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Psychophysical and psychophysiological effects of heat stimulation by electric moxibustion

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ABSTRACT

Objectives: Traditional moxibustion might be not safe due to the excessive heat stimulation or toxic chemical components involved. Electric moxibustion (EM), which has been recently developed as an alternative, offers adjustable and constant heat stimulation. This study aimed to investigate the psychophysical and psychophysiological responses to EM heat stimulation.
Methods: Twenty-seven healthy volunteers received two different levels of heat stimulation using EM. High-temperature (HT) and medium-temperature (MT) heat stimulations were randomly delivered at the TE5 acupoint on the left or right arm. Participants rated the intensity and the spatial information of the heat sensations immediately after each EM stimulation. Local blood flow around the acupoint was measured with Laser Doppler perfusion imaging before and after heat stimulation.
Results: Both HT-EM and MT-EM induced considerable heat sensations and enhanced local blood flow around the acupoints. HT-EM resulted in greater heat sensation compared to MT-EM. HT-EM induced a higher increase in local blood flow around the stimulation site compared to MT-EM. No remarkable adverse effects were noted.
Conclusion: Two different levels of EM heat stimulation induced two different levels of heat sensations and enhanced local blood flow. This preliminary study suggests that the newly developed EM can be further applied to examine the effectiveness of moxibustion in clinical trials.

1. Introduction

Along with acupuncture, moxibustion has been one of the most widely used treatment methodologies in East Asia.[1] It is believed to cure a wide range of diseases.[2,3] Current research categorizes the mechanisms of moxibustion into two subdivisions; thermal and pharmacological actions, which induce changes in the physical and physiological parameters in the body.[4] Although the exact mechanisms of moxibustion remain unclear, heat stimulation is considered to be the leading factor in evoking changes in bodily systems.[5] Heat stimulation has been observed to stimulate polymodal receptors, leading to a cascade of effects, including enhancement of the immune system, stimulation of the central nervous system, and analgesia of pain trigger points.[6–8] Moreover, sham moxibustions were developed to serve as appropriate controls for clinical studies of moxibustion by controlling the thermal sensations.[5,9] Hence, the use of moxibustion to control the temperature is assumed to be the most important factor in moxibustion treatment.

Many studies have raised concerns about the safety of traditional moxibustion due to the excessive heat or toxic components involved.[10,11] Electric moxibustion (EM) has been newly developed to offer adjustable and constant heat stimulation.[12] Devices that thermally stimulate the epidermis and subcutaneous tissues have been reported in *in vivo* models, illustrating the potential of electric moxibustion to minimize the adverse effects of traditional moxibustion while also effectively serving its purpose.[13] Recently, several studies evaluated the efficacy and safety of EM as a treatment for knee osteoarthritis and for cancer-related fatigue.[14,15] EM is believed to act primarily through heat stimulation without any noticeable adverse events.[12] However, despite the accumulating evidence, the psychophysical and psychophysiological characteristics of heat stimulation from EM have not yet been explored.

This study investigated the psychophysical and psychophysiological responses to two different levels of heat stimulation induced by EM. The intensity and the spatial information of the heat sensations were evaluated immediately after high-temperature- (HT-) or medium-temperature- (MT-) EM. We also observed peripheral blood flow changes in response to the two different electric moxibustion stimulations using

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Laser Doppler perfusion imaging (LDPI).

2. Materials and methods

2.1. Participants

In total, 27 healthy volunteers (aged 20–38, average age 24.6) were recruited *via* online advertisements directed at students attending Kyung Hee University and Korea University in Seoul, Republic of Korea. The participants had no history of neurological, cardiac, psychiatric, or dermatological disorders. All participants refrained from consuming medication, alcohol, or caffeine for 12 h prior to the experiment; received a thorough explanation of the experimental procedure; and provided written informed consent. This experiment was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Kyung Hee University (KHSIRB-18-065). All procedures were conducted in a quiet, air-conditioned, dimly lit room (24 ± 1 °C).

2.2. Experimental procedure

The experiments followed a within-subjects cross-over design in which the independent variable was HT *versus* MT EM stimuli on the arm to measure psychophysical and psychophysiological changes. Each participant was asked to extend one of his/her forearms with the palm facing down and to maintain a comfortable position throughout the experiment. The experiment proceeded as follows (Fig. 1A). First, the baseline value of local blood flow was measured by LDPI for 5 min. Heat stimulation was then delivered to the participants for 5 min, and the participants were asked to rate its intensity and spatial characteristics. After the heat stimulation, the post-treatment local blood flow was measured again by LDPI for 5 min. The experimental procedure was repeated with a different type of EM on the other arm. There was 10 min break time between the two sessions. It might be not enough time to recover to the baseline. In order to minimize the carry-over effect of the EM stimulation in two sessions, participants randomly received heat stimulation by EM on either the left or the right arm in each session.

Prior to the experiment, the participants were asked to complete surveys measuring their experiences of moxibustion and their laterality. To measure laterality, a shortened version of the 10-item Edinburgh Handedness Inventory was used.[16] Participants were also informed that the treatment area might become flushed after the EM stimulation; however, they were told that it was temporary and that the area would return to normal within several hours. Participants were informed that they should contact the researchers immediately if the area showed any signs of inflammation or complications.

2.3. Heat stimulation interventions

Participants were told that they would receive two different levels of heat stimulation from EM. They received heat stimulation by EM on either the left or the right arm with two different types of EM devices; high-temperature (HT) and medium-temperature (MT). The order of the location and intensity of the EM were randomly allocated to each participant prior to the experiment. In order to blind participant, the order of the EM stimulations was randomized by using a computer program (Random Allocation software; Revolution Analytics, Mountain View, CA).

Heat stimulations were delivered using the EM device (Cettum, K-medical Co., Daegu, Republic of Korea). Heat stimulation was delivered to the lateral side of the arm (TE5 acupoint: on the posterior aspect of the forearm, at the midpoint of the interosseous space between the radius and the ulna, 2 B-cun proximal to the dorsal wrist crease). The EM was pre-heated for 5 min prior to the stimulation to reach the maximum temperature at the time of adhesion of the EM to TE5. The total duration of the heat stimulation was 5 min. To determine the maximum temperature and the stability and durability of the two EM devices, the temperature of the devices was measured in an isothermal room (24 ± 1 °C) using Thermistor Pods (ADInstruments, Bella Vista, Australia).

At the beginning, we measured the time course changes of the four

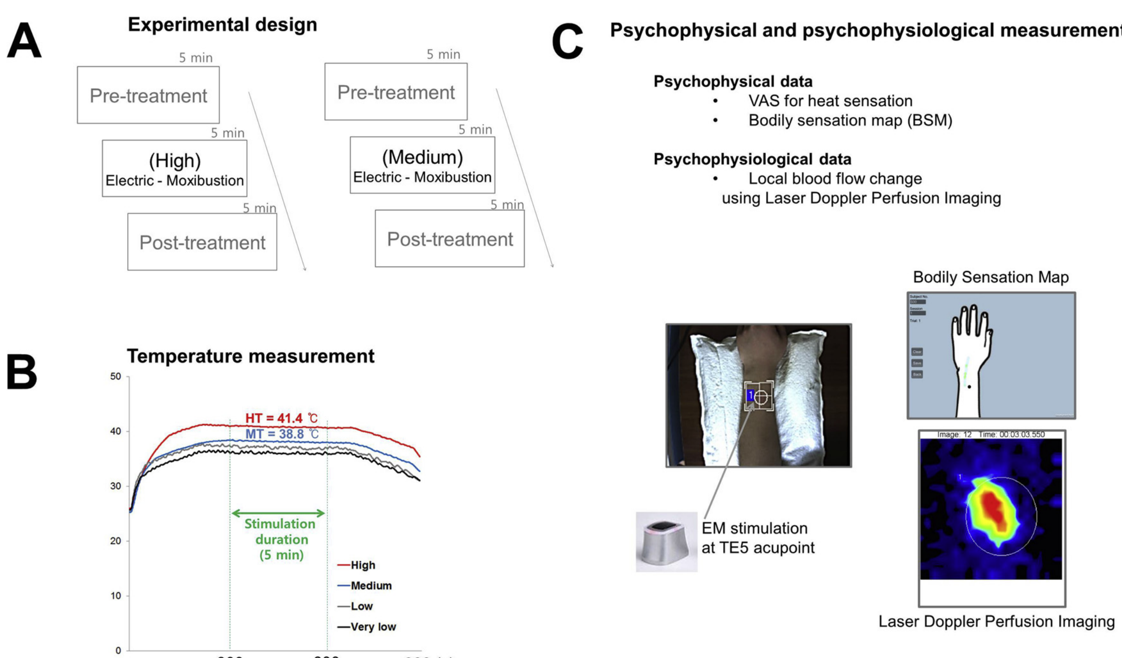

Fig. 1. A: Experimental design. The intensity and spatial characteristics of the perceived heat sensation were measured after electric moxibustion (EM). The local blood flow was measured before and after EM stimulation. High- (HT) and medium-temperature- (MT-) EM were randomly delivered to the lateral side of the arm. B: The temperature characteristics of EM. HT-EM resulted in a peak temperature of 41.4 °C, whereas MT-EM resulted in a peak temperature of 38.8 °C. C: Measurement of perceived heat sensations and local blood flow changes. The intensity and the spatial patterns of the perceived heat sensations were measured using a visual analog scale and the bodily sensation map (BSM) tool. The local blood flow changes after heat stimulation were measured using a Laser Doppler perfusion imager.

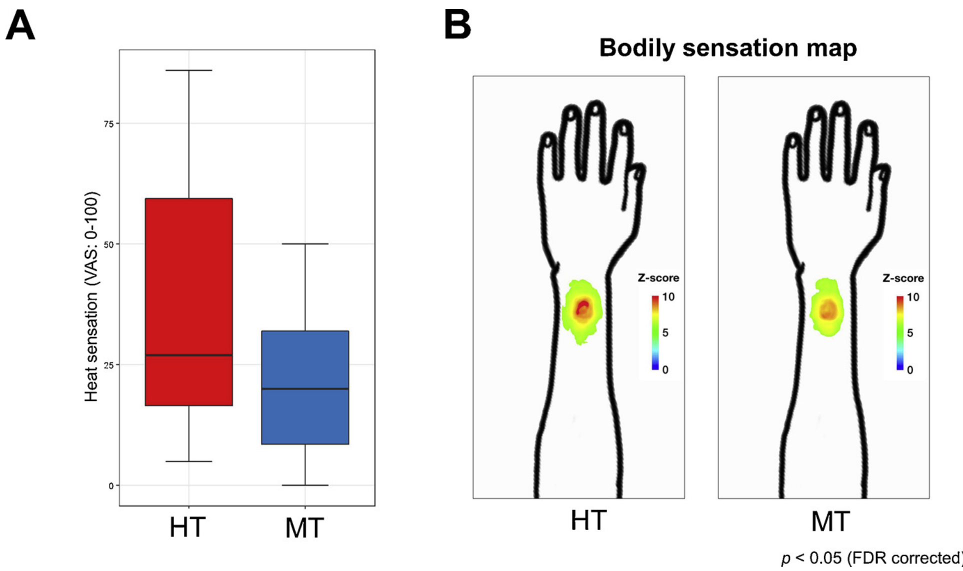

Fig. 2. Psychophysical responses of two different EM heat stimulations. A: The intensity of the perceived heat sensations. HT-EM resulted in greater heat sensation compared to MT-EM ($p < 0.001$). B: The spatial patterns of the perceived heat sensations. Both HT- and MT-EM produced localized heat sensations around the acupoints, but there were no differences in the spatial patterns of the heat sensations.

different EM in our preliminary study. Base on the peak temperature of these EM, we determined the two conditions of EM. It is assumed that the other two conditions of the EM were too low to induce sufficient psychophysical and physiological changes to the stimuli (low temperature peak at 37.7 °C and very low temperature peak at 36.5 °C). The reasons for the determination of the two temperatures are described in the discussion in detail. The surface temperature of the HT/MT EM devices was measured as shown in Fig. 1B. During the total time frame of 15 min, HT-EM resulted in a peak temperature of 41.4 °C, whereas MT-EM showed a peak of 38.8 °C. EM devices displayed the maximum temperature from around 5 min after activation and maintained the temperature for another 5 min. Thus, 5 min of pre-heating time was implemented to ensure that participants received the optimal heat stimulation.

2.4. Measurement of perceived heat sensation

Participants were asked to complete two survey forms during the experiment, the Heat Sensation-Visual Analog Scale (VAS) and the Bodily Sensation Map (BSM) (Fig. 1C). Immediately after the heat stimulation, participants were asked to rate the intensity of the heat stimulation using a 100-mm VAS, with 0 indicating no heat sensation and 100 indicating the strongest heat sensation imaginable.

Participants were also asked to specify the spatial patterns of the perceived heat sensations using the BSM (http://cmslab.khu.ac.kr/downloads/bsm).[17,18] This tool includes templates of the human body as 2D images and lateral views of the left arm. The images were collected in 1024 × 512 matrices on an iPad (Apple Inc., Cupertino, CA, USA). The participants were asked to mark intensity and locations of their sensations changes induced by EM stimulation. They express the intensity of BSM by changing the color of the points on a continuous color map *via* successive strokes with a touch pen (Adonit Inc., Austin, TX, USA).

2.5. Measurement of local blood flow changes in response to heat stimulation

Peripheral blood flow was measured using the LDPI (PeriScan PIM III system; Perimed AB, Järfälla, Sweden). Peripheral blood flow was calculated as the average perfusion during 15 s in the region of interest (a 4 × 4 cm square centered on the TE5 acupoint). Changes in local blood flow were subtracted from the baseline measurements (collected over 5 min) and averaged across the 5 min after EM stimulation. To minimize interference caused by light disturbance, the room was dimly lit. The arms of the participants were successively stabilized in accordance with the experimental procedures by a kapok-filled vacuum cushion to minimize movement.

2.6. Data analysis

The results are expressed as the mean ± standard error (SE). Differences in the heat sensations and local blood flow changes between HT-EM and MT-EM stimulations were analyzed using a paired *t*-test. Statistical analyses were performed using the R software (version 3.4.4., http:cran.r-project.org). Pearson's correlation analysis was also performed to determine the correlation between the heat sensations and the local blood flow changes after EM stimulation. A significance level of $p < 0.05$ was used for all analyses.

We extracted parametric maps of the bodily sensations to determine the spatial patterns of the heat sensations under each condition. Individual datasets for each subject and for each trial were scaled on a range of 0–1. The normalized BSMs were subjected to a group-level analysis of the statistical parametric maps. Random effects analysis and pixel-wise univariate *t*-tests were conducted on a group-level heat sensation pattern map within a mask of the body template (3dttest++, AFNI, https://afni.nimh.nih.gov/). False-discovery-rate (FDR) corrections were carried out to handle false positives due to multiple comparisons (FDR-corrected $p < 0.05$). The statistical *t*-values were transformed into *Z*-scores of the pixels that represented significant spatial information about the heat sensations in response to EM stimulation. The color code was visualized based on the *Z*-score.

3. Results

3.1. Baseline characteristics

In total, 27 participants (12 male, 15 female) took part in this study. The body mass index (BMI) of the participants was 22.5 ± 0.6. Most participants were right-handed, although one was ambidextrous and another was left-handed. Only four participants had prior experience with moxibustion treatment.

3.2. Psychophysical responses of heat stimulation

Both HT-EM and MT-EM induced considerable heat sensations (Fig. 2). HT-EM resulted in greater heat sensations compared to MT-EM (36.3 ± 5.0 *vs.* 21.7 ± 3.0, $t = 2.793$, $p < 0.001$). Additionally, the spatial patterns showed that both HT-EM and MT-EM produced

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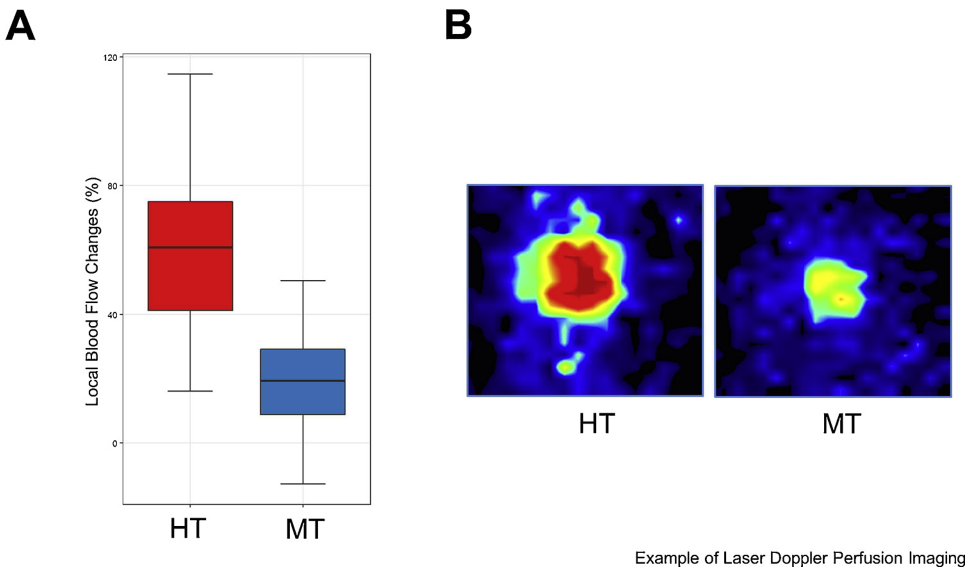

Fig. 3. Psychophysiological responses of two different EM heat stimulations. A: Local blood flow changes after heat stimulation using a Laser Doppler perfusion imager. HT-EM exhibited a higher increase in local blood flow around the stimulation site than MT-EM ($p < 0.001$). B: The representative Laser Doppler perfusion image of the local blood flow changes after heat stimulation.

localized heat sensations around the acupoints, but there were no differences in the spatial patterns of the heat sensations.

3.3. Psychophysiological responses of heat stimulation

Both HT- and MT-EM resulted in enhanced local blood flow around the acupoints (Fig. 3). HT-EM exhibited a greater increase in local blood flow around the stimulation site than MT-EM (60.3 ± 5.1 *vs.* 18.9 ± 3.0, $t = 7.916$, $p < 0.001$).

3.4. Correlation analysis between local blood flow changes and heat sensations

Local blood flow changes were significantly correlated with heat sensations after EM stimulation ($r = 0.447$, $p < 0.001$) (Fig. 4).

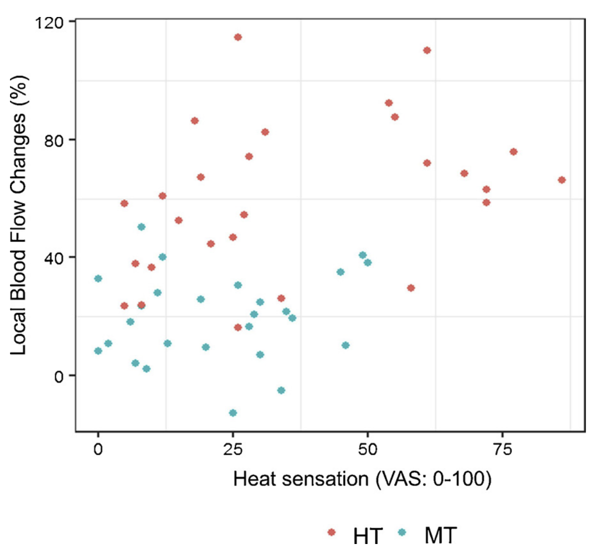

Fig. 4. Correlation analysis between local blood flow changes and heat sensations. Local blood flow changes were significantly correlated with the heat sensations after EM stimulation ($r = 0.447$, $p < 0.001$). Red dot: HT-EM, Blue dot: MT-EM (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

3.5. Adverse events

Adverse events following moxibustion therapy, including burns, inflammation, or infection, were monitored after treatment. None of the participants reported any remarkable signs of adverse events.

4. Discussion

Because moxibustion involves the burning of moxa sticks made of *artemisia vulgar* on the skin, this procedure often produces side effects resulting from the excessive heat of such sticks.[19] Depending on the design, composition, and quantity of the moxa sticks, thermal intensities can differ greatly.[20] The adverse events mainly involved burns, allergic reactions, and infections, with burns being the most prevalent. A systematic review identified 43 cases of burns, 7 cases of allergic reactions, and 6 cases of infections caused by moxibustion.[21] In contrast to the disadvantages of traditional moxibustion, the EM used in the current study can provide adjustable and constant heat stimulation. Both HT- and MT-EM produced constant and safe heat stimulation (41.4 °C and 38.8 °C, respectively). When animal models were treated with heat stimulation above 44 °C, severe epidermal and tissue damage resulted.[22] Additionally, local somatothermal stimulation (LSTS), which is a therapeutic procedure similar to EM that is characterized by applying a heat generator above a certain acupoint, was reported to evoke heat-shock protein expression at 42 °C.[23] Furthermore, when the temperature was set at 42 °C, the local blood flow changes were positively correlated with heart rate variability.[24] Considering these studies, we assumed that 42°C would be the optimal temperature to ensure both the efficacy and safety of EM.

In the current study, both HT-EM and MT-EM resulted in localized heat sensations around the acupoints. In an analysis of the psychophysical responses to two different heat stimulations, HT-EM was associated with greater heat sensations around the stimulation sites than MT-EM. It has been shown that humans can detect changes in heat-pain stimuli as small as 2°C with < 10% error rates.[25] As we applied stimuli with only 2.6°C between the high and medium heat stimulations, participants were able to discriminate the differences between the two stimuli. Although we did not ask participants to discriminate between the two stimuli in the present study, the heat sensations of the two stimuli were distinctive, but there were no differences in their spatial patterns. Thus, we believe that MT-EM can be regarded as an appropriate thermal stimulation for inducing different levels of heat sensation.

The BSM used in our study evaluates the intensity and spatial characteristics of perceived heat sensations from the body.[17] Acupuncture research has reported on the sensations propagated along channels[26] as well as on the remote sensation effects of acupuncture, suggesting that responses to acupuncture stimulation are not limited to local responses.[18] However, the BSM results from our study indicate that peripheral sensations were perceived only around the stimulation site. As acupuncture stimulates innervated nerves under the skin and involves additional sensory receptors in the skin, it can produce a wider range of bodily sensations along the meridians. On the other hand, heat sensations are generally not spatially sensitive. A previous study using infrared thermography failed to find any distinctive spatial patterns related to the meridian system.[27] These results suggest that further studies focused on clarifying the somatosensory and psychophysical responses to acupuncture/moxibustion stimulation should be conducted.

As the heat stimulation of moxibustion can result in vasodilation and increased blood flow to the affected area, local blood flow changes have been regarded as an appropriate index for assessing the effect of the heat stimulation.[28] Triple moxibustions on the abdomen induced greater increases in blood perfusion than a single moxibustion.[29] Different levels of thermal stimulation produced different levels of blood perfusion around the acupoints.[24] Likewise, in our study, HT-EM was associated with a higher increase in local blood flow around the stimulation site than MT-EM. Furthermore, there were significant correlations between perceived heat sensation and local blood flow changes. Therefore, we suggest that changes in local blood flow are good indicators of the physiological changes that occur in response to different thermal stimuli. To establish the efficacy of EM, however, clinical outcomes should be included in future research.

Still, our study possesses several limitations. First, we compared the psychophysical and psychophysiological changes to two different levels of temperatures of EM at the same TE5 acupoint. The heat sensations and local blood flow changes to EM stimuli can be varied with the anatomical distributions of nerves and vessels around acupoints. It will be further necessary to investigate the difference of the psychophysical and psychophysiological changes to the same EM stimuli among different body regions. Second, psychophysical and physiological responses to moxibustions can be varied with ages. Older people can have different characteristics of skin, nerves, vessels or muscles. In order to minimize the variations of these components, we did not include older people over 40 ages. However, it will be further necessary to include older people to generalize our findings. Third, we included only 27 healthy volunteers in this study and the sample size seems to be not large enough. However, the effect size of $d = 0.53$ was calculated based on the mean difference and the standard deviations of heat sensations between the two EM stimuli. The effect size in our study can be regarded as medium. With a standard power of 80%, the total sample size can be estimated as 24 to show statistical significance for the paired *t*-test. Although we had the adequate sample size for the statistical analysis in this study, power may be needed to be increased to draw concrete conclusions in future studies.

In our study, we demonstrated that EM can produce prominent psychophysical and psychophysiological changes in healthy volunteer. Many studies have shown that traditional moxibustion have regulatory effects on the excessive immune responses in ulcerative colitis.[30,31] The present study did not examine the modulatory effects of EM on immune responses, however, it will be interesting to investigate the role of EM in the regulations of the immune system compared with traditional moxibustion in the future study. Furthermore, the physiological responses to traditional moxibustion can be varied based on the different stimulation conditions, such as distance from the indirect moxibustion or number of stimulations.[29,32] Since it is difficult to establish appropriate condition of traditional moxibustion as a positive control, we did not directly compare the physiological responses to EM with traditional moxibustion in this study. If there were standard criteria for the temperature of traditional moxibustion, it might be interesting to compare the psychophysical and physiological response to EM with the traditional moxibustion in the future study.

In summary, HT-EM produced greater heat sensations as well as increased local blood flow changes around the stimulation sites than MT-EM. We clearly showed that two different levels of heat stimulation of EM induced two different levels of heat sensation and enhanced local blood flow. Moreover, the enhanced local blood flow changes were significantly correlated with the heat sensation from EM. This study will contribute to future research on the psychophysical and psychophysiological characteristics of moxibustion in the future.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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