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Partial correlation investigation on the default mode network involved in acupuncture: An fMRI study

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ABSTRACT

Certain clinical reports and researches have shown that acupuncture effects can sustain a period during the post-stimulation state, and modulate the default mode network (DMN). In this study, partial correlation approach was utilized to investigate whether or not electro-acupuncture stimulation (EAS) at the three acupoints (GB37 (Guangming), BL60 (Kunlun) and KI8 (Jiaoxin)) and one sham point on the left leg modulated the DMN and how to change the intrinsic connectivity of the DMN. The results indicated that DMN could be modulated after EAS, and there existed different modulation patterns of the four points. Meanwhile, we found that the posterior cingulate cortex and precuneus (PCC/pC) strongly interacted with other nodes during the pre- and post-stimulation states. The correlation was interrupted between the PCC/pC and anterior cingulate cortex (ACC). The orbital prefrontal cortex (OFC) negatively interacted with the left medial temporal cortex (lMTC) at the acupoints. We suggested that the distinct modulation patterns to the DMN attributed to the different effects evoked by the three acupoints and one sham point.

1. Introduction

Acupuncture, an ancient therapeutic modality in Eastern medicines, has been selected as a complementary therapy in the Western world to [6,7]. However, little is known about the neural mechanisms underlying acupuncture. In the past decade, noninvasive functional magnetic resonance imaging (fMRI) techniques have provided us with more direct information about the anatomy and physiological function involved in acupuncture [4,16,17,19,21].

Previous acupuncture studies investigated the topography of brain activity during the short period of acupuncture stimulation with block designs and the help of fMRI [8,16,17,19,34]. However, certain clinical reports have indicated that the therapeutic effects of acupuncture can last several minutes/hours/days. For example, the effective therapeutic effects last 10 weeks in the treatment of childhood persistent allergic rhinitis [24]. Price et al. demonstrated that the analgesic effects of acupuncture actually peaked long after acupuncture stimulation [28]. Therefore, the sustained effects of acupuncture are really a key point for acupuncture studies. However, it is ignored by previous acupuncture studies with fMRI. Fortunately, there have been more and more neuroscience researches focusing on the sustained effects of acupuncture. One study of our group demonstrated that the time-varied effects of acupuncture could sustain during the multi-block design [35], and we also reported that sustained acupuncture effects modulated the brain networks associated with amygdala [29]. In addition, the DMN has also received attention in the internal activities to cognition and fMRI signal changes in certain diseases [2,9,15]. While, few reports on the modulation to the DMN has been investigated in the field of acupuncture studies. Dhond et al. reported that the sustained effects of acupuncture can alter the DMN [5]. Nevertheless, Dhond et al. adopted one acupoint PC6 (Neiguan), and their study provided little information regarding the differences of the functional interactions in the DMN at different acupoints. Therefore, this raised the questions: whether or not the DMN could be modulated by stimulation at other acupoints. If so, how to change the intrinsic connectivity in the DMN by sustained effects of different acupoints.

In the present study, we adopted partial correlation approach to investigate the changes of the intrinsic connectivity in the DMN at the three acupoints. Partial correlation can evaluate the relation

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between any two network nodes under the circumstance of the removal of the common influences from all other nodes [23]. In other words, if adopting the partial correlation analysis of DMN, we can remove mutual dependencies among related brain areas without taking into account losing potentially interesting information. Furthermore, partial correlation has been implicated in the fMRI data analysis to investigate functional connectivity [22,23,31]. Thereby, partial correlation was applied in the current study.

2. Materials and methods

Fifty-six right-handed volunteers participated in the present study (28 females; 28 males; mean age: 23.8 ± 2.7). Subjects were acupuncture naïve and given informed consent approved by a local review board for human studies.

The 42 subjects participated in the verum acupuncture treatment and were randomly divided into three groups and variances across subjects have been counterbalanced across groups. Each group was only associated with one acupoint. Another 14 subjects were recruited to complement this study as a control group with sham acupuncture treatment. And the control group was matched with each acupoint group by gender, age, handedness and education. A non-repeated event-related (NRER) fMRI design [29] was applied in the current study. The experiment lasted 18 min, which consisted of a 6 min natural resting scan, a 6 min EAS treatment scan and another 6 min resting scan after EAS with needle removed. According to grouping, acupuncture was separately performed at acupoint GB37, BL60, KI8 or sham on the left leg (GB37 on the lateral side of the left leg, 5 cun superior to the prominence of the lateral malleolus, BL60 on the lateral ankle, in the depression midway between the external malleolus and the tendon calcaneus, KI8 located on posterior to the medial border of the tibia, and sham located out any of GB, BL or KI meridian). A professional acupuncturist operated the whole treatment on each subject for 6 min with EAS at 2 Hz pulses and 2–3 mA. After fMRI scanning, each subject was asked to complete a questionnaire that used a 10-point visual analogue scale to rate their experience (or "Deqi") during scanning, as determined by Hui et al. [17].

Subjects were scanned in a GE 3T Signa scanner. Functional images were acquired with a single-shot gradient-recalled echo planar imaging (EPI) sequence. (TR/TE = 2000 ms/30 ms, FOV = 240 mm × 240 mm, matrix size = 64 × 64, flip angle = 90°, slice thickness = 5 mm thick with no gaps, 32 sagittal slices). A set of T1-weighted high-resolution structural images was also collected (TR/TE = 5.7 ms/2.2 ms, FOV = 256 mm × 256 mm, matrix size = 256 × 256, flip angle = 12°, slice thickness = 1 mm with no gaps).

To test the behavioral data, the analysis of variance (ANOVA) was adopted to estimate the differences in each sensation intensity among the three different acupoint and sham groups ($p < 0.01$).

The first 5 time points were discarded to avoid the instability of the initial MRI signal. Data sets were preprocessed using SPM5 (www.fil.ion.ucl.ac.uk/spm). Images were realigned to the first image. The images were then normalized to Montreal Neurological Institute (MNI) template and re-sampled to 3 mm × 3 mm × 3 mm. The resting scans before EAS (R1) contained the images from 0.5 to 5.5 min and the scans from 12.5 to 17.5 min during the post-stimulation sate were extracted and named as R2. R1 and R2 were then processed with a bandpass-filter of 0.01–0.1 Hz. Finally, the filtered images were smoothed with a Gaussian kernel 6 mm × 6 mm × 6 mm FWHM.

The region of interest (ROI) was located in the posterior cingulate cortex and precuneus (PCC/pC), which was widely reported to be connected with other brain regions of the DMN [1,12]. The mean BOLD time course was then extracted from a 6 mm sphere in the PCC/pC (centered Motreal Neuorlogical Institute (MNI) coordinates: 0, −56, 25) of each subject's R1, which was used as a regressor in functional correlation analysis.

The brain network nodes of the DMN were defined from a one sample t-test of functional correlation analysis mentioned above ($p < 0.005$, uncorrected). The center MNI coordinates of the 6 mm sphere DMN nodes were on the base of the peak t score and each center of the clusters was in the targeted cortical region. The similar analysis steps were depicted in the studies from Buchel and Friston [3] and Greicius et al. [12].

For each subject, the mean fMRI time courses of the network nodes were separately extracted from R1 and R2. The functional interactions of the nodes were investigated by partial correlation approach during both the resting state and the post-stimulation state. And partial correlation coefficients were at a threshold $p < 0.05$ under the null hypothesis that no interaction between pairs of network nodes exists, as determined by Marrelec et al. [23] and Fransson and Marrelec [10]. We then used the mean interregional partial coefficients to measure the group-level connectivity related to each of the brain nodes.

3. Results

The prevalence of Deqi sensations was expressed as the percentage of individuals in the group that reported the given sensations (Fig. 1A). And the intensity of sensations was expressed as the mean score ± SD (Fig. 1B). Soreness, numbness and fullness were primary Deqi sensations in the present study. When estimating the difference in the intensity for each sensation among the four groups, the one-way ANOVA results (degree of freedom (df) of between-groups: 3 and df of within-groups: 52) showed that there were not significant differences in intensity of soreness, fullness and dull pain among the four acupoints (soreness: $F = 0.81$, $p = 0.49$; fullness: $F = 1.91$, $p = 0.14$ and dull pain: $F = 0.50$, $p = 0.69$). Nevertheless, the

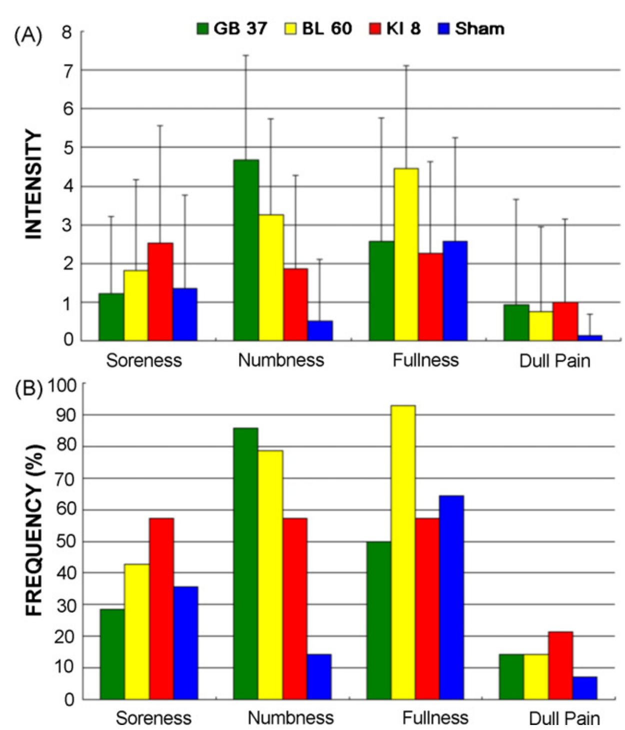

Fig. 1. Results of psychophysical analysis. (A) Soreness, numbness and fullness were primary Deqi sensation. (B) The intensity of each sensation was measured by mean score with standard error bars on a scale from 0 denoting no sensation to 10 denoting an unbearable sensation.

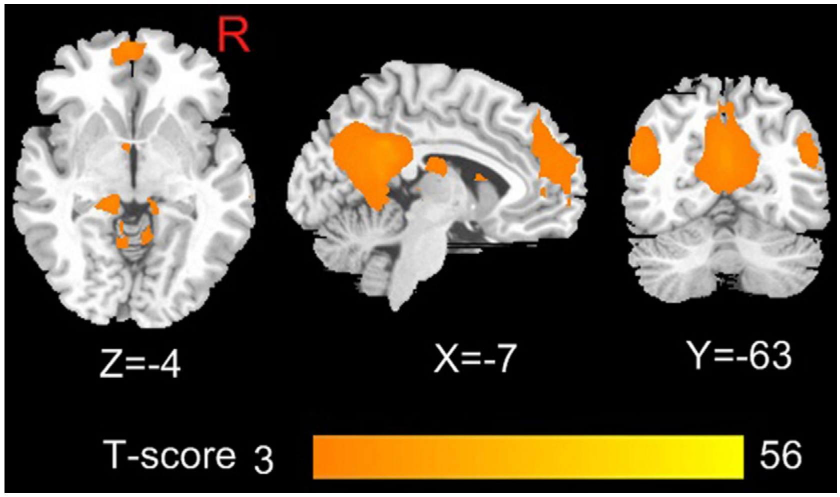

Fig. 2. The functional correlation map associated with PCC/pC as the seed region during the resting state. Positive functional connectivity to the seed region was indicated with warm color.

difference of numbness sensation was detected to be significant ($F = 8.29$, $p < 0.01$).

At the second level, intrinsic connectivity of the DMN was represented by the functional connectivity approach as shown in Fig. 2. The default mode network mainly consisted of the medial prefrontal cortex (MPFC), medial orbital prefrontal cortex (OFC), anterior cingulate cortex (ACC) and bilateral medial temporal cortex (MTC) and PCC/pC, which were associated with our network analysis. On the ground of the peak t score, we chose the MPFC (MNI: (−4, 66, 25), $t = 16.42$), OFC (MNI: (5, 58, −6), $t = 11.32$), ACC (MNI: (−3, 44, 12), $t = 5.38$), and bilateral MTC (MNI: (−51, −66, 21), $t = 11.80$; (48, −57, 27), $t = 9.70$) and PCC/pC (MNI: (0, −56, 25), $t = 30.63$) as our DMN nodes.

During the resting state, the PCC/pC fully interacted with other nodes. After EAS, the patterns of intrinsic connectivity were different. However, PCC/pC still strongly correlated with certain nodes. The correlation was interrupted between the PCC/pC and ACC. Although EAS was utilized at the different acupoints, OFC negatively correlated with left MTC (lMTC), which was not examined in the sham group. In addition, the lMTC extensively associated with other nodes compared to the right MTC (rMTC) (Fig. 3).

4. Discussion

In this pilot study, we used partial correlation approach to investigate the intrinsic connectivity changes of the DMN by stimulation at the three different acupoints and one sham point. We reported that the DMN could be modulated after EAS, and the results indicated that there existed different modulation pattern. Meanwhile, we found that PCC/pC strongly interacted with other nodes during the pre-and post-stimulation states. After EAS, the correlation of ACC to certain nodes was significantly changed. OFC negatively interacted with left MTC, and the left MTC more extensively associated with other nodes.

The varieties of the intrinsic connectivity in the DMN were detected after EAS. It is reported that several interesting differences of the patients' DMN are observed during the process of comparing with healthy control group [11,13,14], which resulted from the variation of the cytoarchitectonics or topographical anatomy. The physiology variation finally disrupts the balance of the DMN. Our present study provided evidence that acupuncture effects also disrupted or modulated the DMN. However, unlike the patients' disruption the acupuncture stimulation was more likely to integrate or segregate the resource of the brain, rather than alter physiological construct. Moreover, the distinct modulation patterns of the intrinsic connectivity may attribute to the different effects of different acupoints. We suggested that different effects of acupoints might lead to the resource redistributions because of different function-guide actions.

The DMN studies have shown that the metabolic is higher in the cingulate cortex and the spontaneous signal changes are stronger in the PCC/pC [30]. In the researches of disease, it was reported that fMRI signal fluctuations in the PCC/pC was altered in schizophrenia [2]. And He et al. indicated that the reductions of the low frequent signal fluctuations are shown in the pC at the early stages of Alzheimer's disease [15]. In the present study, the PCC/pC interacted with all the other nodes during the resting state, and this finding provided another positive evidence to support such a conclusion that PCC/pC plays a pivotal role in the default mode network. In a way, PCC/pC was strongly interacted with other nodes during the post-stimulation state. Moreover, previous acupuncture studies have detected that the PCC/pC is often activated during acupuncture experiments [17,20]. Taken together, we proposed that the PCC/pC might be an important brain area associated with sustained effects modulation of acupuncture.

The correlation was interrupted between the PCC/pC and ACC, which might result from acupuncture stimulation administration. Anatomical studies have detected that ACC connects with several thalamic subnuclei, receiving nociceptive input from the spinal cord [33]. ACC is associated with information processing and regulation in the brain including attention, emotion, visuospatial functions and nociception. Moreover, ACC is a crucial cortical area implicated in cognitive modulation of pain processing [25,26]. Compared to the control group, the correlation patterns and intensity associated with ACC were different among the three acupoint groups. Therefore, we suggested that certain changes related with ACC indicated that sustained effects of acupuncture were involved in both high cognitive networks.After EAS, the negative connectivity between OFC and lMTC was detected at the three acupoints, which did not present in the sham group. Despite the underlying mechanism of acupuncture has not been clear, it is generally accepted that mediation on endogenous opioid is a key component of acupuncture analgesia. Kong et al. found signal changes of [11C] diprenorphine positron emission tomography in the OFC during acupuncture administration [18]. In addition, OFC is implicated in sensory integration, autonomic reactions and certain emotion processing [27,32]. In this study, it was common that OFC negatively interacted with lMTC at the three acupoints during the post-stimulation states, which reflected the general non-specific of acupuncture needling. We further suggested that EAS at the three acupoints were all involved in the task linking with mediation on endogenous opioid and sensory/emotion processing by acupuncture, which was associated with the OFC and lMTC.

Compared to the correlation analysis of the rMTC, the lMTC extensively interacted with certain other nodes, which was due to our acupuncture stimulation on the leg. We speculated that this attributed to the cerebral functional lateralization.

One limitation in the current study was that we only analyzed the network nodes in the DMN but in the whole brain. Although we found that the distinct modulation patterns to the DMN, there was little information about changes of the whole brain network involved in acupuncture modulation. We speculated if more brain network nodes were recruited, more worthy results were indicated. Further study is needed at the point.

Overall, we assessed the interregional interactions related with the DMN before and after acupuncture stimulation by partial correlation approach. We found the distinct modulation patterns of the three acupoints and one sham point. The present results provide neuroimaging data to investigate the relationships between

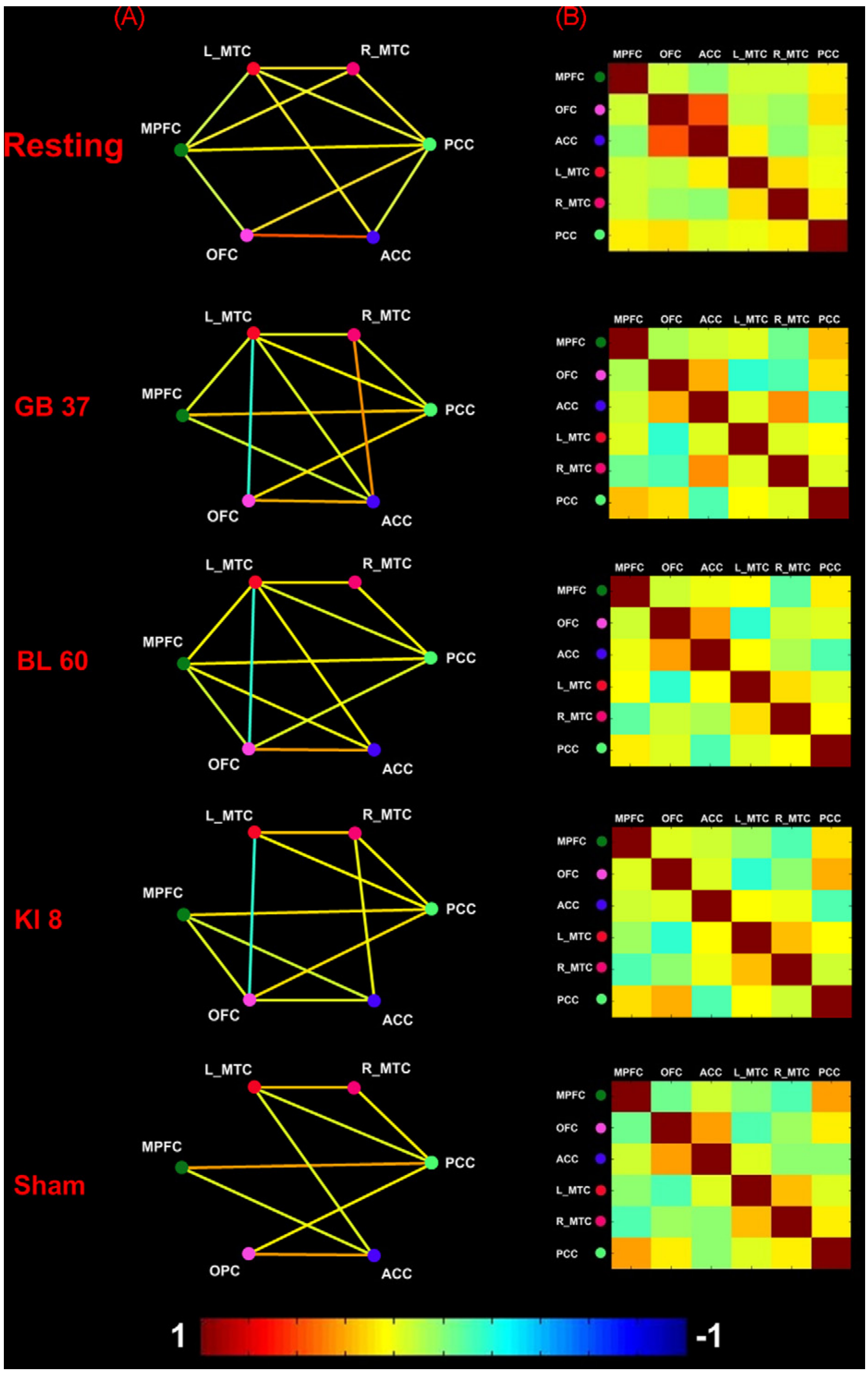

Fig. 3. (A) Partial correlation coefficients were shown in a network graph format, which was for the six brain regions (network nodes) of the DMN during the pre-and post-stimulation states. The correlation strength between any two nodes was color-coded in accord to the partial correlation matrix ($p < 0.05$). (B) The mean partial correlation matrixes were shown during the different sates.

the intrinsic connectivity in the DMN and the stimulation of different body locations, such as the three different acupoints and one sham point mentioned in the current study.

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