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The altered right frontoparietal network functional connectivity in migraine and the modulation effect of treatment

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Abstract

Aims—This study aims to investigate resting-state functional connectivity (rs-fc) of the right frontoparietal network (rFPN) between migraineurs and healthy controls (HCs), and how the rFPN rs-fc can be modulated by effective treatment.

Methods—One hundred patients and forty-six matched HCs were recruited. Migraineurs were randomized to verum acupuncture, sham acupuncture, and waiting list groups. Resting state fMRI data was collected before and after longitudinal treatments.

Results—Independent component analysis found that migraineurs showed decreased outside-network rs-fc with the bilateral precuneus for rFPN, a key node in the default mode network,

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Disclosure

The authors report no disclosures relevant to the manuscript.

Author contributions

F. L. and F. Z. are the corresponding authors. Z. L. and L. L. contributed equally to this article. Study protocol and design: F. L., F. Z., Y. L. and Q. G.; acquisition of data: M. L., L. L., T. G., F. W., Y. G., M. D., and J. Y.; analysis and interpretation of data: Z. L., N. M., J. H., F. Z., and J. K.; drafting of the manuscript: Z. L., L. L., S. S., N. M., and J. K. All authors reviewed the manuscript.

compared with HCs. After treatment (real and sham), outside-network rs-fc with the precuneus for rFPN was significantly reduced. This reduction was associated with headache intensity relief. To explore the role of the precuneus in acupuncture modulation, we performed a seed-based rs-fc analysis using the precuneus as a seed and found that the precuneus rs-fc with key regions in the reward system, cognitive control, and descending pain modulatory systems is significantly enhanced after treatment.

Conclusion—Our results suggest that migraineurs were associated with abnormal rFPN rs-fc. An effective treatment, such as acupuncture, may relieve symptoms by strengthening the cognitive adaption/coping process. Elucidation of the adaption/coping mechanism may open a new window for migraine management.

Keywords

Acupuncture; Migraine without aura; fMRI; Independent component analysis; Frontoparietal network; resting state functional connectivity

Introduction

Migraine, a disabling chronic brain disorder, has become an important public healthcare and social issue due to its high prevalence, large medical burden¹, disabling effects², and serious reduction in quality of life³. Nevertheless, many questions regarding its pathophysiology remain unclear. An improved understanding of the mechanisms underlying migraine and the modulation effect of treatment will open new and promising avenues for discovery of its causes as well as the development of new therapeutic methods.

Despite its high prevalence and social burden, treatments for migraine are far from satisfactory⁴. Previous studies showed that acupuncture may achieve its therapeutic effect by enhancing human body's self-regulation/healing process; and both verum or sham acupuncture, can significantly relieve migraine headache intensity and frequency^{5,6}. Although the mechanism underlying acupuncture is complex, studies have demonstrated that nonspecific effects (including attention, cognition and expectation) play an important role⁷. As a result, acupuncture treatment can be used as an effective treatment to investigate the neural physiopathology of migraine.

Recently, investigators have recently begun to explore the functions of individual brain regions of interest as well as neural networks of migraineurs^{8,9,10,11,12} and found that the brain structure and function of migraineurs differs significantly from that of healthy individuals. These differences can be embodied in their reaction to pain, light and smell, or as an adaptive response to repeated pain (stressor) attacks^{13,14}.

More recently, accumulating evidence has suggested that resting state functional connectivity (rs-fc) may be a valuable tool for understanding brain networks¹⁵. One such brain network is the right frontoparietal network (rFPN), which plays an important role in cognitive control and top-down modulation¹⁶, and has been reliably identified by independent component analysis (ICA)¹⁷. Previous studies suggested that pain and cognition interact reciprocally, i.e., pain can negatively influence cognitive performance, while

cognition can significantly modulate our pain experience^{18,19}. In particular, studies have shown that migraineurs are associated with impaired rFPN rs-fc^{20,21}.

Thus, this study aims to investigate the rFPN resting-state functional connectivity (rs-fc) between migraine patients (during the interictal period when they were free from headache symptoms) and matched healthy controls (HC), as well as how longitudinal acupuncture, an effective treatment, can modulate rFPN rs-fc in migraineurs. We hypothesize that migraineurs will be associated with altered rFPN rs-fc to adapt/cope with repeated headache attacks, an effective non-pharmacological treatment that can further modulate the adaptation/coping process.

Materials and Methods

Participants

The Ethics Committee of the 1st Teaching Hospital of Chengdu University of Traditional Chinese Medicine approved all study procedures. The experiment was performed in accordance with approved guidelines. This study was then registered on clinicaltrial.gov (NCT01152632, June 27, 2010). Patients (n=100) and healthy controls (n=46) were enrolled from the outpatient department of the 3rd Teaching Hospital, local advertisements or the Chengdu University of Traditional Chinese Medicine campus. All participants signed a written consent. The recruitment started in June 2011 and ended in November 2013.

Migraine without aura (MwoA) patients—Migraineur inclusion criteria was as follows:

1) 17–45 years (to improve demographic homogeneity) old and right-handed, 2) matched the diagnosis of MwoA based on the International Classification of Headache Disorders, 2nd Edition ICHD-II MwoA criteria²², 3) had not received any prophylactic headache medicine or acupuncture treatment in the past 3 months, 4) had a migraine duration of at least 6 months, and 5) had at least one headache attack per month in the past 3 months. Exclusion criteria included: 1) alcohol or drug abusers, 2) pregnant or lactating women, 3) suffered from psychiatric, neurologic, cardiovascular, respiratory or renal illnesses, 4) had any other type of headache or a history of head trauma with loss of consciousness, 5) magnetic resonance imaging (MRI) contraindications such as claustrophobia, and 6) acupuncture contraindications such as excessive bleeding.

Healthy controls—Right-handed HCs between 17–45 years, free from headache and other chronic pain conditions, were recruited for this study as controls. Each subject underwent a review of medical history evaluation, physical examination, hepatic function, renal function, and routine analysis of blood, urine, and stool to exclude organic disease carriers.

Individuals with abnormal test results or a history of head trauma with loss of consciousness, pregnancy or lactation were excluded.

Study Design

The total observation period for MwoA patients in this study was 8 weeks. After screening, all MwoA patients were randomized into 5 groups: verum acupuncture (VA) groups 1, 2, 3 (VA1, VA2, VA3), a sham acupuncture group (SA) and the waiting list (WT) group. All

patients were blinded with the group allocation. In this study, we included three verum acupuncture prescriptions to better represent different acupoint selection strategies²³. Weeks 1–4 were the baseline phase during which patients recorded baseline headache diaries. Weeks 5–8 were the intervention phase during which patients in treatment groups received verum or sham acupuncture. All patients continued recording headache diaries during this treatment period. In addition, MRI scans were applied at the end of the 4th and 8th weekends for the migraine patients. All MwoA patients were migraine-free for at least 72 hours at the time of the MRI scan. HCs received only the baseline MRI scan (Figure 1).

Interventions

Two licensed acupuncturists administered all acupuncture treatments. Acupoint and non-acupoint selection were similar to those in our previous RCT studies⁶. Acupoints selected in VA1 included Yanglingquan (GB34), Qiuxu (GB40) and Waiguan (SJ5). VA2 acupoints included Xiyangguan (GB33), Diwuhui (GB42) and Sanyangluo (SJ8). VA3 acupoints included Zusanli (ST36), Chongyang (ST42) and Pianli (L16). SA acupoints included non-acupoints 1, 2, 3 (NAP1, NAP2 and NAP3) (Figure 2).

All acupoints and non-acupoints were punctured bilaterally using disposable needles. The needles were inserted perpendicularly at a penetration of 5 to 15 mm and were gently twisted, lifted, and thrust at an even amplitude, force, and speed to acquire deqi sensation²⁴ (deqi sensation is a complex feeling including soreness, numbness, heaviness, distention or dull pain at the site of needle placement) in all treatment groups. The MwoA patients in acupuncture groups received 20 treatments (30 min each) over a 4-week period: once per day for five weekdays followed by a two-day break. Acupuncture or sham acupuncture treatment was not performed on HCs and migraines in the waiting list group.

MwoA patients were instructed and agreed not to take any regular medications for migraine treatment. In cases of severe pain, ibuprofen (300 mg per capsule with sustained release) was allowed as a rescue medication.

Outcome Measures

The clinical outcomes included: headache intensity (visual analogue scale (VAS) of 0–10) and frequency (number of migraines separated by pain-free intervals of at least 48 hours) in the past month obtained from the headache diary. The metrics obtained were consistent with the guidelines of the IHS for Clinical Trials in Migraine²⁵. In addition, the Self-rating anxiety scale (SAS) and Self-rating depression scale (SDS) were applied to assess the MwoA patients' emotional status^{26,27}.

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 head coil at the West China Hospital MRI center. 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 mm³ employing an axial fast spoiled gradient recalled sequence (TR=1900ms; TE=2.26ms; data matrix, 256×256; field of view, 256×256mm²). The BOLD resting-state functional images were obtained with echo-

planar imaging (30 continuous slices with a slice thickness of 5mm; TR=2000ms; TE=30ms; flip angle, 90°; total volumes, 180; matrix size, 64×64; field of view, 256×256mm²). Subjects were instructed to stay awake and remain motionless during the scan with their eyes closed.

Data Analysis

Clinical data analysis—The clinical variables were analyzed using SPSS16.0 software (SPSS Inc, Chicago, IL). A threshold of $p < 0.05$ (2-tailed) was applied. Continuous variables were presented as the mean (standard deviation) with 95% confidence intervals (CI). Categorical variables were described as n (percentage). χ^2 was applied for categorical variables comparisons. For continuous variables, a paired-t test was applied for within-group comparisons, two-sample t-tests were applied for two-group comparisons, and one-way ANOVA was applied when there were more than three groups.

Independent Component Analysis for resting state fMRI data—Resting state data was processed using FSL (FMRIB Software Library) and AFNI following the same processing steps (pipeline) described previously¹⁷. Previous studies suggested ICA as a reliable method for analyzing resting state functional connectivity, particularly the attention and control network^{28,29}.

Preprocessing of functional images included removal of non-brain structures, motion correction, temporal bandpass filtering at 0.01 to 0.1 Hz, spatial smoothing (6 mm full-width at half-maximum Gaussian kernel), and 8-parameter nuisance signal extraction. Similar to previous study¹⁷, to co-register fMRI images to a standard space, functional images were first registered to each individual's high-resolution T1 anatomical scan and further registered to the MNI152 template using affine transformations with 12 degrees of freedom^{30,31}.

Probabilistic independent component analysis (PICA) at low dimensionality (20 components) was performed (MELODIC, FSL³²) to derive the group's (n=190) resting state networks. Spatial correlations between our group-level networks and the template networks derived from 1414 healthy subjects¹⁷ were calculated. The group-derived network that showed the highest spatial overlap with the rFPN in the template network was assigned to the rFPN.

Then, a dual-regression³³ analysis was applied. Using the rFPN as spatial regressors in a general linear model (GLM), we were able to extract the temporal dynamics associated with each spatial map. The resulting time courses served as temporal regressors in a GLM to generate subject-specific maps of the whole brain for each subject. Finally, group analyses were performed using whole-brain subject-specific network maps from the second GLM. The results represent the strength of the rs-fc for each voxel with the rFPN. A two-sample t-test and paired t-test were applied to compare the between-group and within-group differences.

In addition, we also applied multiple regression analyses on migraine patients to explore the association between baseline functional connectivity and the corresponding migraine intensity as measured by VAS, as well as the association between pre- and post-treatment

functional connectivity changes and corresponding VAS changes in all treatment groups including age, gender, disease duration, SAS and SDS as non-interest covariates. For all analysis, cluster correction threshold at $Z > 2.3$, $P < .05$ was applied.

Seed based functional connectivity—Using ICA analysis, we found that the precuneus plays an important role in the modulation of acupuncture. To further explore the modulation process, we performed a seed based rs-fc analysis using the precuneus as a seed. The fMRI data was preprocessed using Data Processing Assistant for Resting-State fMRI (DPARSF) software (available at: <http://rfmri.org/DPARSF>). The fMRI images were slice timing and head-motion corrected, coregistered to the respective structural images for each subject, segmented, regressed out 6 rigid body motion, white matter, and CSF signal, normalized using structural image unified segmentation, and then re-sampled to 3-mm cubic voxels. After linear detrending, data was filtered using a typical temporal bandpass (0.01–0.08 Hz) to remove low frequency noise (including slow scanner drifts) and influences of higher frequencies reflecting cardiac and respiratory signals. We removed frames with FD > 0.5 mm ('scrubbing'), one time point before 'bad' time points and two time points after 'bad' time points were deleted. Finally, the data was smoothed using a full width half maximum of 6 mm.

Functional connectivity analysis for individual subjects was carried out in DPARSF by applying a seed-region approach using the right precuneus (2, –62, 50, 3mm) so that the coordinate represents the peak of the overlap cluster observed in ICA results. Next, the averaged time course was obtained from the seed and correlation analysis was performed in a voxel-wise manner to generate the FC map. The correlation coefficient map was converted into a Fisher-Z map using Fisher's r-to-z transform by calling functions in REST to improve normality. Group analysis was calculated with a random effect model using SPM8. We first compared the rs-fc difference between MwoA patients and healthy controls using two sample t-tests. Then, we compared the changes of rs-fc difference (post-treatment minus pre-treatment) between acupuncture (verum + sham) groups (AG) and waiting-list group in factorial design module in SPM8. A threshold of voxel-wise $p < 0.005$ (uncorrected) and $p < 0.05$ family wise error (FWE) corrected at cluster level was applied for all the analyses.

Results

One hundred and fifty patients were screened, of which 100 patients were recruited for this study. Forty-six age and gender matched HCs were also recruited. Eighty-eight patients participated in the first fMRI scan and 81 patients participated in the second. Seven 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). Of the 81 patients who participated in the two MRI scans, 9 patients were excluded from data analysis due to incomplete scans (lack of resting state MRI or T1 anatomy, 3 in V1, 1 in V2, 2 in V3, 2 in SA and 1 patient in the waiting list group) (Figure 1).

The baseline characteristics

We found no statistical difference among VA1, VA2, VA3, SA and waiting list groups in age, sex, weight, height, duration of disease, headache intensity (VAS score), headache

frequency, SAS and SDS ($P > 0.05$). There is no statistical difference in age, gender, weight and height between MwoA patients and HCs (Table 1).

The clinical outcomes

Compared with the baseline condition, all three verum acupuncture groups (VA1, VA2, and VA3) showed improvement in headache intensity and headache frequency ($P < 0.05$) after treatment. Participants in the sham acupuncture group only showed improvement in SAS and SDS ($P < 0.05$) and a trend for headache intensity ($p = 0.083$) (Table 2). As expected, we found no significant differences among the VA1, VA2, VA3, and sham acupuncture groups in headache intensity, headache frequency, SAS and SDS improvement ($P > 0.05$), which is consistent with previously published meta-analysis reports^{34,35}, indicating that the specific effect of acupuncture treatment as compared with sham is only moderate. Because both verum and sham acupuncture treatments reduced the headache intensity in migraine patients we merged all acupuncture groups (AG) and found that AG showed significantly greater improvements than the waiting list group in headache intensity and frequency improvement ($P < 0.05$) (Table 2). Since the aim of this study is to use acupuncture treatment as a mediator to investigate the neural mechanism of migraine development; thus, we merged all acupuncture treatment groups (verum and sham) in the following rs-fc analyses to investigate the modulation effect of an effective treatment.

Independent Component Analysis results

As expected, ICA analysis including all subjects/scans have produced a right frontoparietal network, which mainly covers the right DLPFC, VLPFC, bilateral inferior/superior parietal lobules, MPFC, insula and left cerebellum (Figure 3). This component is consistent with findings from previous studies³⁶.

Compared with healthy controls, MwoA patients showed significant decreased outside-network rs-fc with the bilateral precuneus, lingual gyrus, middle temporal gyrus, and superior temporal gyrus; left fusiform and secondary somatosensory cortex (S2); right cerebellum, inferior occipital gyrus, inferior temporal gyrus and cuneus for rFPN (Figure 4 and Table 4); no abnormal intra-network functional connectivity for rFPN was found. Regression analysis showed that the outside-network rs-fc with the bilateral precuneus, and left superior frontal gyrus and intra-network rs-fc within rACC/MPFC for rFPN were positively associated with migraine headache intensity (VAS) at the baseline. The outside-network rs-fc with the right inferior temporal gyrus for rFPN was negatively associated with headache intensity (Figure 4 and Table 4).

Paired t-tests showed that after longitudinal treatment (real and sham), the outside-network rs-fc with the right precuneus and intra-network rs-fc within left middle frontal gyrus for rFPN was significantly reduced; the outside-network rs-fc with the bilateral posterior cingulate cortex (PCC) for rFPN was significantly increased (Figure 4 and Table 4). Regression analysis showed that after treatment, the decrease of outside-network rs-fc with the bilateral precuneus, right paracentral gyrus and postcentral gyrus for rFPN was positively associated with a decrease in headache intensity (Figure 4 and Table 4).

In waiting list group, we found the intra-network rs-fc within the left inferior frontal gyrus (peak MNI coordinates: -52, 30, 8, cluster size 351) and bilateral MPFC (peak MNI coordinates: 0, 44, 28, cluster size 273) for rFPN was significantly reduced; the outside-network rs-fc with the middle temporal gyrus/angular gyrus (peak MNI coordinates: -52, -68, 38, cluster size 208) for rFPN was significantly increased in MwoA patients (second time–first time). The comparison between the acupuncture treatment (real and sham) (post minus pre-treatment) and the waiting list group showed a significant difference at the left cerebellum (peak MNI coordinates: -6, -46, -30, cluster size 163) and right middle frontal gyrus (peak MNI coordinates: 38, 6, 46, cluster size 123). In addition, we also compared sham acupuncture group and waiting list group. The comparison between the sham group (post minus pre-treatment) and the waiting list group showed a significant difference at the left precentral gyrus (peak MNI coordinates: 42, -4, 60, cluster size 523) and left insula (peak MNI coordinates: 46, -8, 12, cluster size 122).

Seed-based rs-fc analysis results

We found that the right precuneus plays an important role in pathophysiology of migraine, specifically that: 1) reduced outside-network rs-fc with the right precuneus for rFPN in MwoA patients as compared with healthy controls; 2) outside-network rs-fc with right precuneus for rFPN was associated with headache intensity in baseline MwoA patients; and 3) the decrease of outside-network rs-fc with the right precuneus for rFPN was positively associated with a decrease in headache intensity due to acupuncture treatment. To further explore the role of the right precuneus in the pathology of migraine and its role in treatment, we applied a functional connectivity analysis using the peak of the overlapped cluster at right precuneus (2, -62, 50, 3mm) as the seed. We found that compared with HCs, MwoA patients showed reduced right precuneus rs-fc with the left precuneus, supramarginal gyrus and inferior temporal gyrus. After longitudinal acupuncture treatment (verum + sham), MwoA patients showed increased right precuneus rs-fc with the bilateral rACC/MPFC, ventral striatum, middle/inferior occipital gyrus, cuneus, DLPFC and cerebellum, and left VLPFC and right superior temporal gyrus (Figure 5, Table 4).

Discussion

In this study, we found that MwoA patients showed reduced outside-network rs-fc with the bilateral precuneus for rFPN during the interictal period compared with healthy controls. The outside-network rs-fc with precuneus and intra-network rs-fc within MPFC/rACC for rFPN were positively associated with headache intensity in MwoA patients at baseline. Interestingly, acupuncture (both real and sham), could significantly reduce outside-network rs-fc with the precuneus for rFPN. Greater headache intensity relief was associated with greater reduced outside-network rs-fc with the right precuneus for rFPN. Seed-based functional connectivity analysis (using the right precuneus as the seed) showed that longitudinal acupuncture treatment significantly enhanced precuneus rs-fc with MPFC/rACC, ventral striatum³⁷, and DLPFC/VLPFC^{38,39}.

Our result is partly consistent with previous studies in which investigators found impaired rFPN rs-fc in MwoA patients^{20,21}. Xue and colleagues²⁰ found that migraineurs (n=23)

showed increased rFPN rs-fc in the middle frontal gyrus and anterior insula and in another study, Russo and colleagues²¹ found that MwoA patients (n=14) had reduced rFPN rs-fc with the middle frontal gyrus and dorsal anterior cingulate cortex compared to healthy controls. The different rFPN rs-fc changes in migraineurs between our study and previous studies may not necessarily be contradictory, as we believe the differences reflect the complexity of the neural physiopathology of migraine⁴⁰.

Previous studies have suggested^{38,39} that the key regions of rFPN including VLPFC, DLPFC and the parietal gyrus are involved in the cognitive control of pain, and that all these regions have direct connections with brain regions involved in affective (i.e., ACC, MPFC, amygdala) and sensory (i.e., SI, S2/insula) pain process components. We find that MwoA patients showed reduced outside-network rs-fc with the precuneus for rFPN, which is associated with reduced headache intensity. This result is consistent with previous studies showing that the precuneus is closely connected with the rFPN both anatomically and functionally^{41,42}. The precuneus is a key node in the default mode network (DMN)³⁶, a brain network associated with self-referential processing^{43,44} and mind-wandering⁴⁵ whereas the rFPN plays an important role in attention, memory process and cognitive control¹⁶. We thus speculate that the reduced rs-fc between the rFPN and the precuneus may represent the brain's self-compensatory adaptation/coping responses to continued attacks of migraine^{46,47}. Specifically, paying attention to pain⁴⁸ results in more suffering while distraction⁴⁹ from pain results in a less painful experience. The body may automatically apply a distraction strategy as a natural response to avoid suffering.

Interestingly, we found that longitudinal acupuncture treatment could further reduce outside-network rs-fc with the right precuneus for rFPN, and that reduced right precuneus-rFPN rs-fc was associated with migraine headache intensity reduction. Previous studies suggested that expectation, attention and reappraisal are crucial components of the non-specific effect of treatments^{38,39,50}. And studies have also shown that the non-specific effect plays an important role in acupuncture's treatment of chronic pain^{51,52,53}. Taken together, our results suggest that acupuncture may relieve headache intensity by enhancing the self-compensatory adaptation/coping process. This finding is consistent with a previous brain imaging cognitive behavioral therapy on fibromyalgia showing that rather than reducing pain response in patients with fibromyalgia, cognitive behavioral therapy increases access to executive regions for reappraisal of pain⁵⁴.

Seed-based functional connectivity analysis showed that after longitudinal acupuncture treatments, the right precuneus rs-fc with the MPFC/rACC significantly increased. MPFC/rACC have wide functional connections⁵⁵ and involvement in many functions; several studies have suggested that the MPFC/rACC is functionally connected with PAG^{56,57}, a key region in the descending pain modulatory regions. We thus speculate that the increased precuneus rs-fc and MPFC/rACC imply an enhancement between the self-referral system and pain modulation process.

We also found increased precuneus rs-fc with cognitive control brain regions (i.e., VLPFC and DLPFC) and reward regions (i.e., ventral striatum/nucleus accumbens). A previous study⁵⁸ showed that pain relief could produce negative reinforcement through activation of

the mesocorticolimbic reward-valuation circuitry. A recent human fMRI-PET study⁵⁹ found that increased endogenous opioid releases were at nucleus accumbens during pressure pain. Taken together, our results suggest that the cognitive control network, reward system, and descending pain modulatory network may all be involved in the modulation process of acupuncture treatment.

There are several limitations to this study. 1) The sample size in each acupuncture treatment group is small, which prevents us from testing clinical outcome differences between different acupuncture treatment groups. In addition, the dropout rate is 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 is to explore the neural physiopathology of migraine so using the treatment as a mediator is intended to investigate how an effective treatment can modulate the rFPN rs-fc rather than test the efficacy of acupuncture itself. 2) Although the patients were migraine-free for at least 72 hours at the time of the MRI scan, they could have been in different stages with regards to the upcoming migraine attack⁶⁰. 3) We do not have a second fMRI scan for the matched healthy controls. Thus, we can not completely rule out the result observed in drift effects over time or habituation to the scanning environment.

Conclusion

Migraine is associated with abnormal rFPN rs-fc during the interictal period. The reduced rFPN rs-fc with the DMN is associated with lower headache intensity, suggesting an adapting/coping cognitive mechanism in migraine patients. An effective treatment, such as acupuncture, may achieve symptom relief by strengthening the cognitive adapting/coping mechanism.

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Clinical Implications

Migraineurs might be associated with abnormal rFPN rs-fc. An effective treatment, such as acupuncture, may relieve symptoms by strengthening the cognitive adaption/coping process. Elucidation of the adaption/coping mechanism may open a new window for migraine management.

Figure 1.
Study flow chart. HC, healthy controls; MRI, magnetic resonance image; n, number; VA, verum acupuncture; SA, sham acupuncture; WT, waiting list.

Figure 2.

Acupoint locations. GB, Gallbladder meridian; LI, Large intestine meridian; NAP, non acupoints; SA, sham acupuncture; SJ, Sanjiao meridian; ST, Stomach meridian; VA, verum acupuncture; WT, waiting list.

Figure 3.
rFPN revealed by independent component analysis in this study.

Figure 4.

rFPN resting state functional connectivity (rs-fc) results. 4A. MwoA showed reduced rFPN rs-fc with the precuneus at baseline compared with HC; 4B. fFPN rs-fc between the precuneus and MPFC/rACC was associated with headache VAS at baseline; 4C. The reduced rFPN rs-fc with the precuneus due to acupuncture treatment (verum + sham); 4D. The greater reduction of rFPN rs-fc with the right precuneus was associated with greater headache intensity relief. A threshold of $Z > 2.3$, $P < 0.05$ was applied. AG, acupuncture groups; HC, healthy controls; MwoA, migraine without aura; R, right side; rFPN, right frontoparietal network; VAS, visual analogue scale.

Figure 5.

Precuneus resting state functional connectivity (rs-fc) results. 5A. MwoA showed reduced precuneus rs-fc with the supramarginal gyrus and inferior temporal gyrus, compared with HC. 5B. MwoA patients showed increased right precuneus rs-fc with the bilateral rACC/MPFC, ventral striatum, DLPFC and VLPFC, due to acupuncture treatment (verum + sham). A threshold of Voxelwise $P < 0.005$ and $p < 0.05$ FWE corrected was applied. AG, acupuncture groups; DLPFC, dorsolateral prefrontal cortex; HC, healthy controls; Inf, inferior; L, left side; MPFC, medial prefrontal cortex; MwoA, migraine without aura; Mid, middle; R, right side; rACC, rostral anterior cingulate cortex; VLPFC, ventrolateral prefrontal cortex.

Table 1

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

Characteristics	VA1, n=12	VA2, n=14	VA3, n=15	SA, n=13	WT, n=18	P value *	MwoA, n=72	HC, n=46	P value **
Female n(%)	10 (83.3%)	10 (71.4%)	12 (80.0%)	11 (84.6%)	14 (77.8%)	0.925	57 (79.2%)	36 (78.3%)	0.907
Age (y)	21.75 (20.70; 22.80)	20.93 (19.74; 22.12)	20.87 (19.89; 21.85)	21.38 (20.75; 22.02)	21.61 (20.54; 22.68)	0.605	21.30 (20.89; 21.73)	21.24 (20.98; 21.50)	0.789
Height (cm)	159.0 (154.50; 163.40)	161.93 (157.52; 166.24)	159.1 (155.13; 163.01)	157.9 (154.84; 161.00)	162.3 (157.91; 166.76)	0.390	160.22 (158.49; 161.96)	161.11 (158.49; 161.96)	0.493
Weight (kg)	52.50 (48.09; 56.91)	55.21 (49.23; 61.20)	50.17 (47.64; 52.70)	50.23 (45.96; 54.50)	53.95 (49.01; 58.88)	0.375	52.49 (50.56; 54.42)	51.13 (49.33; 52.93)	0.335
Duration (mo)	61.67 (44.38; 78.95)	69.57 (56.10; 100.19)	62.27 (42.79; 82.54)	58.69 (34.29; 64.63)	64.73 (58.52; 95.81)	0.140	-	-	-
Headache intensity	5.33 (4.46; 6.20)	5.32 (4.77; 5.87)	5.80 (5.20; 6.40)	5.46 (4.52; 6.40)	5.58 (5.14; 6.03)	0.799	-	-	-
Headache frequency	5.75 (3.89; 7.61)	7.50 (5.61; 9.39)	5.73 (3.58; 7.88)	6.00 (4.04; 7.96)	4.50 (3.07; 5.93)	0.164	-	-	-
SAS score	44.63 (39.74; 49.51)	44.86 (40.36; 49.35)	47.02 (41.69; 52.34)	47.21 (42.23; 52.20)	47.10 (41.92; 52.26)	0.885	-	-	-
SDS score	42.13 (35.01; 49.24)	48.98 (43.97; 53.99)	44.80 (38.22; 51.38)	45.06 (39.25; 50.86)	46.88 (42.01; 51.74)	0.516	-	-	-

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;

* χ^2 test applied for gender comparison, one-way ANOVA applied for the rest comparisons, among VA1, VA2, VA3, SA and WT groups;

** χ^2 test was applied for gender comparison, two-sample t test applied for the rest comparisons, between MwoA and HC.

Clinical outcomes before and after treatment in different groups. AG, acupuncture group including both verum acupuncture and sham acupuncture; VA, verum acupuncture; SA, sham acupuncture group; SAS, self-rating anxiety scale; SDS, self-rating depression scale; WT, waiting list. Pair-t test was applied for comparisons in each group.

Table 2

Outcome measures	VA1, n=12	VA2, n=14	VA3, n=15	SA, n=13	WT, n=18	AG, n=54
Headache intensity						
Mean (95%CI)						
Baseline	5.33 (4.46; 6.20)	5.32 (4.77; 5.87)	5.80 (5.20; 6.40)	5.46 (4.52; 6.40)	5.58 (5.14; 6.03)	5.49 (5.15; 5.83)
End of treatment	3.25 (2.39; 4.11)	3.57 (2.83; 4.31)	2.87 (2.01; 3.72)	4.19 (3.34; 5.04)	5.53 (4.69; 6.36)	3.45 (3.06; 3.85)
P value	0.003	0.000	0.000	0.083	0.869	0.000
Headache frequency						
Mean (95%CI)						
Baseline	5.75 (3.89; 7.61)	7.50 (5.61; 9.39)	5.73 (3.58; 7.88)	6.00 (4.04; 7.96)	4.50 (3.07; 5.93)	6.26 (5.34; 7.18)
End of treatment	3.92 (2.37; 5.46)	5.93 (4.38; 7.47)	4.20 (2.42; 5.98)	6.15 (4.03; 8.27)	8.17 (5.81; 10.52)	5.06 (4.21; 5.90)
P value	0.014	0.021	0.013	0.895	0.001	0.003
SAS score						
Mean (95%CI)						
Baseline	44.63 (39.74; 49.51)	44.86 (40.36; 49.35)	47.02 (41.69; 52.34)	47.21 (42.23; 52.20)	47.10 (41.92; 52.26)	46.00 (43.71; 48.23)
End of treatment	38.13 (31.15; 45.10)	41.45 (37.12; 45.78)	37.98 (32.61; 43.36)	37.37 (33.09; 41.64)	41.39 (37.83; 44.94)	38.76 (36.36; 41.17)
P value	0.055	0.117	0.005	0.019	0.017	0.000

Outcome measures		VA1, n=12	VA2, n=14	VA3, n=15	SA, n=13	WT, n=18	AG, n=54
SDS score							
Mean (95%CI)							
Baseline		42.13 (35.01; 49.24)	48.98 (43.97; 53.99)	44.80 (38.22; 51.38)	45.06 (39.25; 50.86)	46.88 (42.01; 51.74)	45.35 (42.51; 48.20)
End of treatment		40.63 (32.17; 49.08)	42.68 (37.07; 48.28)	39.15 (33.41; 44.89)	37.56 (32.06; 43.06)	41.18 (36.57; 45.80)	40.01 (37.14; 42.88)
P value		0.518	0.040	0.023	0.049	0.066	0.000

Table 3

Comparisons of the therapeutic effects between different groups.

Outcome measures	VA1, n=12	VA2, n=14	VA3, n=15	SA, n=13	P value *	WT, n=18	AG, n=54	P value **
Headache intensity								
Mean (95%CI)								
End of treatment	3.25 (2.39; 4.11)	3.57 (2.83; 4.31)	2.87 (2.01; 3.72)	4.19 (3.34; 5.04)	0.101	5.53 (4.69; 6.36)	3.45 (3.06; 3.85)	0.000
End - baseline	-2.08 (-3.31; -0.86)	-1.75 (-2.42; -1.08)	-2.93 (-4.01; -1.86)	-1.27 (-2.73; -0.19)	0.139	-0.06 (-0.75; 0.64)	-2.04 (-2.57; -1.50)	0.000
Headache frequency								
Mean (95%CI)								
End of treatment	3.92 (2.37; 5.46)	5.93 (4.38; 7.47)	4.20 (2.42; 5.98)	6.15 (4.03; 8.27)	0.132	8.17 (5.81; 10.52)	5.06 (4.21; 5.90)	0.016
End - baseline	-1.83 (-3.21; -0.46)	-1.57 (-2.87; -0.28)	-1.53 (-2.69; -0.37)	0.15 (-2.32; 2.63)	0.250	3.67 (1.63; 5.70)	-1.20 (-1.96; -0.44)	0.000
SAS score								
Mean (95%CI)								
End of treatment	38.13 (31.15; 45.10)	41.45 (37.12; 45.78)	37.98 (32.61; 43.36)	37.37 (33.09; 41.64)	0.626	41.39 (37.83; 44.94)	38.76 (36.36; 41.17)	0.257
End - baseline	-6.50 (-13.16; 0.17)	-3.41 (-7.79; 0.97)	-9.03 (-14.78; -3.28)	-9.85 (-17.78; -1.92)	0.379	-5.71 (-10.26; -1.16)	-7.21 (-10.08; -4.33)	0.591
SDS score								
Mean (95%CI)								
End of treatment	40.63 (32.17; 49.08)	42.68 (37.07; 48.28)	39.15 (33.41; 44.89)	37.56 (32.06; 43.06)	0.638	41.18 (36.57; 45.80)	40.01 (37.14; 42.88)	0.675

Outcome measures	VA1, n=12	VA2, n=14	VA3, n=15	SA, n=13	P value *	WT, n=18	AG, n=54	P value **
End - baseline	-1.50 (-6.44; 3.44)	-6.30 (-12.26; -0.35)	-5.65 (-10.38; -0.92)	-7.50 (-14.96; -0.05)	0.469	-5.69 (-11.81; 0.43)	-5.34 (-5.34; -8.03)	0.902

AG, acupuncture groups; HC, healthy controls; VA, verum acupuncture; 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, SA and WT groups;

** two-sample t test was applied for the comparisons between MwoA and HC.

The rFPN resting state functional connectivity (ICA). AG, healthy controls; G, gyrus; HC, healthy controls; Inf, inferior; L, left side; MwoA, migraine without aura; Mid, middle; PCC, posterior cingulate cortex; R, right side; rFPN, right frontoparietal network; Sup, superior; SII, secondary somatosensory cortex; VAS, visual analogue scale

Table 4

rFPN resting state functional connectivity differences between MwoA patients and healthy controls at baseline					Association between VAS and rFPN resting state functional connectivity in MwoA patients at baseline						
Contrast	Voxels	Brain Region	MNI (x, y, z)	Z	Contrast	Voxels	Brain Region	MNI (x, y, z)	Z		
HC>MwoA	884	L/R Precuneus	-6	-58	46	4.12	L/R precuneus	4	-60	54	3.78
	595	L SII	-54	-32	22	4.17	L Sup Frontal G	-14	68	10	4.14
	689	L Lingual G	-10	-98	-16	4.54	R/L pgACC/mPFC	-4	44	0	3.54
	829	L Fusiform G/Mid/Sup Temporal G	-46	-52	-10	4.48					
	426	R Lingual/Cuneus	18	-84	4	4.17					
1086	R Sup/Mid/Inf Tempotal G	38	-74	-4	4.57						
273	R Cerebellum	40	-40	-28	4.72						
MwoA>HC	No brain region above the threshold										
Changes of rFPN resting state functional connectivity in MwoA patients before and after acupuncture treatment											
Contrast	Voxels	Brain Region	MNI (x, y, z)		Z	Association between VAS changes (post minus pre) and corresponding rFPN functional connectivity changes in MwoA patients					
Pre>Post	569	R Precuneus	22	-62	40	4.02	Brain Region	MNI (x, y, z)		Z	
	195	L Mid Frontal G	-38	34	14	3.59	L/R Precuneus	-2	-70	34	3.39
Post>Pre	183	R/L dorsal PCC	10	-38	24	3.74	R Postcentral G	14	-34	72	3.87
No brain region above the threshold											

Results from seed-based functional connectivity analysis. The altered right precuneus resting state functional connectivity in MwoA as compared with healthy controls, and pre- and post-treatment resting state functional connectivity differences across patients. DLPFC, dorsolateral prefrontal cortex; Inf, inferior; L, left side; MPFC, medial prefrontal cortex; MwoA, migraine without aura; Mid, middle; R, right side; rACC, rostral anterior cingulate cortex; rFPN, right frontoparietal network; Sup, superior; VLPFC, ventrolateral prefrontal cortex.

Table 5

The right precuneus resting state functional connectivity Difference between MwoA patients and healthy controls						
Contrast	Voxels	Brain Region	MNI (x, y, z)	Z		
HC>MwoA	322	L Precuneus	42	-63	39	4.68
		L Supramarginal G/Inf Temporal G	51	-42	36	3.77
MwoA>HC	No brain region above the threshold					
Resting state functional connectivity changes before and after acupuncture treatment						
Contrast	Voxels	Brain Region	MNI (x, y, z)			Z
Post>Pre	1693	L MPFC/rACC	-6	66	3	4.62
		L VLPFC	-3	54	-24	4.57
		L Ventral stratum	-12	18	-9	3.55
		L DLPFC	-33	-63	0	4.1
		R MPFC/rACC	9	69	6	4.2
		R Ventral stratum	15	15	-12	4.16
		R DLPFC	18	69	-3	3.96
		R Sup Temporal G	36	6	-33	3.87
		L Cerebellum	-42	-63	-48	4.32
		L Mid/Inf occipital G	-27	-99	-9	4.3
Pre>Post	347	R Cerebellum	51	-69	-39	4.36
		R Mid/Inf occipital G	21	-102	12	4.51
No brain region above the threshold						