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Original Research Article

The Modifying of Functional Connectivity Induced by Peripheral Nerve Field Stimulation using Electroacupuncture for Migraine: A Prospective Clinical Study

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Abstract

Objective. We examined the functional connectivity (FC) in patients with migraine compared with healthy subjects before and after C2 peripheral nerve field stimulation with electroacupuncture (EA-C2-PNfS) to evaluate the effect of EA-C2-PNfS and elucidate the mechanism of migraine. **Methods.** Twenty-six patients with migraine and 24 healthy controls were recruited. All patients underwent resting state functional magnetic resonance imaging before and after 3 months of EA-C2-PNfS. We evaluated a numerical rating scale, the Headache Impact Test, and the Self-Rating Depression Scale, which assesses depression. Healthy controls underwent magnetic resonance imaging twice at a 3-month interval without acupuncture. An analysis of FC in the region of interest in the pain matrix was performed. **Results.** Twenty patients with migraine and 23 healthy controls (mean ± standard deviation: 44.9 ± 12.9 years of age) were included. Three patients had migraine with aura (55.0 ± 18.0 years of age), 11 patients had migraine without aura (MWoA) (45.6 ± 14.6 years of age), and six patients had chronic migraine (40.8 ± 13.9 years of age). The clinical assessments significantly improved after EA-C2-PNfS in the MWoA group only. In FC analysis, the MWoA group showed a significant decrease after EA-C2-PNfS in FC between the right hypothalamus and left insula. Right hypothalamus–related FC was lower before acupuncture in the chronic migraine group than in the MWoA group. **Conclusion.** After EA-C2-PNfS for MWoA, significant changes in FC were observed at the hypothalamus and insula. Our results indicate that EA-C2-PNfS could improve migraine headache by modifying pain-related FC.

Key Words: Acupuncture; Migraine; Peripheral Nerve Field Stimulation; Functional Connectivity

Introduction

Brain dysfunction has been identified as one of the pathologies of migraine [1]. In patients with migraine, activation of several pain-related regions, such as the insula, thalamus, and cingulate cortex, has been reported [1]. Allodynia that accompanies migraine attacks has been suggested to be caused by central sensitization of pain-related regions [2]. Recently, there have been several reports on the study of migraine with resting state functional magnetic resonance imaging (rsfMRI), which can be used to analyze several parameters, one of which is functional connectivity (FC). FC is defined as the temporal coherence of the activity of different neurons and is measured by cross-correlating their spike trains [3]. In clinical research on migraine, FC was observed to be significantly decreased at the default mode network and visuo-spatial network of patients with migraine relative to the FC in healthy controls [4]. The change of FC in migraine was affected by the disease duration [5], the presence of aura [6], and ictal/interictal periods [7, 8]. Recently, the FC has been analyzed not only to investigate the pathophysiology of migraine and chronic pain, but also to determine the diagnosis and predict the prognosis [9, 10]. Chong et al. examined rsfMRI to distinguish individual patients with migraine from healthy controls [9]. Patients with disease durations >14 years were more accurately defined than were patients with shorter disease durations [9]. Patients with persistent chronic back pain showed higher white matter FC of the corticolimbic system (dorsal medial prefrontal cortex [mPFC]–amygdala– accumbens) than did the patients who showed early recovery [10].

Acupuncture is a nonmedication therapy for migraine. In a randomized clinical trial, acupuncture reduced the frequency of migraine attacks in a 24-week period in comparison with a sham group and patients on a waiting list [11]. Another option for nonmedication therapy is neuromodulation [12]. C2 peripheral nerve field stimulation (C2-PNfS) is a method of stimulating the C2 dermatome area in the occipital region, innervated by the greater occipital nerve, subcutaneously with implanted electrodes [13]. It is considered to stimulate the small branches of the nerve within the subcutaneous tissue. We use acupuncture needles as percutaneously inserted electrodes to stimulate the subcutaneous tissue of the C2 area—i.e., C2 peripheral nerve field stimulation with electroacupuncture (EA-C2-PNfS). We reported that EA-C2-PNfS improved headache intensity and the quality of daily life [14]. However, the mechanism of EA-C2-PNfS has not been clarified. In the present study, we examined the FC in patients with migraine compared with healthy subjects before and after EA-C2-PNfS to evaluate the effect of EA-C2-PNfS and elucidate the mechanism of migraine.

Methods

Participants

The patients were recruited from July 2017 to August 2019. All patients received an explanation of the study and gave their written informed consent. Our study was registered in the clinical trial database of the University Hospital Medical Information Network (ID 000028222) and received approval from the ethics committee of our hospital (No. 17-14).

Patients with Migraine

A board-accredited headache specialist (YS) diagnosed participants' headaches on the basis of The International Classification of Headache Disorders, 3rd edition (beta version) [ICHD-3β] [15]. The inclusion criteria were as follows: Patients 1) had migraine, 2) could be treated with acupuncture therapy once a week for 3 months, 3) had no history of other neurological disease, 4) had no other type of primary or secondary headache, 5) had been diagnosed with migraine more than 3 years previously, and 6) had no another acupuncture treatment during the study period.

The exclusion criteria were as follows: 1) other type of headache (e.g., tension-type headache), 2) other neurological disorders (e.g., stroke, dementia, epilepsy) or malignancy, 3) migraine attack or headache during magnetic resonance imaging (MRI) examination, 4) claustrophobia, 5) pregnancy, and 6) prophylactic medications added or changed during the study period.

Age- and sex-balanced healthy controls (male, n = 6; female, n = 17) were recruited. The exclusion criteria for healthy controls were 1) history of migraine or other chronic headache and 2) hypertension, stroke, concussion, epilepsy, diabetes, or psychiatric disease.

All patients with migraine underwent MRI in two interictal periods, before and after 3 months of acupuncture (Figure 1). The control groups underwent MRI two times with a 3-month interval in our hospital.

Electroacupuncture Therapy (EA-C2-PNfS)

Acupuncture was performed in the lateral position. The acupuncture needles (length, 50 mm; diameter, 0.18 mm; SEIRIN, Shizuoka, Japan) were subcutaneously inserted approximately 15 to 20 mm into the bilateral occipital scalp regions (Figure 2) [14]. Our technique stimulates the area innervated mainly by the greater occipital nerve. Biphasic electrical pulse waves were applied for 15 minutes at the frequency of 50 Hz through the use of an electrical stimulator (OhmPulser LFP-4000A, Zen Iryoki, Fukuoka, Japan). The intensity of electrical stimulation was adjusted to just below the threshold of muscle contraction. Four needles were used for each patient. The basic procedure is completely the same as ordinary electroacupuncture, except the acupuncture needles were not placed at any acupoints in our method. EA-C2-PNfS was performed once a week for 3 months. An acupuncturist (SI) with 9 years of experience performed all of these procedures.

Clinical Assessments

The numerical rating scale (NRS) ranged from 0 to 10, with 0 defined as no pain and 10 defined as the worst

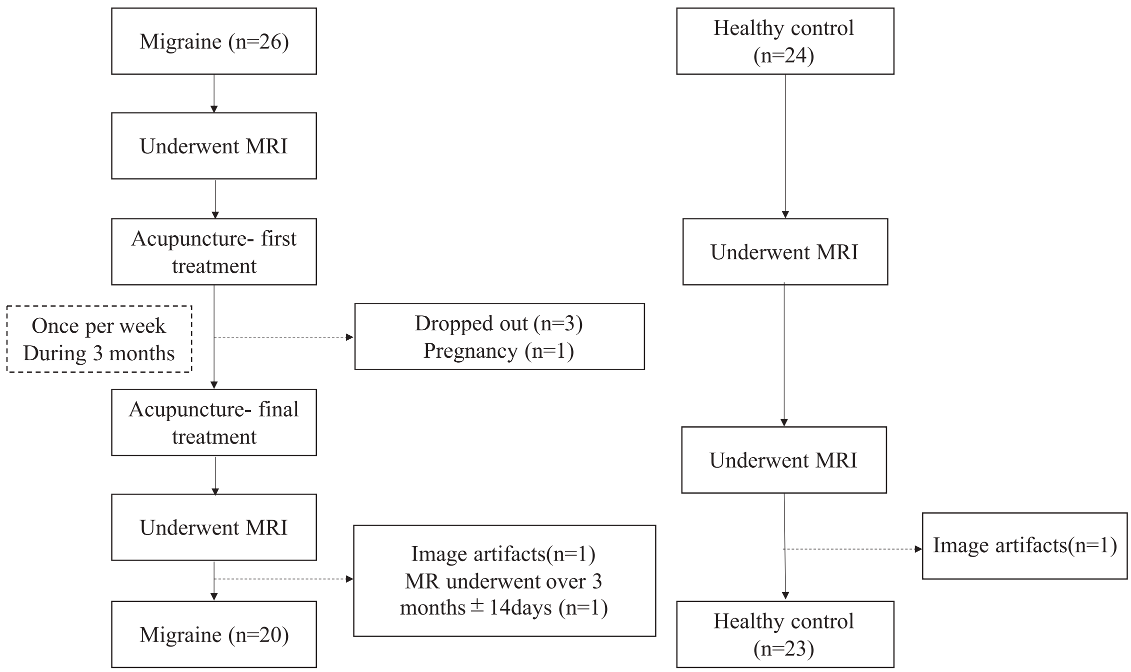

Figure 1. Flow chart.

pain. The headache intensity before the patient took triptan and/or nonsteroidal anti-inflammatory drugs was assessed every week by use of the NRS. The patients rated their maximum headache during the week on the NRS. The Headache Impact Test (HIT-6) consists of six questionnaires and is a tool for measuring the effect of headaches on an individual's ability to function at their job, at school, at home, and in social situations [16, 17]. The Self-Rating Depression Scale (SDS) is a 20-item questionnaire about the symptoms of depression developed by Zung et al., and it assesses the frequency of depression with four classifications: a short time, some time, a good length of time, and most of the time [18]. If the score is higher, the patients are more depressed. The HIT-6 and SDS were assessed every month.

The patients were instructed to keep a headache diary for 1 month before starting acupuncture. The numbers of headache days and acute medication days per month during the study were obtained from diaries.

Imaging Protocols

All patients underwent MRI with a 3.0-Tesla MR scanner (Siemens, Erlangen, Germany) with a 32-channel head coil. All participants were instructed to close their eyes, to not fall asleep, and to not think about anything.

Structural imaging, including T1-weighted volume with magnetization-prepared rapid acquisition with gradient echo and T2 (fluid-attenuated inversion recovery), was performed. For T1-weighted imaging, the following parameters were used: repetition time (TR) / echo time (TE) = 2,300/2.32 ms, 192 slices, and slice thickness = 0.9 mm.

For the rsfMRI, we used T2*-weighted imaging (TR/TE = 437/11 ms, slice thickness = 4 mm, field of view = 220 mm). The following function image parameters were used: TR/TE = 2,500/35 ms, number of slices = 40, voxel size = $3 \times 3 \times 4$ mm, and scan duration = 7 minutes.

Data Processing and Analysis of fMRI

The statistical analysis of fMRI data to evaluate preprocess and FC was performed with the CONN v17b toolbox (Cambridge, MA, USA, www.nitrc.org/projects/conn) [19] in MATLAB (MathWorks, Inc, Natick, MA, USA).

Registration of the structural data (T1 imaging) and functional data was performed. Pre-processing included the following steps: 1) slice time correction, 2) head motion correction, 3) nonbrain tissue removal, 4) spatial smoothing with a 5-mm Gaussian kernel, and 5) normalization. After these pre-processing steps, the noise coming from the white matter and cerebrospinal fluid were removed from the fMRI data. An FC analysis was performed with the region of interest (ROI)–to–ROI method. We selected a total of 13 ROIs at the anterior/posterior cingulate cortex (ACC/PCC), bilateral insula, bilateral thalamus, bilateral amygdala, bilateral postcentral gyrus (post-CG), bilateral hypothalamus, and brainstem as pain regions (Figure 3). The hypothalamus has shown an association with migraine attacks in previous studies [8, 20]. We therefore used $X = -6$, $Y = -2$, $Z = -8$ as the ROI of the hypothalamus, in accordance with the methods of a previous study [20].

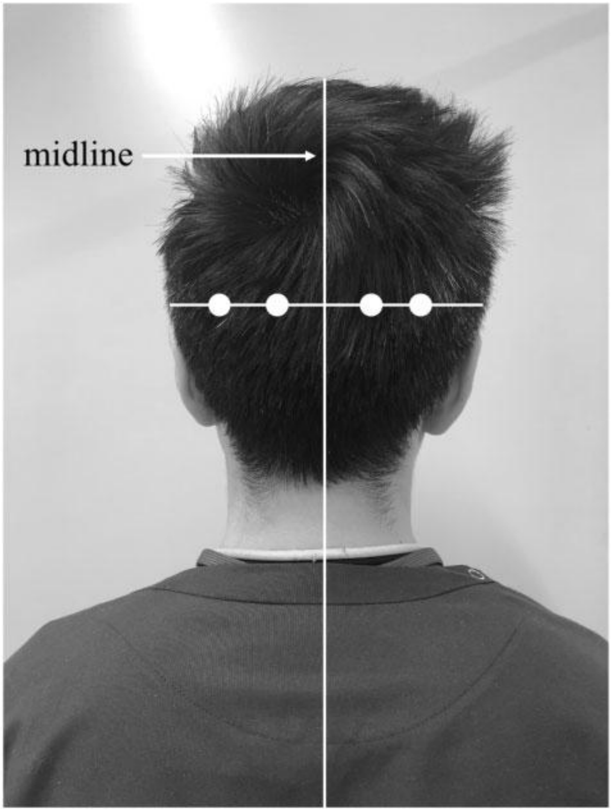

Figure 2. EA-C2-PNfS. Acupuncture needles were subcutaneously inserted bilaterally, midway between the midline and the top of the ear, the second needles were subcutaneously inserted bilaterally, midway between the midline and first needle points [14].

Statistical Analysis

We used the Kruskal-Wallis test to compare ages among four groups (migraine without aura [MWoA], migraine with aura [MWA], chronic migraine [CM], and controls) and to compare disease durations among three groups (MWoA, MWA, and CM). The NRS, HIT-6, SDS, and number of headache days, which were used for clinical assessments, were analyzed with the Wilcoxon signed-rank test. In the analysis of rsfMRI, $P < 0.05$ was the threshold of significance when the corrected false discovery rate was used.

Results

Twenty-six patients with migraine were recruited into our study. Among the 26 patients, one patient was excluded because of image artifacts. Three patients failed to attend weekly visits for acupuncture and therefore dropped out. In one case, MRI could not be acquired in a timely manner. One patient was excluded from the study because of pregnancy. In the control group, one patient was excluded because of image artifacts.

Ultimately, 20 patients with migraine (MWA: n = 3, female n = 3, age 55.0 ± 18.0 [mean ± standard deviation] years; MWoA: n = 11, male n = 1, female n = 10, age 45.6 ± 14.6 years; CM: n = 6, female n = 6, age 40.8 ± 13.9 years) and 23 control subjects (male n = 6, female n = 17, age 44.9 ± 12.9 years) were included and analyzed (Table 1). Age and sex did not differ significantly ($P > 0.05$) among the four groups (MWoA, MWA, CM, and controls).

None of the patients had a migraine attack during the scanning. All imaging was reviewed by a certified neurosurgeon, and no abnormal findings were obtained.

Clinical Assessments

The clinical outcomes of the 20 patients at baseline and after 3 months therapy are summarized in Table 2. The NRS significantly decreased after EA-C2-PNfS, from a median of 7 (range: 4–10) to 4 (1–10) in the MWoA group ($P = 0.019$). In addition, the SDS improved from 46.0 (31–58) to 45 (29–54; $P = 0.028$). The HIT-6 did not show clinical improvement, changing from 61 (49–74) to 58 (48–76; $P = 0.168$).

In the CM group, none of the clinical outcomes changed significantly (Table 2). Patients whose headache intensity on the NRS decreased by more than 50% relative to baseline were defined as responders, and eight patients were responders. Six patients had SDS >50 points before EA-C2-PNfS, and this decreased to three patients after 3 months. There were no severely depressed patients with SDS >60 points.

Number of Headache Days and Acute Medication Days per Month

Ten of 20 patients (MWA, n = 2, 66.7%; MWoA, n = 4, 36.4%; CM, n = 4, 66.7%) had completed diaries during the period from 1 month before EA-C2-PNfS to the time of the final acupuncture session.

We then compared the number of severe headache days, moderate/mild headache days, and acute medication days after 3 months compared with those 1 month before EA-C2-PNfS. The number of severe headache days per month did not significantly improve, changing from a median (range) of 1 (0–7) to 1 (0–2). Similarly, the number of moderate/mild headache days per month did not change significantly, changing from 9.5 (0–20) to 12.5 (1–20). There was no significant change in the number of acute medication days, which increased from 12.25 (1–24) to 15.5 (0–24).

FC Results

The MWoA group showed a significant decrease in right hypothalamus–left insula FC after acupuncture (Figure 4, Table 3). In contrast, the CM group showed no significant change in FC from before to after acupuncture.

In addition, pre-acupuncture patients with CM showed lower FC of the right hypothalamus–right insula,

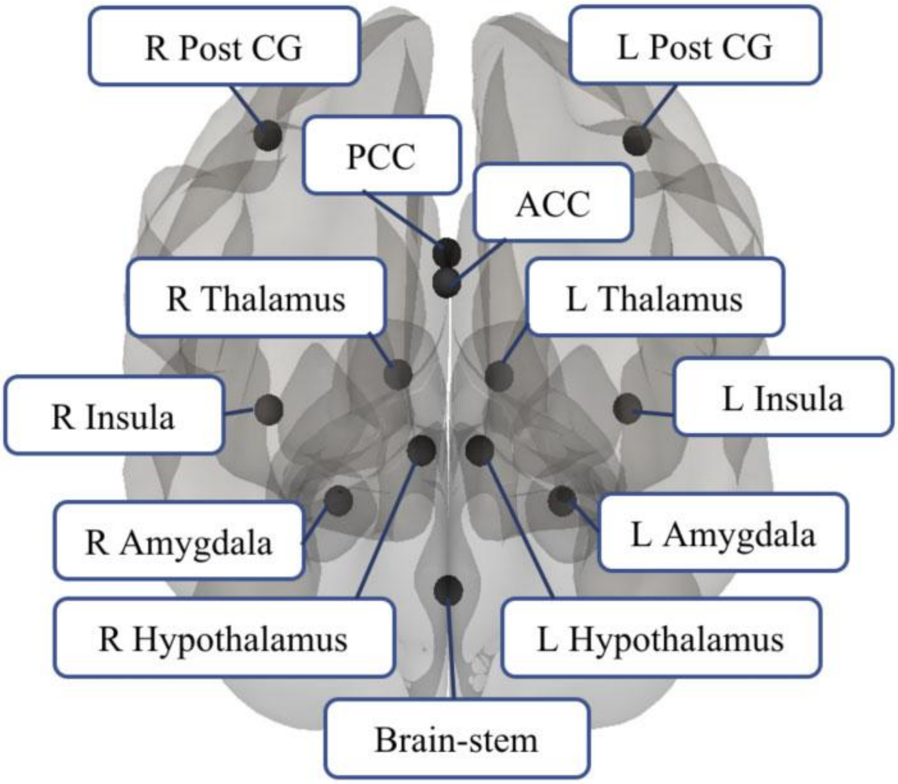

Figure 3. The ROIs as regions responsible for pain.

Table 1. Patients' characteristics

	Migraine				
	MWA	MWoA	CM	Healthy Control	*P* Value
n	3	11	6	23	
Age, years, mean±SD	55.0±18.0	45.6±14.6	40.8±13.9	44.9±12.9	0.618
Sex, n, male/female	0/3	1/10	0/6	6/17	0.285
Duration of migraine, years, mean±SD	37.7±13.7	22.5±16.7	21.8±18.6		0.307

SD = standard deviation.

Table 2. The clinical outcome at baseline and after 3 months

	MWoA			CM		
	Baseline	After Therapy	*P* Value	Basline	After Therapy	*P* Value
NRS			0.019			0.078
Median (range)	7 (4–10)	4 (1–10)		7.5 (5–9)	6 (0–9)	
Mean±SD	6.9±1.9	4.2±2.6		7.3±1.4	4.8±3.6	
HIT-6			0.168			0.293
Median (range)	61 (49–74)	58 (48–76)		64 (60–74)	65 (42–70)	
Mean±SD	61.7±6.5	58.9±8.2		65.7±5.3	61.3±10.0	
SDS			0.028			0.172
Median (range)	46.0 (31–58)	45 (29–54)		39.5 (37–59)	39.5 (27–48)	
Mean±SD	45.6±9.6	42.2±8.8		43.0±8.6	39.0±7.0	

SD = standard deviation.

bilateral postcentral gyrus, and amygdala than did the MWoA group (Figure 5, Table 4). Pre-acupuncture patients with CM showed significantly higher FC of the left amygdala with the bilateral thalamus and PCC than did healthy controls. Moreover, FC of the right hypothalamus with the bilateral post-CG and right amygdala was lower in the CM group than in healthy controls (Figure 6, Table 4). The comparison of the MWoA group

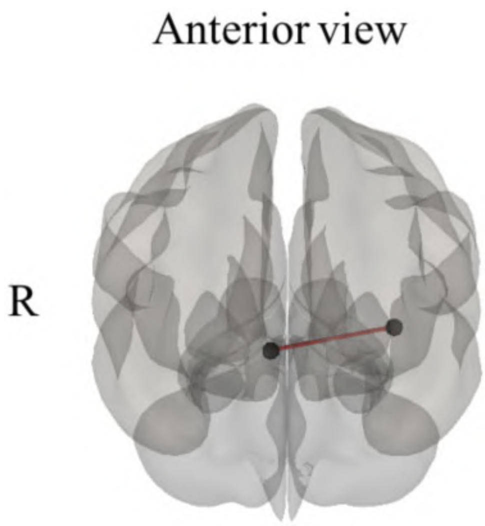

Figure 4. The change in in FCs of the left insula and right hypothalamus before and after acupuncture in patients with MWoA. The red line shows significantly decreased FCs after acupuncture.

Table 3. Comparison of the FC before and after acupuncture

MWoA		
Seed Hypothalamus (R)	*T(10)*	*p-FDR*
Insula (L)	4.06	0.0275

T= t-values; p-FDR = false discovery rate.
The FC of positive T values showed a significant decrease after acupuncture.

and healthy controls before acupuncture did not show any significant difference in FC.

The comparison of the second images between post-acupuncture patients with migraine and healthy controls also revealed no significant differences in FC. In addition, the CM and MWoA groups did not show any changes between control and post-acupuncture imaging.

No significant change in pain-related FC was found in healthy controls from before to after the 3-month interval. Because of the small sample size of the MWA group, we excluded MWA from the analysis.

Discussion

The main results in our study were as follows: 1) The NRS and SDS significantly improved in the patients with MWoA, but patients with CM did not show significant improvements; 2) after acupuncture, patients with MWoA showed a significant decrease of FC between the left insula and right hypothalamus; 3) in pre-acupuncture patients with CM, right amygdala–related FC was lower than that of healthy controls, whereas left amygdala–related FC was higher than that of healthy controls; and 4) patients with CM showed lower FC associated with the hypothalamus and higher FC associated with the left amygdala than did the other groups.

Functional Change After EA-C2-PNfS

We observed changes in FC between the right hypothalamus and left insula after EA-C2-PNfS in the MWoA group; however, the CM group did not show significant changes. The hypothalamus was reported as a key region of migraine attacks, and activation of the hypothalamus has been shown 48 hours before the onset of an attack but not in the early or ictal phases [8]. A previous study reported a relationship between chronic pain and the abnormal sensitization of the spinal trigeminal nucleus [2]. The spinal trigeminal nucleus strongly connects to the pain-related regions of the thalamus and hypothalamus [2]. We consider that EA-C2-PNfS could modify the activity of pain-related regions via the spinal trigeminal nucleus and hypothalamus in patients with MWoA (Figure 7). In the CM group, FC was not significantly changed by EA-C2-PNfS. Additionally, the CM group did not show clinical improvements after EA-C2-PNfS. Clinical assessments, such as HIT-6, in the CM group were more severe than those in the MWoA group. The results could be influenced by the small number of patients and might indicate a limitation of this therapy.

Acupuncture is a nonmedication therapy for migraine; however, the mechanism of its effects is unclear. In multicenter randomized controlled trials of acupuncture as prophylaxis against migraine, acupuncture was reported to reduce the number of migraine days in comparison with sham and standard therapy groups [21, 22]. However, the sham acupuncture group showed a significant reduction in migraine attacks in comparison with patients who received usual care [22]. In the sham group, acupuncture needles were inserted into non-acupoints [21, 23] or subcutaneous acupoints not related to migraine treatment [24]. As noted previously, it was difficult to determine whether this was an effect of acupuncture or a placebo effect. Zhao et al. examined the change in the brain activity of patients with migraine after acupuncture with acupoints and non-acupoints [24]. Both groups showed significant improvements in pain intensity and frequency of migraine attacks; however, the average regional homogeneity of the acupoint group increased in only some regions, such as the bilateral insula, thalamus, and brainstem [24]. In the non-acupoint group, the regional homogeneity of these regions did not change. Regional homogeneity indicates the local function of the brain based on data-driven methods. Additionally, the ACC was significantly activated between the acupoint and non-acupoint groups, because they suggested that the ACC might be an acupuncture-specific region [24]. The insula, which was activated only in the acupoint group, showed significant changes after EA-C2-PNfS. However, the ACC showed no significant difference in our study. Most previous studies of acupuncture treatment involved traditional acupuncture of the neck, back, forearm, and leg acupoints and muscles [21, 24]. Still, in EA-C2-PNfS, needles were inserted into only C2 areas. We could consider that the activity of ACC was a different type of acupuncture treatment.

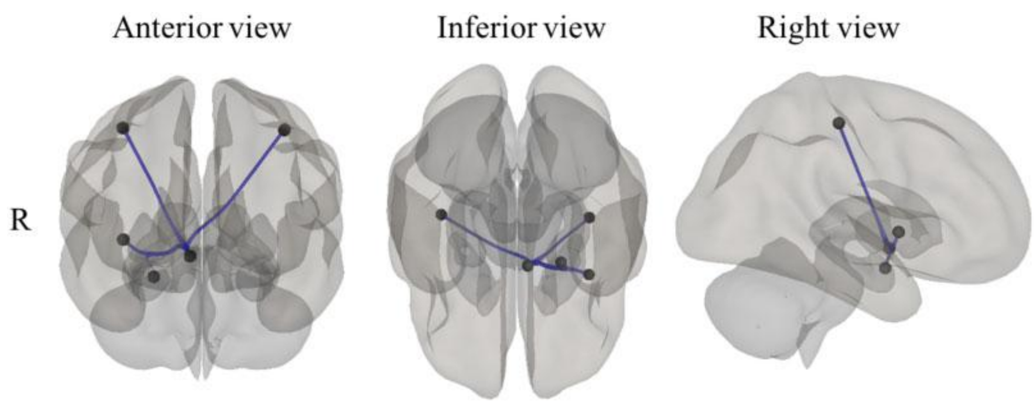

Figure 5. First imaging of pre-acupuncture patients with MWoA in comparison with first imaging of pre-acupuncture patients with CM. The blue line shows that the FC on first imaging of pre-acupuncture patients with CM was significantly lower than that of patients with MWoA.

Table 4. The comparison to first imaging of control subjects and pre-acupuncture patients with MWoA and CM

CM < Control		
Seed Hypothalamus (R)	*T(27)*	*p-FDR*
Amygdala (R)	–3.23	0.016
Post-CG (R)	–3.18	0.016
Post-CG (L)	–3.15	0.016
CM > Control		
Seed Amygdala (L)	*T(27)*	*p-FDR*
Thalamus (R)	3.08	0.0463
Thalamus (L)	2.88	0.0463
PCC	2.68	0.0498
MWoA > CM		
Seed Hypothalamus (R)	*T(15)*	*p-FDR*
Insula (R)	–2.72	0.0477
Amygdala (R)	–3.52	0.0185
Post-CG (R)	–3.12	0.0283
Post-CG (L)	–3.59	0.0185

T= t-values; p-FDR= false discovery rate; PCC= posterior cingulate cortex; Post-CG= postcentral gyrus.

Recently Liu et al. reported the effect of placebo treatments for acupuncture using voxel-based morphometry and an FC analysis [25]. After placebo acupuncture, patients with recovering migraine pain showed a significantly smaller mPFC volume than did patients with persistent migraine pain [25]. This suggested that the brain structure volume in the mPFC could predict the placebo responses in migraine [25]. In our study, we did not establish a sham therapy group; thus, the possibility of placebo effects underlying the change of FC after EA-C2-PNfS cannot be excluded.

FC of Patients with Migraine in Comparison with Healthy Controls

Compared with the pre-therapeutic MWoA group, the FC values between the right hypothalamus and right amygdala, bilateral post-CG, and right insula were lower in the pre-therapeutic CM group. Those FC values were also lower in the CM group than in healthy controls. Additionally, the FC between the left amygdala and bilateral thalamus and PCC was higher in the CM group than in healthy controls. Thus, the amygdala could have a critical function in preventing chronic pain. Vachon-Presseau et al. reported that patients with persistent chronic back pain showed higher white matter FC of the corticolimbic system than did patients with early recovery [10]. Furthermore, the amygdala volume in patients with persistent pain was smaller than that in patients with early recovery and in healthy controls [10]. The amygdala is associated with the pain process via the thalamus [26]. Chen et al. reported that the right amygdala was associated with CM chronification, whereas the left amygdala was associated with the genesis of episodic migraine (EM) [27]. In our study, right amygdala–associated FCs showed decreases in the CM group, which suggests central sensitization in CM. Additionally, left amygdala–related FCs were higher than those in healthy controls in the CM group but not in patients with MWoA. These results differ from the results of Chen et al., who reported high left amygdala–related FC only in EM and not in CM [27]. Our results showed high left amygdala–related FCs only in the CM. The different analysis methods and patient populations could be the causes of these discrepancies.

Hadjikhani et al. reported that patients with migraine have increased FC between the bilateral amygdala, anterior insula, secondary somatosensory cortex, and thalamus in comparison with healthy controls [28]. These FC findings were migraine specific, because other chronic pain disorders were not associated with FC abnormality [28]. Also, the FCs between the right hypothalamus and the bilateral post-CG, right insula, and right amygdala of patients with CM were lower than those of patients with MWoA before EA-C2-PNfS. In CM, hypothalamus and pain matrix such as thalamus and insula were stronger than in EM [29]. In

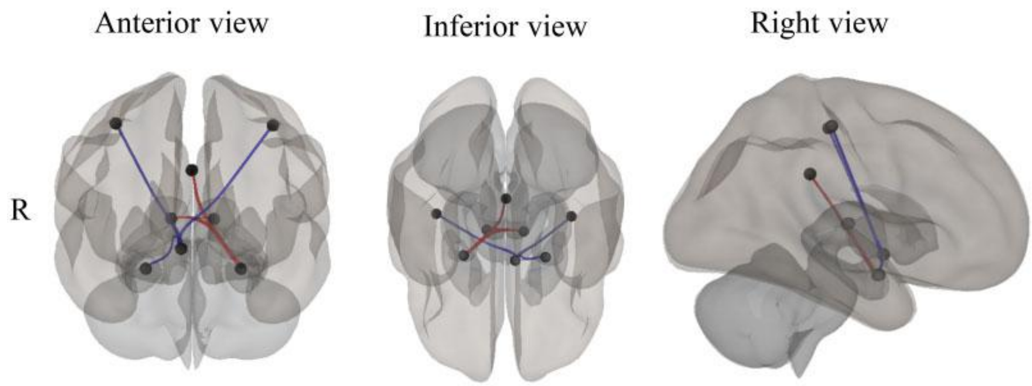

Figure 6. First imaging of pre-acupuncture patients with CM in comparison with first imaging of healthy control subjects. The blue line shows significantly lower CM than control, and the red line shows significantly higher CM.

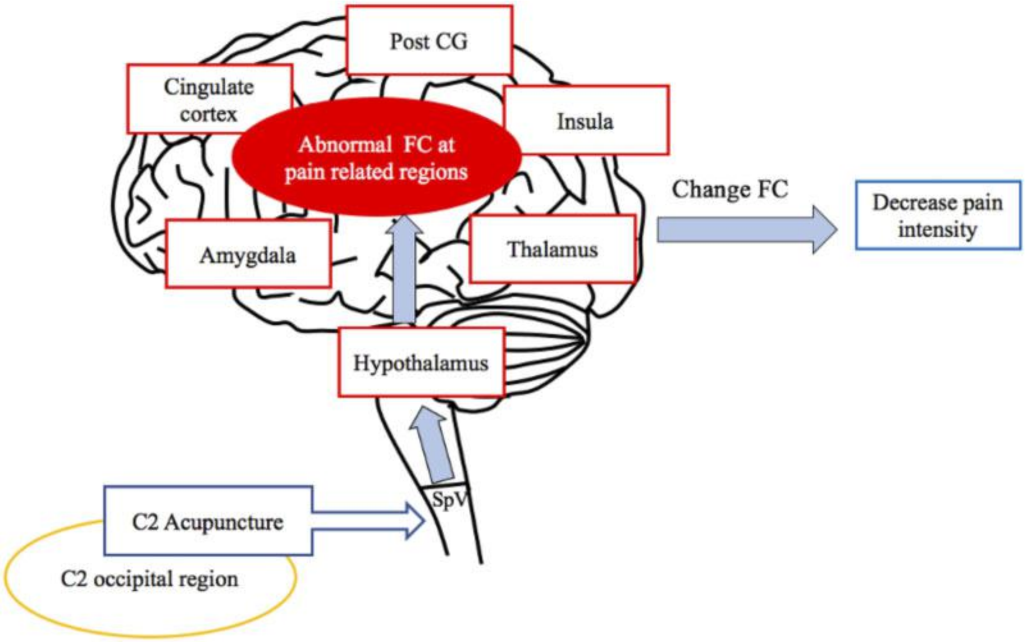

Figure 7. Propo sed mechanism of the effects of EA-C2-PNfS in patients with migraine. Migraine showed FC abnormality of pain-related regions. EA-C2-PNfS could modify the activity of pain-related regions via the SpV and hypothalamus. SpV = spinal trigeminal nucleus; Post CG = post-central gyrus.

our study, we did not observe the difference in FC between CM and EM, and the pre-therapeutic difference in FC between CM and MwoA disappeared after EA-C2-PNfS. In our study, the chronic migraine groups did not show significant FC changes after acupuncture. We might consider that the FCs are normalized by EA-C2-PNfS.

The natural course of FCs in healthy controls has not been reported in our literature search. We examined the rsfMRIs of healthy controls after a 3-month interval and found no significant change in pain-related FC.

Limitations

The present study had some limitations. First, we must emphasize that this study was open label and did not have a sham electroacupuncture group. We could not rule out a placebo effect due to the expectations of patients and regular meetings with therapists. To validate the efficacy of acupuncture, we need to perform a prospective study that includes a waiting list. It is difficult to perform electroacupuncture in a blinded setting. Chen et al. analyzed previous randomized controlled trials of electroacupuncture and reported that several sham methods can be applied [30]. In the future, the effects of needle position, needle insertion, and electrical stimulation by sham acupuncture must be considered. Second, this was a single-center study with a relatively small number of patients, and the long-term effect is still unknown. In the future, we need to perform a multicenter study with a large population. Third, some patients did not complete diaries for 3 months. Ten patients (50.0%) had completed diaries from 1 month before EA-C2-PNfS to the final acupuncture session, but the number of acute medication days and headache days showed no significant changes. Those results could have been influenced by two factors. First, 10 patients did not complete their diaries because the patients were confused and recorded only the medication days and not the headache days. The other factor was that patients with response did not need to write in the diary, so there were several cases of loss of diaries by the final session. The five of 10 patients with loss of diaries were responders whose NRS scores improved 50% over baseline. In addition, we had planned to perform MRI in the interictal period. Subjects experiencing a migraine attack were excluded; however, some patients might have experienced a migraine attack after MRI acquisition. Also, there were no significant differences between patients with migraine and healthy controls, and the numbers of each sex were not controlled, which might have influenced the results. For the FC analysis, we performed ROI-to-ROI analysis using the CONN toolbox. We did not manually select the ROIs; however, some ROIs were simple and large. In the future, we will consider performing a voxel-based method for more detailed analysis. Finally, no attempt was made to change the frequency or intensity of the electroacupuncture stimulation in this study. Further studies are needed to investigate suitable stimulation parameters.

Conclusion

We performed EA-C2-PNfS for patients with migraine and analyzed the FC findings before and after 3 months. EA-C2-PNfS improved the pain intensity in patients with MWoA. In the FC analysis, patients with MWoA showed significant changes in FC between the left insula and right hypothalamus after EA-C2-PNfS. The control group demonstrated no change in FC after a 3-month interval. Our results suggested that EA-C2-PNfS improves migraine headache by modifying pain-related FC.

Authors' Contributions

Dr. Ayuzawa developed EA-C2-PNfS with Dr. Ishiyama. Dr. Ishiyama and Dr. Shibata designed and conducted all steps of the study, including patient recruitment, diagnosis, acupuncture, data collection, and analyses. Dr. Matsushita supported MRI analysis. Dr. Matsumura and Dr. Ishikawa helped conduct the study. Dr. Ishiyama prepared the manuscript draft with intellectual input from Dr. Ayuzawa. All authors approved the submitted manuscript.

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