77)	(4.13; 8.03)	(2.40; 5.76)	(3.97; 8.94)	(3.83; 5.71)	(6.14; 11.11)
P value	0.029	0.111	0.038	0.999	0.009	0.000
SAS score						
Mean (95%CI)						
Baseline	45.05	45.27	46.75	45.68	45.75	46.81
	(39.72; 50.37)	(39.71; 50.83)	(40.50; 53.00)	(40.35; 51.01)	(42.74; 48.76)	(41.52; 52.11)
End of treatment	39.20	41.77	37.96	38.02	39.55	41.64
	(31.93; 46.48)	(36.43; 47.11)	(31.68; 44.25)	(32.97; 43.08)	(36.22; 42.88)	(37.76; 45.52)
P value	0.101	0.180	0.015	0.081	0.001	0.040
SDS score						
Mean (95%CI)						
Baseline	42.41	50.86	43.90	44.27	45.37	47.34
	(34.55; 50.27)	(45.14; 56.59)	(36.43; 51.38)	(37.41; 51.14)	(41.53; 49.21)	(42.48; 52.21)
End of treatment	41.93	43.86	38.92	37.34	41.03	41.25
	(33.11; 50.75)	(36.67; 51.05)	(32.31; 45.53)	(30.69; 43.98)	(37.17; 44.89)	(35.99; 46.51)
P value	0.832	0.071	0.070	0.118	0.011	0.065

3.3.2. Modulation effects of treatment (acupuncture)

We then compared post- and pre-treatment differences in all treatment groups. Results revealed that after longitudinal verum acupuncture treatments, MwoA patients showed significant ALFF increases in the bilateral OFC, bilateral RVM/TCC (Stankewitz et al., 2011; Schulte et al., 2016) and bilateral rostral midbrain, and ALFF decreases in left middle occipital cortex/cuneus (Fig. 2A and B, Table 4B). Interestingly, this finding partially overlapped with the ALFF differences between healthy controls and MwoA patients at RVM/TCC (Fig. 2C). To further explore the ALFF value changes at different conditions, we extracted the ALFF value in the overlapping RVM/TCC region and found that effective treatment can normalize the decreased RVM/TCC ALFF value in MwoA patients (Fig. 2D).

In the waiting-list group, comparison between the first and second fMRI scan showed increased ALFF only in the right rostral anterior cingulate cortex (Table 4C). Compared with the waiting-list group, the verum acupuncture treatment group (VA1 + VA2 + VA3) showed greater ALFF increases in the bilateral OFC and bilateral RVM/TCC after verum acupuncture treatments (Fig. 3A and Table 4D). The opposite comparison found the waiting-list group showed greater ALFF increases in the bilateral PCC and left middle occipital cortex/cuneus (Fig. 3B and Table 4D).

We also compared the differences between verum acupuncture group and sham acupuncture group. The results indicated that, compared with the sham acupuncture group, the verum acupuncture group (VA1 + VA2 + VA3) showed greater ALFF increases in the bilateral RVM/TCC (peak MNI, x = − 12, y = − 36, z = − 36, z = 4.72, cluster size = 92) (Fig. 3C). We extracted the ALFF value of the RVM/TCC (peak MNI, x = − 12, y = − 36, z = − 36, sphere, 2 mm) in each group, and found that verum acupuncture could increase the ALFF value of RVM/TCC in MwoA patients while sham acupuncture decreases the ALFF value (Fig. 3D).

4. Discussion

In this study, we investigated the ALFF changes between migraine patients and healthy controls, the modulation effects of an effective treatment (verum acupuncture treatment) as well as the different modulation effects between verum and sham acupuncture. We found that migraine symptoms are associated with reduced ALFF in the RVM/TCC as compared with healthy controls, and longitudinal verum acupuncture treatment can normalize the decreased ALFF of the RVM/TCC in migraine patients. And verum acupuncture and sham

Table 3

Comparisons of the therapeutic effects between different groups.

HC, healthy controls; VA, verum acupuncture (VA1 + VA2 + VA3); SA, sham acupuncture; SAS, self-rating anxiety scale; SDS, self-rating depression scale; WT, waiting list; *, one-way ANOVA was applied for the comparisons among VA1, VA2, VA3 and SA groups; **, two-sample *t*-test was applied for the comparisons between VA and WT groups. A P value < 0.05 was considered statistically significant.

| Outcome measures	VA1, n = 11	VA2, n = 11	VA3, n = 13	SA, n = 11	P value*	VA, n = 35	WT, n = 16	P value**
Headache intensity Mean (95%CI)								
End of treatment	3.18 (2.24; 4.12)	3.73 (2.82; 4.63)	3.15 (2.31; 3.99)	4.04 (3.09; 5.00)	0.351	3.34 (2.87;3.81)	5.72 (4.84; 6.59)	0.000
End - baseline	− 2.27 (− 3.55; − 0.99)	− 1.59 (− 2.42; − 0.75)	− 2.54 (− 3.41; − 1.66)	− 1.14 (− 2.80; 0.52)	0.242	− 2.16 (− 2.69; − 1.62)	0.06 (− 0.68; 0.81)	0.000
Headache frequency Mean (95%CI)								
End of treatment	4.18 (2.60; 5.77)	6.18 (4.13; 8.03)	4.08 (2.40; 5.76)	6.45 (3.97; 8.94)	0.107	4.77 (3.83; 5.71)	8.63 (6.14; 11.11)	0.001
End - baseline	− 1.73 (− 3.23; − 0.22)	− 1.27 (− 2.89; 0.35)	− 1.46 (− 2.83; − 0.10)	0.00 (− 2.75; 2.75)	0.493	− 1.49 (− 2.26; − 0.72)	4.31 (2.26; 6.37)	0.000
SAS score Mean (95%CI)								
End of treatment	39.20 (31.93; 46.48)	41.77 (36.43; 47.11)	37.96 (31.68; 44.25)	38.02 (32.97; 43.08)	0.745	39.55 (36.22; 42.88)	41.64 (37.76; 45.52)	0.399
End - baseline	− 5.84 (− 13.05; 1.37)	− 3.50 (− 8.91; 1.91)	− 8.79 (− 15.54; − 2.04)	− 7.66 (− 16.46; 1.14)	0.670	− 6.20 (− 9.67; − 2.73)	− 5.17 (− 10.07; − 0.27)	0.722
SDS score Mean (95%CI)								
End of treatment	41.93 (33.11; 50.75)	43.86 (36.67; 51.05)	38.92 (32.31; 45.53)	37.34 (30.69; 43.98)	0.520	41.03 (37.17; 44.89)	41.25 (35.99; 46.51)	0.944
End - baseline	− 0.48 (− 5.35; 4.40)	− 7.00 (− 14.72; 0.72)	− 4.98 (− 10.44; 0.48)	− 6.93 (− 15.95; 2.09)	0.432	− 4.34 (− 7.62; − 1.07)	− 6.09 (− 12.61; 0.42)	0.617
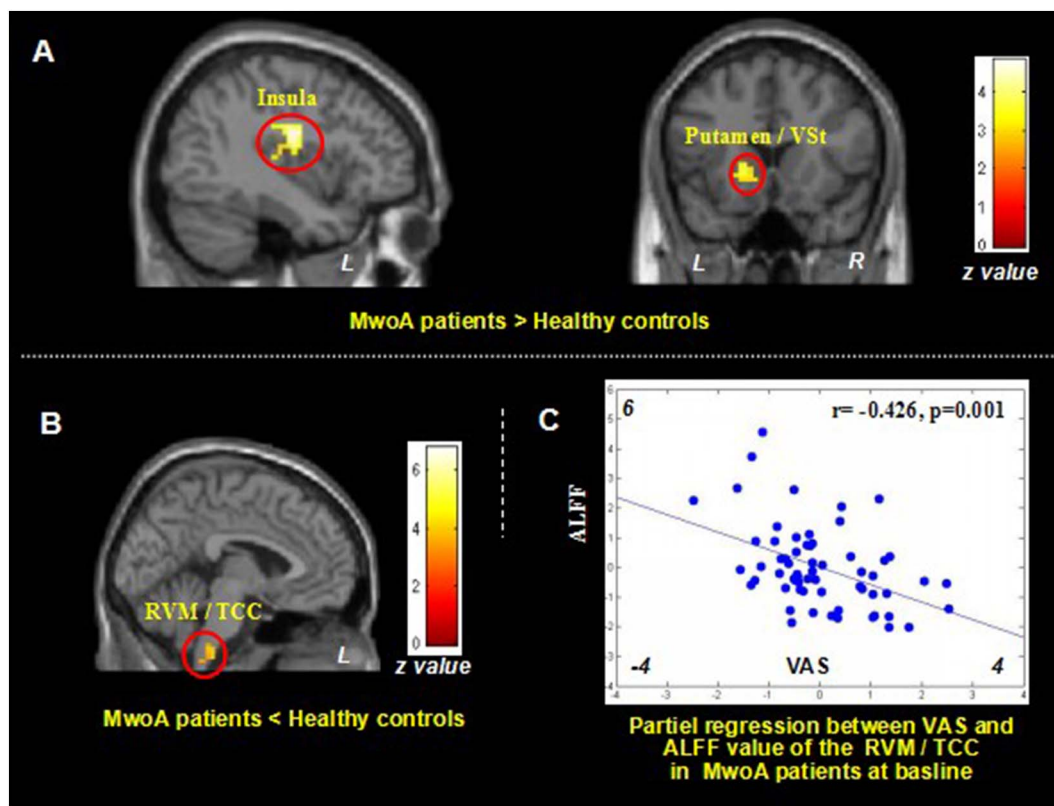
Fig. 1. Altered resting state ALFF in MwoA patients.

1A. Brain regions showed increased resting state ALFF in MwoA patients compared to healthy controls; 1B. Brain regions showed reduced resting state ALFF in MwoA patients, compared to healthy controls; 1C. Reduced ALFF value in RVM/TCC is negatively associated with increased headache intensity as indicated by VAS scores in MwoA patients at baseline, controlled for age, gender, disease duration, SAS and SDS. ALFF, amplitude of low frequency fluctuation; L, left side; MwoA, migraine without aura; R, right side; RVM, rostral ventromedial medulla; TCC, trigeminocervical complex; VAS, visual analogue scale; Vst, ventral striatum.

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Table 4
The ALFF in MwoA patients and the changes in different groups.

4A. ALFF comparison between MwoA and HCs; 4B. ALFF changes in MwoA patients in acupuncture group; 4C. ALFF changes in MwoA patients in waiting-list group; 4D. ALFF modulation difference in MwoA patients between acupuncture group and waiting-list group. ALFF, amplitude of low frequency fluctuation; B, bilateral; L, left side; HCs, healthy controls; MwoA, migraine without aura; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; R, right side; rACC, rostral anterior cingulate cortex; RVM, rostral ventromedial medulla; TCC, trigeminocervical complex; WT, waiting-list. A threshold of a voxel-wise P < 0.001 uncorrected and P < 0.05 family wise error (FWE) correction at cluster level were applied.

A. ALFF difference between MwoA and HCs

Contrast	Voxels	Brain region	MNI (x, y, z)			Z
MwoA > HC	132	L posterior insula	− 39	− 12	24	5.05
	128	L putamen/caudate	− 15	18	0	4.03
MwoA < HC	287	R middle occip/cuneues	30	− 75	24	6.16
	153	L middle occip/cuneues	− 27	− 69	24	5.35
	59	B RVM/TCC	− 3	− 33	− 57	3.93

B. ALFF changes in verum acupuncture group

Contrast	Voxels	Brain region	MNI (x, y, z)			Z
Pre > Post	178	L middle occip/cuneues	− 30	− 72	30	5.21
Pre < Post	88	B RVM/TCC	− 12	− 39	− 39	5.40
	83	B OFC	− 6	27	− 30	5.15
	41	B rotral midbrain	0	− 24	− 25	4.33

C. ALFF changes in waiting-list group

Contrast	Voxels	Brain region	MNI (x, y, z)			Z
Pre > Post		None				
Pre < Post	35	R rACC	9	24	− 3	4.02

D. ALFF difference between verum acupuncture group and waiting-list group

Contrast	Voxels	Brain region	MNI (x, y, z)			Z
VA > WT (Post-Pre)	55	B OFC	− 6	27	− 30	4.78
	60	B RVM/TCC	− 12	− 39	− 39	4.70
VA < WT (Post-Pre)	124	L middle occip/cuneues	− 30	− 72	30	4.95
	91	B PCC	− 6	− 45	27	4.58

acupuncture have different modulation effects on ALFF of RVM/TCC in migraine patients.

In this study, we found an increased ALFF at the insula, putamen and caudate in MwoA patients, compared with HCs. Previous studies suggested that these regions are involved in pain information processing in the brain (Kong et al., 2006; Kong et al., 2010; Schwedt et al., 2015). We thus speculate these changes may represent an adaptive response to repeated migraine attacks in these patients.

We also found decreased ALFF in RVM and TCC. The decreased ALFF value of RVM/TCC was associated with increased headache intensity. RVM is a key region of the descending pain modulatory system (Millan, 2002; Fields, 2004; Kong et al., 2010), while TCC comprises the second-order neurons of the trigeminovascular nociceptive pathway. Animal studies show that the descending modulation of the TCC, through the PAG and RVM, could cause the activation of 'on' cells and the inhibition of 'off' cells in the RVM, which is critical for
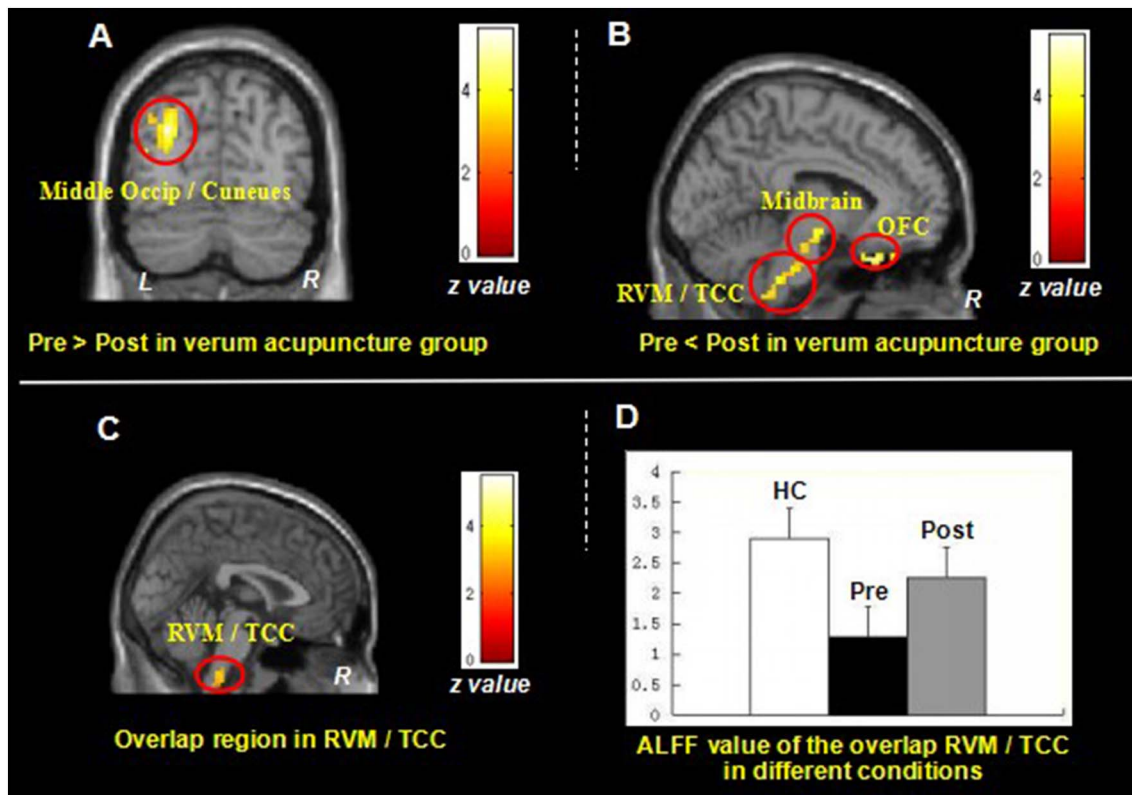

Fig. 2. Resting state ALFF changes of MwoA patients in verum acupuncture group.

2A. Brain regions showed decreased ALFF value in MowA patients after verum acupuncture treatment; 2B. Brain regions showed increased ALFF value in MowA patients after verum acupuncture treatment; 2C. Brain regions (RVM/TCC) showed overlap between Fig. 1B and Fig. 2B; 2D. The Fisher-z value of the overlap RVM/TCC in healthy controls and MwoA patients before and after verum acupuncture treatment respectively (mean ± SE). ALFF, amplitude of low frequency fluctuation; L, left side; MwoA, migraine without aura; OFC, orbital frontal cortex; R, right side; RVM, rostral ventromedial medulla; TCC, trigeminocervical complex; VAS, visual analogue scale.
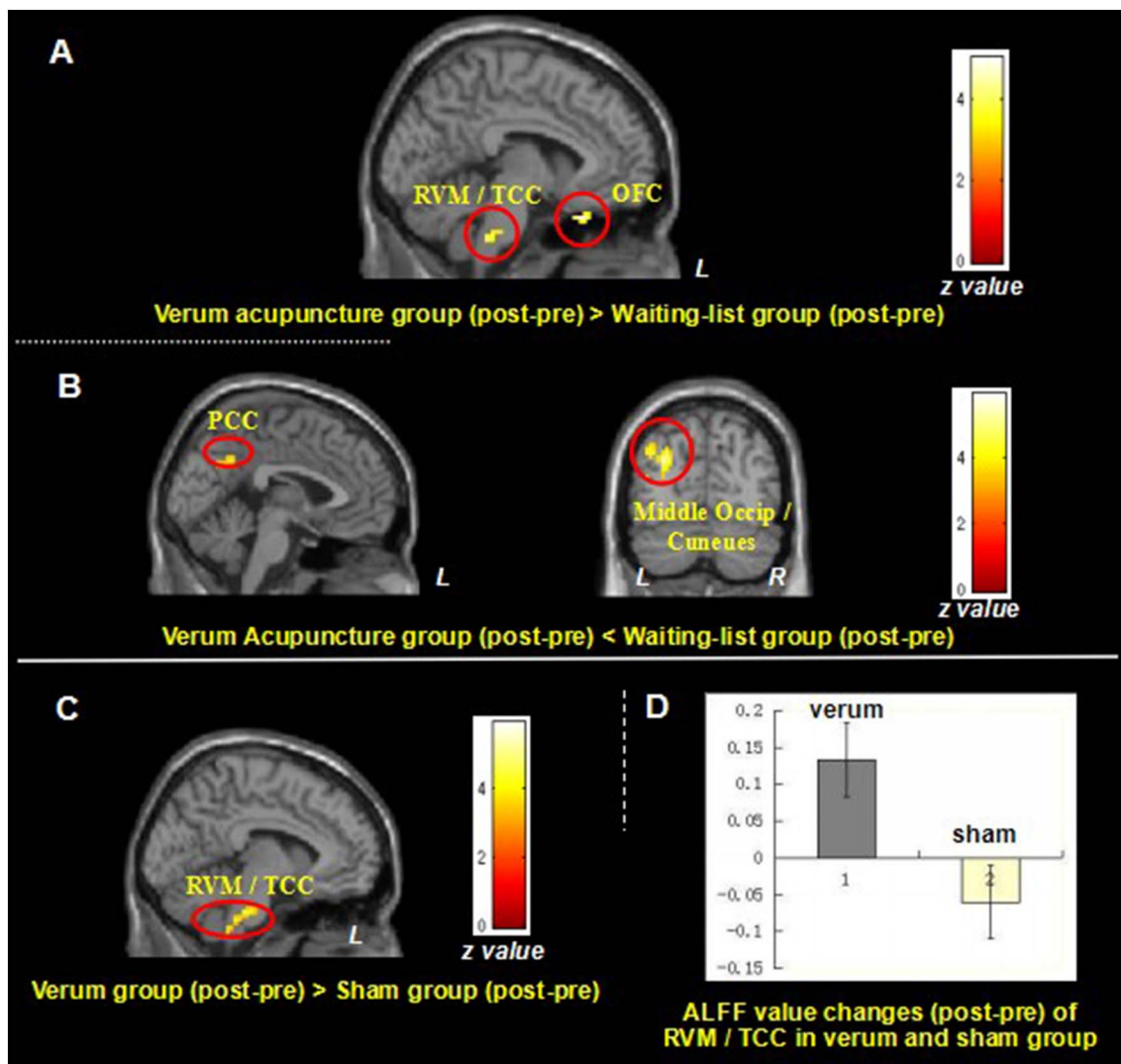
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Fig. 3. The Difference of resting state ALFF changes of MwoA patients in verum acupuncture group VS. waiting-list group and verum acupuncture group VS. sham acupuncture group. 3A. Brain region showed greater ALFF value increase (post- minus pre-treatment) in the verum acupuncture treatment group compared to waiting-list control; 3B. Brain region showed greater ALFF value increase (post- minus pre-treatment) in the waiting-list control compared to verum acupuncture treatment group; 3C. Brain regions showed greater ALFF value increase (post- minus pre-treatment) in the verum acupuncture group compared to sham acupuncture group; 3D. ALFF value changes of RVM/TCC in verum and sham group. L, left side; MwoA, migraine without aura; OFC, orbital frontal cortex; PCC, posterior cingulate cortex; R, right side; TCC, trigeminocervical complex.

activation of TCC and development of migraine headaches (Akerman et al., 2011). Our results provide direct evidence in patient population in favor of findings from animal studies.

Our findings of the decreased ALFF in RVM are also in line with many human brain imaging studies reporting that migraine is associated with an impaired descending pain modulatory system (May, 2008; Mainero et al., 2011; Schwedt et al., 2014). In a previous study, investigators also found that migraine patients in the interictal phase revealed lower BOLD-fMRI signals in the TCC compared with healthy controls (Stankewitz et al., 2011).

Recent studies suggested that the neuropeptide calcitonin gene-related peptide (CGRP) may play a critical role in the central and peripheral pathways leading to a migraine attack (Wrobel Goldberg and Silberstein, 2015). CGRP and its receptor components were found in different subregions of TCC in both humans and rats (Unger and Lange, 1991; Van Rossum et al., 1997). A more recent study showed an inhibitory effect of CGRP on mechanically evoked activity in the spinal trigeminal nuclei after pretreatment with glyceryl trinitrate in rats (Covasala et al., 2012). Taken together, these results support the crucial role of TCC in the pathology of migraine, and provide direct support for our findings indicating reduced ALFF value in TCC.

In this study, we also found that verum acupuncture treatments can normalize the decreased ALFF of the RVM and TCC in migraine patients, compared with the waiting-list group. This finding is in line with many brain imaging studies reporting that acupuncture treatment could normalize the impaired descending pain modulatory system in migraine (Li et al., 2016) and other chronic pain conditions (Chen et al., 2014; Chen et al., 2015; Egorova et al., 2015). It is well accepted that the endogenous opioid system is involved in mediating acupuncture analgesia (Han, 2011; Zhang et al., 2014; Dougherty et al., 2008). Specifically, in the RVM level, 'on' cells facilitate the firing of neurons that receive nociceptive inputs and are inhibited by opioids, whereas 'off' cells are tonically active, inhibit nociceptive responses, and are activated by opioids (Fields and Heinricher, 1985). This might be the one of the underlying mechanisms of verum acupuncture treatment for migraine (Vickers and Linde, 2014; L Zhao et al., 2014; Yang et al., 2012; Li et al., 2015).

Recently, an neuroimaging study found that triptans (a class of migraine-specific medication) could significant increase the BOLD signal in the trigeminal nuclei in migraine patients compared with placebo or a nonsteroidal anti-inflammatory drug (broad spectrum pain killer) (Kröger and May, 2015). The study further illuminated that the

increase in BOLD signal changes after triptan administration could be attributable to an inhibition of the inhibitory action of CGRP on trigeminal neurons in the brainstem, and concluded that a specific functional inhibition of trigemino-cortical projections might be one of the reasons that triptans, unlike pain killers, act specifically on migraine but not pain (Kröger and May, 2015). Therefore, we speculate that verum acupuncture might also work through the CGRP system to achieve treatment effects. Future studies are needed to elucidate the details of this process.

Although, due to small sample size in each group, insignificant differences were found in the changes of VAS score, changes in headache frequency, the SAS and SDS improvement between verum acupuncture (VA1 + VA2 + VA3) and sham acupuncture group in this study. Our previous RCTs reporting that puncturing at true acupoints, compared with puncturing at non-acupoints, showed better clinical improvement for migraine prevention (Li et al., 2012; Zhao et al., 2017). Thus, we compared verum acupuncture with sham acupuncture, and found that verum acupuncture showed an increase, but sham acupuncture showed a decrease in the RVM/TCC in migraine patients, which suggested that verum and sham acupuncture may have different modulation effects at RVM/TCC. Although the superiority of verum acupuncture over sham control remains a global controversy, accumulating neuroimaging studies suggest that verum acupuncture works in a more targeted and special manner on migraine patients, compared with sham acupuncture (Yang et al., 2012; Ling Zhao et al., 2014; Yang et al., 2014). Further studies with larger sample sizes are needed to validate this finding.

There are several potential limitations in this study. 1) Sample size in each group was relatively small, which prevented us from testing the clinical outcome differences between different treatment groups. 2) Dropout rate in each group was relatively high; however, we would like to emphasize that the reasons for dropout do not seem to be associated with treatment response. Also, the aim of this study was to explore if an effective treatment could modulate the ALFF in migraine patients rather than to test the efficacy of acupuncture treatment. 3) We did not quantitatively record intensity of 'deqi' sensation, which is thought to be an important contributor to acupuncture effect (Kong et al., 2007). Studies with larger sample size and quantitative 'deqi' records are needed in the future.

5. Conclusion

Our results demonstrate that impairment of the descending pain modulatory system and ascending nociceptive pathway at RVM/TCC are associated with neural pathophysiology of migraine during the interictal period. Verum acupuncture treatment can normalize (increase) the reduced ALFF of RVM/TCC in migraine patients. Verum acupuncture and sham acupuncture have different modulation effects on ALFF of RVM/TCC in migraine patients.

Conflicts of interest

None of the authors have any conflict of interest.

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