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Interaction of acupuncture treatment and manipulation laterality modulated by the default mode network

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Abstract

Appropriate selection of ipsilateral or contralateral electroacupuncture (corresponding to the pain site) plays an important role in reaching its better curative effect; however, the involving brain mechanism still remains unclear. Compared with the heat pain model generally established in previous study, capsaicin pain model induces reversible cutaneous allodynia and is proved to be better simulating aspects of clinical nociceptive and neuropathic pain. In the current study, 24 subjects were randomly divided into two groups with a 2×2 factorial design: laterality (ipsi- or contralateral side, inter-subject) $\times$ treatment with counter-balanced at an interval of one week (verum and placebo electroacupuncture, within-subject). We observed subjective pain intensity and brain activations changes induced by capsaicin allodynia pain stimuli before and after electroacupuncture treatment at acupoint LI4 for 30 min. Analysis of variance results indicated that ipsilateral electroacupuncture treatment produced significant pain relief and wide brain signal suppressions in pain-related brain areas compared with contralateral electroacupuncture. We also found that verum electroacupuncture at either ipsi- or contralateral side to the pain site exhibited comparable significant magnitudes of analgesic effect. By contrast, placebo electroacupuncture elicited significant pain reductions only on the ipsilateral rather than contralateral side. It was inferred that placebo analgesia maybe attenuated on the region of the body (opposite to pain site) where attention was less focused, suggesting that analgesic effect of placebo electroacupuncture mainly rely on the motivation of its spatial-specific placebo responses via attention mechanism. This inference can be further supported by the evidence that the significant interaction effect of manipulation laterality and treatment was exclusively located within the default mode network, including the bilateral superior parietal lobule, inferior parietal lobule, precuneus, and left posterior cingulate cortex. It is also proved that disruptions of the default mode network may account for the cognitive and behavioral impairments in chronic pain patients. Our findings further suggested that default mode network participates in the modulation of spatial-oriented attention on placebo analgesia as a mechanism underlying the degree to which treatment side corresponding to the pain.

Keywords

Interaction effect, laterality, electroacupuncture, capsaicin pain model, default mode network, placebo analgesia

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Introduction

It has been widely accepted that electroacupuncture is well practiced to treat and prevent various diseases and disorders especially for its analgesic effects.[1] According to the theory of the Traditional Chinese Medicine, acupuncture stimulation, at either ipsilateral (local) or contralateral (distal) side corresponding to the pain site, can be applied to different pain states. Appropriate selection of ipsilateral or contralateral electroacupuncture plays an important role in reaching its better curative effect.[2] However, potential neural mechanisms underlying laterality of electroacupuncture manipulation still remains unclear.

One recent study has discovered that local adenosine, acting as an anti-nociceptive transmitter, can be enhanced during acupuncture manipulation in a mouse model of inflammatory and neuropathic pain.[3] It is suggested that ipsilateral acupuncture plays its greater analgesic effects than that of contralateral side mainly through the local pain modulatory process. By establishing capsaicin-induced hyperalgesia pain model in rats, evidence confirms that electroacupuncture (EA) applied on the ipsilateral SI3-TE8 has more significant analgesic effect over the contralateral side, possibly due to the activation of the ipsilateral descending inhibitory system.[4] Furthermore, Yi et al.[5] have also revealed that the intact of the rostral anterior cingulate cortex (ACC) is crucial for the anti-nociceptive effect of contra- but not ipsilateral EA; thus, they infer that there are divergent modulatory pain pathways between distinct laterality electroacupuncture. Taken together, different neural mechanism has been found underpinning the laterality effect of electroacupuncture in animals, whereas its neurophysiological basis and modulatory component contributing to distinct analgesic effects has not been examined in human beings.

Emerging evidence has demonstrated that cognitive component (spatial-specific attention) exerts great influence on placebo analgesia. For instance, behavioral studies have shown that placebo analgesia is limited to the location where pain relief is expected.[6] Similarly, Kong et al.[7] have designed a sophisticated experiment performed in human subjects, it also manifests that acupuncture analgesia was only found on the high expectancy side rather than the control side. More interesting, abundant clinical reports show that invasive placebo treatments such as sham acupuncture and sham surgery enhance clinical benefits over the non-invasive oral pharmacological placebo for simultaneously manipulating of sensory, cognitive, and emotional factors to elicit placebo responses.[8,9] On the basis of these findings, Liu[10] reasonably hypothesize that needle manipulations work through the spatially directed expectancy to the certain sites of the body where the invasive acupuncture treatment performed, thus producing the spatial specific placebo analgesia. Along the same line, it has been revealed that spatial information of nociceptive stimulation can be represented in higher order cortical structures, suggesting a spatial specificity of pain control.[11] Given that both behavioral and neuroimaging findings discovered pain modulatory control is spatially specific, it is assumed that spatial-specific attention plays a pivot role in the cognitive component of electroacupuncture placebo analgesic effect. In the present study, we established attention modification model by laterality acupuncture, inferring that enhanced attention and expectation is directed to the same side of capsaicin-induced pain for the ipsilateral electroacupuncture stimulation comparing to the opposite side for the contralateral manipulation.

In this study, 24 healthy volunteers were randomized into two groups with a 2×2 factorial design: electroacupuncture at the ipsi- or contralateral side corresponding to the pain site (inter-subject)$\times$verum and placebo electroacupuncture (PA) treatment (within-subject) with counter-balanced stimulation at an interval of one week. Previous research widely used heat pain model to explore the interaction between electroacupuncture analgesia and expectancy effects. Here, we designed capsaicin-induced allodynia model on human body with better mimicing chronic neuropathic pain for its further clinical implication.[12] We hypothesize that analgesic effect and brain response patterns involved in laterality electroacupuncture differed between treatment modalities, which will help us to understand how spatial-specific placebo analgesia affect pain perception under different treatment modalities and their interactions.

Methods

This was a randomized, controlled, single blind, and crossover study. At the beginning, subjects were informed that this was a study about electroacupuncture analgesia. In order to elicit a full range of expectations that would allow the study of inter-individual differences in these phenomena, we also asked subjects to read a script stating the following: (i) responses to electroacupuncture can be positive or negative. Some persons have a very positive response to electroacupuncture treatment and are called ''good electroacupuncture responders'' whereas some people do not respond well to electroacupuncture and are called ''poor electroacupuncture responders;'' (ii) a given subject's response tends to remain consistent across sessions. At the end of all sessions, subjects were informed of the rationale for deception, and the final datasets were only included after the consent from the subjects (Figure 1).

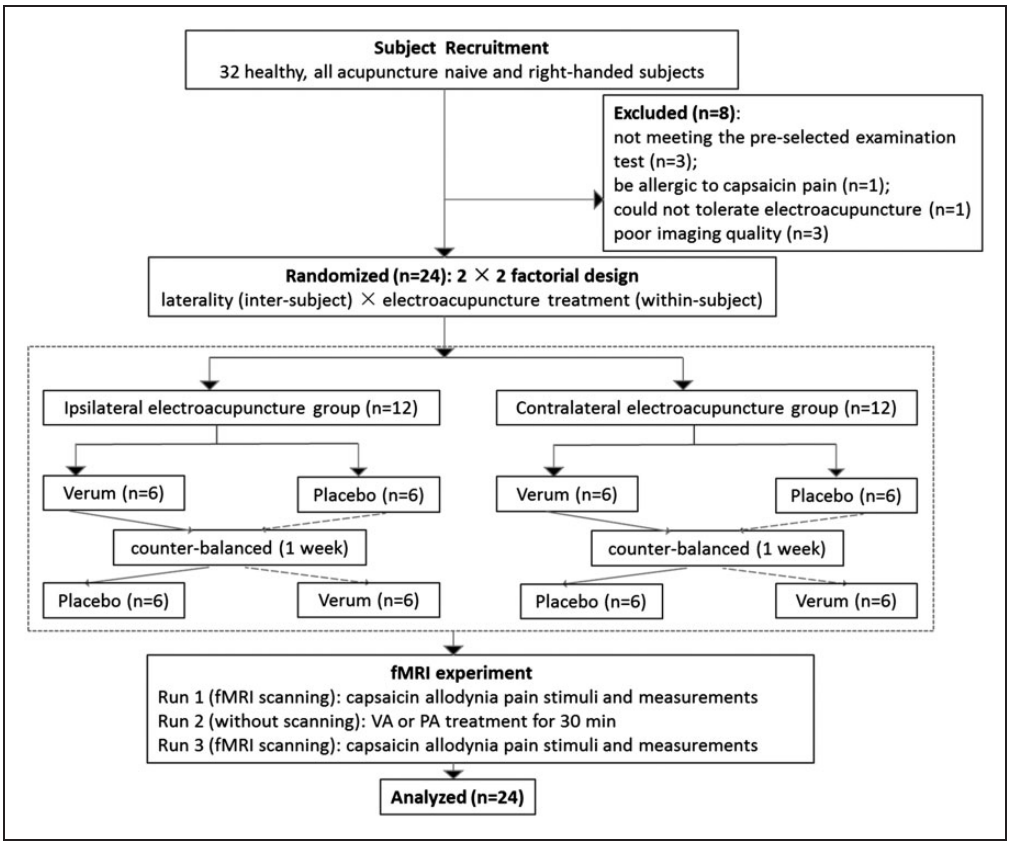

Figure 1. Experimental design. A total of 32 healthy subjects were recruited in this experiment. Three subjects did not meet the inclusion criteria of pre-selected examination and one was allergic to capsaicin pain. One in ipsilateral electroaupuncture group could not tolerate electroacupuncture treatment. Three subjects were also excluded due to poor quality (head movement exceeded 2.5 mm), one of them was in ipsilateral group, and the others were in contralateral group. Finally, 24 subjects completed the randomized, controlled, crossover study and were used for data analysis, 12 subjects for ipsilateral electroacupuncture group, and 12 subjects for contralateral electroacupuncture group. VA = verum electroacupuncture, PA = placebo electroacupuncture.

Subjects

Thirty-two healthy, all electroacupuncture naïve, and right-handed subjects (16 males and 16 females, ages of 24.01 ± 1.74, mean $\pm$ SD), took part in this experiment. Each subject underwent a pre-selected examination with the normal pain sensitivity levels (pain threshold [PT] and pain tolerance limit [PTL]). The assessment was carried out independently two weeks prior to the present study and involved a separate session. The data acquired were also used to verify the stability of pain sensitivity within the same person. The subjects were excluded when their PT or tolerance scores were 2SD above the group mean ($n = 32$; mean score $\pm$ SD $= 1.07 \pm 0.22$ for PT; mean score $\pm$ SD $= 0.91 \pm 0.26$ for pain tolerance [upper limit score-PT]). And all the subjects were also screened and excluded for major medical illnesses, head trauma, neuropsychiatric disorders, intake of prescription medications within the last month, and any contraindications for exposure to a high magnetic field. To control for menstrual cycle effects on pain sensitivity, women were only tested during the follicular phase (days 1–10) of the menstrual cycle. None of the subjects had taken any drugs for pain relief within the past one month. All subjects signed their written informed consent approved by the Tiantan Hospital Subcommittee on Human Studies before the start of the experiments. The experiment was also conducted in accordance with the guidelines of Declaration of Helsinki.

Randomization and blinding

Eligible subjects were randomized into the ipsilateral and contralateral electroacupuncture group in a 1:1, which was performed using predictive analytics software Statistics 20 (International Business Machines Corporation, Beijing, China). For each group, half of the subjects were firstly received the verum electroacupuncture (VA) at the acupoint LI4 and then PA treatment counter-balanced at an interval of one week, while the other half of subjects were conducted the opposite sequence VA and PA. The presentation sequence of

these two treatments was randomized throughout the population. In order to facilitate blinding, several procedures had also been performed: (i) all participants were not informed of the order in which the VA and PA runs would be performed; (ii) they were also instructed to keep their eyes closed to prevent from actually observing the procedures; (iii) to validate the blinding of our study, the subjects were also asked to the question ''Did you think the treatment you just had was real?'' at the end of experiment.

Quantitative somatosensory testing

After instructions to subjects, PT and PTL were measured on the right medial aspect of the forearm with potassium iontophoresis.[13] Prior to the fMRI scanning, subjects had a training session to be familiar with the stimulus rating scales and selected according to the value of PT and PTL in a moderate range of pain sensitivity. The probe of the stimulator was moved to a new skin site between the trials to prevent changes in skin sensitivity. When the participants indicated that they were ready to begin the experiment, the first electrical pulse was sent. Beginning at 0 mA, an electrical pulse of 1 s duration was delivered and increased the pulse intensity by 0.10 mA each time with inter-stimulus intervals of 1 s until the participant wanted to stop. To avoid the physical injury, the pain tolerance measurement stopped automatically at the upper limit of 5.0 mA. During the procedure, participants made three responses. When participants initially perceived as the lowest perceived pin prick, the experimenter recorded the pulse magnitude. Similarly, when the pulse reached a level where it was uncomfortable enough to be described as painful, the participant indicated pain (i.e., PT). Finally, when the pulse magnitude reached a point where the participant no longer wanted to continue receiving pulses, the participant indicated stop (i.e., upper limit score). To control for individual differences in participants' ratings of PT, pain tolerance was computed by subtracting participants' threshold from their upper limit score.[14] These procedures were repeated five times and with an inter-stimulus interval of 20 s for each stimulus presentation. At the beginning of both the training session and fMRI scanning, PT and PTL assessments were performed and determined as the average of five successive stimuli. In addition, subjects were also tested whether they were allergic to capsaicin by applying a test dose of capsaicin (250 mg in 20 ml, intradermal) two weeks prior to the MRI experiment.

Measurement of suggestibility, anxiety, and depression level

Each participant also filled in the personal trait questionnaires concerning anxiety (State Trait Anxiety Inventory),[15] depression (Beck Depression Inventory),[16] and suggestibility[17] prior to the fMRI scanning. Participants were further screened as the outliner of norm ratings adjusted by age, sex, and education level. The difference was also tested between groups to avoid confound effects. There were no significant differences on depression, anxiety, and suggestibility between the two groups ($P > 0.1$)

Capsaicin pain model of neuropathic pain[18] and assessment of noxious mechanical stimuli

A detailed overview of the experimental design conducted for capsaicin allodynia was presented in the Figure 2. Initially, the topical application of 10% capsaicin cream were delivered to the skin of the medial aspect of left forearm using capsaicin cream within a 3 cm × 3 cm small box. After 30 min, allodynia can be induced, and capsaicin solution (2.5% w/v in 70% ethanol) was used to remove the capsaicin cream.

A 20.9 g von Frey hair was used to stimulate along four linear paths, which are vertical and horizontal to the axis of the left forearm. Stimulation along each path started in steps of 5 mm from the outside the hyperalgesic area towards the capsaicin-treated skin area, until the subjects reported unpleasant sensations, indicating the presence of allodynia (sensory testing).[19] These sites were marked on the skin to delineate the border of secondary hyperalgesia area. To provoke allodynia during the MR scanning, an eight-block paradigm of mechanical stimulation testing was performed within the area of secondary hyperalgesia. Each stimulation lasted 30 s interrupted by a resting condition of 30 s. The brain activation signals in response to capsaicin allodynia stimuli were recorded before and after electroacupuncture treatment.

Subjective pain perception was evaluated using the McGill Pain Questionnaire (MPQ) after fMRI scanning. The MPQ[20] as a well-validated pain measurement was applied to assess subjective pain perception on capsaicin allodynia stimuli.

Measurement of internal emotional states

Subjects were asked to rate their current moods (state affect) by using the positive affectivity-negative affectivity scale (PANAS). The PANAS is conceptualized as a state measure of general mood.[21] It consists of 20 descriptors of various positive and negative affective states divided into two 10-item subscales: Positive Affect and Negative Affect. Individuals indicate how much each mood descriptor applies to them using a 5-point likert scale ''very slightly or not at all'' to ''extremely.''

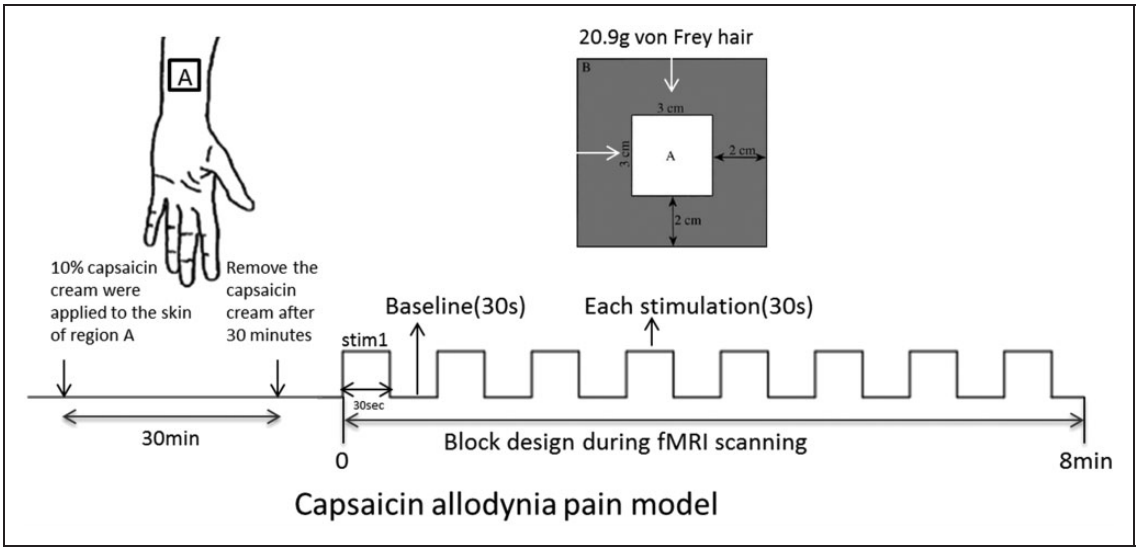

Figure 2. Schematic illustration of the fMRI experimental sessions. Capsaicin pain was established at the medial aspect of left forearm by using capsaicin cream within region A. After 30 min, the cream was removed. Then, an eight-block paradigm of mechanical stimulation testing with MRI scanning was performed in the secondary hyperalgesia shown as region B by 20.9 g von Frey hair to provoke allodynia. Each stimulation lasted 30 s interrupted by a baseline of 30 s.

Electroacupuncture administration

All subjects were randomized to receive two electroacupuncture stimulation paradigms (VA and PA) in a counter-balanced order. Every participant performed only one session (VA or PA) in a separate day in order to minimize potential long-lasting effects of acupuncture.[22,23] Two scanning sessions were performed at an interval of at least one week, depending on scanner availability and the scheduling needs of the subjects.

For VA, the needle (sterile disposable 38 gauge stainless, 0.2 mm in diameter and 40 mm in length) was inserted through the plastic needle guiding tube at the acupoint LI4 (Hegu, located at the first dorsal interosseus space) about 2–3 cm in depth on the hand and maintained until evoked subjective *deqi* but not sharp pain. LI4 was selected due to its wide application for analgesia.[24] Needles were then connected to an electroacupuncture device passing a 2 Hz current (Han's acupoint nerve stimulator LH-202, Beijing, China). Current intensity adjusted by the participant report rated as "moderately strong, but comfortable." The stimulation level varied between 1.6 mA and 2.9 mA (2.13 ± 0.74 mA) for participants.

For PA, the Streitberger needle[25] with a blunt tip was tapped through the same plastic needle guide-tube as VA on the surface of the skin of acupoint LI4, but without needle insertion into the skin. The non-penetrating placebo needle has been demonstrated as a successful blinding effect[26] and widely used in both neuroimaging and clinical studies.[27] The needle was then connected to a electroacupuncture device passing a 2-Hz current. The intensity corresponds to a threshold value of tingling sensation to ensure blinding as much as possible. The stimulation location, intensity, and duration were exactly as conducted in VA. The procedure was performed by the same experienced and licensed acupuncturist (with 6 years of experience) on all subjects. In order to induce satisfactory analgesia, every subject received a 30-min electroacupuncture treatment (VA and PA) without fMRI recording. It is proven that longer durations of electroacupuncture stimulation (at least 15 min) provide a more sustainable analgesic benefit to noxious stimulation than a shorter duration of stimulation (i.e., 5 min).[28]

For ipsilateral electroacupuncture group, the acupoint LI4 was selected in the same side of capsaicin-induced pain while opposite side for the contralateral manipulation.

Evaluation of deqi sensations

After electroacupuncture treatment, subjects completed a questionnaire that used a 10-point visual analogue scale (VAS) to rate their experience (or "deqi") of tingling, soreness, warm, heaviness, numbness, fullness, cold, itchy, aching, deep-pressure, dull, or sharp pain they felt during the electroacupuncture administration. The VAS was scaled at 0 = no sensation, 1–3 = mild, 4–6 = moderate, 7–8 = strong, 9 = severe, and 10 = unbearable sensation. The questionnaire also had one blank row for subjects to add their own words if the above descriptors did not embody the sensations they experienced during the stimulation.

Behavioral data analysis

After mechanical allodynia stimuli, subjects were asked to report the pain intensity on a MPQ scale. Analyses of variance (ANOVA) with repeated measures was performed on pre- and post-treatment subjective pain rating differences across the two groups (ipsi- and contralateral electroacupuncture) and two treatment modalities (VA and PA), where the former factor was between-subject and the latter within-subject. The main effects of treatment, manipulation laterality, and their interactions on pain rating changes were examined. Paired-t tests were employed by comparing pre- and post-treatment pain ratings between VA and PA for ipsi- and contralateral treatment group separately. To examine the effect of manipulation laterality on analgesia, we compared pre- and post-treatment subjective pain ratings between the two groups under VA and PA, respectively, by using two sample t-tests.

Statistical analysis

Continuous variables were compared using the t-test. Fisher's exact tests or chi-square tests were used for categorical variable. The level of statistical significance was set at $P < 0.05$ with a two-tailed test. All statistical analyses were performed using SPSS statistical software (version 20.0).

fMRI data acquisition and analysis

Images were acquired on a 3 T GE Signa scanner. A custom-built head holder was used to prevent head movements. Thirty-two axial slices (FOV = 240 mm × 240 mm, matrix = 64 × 64, thickness = 5 mm) parallel to the AC-PC plane and covering the whole brain were obtained using a T2-weighted single-shot, gradient-recalled echo planar imaging sequence (TR = 1500 ms, TE = 30 ms, flip angle = 90°). Prior to the functional run, high-resolution structural information on each subject was also acquired using 3D MRI sequences with a voxel size of 1 mm^3 for anatomical localization (TR = 2000 ms, TE = 3.39 ms, matrix = 256 × 256, FOV = 256 mm × 256 mm, flip angle = 7°, slice thickness = 1 mm).

All preprocessing steps were carried out using statistical parametric mapping (SPM 8, http://www.fil.ion.ucl.ac.uk/spm/). The images were first slice-timed and then realigned to correct for head motions (none of the subjects had head movements exceeding 1.5 mm on any axis and head rotation greater than one degree). The image data were further processed with spatial normalization based on the MNI space and re-sampled at 2 mm × 2 mm × 2 mm. Finally, the functional images were spatially smoothed with a 6-mm full-width-at-half maximum Gaussian kernel. The statistics were color coded and mapped in standard Talairach-Daemon based atlas.[29]

For each participant, fMRI signal differences (pre- minus post-treatment) evoked by capsaicin allodynia stimuli were obtained by a general linear model. Then, we compared all pre-treatment brain fMRI changes in a block design with two conditions (stimulus vs. baseline), yielding a mask of capsaicin-induced pain associated brain regions for the following analysis.[30–32] Then, we performed the following analysis within and without the region of interest mask produced above, by: (1) comparing differential pre- and post-treatment fMRI signal changes (pre- minus post-treatment) between the two groups for VA and PA separately using a two sample t-test; (2) comparing pre- and post-fMRI signal change differences between VA and PA within the same group by using a paired t-test. Finally, we investigated the interaction effect between laterality electroacupuncture (ipsi- vs. contralateral electroacupuncture) and treatment modalities (VA vs. PA). This interaction was calculated by comparing fMRI signal changes during mechanical allodynia stimuli between ipsilateral and contralateral electroacupuncture paired with verum and placebo modalities separately.

Results

Subjects

Twenty-eight of thirty-two consenting subjects were randomized into two groups to receive ipsilateral and contralateral electroacupuncture treatment separately. Three subjects did not fit the inclusion criteria of pre-selected examination, one was allergic to capsaicin pain. Of 28 subjects, one could not tolerate electroacupuncture treatment. Three subjects were also excluded due to poor quality (head movement exceeded 2.5 mm). Finally, 24 subjects completed all sessions, 12 subjects for ipsilateral electroacupuncture group (6 male; mean ± SD, ages of 23.98 ± 1.87) and 12 subjects for contralateral electroacupuncture group (6 male; mean ± SD, ages of 23.74 ± 1.90). There were no significant differences in the sex, ages, and educational levels between these two groups ($P > 0.1$). There were also no differences in the pain sensitivity (PT and tolerance) ($P = 0.25$ and $P = 0.28$). State Trait Anxiety Inventory, Beck Depression Inventory, and suggestibility score also presented no significant differences between two groups ($P > 0.1$).

Subjective ratings of pain

We used fMRI experiment pre- and post-treatment pain rating changes in response to capsaicin-induced allodynia to test the analgesia effect of different electroacupuncture interventions. Subjects' pre- and

post-treatment MPQ ratings for verum and placebo electroacupuncture across the two groups were shown in Table 1. ANOVA revealed a significant main effect on treatment ($F(1, 22) = 5.18$, $P = 0.03$). VA evoked more significantly pain rating changes (mean ± SD: 104.17% ± 80.65%, ranging from 70.11% to 138.22%) than that of PA ($P < 0.001$). In contrast, the pain rating changes for PA was in the range of −17.94% to 101.28% (mean ± SD: 41.67% ± 141. 17%, $P = 0.16$). The main effect for laterality (ipsilateral versus contralateral) was also significant ($F(1, 22) = 7.27$, $P = 0.01$) but not for the interaction effect ($F(1, 22) = 1.50$, $P = 0.23$). Ipsilateral group reported more pain reductions than that of the contralateral group. They were not significant for other main effects or interaction effect.

There were significant reductions in pain rating (pre- and post-treatment pain rating changes) on VA for both ipsi- and contralateral group ($P < 0.001$ and $P = 0.02$ for ipsilateral and contralateral group). By contrast, PA can only induce significant pain reductions only on the ipsilateral side ($P = 0.005$) but not on the contralateral side ($P = 0.82$) (Table 1 and Figure 3). PA stimuli on the ipsilateral side of pain site showed prominently greater pain attenuations, compared with that of the contralateral side ($P = 0.02$). Nevertheless, no significant differences were found between the two groups for VA treatment ($P = 0.08$) (Figure 4).

Subjective internal emotion states

In addition, the question "did you think the treatment you just had was real electroacupuncture?" elicited similar answers for both VA and PA ($P > 0.05$), inferring the successful blind to all subjects. There were no significant

Table 1. Average pain ratings of capsaicin stimuli before and after the acupuncture treatment.

	Ipsilateral electroacupuncture		Contralateral electroacupuncture	
	Verum	Placebo	Verum	Placebo
Pre	4.08 ± 1.44	4.25 ± 1.82	3.83 ± 1.19	3.42 ± 1.38
Post	2.75 ± 1.29	3.16 ± 1.70	3.08 ± 1.31	3.50 ± 1.57
Difference	1.33 ± 0.49	1.08 ± 1.08	0.75 ± 0.97	−0.08 ± 1.24
P value*	<0.001	0.005	0.02	0.82

Mean ± standard deviation are reported. Paired t-tests.
*$P < 0.05$ was considered statistically significant.

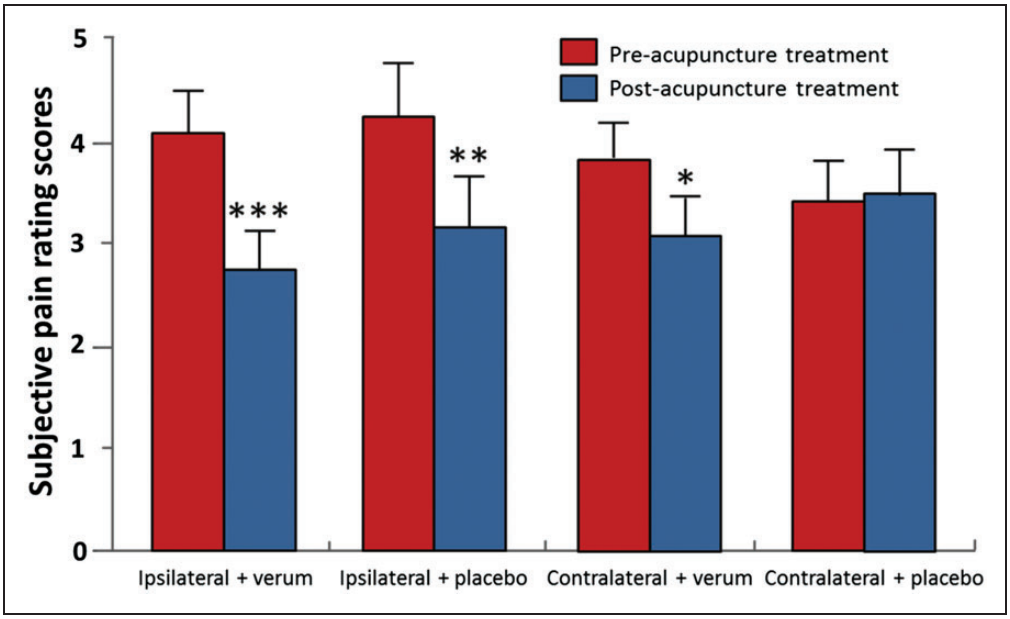

Figure 3. Subjective pain rating changes of pre- and post-acupuncture treatment. Each bar represents the mean of pain ratings scores, and error bars denote standard devation. Significant group differences between pre- and post- acupuncture treatment shown by *$P < 0.05$, **$P < 0.01$, and ***$P < 0.005$.

differences on PANAS score between ipsilateral and contralateral electroacupuncture group ($P = 0.1$).

Subjective electroacupuncture sensation evoked by verum and placebo electroacupuncture

The sensations evoked by electroacupuncture were also measured using the VAS to rate subject's experience, including tingling, soreness, warm, sharp-pain, heaviness, numbness, dull pain, fullness, cold, itchy, aching, and deep-pressure. A summary of the sensation scale was shown as the mean (standard deviation) in Table 2.

fMRI results

To verify the success of establishing pain model, we calculated the brain activities between capsaicin allodynia pain stimulation and rest condition by combining two groups. Capsaicin pain induced significant activations within an extensive brain network within the "pain matrix," such as the bilateral insula, thalamus, hippocampus (Hypo), ACC, medial prefrontal cortex, secondary somatosensory cortex (SII), and dorsolateral prefrontal cortex (DLPFC) (voxel-wise $P < 0.005$, corrected with 10 contiguous voxels). Accumulating evidence from fMRI studies demonstrated that acupuncture can modulate a wide brain regions,[22,33] largely overlapping with the neural activities for pain experience.[30] Our further analysis was only limited to these brain regions elicited by capsaicin pain stimulation (shown in Figure 5).

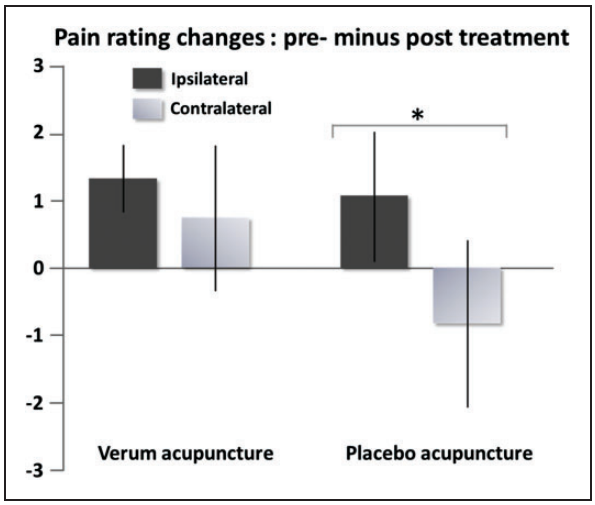

Figure 4. Subjective pain ratings changes (pre- minus post-treatment, mean ± SD) between the ipsilateral and contralateral groups for verum and placebo acupuncture. Each bar represents the mean of pain ratings difference, and error bars denote standard devation. *$P < 0.05$.

For both VA and PA, signal changes of pre- and post-treatment was compared between ipsilateral and contralateral electroacupuncture separately (Table 3). For VA, contralateral stimulation produced significantly less deactivations in brain regions than that of ipsilateral electroacupuncture, including the right supplementary motor area (SMA), posterior ACC (pACC), and DLPFC. No region was found above the threshold for the opposite comparison. For PA, ipsilateral stimulation induced more brain activations primarily in the bilateral SMA, right ACC, and orbitofrontal cortex (OFC), while no brain region above threshold for the contrast of contralateral versus ipsilateral-stimulation. For each laterality side, comparison of brain signal changes between pre-post VA and PA was shown in Table 4. For ipsilateral side, the contrast of VA versus PA showed no region above the threshold, while PA reduced more brain signal changes compared with VA, primarily including the bilateral SMA, amygdala, and right premotor cortex; For the contralateral side, much significantly greater decreased changes in the comparison of VA versus PA, including the bilateral SMA, primary somatosensory cortex (SI), and insula. No region was discovered above the threshold for either contrast (PA vs. VA).

fMRI analysis for the main effects of laterality electroacupuncture (e.g., VA and PA on ipsilateral side (pre-post) –VA and PA on contralateral side (pre-post)) showed that ipsilateral electroacupuncture produced greater fMRI signal decreases in pain related brain regions than contralateral treatment group, such as the bilateral thalamus, DLPFC, left SMA, and ventrolateral prefrontal cortex (VLPFC) (Table 5). In addition,

Table 2. Average VAS ratings for verum ipsilateral, verum contralateral, placebo ipsilateral, placebo contralateral groups.

	Soreness	Numbness	Fullness	Cold	Warm	Sharp-pain	Dull-pain	Heaviness	Tingling	Itchy	Aching	Deep-pressure
V I	2.7 ± 3.1	3.3 ± 3.1	6.1 ± 3.0	0.6 ± 1.1	2.3 ± 1.1	6.1 ± 3.2	4.4 ± 2.5	3.9 ± 3.0	5.0 ± 2.3	1.8 ± 1.4	7.0 ± 2.1	3.6 ± 3.2
V C	4.8 ± 2.4	4.7 ± 1.8	5.5 ± 2.1	1.1 ± 0.9	2.5 ± 1.9	6.2 ± 1.7	5.0 ± 2.4	4.1 ± 1.3	4.8 ± 2.9	1.2 ± 1.8	5.8 ± 2.9	3.8 ± 2.2
P I	1.9 ± 2.0	2.2 ± 2.1	2.4 ± 1.6	1.3 ± 2.3	1.9 ± 2.4	4.0 ± 2.5	3.2 ± 2.5	2.1 ± 2.2	2.9 ± 2.6	1.3 ± 1.7	2.9 ± 2.5	3.1 ± 2.6
P C	2.2 ± 1.7	2.5 ± 1.7	2.0 ± 1.9	1.4 ± 1.3	1.1 ± 0.6	2.4 ± 2.3	2.8 ± 1.8	1.6 ± 0.6	1.9 ± 0.6	0.8 ± 1.1	1.2 ± 1.1	1.4 ± 1.0

The data are presented as mean ± standard deviation. VAS = visual analogue scale; VI = verum ipsilateral; VC = verum contralateral; PI = placebo ipsilateral; PC = placebo contralateral.

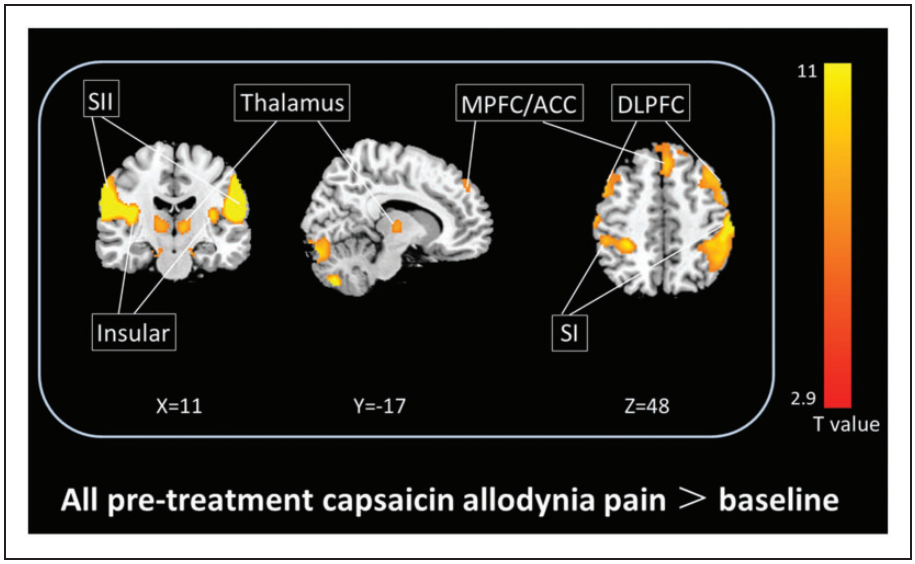

Figure 5. Brain activations in response to all pre-treatment capsaicin allodynia pain stimulation. Significant activations occurred in the bilateral insular, thalamus, ACC/MPFC, SI, SII, and DLPFC (voxel-wise $P < 0.005$ corrected with 10 contiguous voxels). ACC/MPFC = medial prefrontal cortex, SI = primary somatosensory cortex, SII = secondary somatosensory cortex, DLPFC = dorsolateral prefrontal cortex.

Table 3. Between-group comparison in fMRI signal change differences (pre- minus post-treatment).

Comparisons			Area (Brodmann area)	t score	Cluster size	Peak coordinate (x, y, z)
Lateral effect in verum acupuncture	IA > CA	ROI	Right SMA(6)	−5	590	5 4 48
			Right pACC(25)	−3.31	34	3 8 −4
			Right DLPFC(9)	−3.59	16	4 51 16
		Others	No regions above threshold			
	IA < CA	ROI	No regions above threshold			
		Others	No regions above threshold			
Lateral effect in placebo acupuncture	IA > CA	ROI	Bilateral SMA(6)	4.58	52	−53 1 17
			Right ACC(24,32)	3.31	31	6 32 15
			Right OFC(10)	3.48	28	26 50 −6
		Others	No regions above threshold			
	IA < CA	ROI	No regions above threshold			
		Others	No regions above threshold			

The threshold is set to voxel-wise $P = 0.005$ with 20 continuous voxels for predefined ROIs. The threshold for other regions (Others), were set to voxel-wise $P = 0.005$ with 15 contiguous voxels for other regions. Peak coordinates refer to the Talairach atlas. IA = ipsilateral electroacupuncture; CA = contralateral electroacupuncture; SMA = supplementary motor area; pACC = posterior anterior cingulate cortex; ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex.

significant fMRI signal changes were only found in the right cerebrum ACC for the opposite calculation (e.g., VA and PA on contralateral side (pre-post)—VA and PA on ipsilateral side (pre-post)).

For the main effects of treatment modalities (i.e., ipsilateral and contralateral with VA (pre-post)—ipsilateral and contralateral with PA (pre-post)), VA produced greater fMRI signal decreases than that of PA only in the DLPFC. The opposite calculation (e.g., PA (pre-post)-VA (pre-post) was not found any brain regions above the same threshold. Further analysis of the interaction effect between treatment modalities and laterality electroacupuncture showed significant fMRI signal changes within the default mode network (DMN), mainly in the bilateral superior parietal lobule, inferior parietal lobule, and precuneus as well as the left DLPFC, DMPFC, and PCC (Figure 6).

Table 4. Within-group comparison in fMRI signal change differences (pre- minus post-treatment) between verum and sham acupuncture in two groups.

Comparisons			Area (Brodmann area)	t score	Cluster size	Peak coordinate (x, y, z)		
Effects of acupuncture treatment in IA	VA > PA	ROI	No regions above threshold					
		Others	No regions above threshold					
	VA < PA	ROI	Bilateral SMA(6)	−5.53	118	−55	−3	13
			Bilateral amygdala	−3.68	31	30	−5	−15
			Right premoter(4)	−3.85	15	51	−5	46
		Others	No regions above threshold					
Effects of acupuncture treatment in CA	VA > PA	ROI	Bilateral insula(13)	5.19	136	−30	−28	20
			Bilateral SMA(6)	4.53	69	−30	4	46
			Left SI(2,3)	4.08	16	−46	−26	31
	VA < PA	ROI	No regions above threshold					
		Others	No regions above threshold					

The threshold is set to voxel-wise P = 0.005 with 20 continuous voxels for predefined ROIs. The threshold for other regions (Others), were set to voxel-wise P = 0.005 with 15 contiguous voxels for other regions. Peak coordinates refer to the Talairach atlas. VA = verum electroacupuncture; PA = placebo electroacupuncture; SMA = supplementary motor area; SI = primary somatosensory cortex.

Table 5. ANOVA results on fMRI signal change differences on the 2 × 2 factorial design: Ipsilateral or contralateral acupuncture (inter-subject) × verum or placebo acupuncture treatment (within-subject).

fMRI signal change			Area (Brodmann area)	t score	Cluster size	Peak coordinate (x, y, z)		
Main effect of lateral Acupuncture	IA > CA	ROI	Right thalamus	−3.78		16	−11	6
			Left thalamus	−3.37		−10	−15	8
			Left SMA(6)	−3.86	118	−59	1	24
			Left VLPFC(44)	−3.83	44	−55	16	7
			Left DLPFC(9)	−3.37	46	−53	15	31
			Right DLPFC(9)	−3.44	21	51	31	32
		Others	No regions above threshold					
	IA < CA	ROI	Right ACC(24)	3.03	10	58	4	29
		Others	No regions above threshold					
Main effect of Acupuncture modilaty	VA > SA	ROI	Right DLPFC(9)	−3.21	24	8	44	16
		Others	No regions above threshold					
	VA < SA	ROI	No regions above threshold					
		Others	No regions above threshold					
Interaction		ROI	Left PCC, precuneus (23)	3.85	56	−4	−28	22
			Left cingulate cyrus(23)	3.18	25	−4	−24	27
			Left superior parietal lobule(7)	3.07	15	−32	−50	49
			Left inferior parietal lobule (40)	3.84	100	−48	−44	48
			Right superior parietal lobule(7)	3.09	17	34	−51	62
			Right inferior parietal lobule(40)	3.39	36	46	−46	56
			Right precuneus(7)	3.37	77	12	−68	42
			Right lentiform nucleus	3.29	36	16	−4	0
		Others	No regions above threshold					

The threshold is set to voxel-wise p = 0.01 with 10 continuous voxels for predefined ROIs. The threshold for other regions (Others), were set to voxel-wise p = 0.005 with 15 contiguous voxels for other regions. Peak coordinates refer to the Talairach atlas. IA = ipsilateral electroacupuncture; CA = contralateral electroacupuncture; SMA = supplementary motor area; VLDFC = ventrolateral prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex; PCC = posterior anterior cingulate cortex.

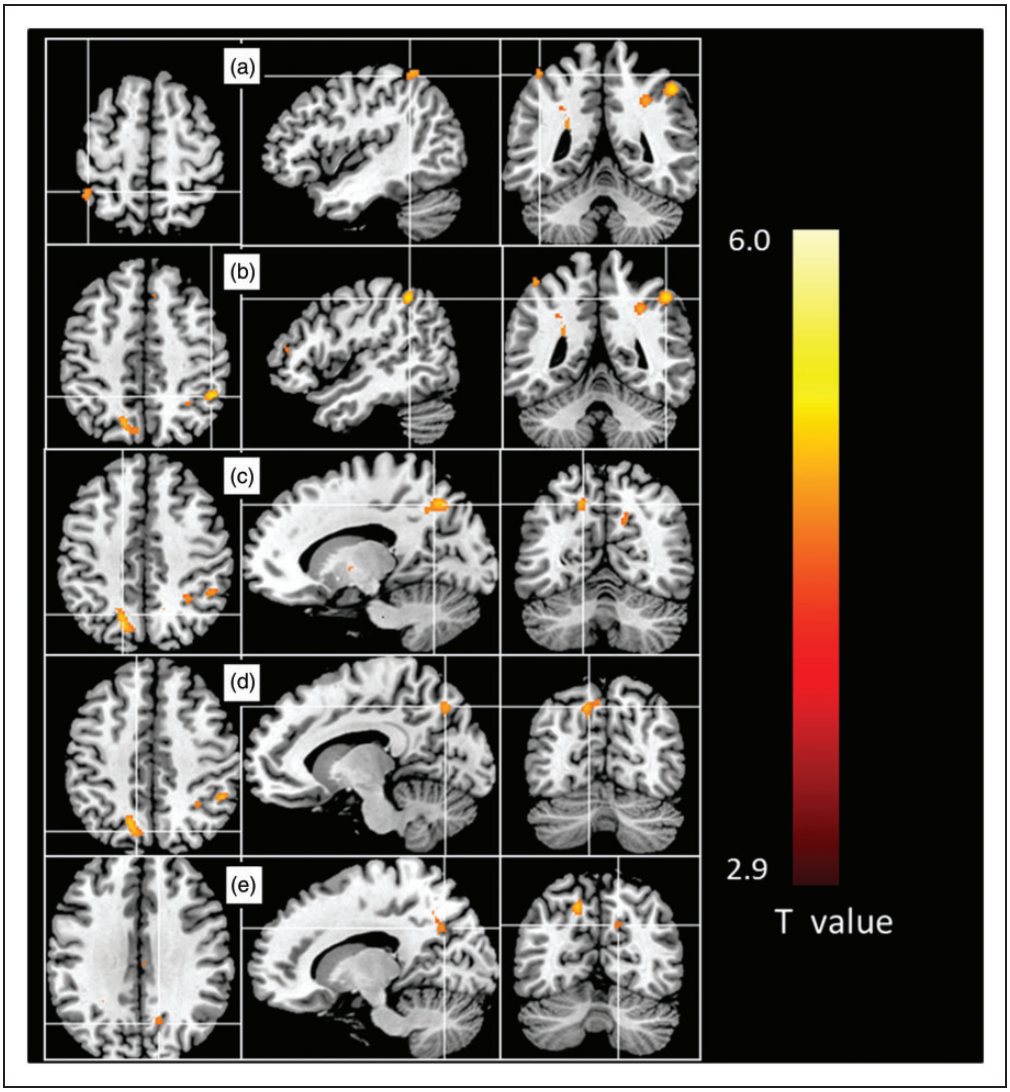

Figure 6. Interaction effect of laterality manipulation and acupuncture modality by ANOVA analysis. Significant brain signal changes were mainly located within the DMN, inclucding the right inferior parietal lobule (a), left inferior parietal lobule (b), right superior parietal lobule (c), right precuneus (d), left precuneus (e), respectively (voxel-wise $P < 0.005$ corrected with 15contiguous voxels). ANOVA = analysis of variance, DMN = default mode network.

Discussion

In the current study, our findings showed that laterality electroacupuncture (needling at ipsi- or contralateral side of pain site) could produce different analgesia responses and may implicate heterogeneous neural mechanisms. More specifically, ipsilateral electroacupuncture was superior to contralateral modality on pain relief. Results also revealed that such lateralized analgesic effect was modulated by different treatment modalities (VA and PA). The DMN is one of the most widely studied intrinsic connectivity networks (ICNs) and includes a set of brain regions such as the medial prefrontal cortex, the parietal cingulate cortex (PCC), and the precuneus.[34] Furthermore, there was a significant interaction effect of laterality manipulation and acupuncture modalities mainly located within the DMN. This interaction effect inferred that the different analgesic effects between treatment modes caused by laterality electroacupuncture can be mediated by the higher cortical areas within the DMN.

The main effect of laterality manipulation indicated that ipsilateral electroacupuncture exhibited more pain relief on subjective pain rating ($F(1, 22) = 7.27$, $P = 0.01$) and greater brain regions deactivation compared with contralateral electroacupuncture manipulation ($P = 0.01$ with 10 continuous voxels). Ipsilateral electroacupuncture produced more signal decreases to calibrated noxious stimuli in brain regions including the bilateral thalamus, DLPFC, left SMA, VLPFC, amygdala, and hippocampus. The regions including the

DLPFC, SMA, and VLPFC are known to participate in the modulation of expectation evoked placebo analgesia in previous studies.[30,32,35] Thalamus is the crucial station for transferring afferent sensory inputs into cerebral cortex. Also, some studies have been reported that spatial somatosensory tract can be organized at the thalamic level in the human brain,[36] suggesting that thalamus mediates the sensory transmission of somatotopic needling stimulation site (ipsilateral vs. contralateral). In the contrast of contralateral side and ipsilateral side, fMRI signal decreased only occurred in the ACC, which is consistent with previous study that ACC is only involved in the anti-nociceptive effects for contra- but not ipsilateral electroacupuncture.[5] Notably, thalamus, amygdala, and hippocampus are part of the limbic-paralimbic neocortical network, which modulates the cognitive and affective dimensions of pain.[37,38] In this point of view, limbic system affects the anti-nociceptive effects of ipsi- and contralateral electroacupuncture through different neural mechanism. Taken together, we speculated that the ipsilateral electroacupuncture may exert its greater analgesic effects through potential beneficial mechanism of enhanced attention and expectation to the same side of pain, in order to achieve a spatial-specific placebo analgesia as previously reported.[39] Moreover, there is evidence that medical devices potentially exerted an elevated placebo effect compared with other noninvasive placebo controls.[40] One meta-analyses suggested that physical placebo (i.e., sham acupuncture) can produce greater effects than pharmacological and other physical placebos.[41] It is natural to assume that this enhanced placebo effects involved in electroacupuncture acupuncture compared with oral or no treatment procedure maybe pertinent to the concentrated attention and expectation around the electroacupuncture site.[42]

Furthermore, we found the analgesic effects of spatial oriented attention modulation can vary under different treatment modalities. VA exhibits significant magnitudes of reported analgesic efficacy, regardless where the needling stimulation was applied (ipsilateral and contralateral side). For PA, significant pain relief only occurred after acupuncture on the same side where capsaicin aroused ($P = 0.02$), while no significant differences (pre- and post-treatment) on pain rating was observed on the contralateral side ($P = 0.82$). Therefore, we inferred that the pain alleviation of PA rely more on the motivation of its placebo effect triggered by spatial-specific attention. Furthermore, brain activation patterns involved for the stimulation laterality can vary under different treatment. For VA, when we compared ipsilateral with contralateral electroacupuncture, small fMRI signal differences were detected in the right SMA, pACC, and DLPFC. For PA, electroacupuncture at the ipsilateral side where attention-directed expectation is enhanced, exhibited more extensive fMRI signal decreases compared with that of the contralateral side, including the bilateral SMA, right ACC, and OFC. Previous study also indicates that there were greater fMRI signal changes in pain related regions when electroacupuncture on the high expectation side compared with the control side only in PA rather than VA group.[27] These regions included the left operculum, right insula, right inferior frontal gyrus (BA 47, 44), medial frontal gyrus, and superior frontal gyrus (BA 10). Similar evidence have been supported in various treatments such as buprenorphine, tramadol, ketorolac, and metamizol, called ''ceiling effect,'' meaning that the therapeutic effect can reaches its ceiling limit value. In this case, one possibility is that VA may possess high proportion of genuine effect to achieve almost equal analgesic effect in both ipsi- and contralateral acupuncture, while ceiling effect restrict sufficient space for the matching placebo effect. For PA, placebo component is an important contributor to its anti-nociceptive effects might be modified by spatial-oriented attention involved in laterality electroacupuncture.

Our findings showed that the interaction effect of laterality manipulation and electroacupuncture modalities (laterality × treatment) was statistically significant, primarily located within the DMN, including the bilateral superior parietal lobule, inferior parietal lobule, precuneus, and left PCC. DMN is known to be associated with the changes of internal mentation, which is engaged in the function of maintaining an individual's spontaneous attentional fluctuations toward and away from pain.[43] In fact, converge evidence has also found that dysfunction of the DMN is related to the impairments in patients with multiple chronic pain. It is further suggested that the DMN plays a prominent role in modulating pain experience.[44] Our results presented that manipulation laterality exert different influence on the treatment modalities (VA and PA), and the interaction effect is mainly modulated through the DMN. This evidence may infer that DMN can induce the top-down attention regulation of internal and external environment in the cognitive dimension of pain perception.

In conclusion, brain mechanism involved in the interaction of placebo effect and electroacupuncture analgesia is located within the DMN, considering as a critical system for the pain modulation particularly in cognitive aspect. It further supported the assumption that placebo analgesia may rely larger on its spatial-specific attention modulation. Notably, for the advancement of clinical practice in the future, this paper also provides a way to improve acupuncture analgesia by motivating spatial attention induced by the placebo effect appropriately. The current study might elucidate the possible neural mechanism underlying the modulation of laterality-induced placebo on treatment, and especially the neural substrate is primarily located within the DMN. In addition, it may possibly reflect individual variation in

placebo response, thus, as a valuable neural biomarker to predict clinical curative effect in acupuncture treatment.

Declaration of Conflicting Interests

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