Investigation of the large-scale functional brain networks modulated by long-time transcutaneous electric acupoint stimulation

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Introduction Acupuncture, a traditional Chinese Medicine (TCM), has been worldwide used to against many disorders since the NIH consensus in 1997[1].However, the neural mechanism underlying acupuncture is still unclear. Now it has been quite accepted that the analgesic effects of acupuncture could last for a long time even hours after removing the needles [2,3]. And many studies have paid close attention to the sustained effects using short-time acupuncture (no more than 6 min) for healthy subjects [4, 5], which may be not long enough to satisfy the treatment effects. More recently, a period of 30 minutes electroacupuncture (EA) treatment was suggested to achieve the full expression of analgesic effect in healthy human [6]. At the same time, there is very few studies have yet investigated the topological organization of functional networks in the whole brain modulated by long-time acupuncture. Small-world is an attractive model for the description of complex brain networks, and we hypothesize that the small-world properties of brain functional networks would be modulated by long-time acupuncture.

Materials and Methods To test the hypothesis, we used functional magnetic resonance imaging (fMRI) to construct brain functional networks of subjects during the resting state. This study was approved by the local ethics committee, all subjects provided informed written consent, in line with the Declaration of Helsinki. Ten healthy subjects were analyzed (5 males, age: 23~34 (28.0±4.37) years). All subjects were enrolled to participate in two fMRI scanning sessions, TEAS (transcutaneous electric acupoint stimulation) and MTEAS (minimal TEAS). Both TEAS and MTEAS sessions consisted of a total of 30 min stimulation. An 8.5 min rest run was completed before, and after, each stimulation state (beforeMTEAS , beforeTEAS, afterMTEAS and afterTEAS). TEAS or MTEAS was performed by placing a pair of electrodes on Left IL-4 (Hegu) and PC-8(Laogong). The intensity of TEAS for each subject was adjusted to a maximal but comfortable level (8mA~25mA). And the current output of MTEAS was discontinuous and fixed on 5 mA, just above the detectable threshold (3 or 4 mA) [7]. The frequency of stimulation was set to 2 Hz, lasting 30 min. During the scanning time, all of the subjects were instructed to keep their eyes closed, their minds clear, and remain awake.

All MRI experiments were performed on a General Electric 3T Signa system (GE Medical Systems, Waukesha, WI) with a standard head coil. Functional data were acquired using a double readout spiral-out sequence with simultaneous Gradient-echo CBF and BOLD acquisitions, at short and long TEs, respectively [8]. Both readouts utilized slice thickness / gap (THK) of 8.0 / 2.0 mm with 3.6 x 3.6 mm^2 in-plane resolution, using a 230 mm^2 field of view (FOV) with a 64 x 64 acquisition matrix, a repetition time (TR) of 3000 ms and a 90° flip angle. CBF/BOLD readouts were acquired at TEs of 3.1/30 ms, respectively, covering 10-12 axial slices of the whole cerebrum. The set consisted of 170 functional contiguous axial images.

SPM2 (Wellcome Department, University College of London, UK) and MATLAB were used for data processing. Only the BOLD results were analyzed in this study. The first 10 images were discarded. The remaining 160 functional images were pre-processed including slice timing, motion correction, normalization, smoothness with a Gaussian kernel of 8 mm at full-width half-maximum, detrended linearly and temporally band-pass filtered (0.01~0.08 Hz).

The preprocessed data sets were first divided into 90 regions of interest (ROIs) using the AAL-atlas [9]. The mean time series of each region was then calculated. Several sources of spurious variances (six motion parameters , signal averaged from the region in cerebrospinal fluid, signal averaged from the region in the white matter) were further removed by multiple linear regression analysis. The Pearson correlation coefficients between every possible pair of the regional residual time series was calculated, and the 90*90 correlation matrices were obtained for each subject. Finally, each correlation matrix was thresholded into an undirected binarized graph for further analysis using graph theoretical approaches, in which nodes represent brain regions and edges represent links between regions. In this study, network cost was used as a threshold measurement. Several small-world parameters of the networks were calculated, including global efficiency(E_{glob}) and local efficiency(E_{loc}) [10].

In the present study, we compared E_{glob} and E_{loc} at each cost value to evaluate the small-world topological differences between the groups(including group1: before_MTEAS and before_TEAS, group2: after _MTEAS and after _TEAS, group3: diff _MTEAS and diff _TEAS, the diff _MTEAS means the difference of small-world parameters between the after _MTEAS and before _MTEAS ,similar to diff _TEAS) using a two-sample paired t-test($p<0.05$).

RESULTS The local efficiency (E_{loc}) and global efficiency (E_{glob}) of the random, group1,group2,and group3 brain networks as a function of cost(0.05~0.5) are illustrated in Figure 1. There were no significant differences in E_{loc} or E_{glob} between before_MTEAS and before_TEAS. At a wide range of cost threshold, the brain networks of the after_TEAS group demonstrated increased local efficiency compared with after_ MTEAS(cost=0.1275, 0.1825~0.1875). Whereas there were no significant differences in global efficiency between the two groups. At a wide range of cost threshold, the brain networks of the diff _TEAS group demonstrated increased local efficiency compared with diff _ MTEAS(cost=0.07, 0.115~0.1275). Whereas there were no significant differences in global efficiency between the two groups.

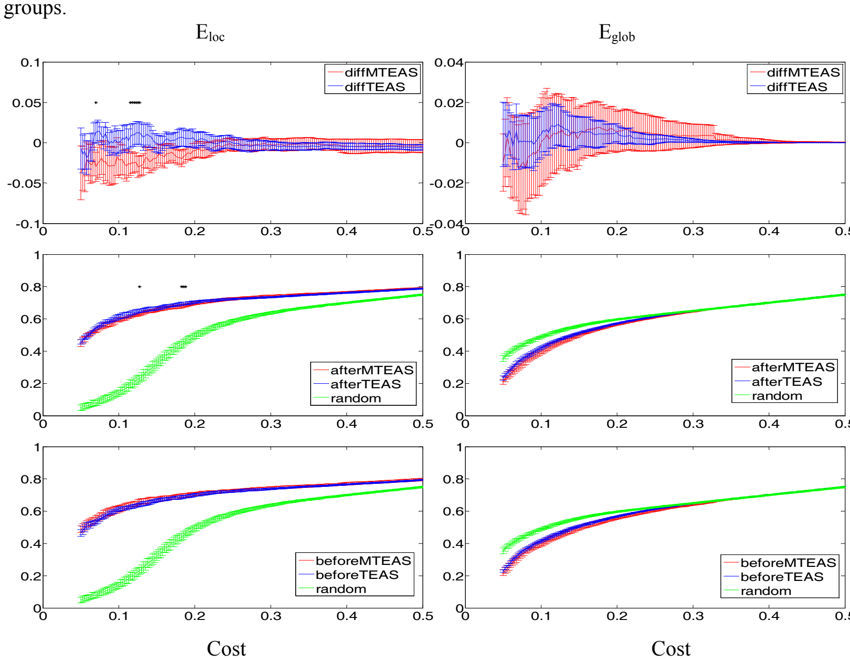

Figure1 The local efficiency (E_{loc}) and global efficiency (E_{glob}) of the random, group1,group2,and group3 brain networks as a function of cost(0.05~0.5). left columns denotes (E_{loc}) and right columns denotes (E_{glob}), black Asterisk denotes significant difference.

Conclusion This is the first study, to our knowledge, to investigate small-world properties of brain functional networks modulated by long-time acupuncture. An altered functional network, however, was found in the brain modulated by long-time acupuncture. In particular, a tendency of increasing local efficiency was demonstrated in TEAS when compared with MTEAS. Local efficiency is predominantly associated with short-range connections between nearby regions that mediate modularized information processing or fault-tolerance of a network [11]. The higher value of local efficiency for TEAS compared with MTEAS observed here might suggest higher fault-tolerance for brain network after long-time acupuncture. These results lead us to believe that this method could be helpful for understanding the mechanism of acupuncture.

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