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Long-duration transcutaneous electric acupoint stimulation alters small-world brain functional networks☆,☆☆,★,★★

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ABSTRACT

Acupuncture, which is recognized as an alternative and complementary treatment in Western medicine, has long shown efficiencies in chronic pain relief, drug addiction treatment, stroke rehabilitation and other clinical practices. The neural mechanism underlying acupuncture, however, is still unclear. Many studies have focused on the sustained effects of acupuncture on healthy subjects, yet there are very few on the topological organization of functional networks in the whole brain in response to long-duration acupuncture (longer than 20 min). This paper presents a novel study on the effects of long-duration transcutaneous electric acupoint stimulation (TEAS) on the small-world properties of brain functional networks. Functional magnetic resonance imaging was used to construct brain functional networks of 18 healthy subjects (9 males and 9 females) during the resting state. All subjects received both TEAS and minimal TEAS (MTEAS) and were scanned before and after each stimulation. An altered functional network was found with lower local efficiency and no significant change in global efficiency for healthy subjects after TEAS, while no significant difference was observed after MTEAS. The experiments also showed that the nodal efficiencies in several paralimbic/limbic regions were altered by TEAS, and those in middle frontal gyrus and other regions by MTEAS. To remove the psychological effects and the baseline, we compared the difference between diffTEAS (difference between after and before TEAS) and diffMTEAS (difference between after and before MTEAS). The results showed that the local efficiency was decreased and that the nodal efficiencies in frontal gyrus, orbitofrontal cortex, anterior cingulate gyrus and hippocampus gyrus were changed. Based on those observations, we conclude that long-duration TEAS may modulate the short-range connections of brain functional networks and also the limbic system.

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1. Introduction

Acupuncture, a traditional Chinese medicine, has long been used for drug addiction treatment, asthma and chronic pain relief, stroke rehabilitation, etc., and has also been recognized as an alternative and complementary treatment in Western medicine since the National Institutes of Health consensus in 1998 [1]. However, the neural mechanism underlying acupuncture is still unclear. Electrical acupoint stimulation (EAS) has been commonly used in acupuncture studies for its controllability and repeatability, companying with optimized parameters (frequency, pulse width, and intensity) to produce a similar effect to manual acupuncture. In this study, transcutaneous electric acupoint stimulation (TEAS), one form of noninvasive EAS, was applied to investigate the acupuncture mechanisms [2–7].

It has been generally accepted that the treatment effects of acupuncture could last for a long time even after the removal of the needles which acted for a duration [8,9]. Many studies have focused on the sustained effects of acupuncture on healthy subjects with short duration of stimulation (no more than 6 min) using functional magnetic resonance imaging (fMRI) [10,11]. They found that acupuncture modulated the connectivity of several brain regions, including antinociceptive, memory and affective brain regions, with the default mode network (DMN), sensorimotor network (SMN) and amygdala-associated brain network. It was also reported that the connectivity between different regions and the hubs of the functional brain networks were altered by short-duration acupuncture [11–15]. While the long-duration acupuncture (20–45 min) is often used in conventional clinical practice [3,16–18], a recent study has revealed that a 30-minute TEAS may result in decreased cerebral blood flow (CBF) in several specific regions and in the brain globally, and more spatially extended connectivity of the DMN and SMN in comparison with minimal TEAS (MTEAS) [2]. However, fMRI studies of long-duration acupuncture are still limited.

Graph theoretical approaches can characterize the overall functional connectivity pattern among all brain regions and capture the topological structure of the functional brain networks [19]. It can measure the relationships among all brain regions compared with seed-based connectivity analysis [12], which merely takes into account the functional connectivity with a predefined region of interest (ROI). Independent component analysis [2] can identify separable sets of connected brain regions (i.e., components), but it does not provide the connectivity information between these components. The graphs with dense local connections and with few long connections can be characterized as small-world networks using the graph theoretical approaches [19]. Recent studies have revealed that there exists a small-world topology in large-scale structural and functional brain networks of humans [20,21]. It has also been demonstrated that the small-world properties of brain networks could be affected by normal aging and brain diseases [22–26]. As an attractive model to describe complex networks by providing quantitative parameters, the small-world brain functional networks are used in this study to investigate the effects of long-duration TEAS on the brain. The functional networks examined here are derived from the spontaneous low-frequency fluctuations in resting state fMRI data [23]. Given that functional connectivity between different brain regions was found to be modulated by TEAS [2], we hypothesized that the properties of small world would be modulated by long-duration TEAS.

2. Materials and methods

2.1. Subjects

This study was approved by the local ethics committee. All subjects provided informed written consent according to the Declaration of Helsinki. Eighteen right-handed subjects (9 males, 9 females; mean age 28 years; range 24–34) participated in the study. All subjects were free to withdraw from the experiment at any time. No subjects had a history of psychiatric or neurological disorder. No subject was excluded due to excessive head motion (maximum displacement in any direction larger than 1 mm or head rotation larger than 1°).

2.2. Experimental design

During the MR scanning, all subjects were instructed to keep their eyes closed, keep their minds clear and be awake all the time. All subjects received 30-min TEAS and MTEAS. These two runs were randomized and balanced throughout the subjects, and every subject performed only one run each day, 1 week apart. The period of resting state acquisition was 6.5 min, performed both before and after the stimulation (Fig. 1).

TEAS or MTEAS was performed at acupoints of LI-4 (Hegu) and PC-8 (Laogong) on the left hand with a pair of skin electrodes placed on them. Han's acupoint nerve stimulator (HANS model LH-202H, Neuroscience Research Center, Peking University, Beijing, China) was used to deliver the stimulation to the TEAS group with a frequency of 2 Hz. The intensity of current for TEAS was adjusted to a maximal but comfortable level for each subject [2–4]. In this study, the current intensities were 8–25 (16.7±3.6) mA. For the MTEAS group, a new machine called "Mock HANS," with an appearance identical to that of the HANS LH-202H, was used to produce 2-Hz stimulation. The current output of "Mock HANS" was fixed at 5 mA [just above the sensory threshold (3 or 4 mA)] [4] and intermittent with 10 s on and 20 s off [2,3]. No noxious feelings were allowed for either TEAS or MTEAS sessions. The feelings of "deqi" (including soreness, numbness, fullness, heaviness and dull pain) and intensities of all sensations (using a visual analogue scale from 0 to 100) were recorded [2].

2.3. Image acquisition

All MRI experiments were performed using a General Electric 3-T Signa system (GE Medical Systems, Waukesha, WI, USA) with a standard head coil. Functional data were acquired using a double readout spiral-out sequence with simultaneous gradient-echo blood oxygenation level dependent (BOLD) and CBF acquisitions at short and long echo times (TEs), respectively [27,28]. Both readouts utilized slice thickness/gap (THK) of 8.0/2.0 mm with 3.6×3.6-mm^2 in-plane resolution, using a 230-mm^2 field of view (FOV) with a 64×64 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 brain. The set consisted of 130 functional contiguous axial images.

A T1-weighed three-dimensional fast spoiled gradient echo (FSPGR) sequence was used to acquire the high-resolution structural images with the following parameters: TR/TE=25/4 ms, FOV=230 mm^2, THK of 2.0 mm with no gap, resolution=1×1 mm^2.

2.4. Data analyses

SPM5 (Wellcome Department, University College of London, UK) and MATLAB were used for data processing. Only the BOLD data were

Fig. 1. Experimental paradigm: functional scanning incorporated with two independent 6.5-min rest runs (REST 1, REST 2), separated by a 30-min TEAS or MTEAS without scanning.

analyzed in the current work. The first 10 functional images were discarded to ignore image acquisition during the approach to steady state and to allow for their adaptation to the circumstances for the subjects. The remained 120 functional images were first corrected to remove acquisition time delay among different slices, motion corrected and then coregistered with the corresponding anatomical image to facilitate transformation to Montreal Neurological Institute space and resampled to isotropic 2×2×2-mm^3 voxels. Several sources of spurious variances, including six motion parameters, the signal averaged from the region in cerebrospinal fluid and the signal averaged from the region in the white matter, were further removed from the data of each voxel through multiple linear regression [13,25]. The data were then detrended to remove linear drift and temporally filtered by a band-pass (0.01–0.08 Hz) filter to reduce the effects of low-frequency drift and high-frequency noise [29–31].

The data sets preprocessed above were divided into 90 ROIs (45 for each hemisphere) based on the automated anatomical labeling (AAL) atlas [32]. The mean time series of each region were then obtained by averaging the time series of all voxels in that area. The Pearson correlation coefficients between each possible pair of the regional time series were calculated, and a 90×90 correlation matrix was obtained for each subject. Subsequently, a Fisher's *r*-to-*z* transformation was applied to the correlation matrices to improve the normality of the correlation coefficients, and the *z*-score matrices were obtained. Finally, each absolute *z*-score matrix was thresholded into an undirected binary graph (network) for further analysis using graph theoretical approaches with the nodes representing brain regions and the edges representing the links between the regions.

In the study, the network cost was used for threshold measurement [22,33]. C_G, the cost of a graph G, is defined as:

$$C_G = K/(N\,(N-1)/2), \tag{1}$$

where N and K are the total number of nodes and edges in the graph, respectively, and $N(N-1)/2$ is the number of all possible edges of G. C_G quantifies how expensive it is to build the network. Different cost thresholds may lead to distinct topologies of graphs (higher thresholds for sparser graphs and lower thresholds for denser ones). Given that there is no definitive way to select a special threshold, a wide range of threshold values, from 0 to 1 with an incremental interval of 0.01, was used to investigate the properties of the complex brain networks in this study [34,35].

Several network measures were calculated, including global efficiency (E_{glob}), local efficiency (E_{loc}), regional nodal efficiency (E_{nodal}) and the cost efficiency.

Compared with the conventional small-world parameters [clustering coefficient (C_{p}), characteristic path length (L_{p})], the network efficiencies, including E_{glob} and E_{loc}, can be applied to disconnected or nonsparse graphs [21,33]. For a graph G with N nodes, they are:

$$E_{\text{glob}}(G) = \frac{1}{N(N-1)} \sum_{j \neq i \in G} \frac{1}{L_{i,j}} \tag{2}$$

and

$$E_{\text{loc}}(G) = \frac{1}{N} \sum_{i \in G} E_{\text{glob}}(G_i), \tag{3}$$

where G_i is the subgraph composed of the nearest neighbors of node i, and $L_{i,j}$ denotes the minimal number of the edges between node i and node j. These parameters can be employed to measure the ability of information transmission of the network at global and local levels. To estimate the small-world properties, 100°-matched random networks were generated [36]. In this study, the ratios of local efficiency ($E_{\text{loc}}/E_{\text{loc-s}}$) and global efficiency ($E_{\text{glob}}/E_{\text{glob-s}}$) between the real brain functional networks and random networks were obtained to assess small-world properties of brain functional networks. Actually, there are a relatively higher local efficiency ($E_{\text{loc}}/E_{\text{loc-s}}>1$) and an approximately equivalent global efficiency ($E_{\text{glob}}/E_{\text{glob-s}} \approx 1$) in small-world networks as compared to the random networks [22]. To provide a threshold-independent assessment, the integrated local efficiency and global efficiency (i.e., the area under the curve with the cost ranging from 0 to 1) were also obtained [34,35].

The regional nodal efficiency $E_{\text{nodal}}(i)$ was also investigated, which is defined as the inverse of the minimum length of the path among node i and all other nodes [22]:

$$E_{\text{nodal}}(i) = \frac{1}{N-1} \sum_{j \in G} \frac{1}{L_{i,j}}. \tag{4}$$

The nodal efficiency represents the communication efficiency between them. The integrated nodal efficiency (i.e., the area under the curve with the cost ranging from 0 to 1) was calculated to characterize nodal properties with a threshold-independent assessment [34,35].

The cost efficiency, which represents the difference between global efficiency and cost, i.e., $E_{\text{glob}}(G) - C_G$, was also evaluated in the study and should be positive for an economical network [22].

2.5. Statistical analysis

Six groups including beforeTEAS (subjects before TEAS), afterTEAS (subjects after TEAS), beforeMTEAS (subjects before MTEAS), afterMTEAS (subjects after MTEAS), diffTEAS (afterTEAS−beforeTEAS, by subtracting the $E_{\text{loc}}/E_{\text{glob}}$ value at each cost or integrated nodal efficiency of each brain region of afterTEAS from that of beforeTEAS) and diffMTEAS (afterMTEAS−beforeMTEAS, by subtracting the $E_{\text{loc}}/E_{\text{glob}}$ value at each cost or integrated nodal efficiency of each brain region of afterMTEAS from that of beforeMTEAS) were then analyzed. The differences in the integrated global metrics (E_{glob} and E_{loc}), global metrics at each cost value and integrated nodal efficiency (E_{nodal}) of each region between groups were compared using a two-tailed paired *t* test.

3. Results

3.1. General results of experimental performance

All 18 subjects in this study completed the two experiments (TEAS and MTEAS), and all reported the feeling of “deqi” but no sharp pain during the stimulation. The frequency of “deqi” feelings, including soreness, numbness, fullness, heaviness and dull pain, was not significantly different between TEAS and MTEAS (Fig. 2, χ^2, $P>.05$). TEAS did not result in more significant sensation intensities than MTEAS (Fig. 2, two-way repeated analysis of variance, $P>.05$). The mean intensities of all sensations for the two groups showed no significant difference (Fig. 2, two-sample two-tailed *t* test, $P>.05$).

3.2. Small-world topology of brain functional networks altered by TEAS/MTEAS

3.2.1. Integrated global metrics (0<cost<1)

Compared to beforeTEAS, afterTEAS demonstrated decreased integrated local efficiency ($P=6.8731\times10^{-4}$) with no statistically significant change in the integrated global efficiency. There is no significant difference in integrated local efficiency or integrated global efficiency between afterMTEAS and beforeMTEAS or between diffTEAS and diffMTEAS (Table 1).

3.2.2. Global metrics at each cost value

Over the whole range of cost (0–1, including 101 cost values), there is no significant difference (false discovery rate [FDR] corrected $P<.05$) in E_{loc} or E_{glob} between afterMTEAS and beforeMTEAS (Fig. 3).

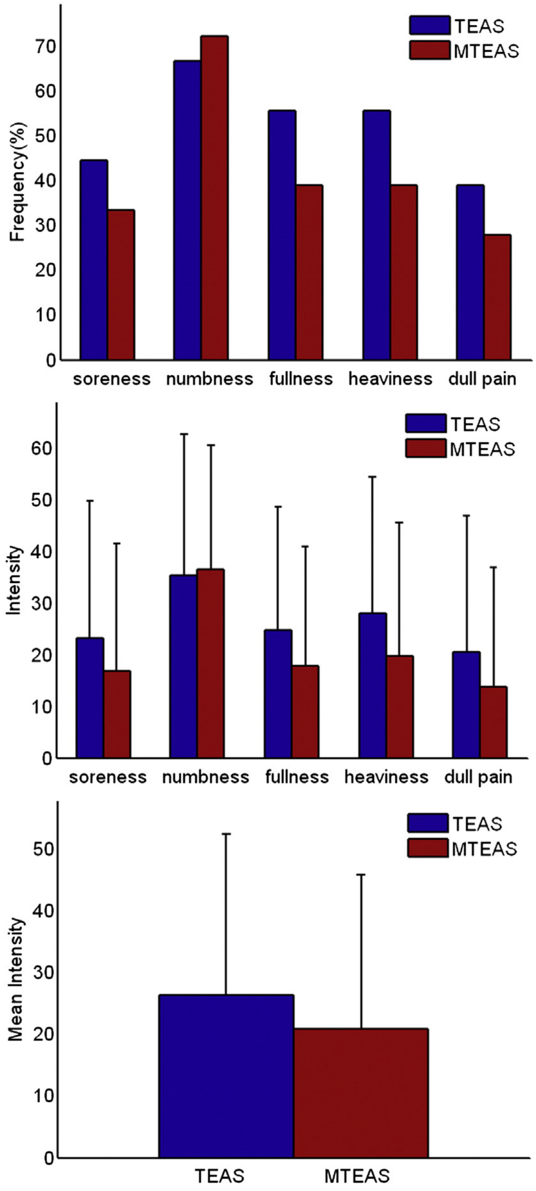

Fig. 2. The frequency (A), the intensity (B, mean±S.E.M.) and the mean intensity (C, mean±S.E.M.) of reported "deqi" sensations for the TEAS and MTEAS.

With a wide range of cost thresholds, the brain networks of afterTEAS demonstrated lower local efficiencies than those of beforeTEAS. Statistical analysis further revealed that there was a significant difference (FDR corrected $P<.05$) in local efficiencies ($0.23<\text{cost}<0.56$, black asterisks in Fig. 3), whereas there was no significant difference in global efficiencies between the two groups. Furthermore, the most significant difference occurred at the cost of 0.33 for local efficiency ($P=.0013$).

Table 1
The integrated local efficiency and global efficiency of beforeMTEAS, afterMTEAS, beforeTEAS, afterTEAS, diffMTEAS and diffTEAS ($0<\text{cost}<1$).

Integrated local efficiency	beforeMTEAS	afterMTEAS	*P* value
	0.7738	0.7717	>.05
	beforeTEAS	afterTEAS	*P* value
	0.7737	0.7684	6.8731e-004
	diffMTEAS	diffTEAS	*P* value
	−0.0021	−0.0053	>.05
Integrated global efficiency	beforeMTEAS	afterMTEAS	*P* value
	0.7049	0.7059	>.05
	beforeTEAS	afterTEAS	*P* value
	0.7053	0.7072	>.05
	diffMTEAS	diffTEAS	*P* value
	0.0011	0.0019	>.05

For the comparison between diffTEAS and diffMTEAS, only the cost values showing significant difference between afterMTEAS and beforeMTEAS or between afterTEAS and beforeTEAS (i.e., $0.23<\text{cost}<0.56$) were examined. The brain networks of the diffTEAS demonstrated a significant decrease in local efficiencies, but no significant change in global efficiencies, as compared with diffMTEAS in the chosen range of cost thresholds. There was a significant difference ($P<.05$) in local efficiencies ($0.32<\text{cost}<0.35$, black asterisks in Fig. 3). The most significant difference ($P=.0251$) was found at the cost of 0.35. In this case, the mean values of local efficiency and global efficiency for diffMTEAS were −0.0024 and 0.0010, respectively, and those for diffTEAS were −0.0128 and 0.0007, respectively. For the integrated global metrics ($0.23<\text{cost}<0.56$), lower integrated local efficiency (mean values of diffMTEAS and diffTEAS were −0.0007 and −0.0032, $P=.046$) but no significantly different integrated global efficiency (mean values of diffMTEAS and diffTEAS were 2.69×10^{-4} and 3.06×10^{-4}, $P>.05$) were demonstrated for diffTEAS compared to diffMTEAS.

3.3. Altered nodal efficiency by TEAS/MTEAS

To further examine the influence on regional nodal characteristics of the brain networks, group comparisons of integrated nodal efficiency (two-tailed paired *t* test, FDR corrected $P<.05$) were performed.

Compared to the case of beforeMTEAS, the afterMTEAS case demonstrated a significant decrease of nodal efficiency in the right middle frontal gyrus and supramarginal gyrus, while showing an increase in the left rolandic operculum, Heschl gyrus and superior temporal gyrus (Table 2).

In the comparison of afterTEAS versus beforeTEAS (Table 3), significant decrease of nodal efficiency was found in the right middle orbitofrontal cortex (OFC), rectus gyrus, inferior temporal gyrus and left anterior cingulate gyrus, while increased nodal efficiency was seen in the left hippocampus, parahippocampal gyrus, superior temporal gyrus and superior temporal pole. These results suggested that the nodal efficiency of brain functional networks was profoundly affected by both TEAS and MTEAS.

To remove the psychological effects and the influence of the baseline (the delta between beforeTEAS and beforeMTEAS), the comparison between diffTEAS and diffMTEAS was performed to examine the central effects of long-duration TEAS by comparing only the nodes with significant difference between afterMTEAS and beforeMTEAS or between afterTEAS and beforeTEAS (those nodes in Tables 2 or 3). It was observed that diffTEAS resulted in significant increases of nodal efficiency in the right middle frontal gyrus, supramarginal gyrus and left hippocampus, but decreases in right rectus gyrus, middle OFC and left anterior cingulate gyrus, than diffMTEAS (Table 4, two-tailed paired *t* test, FDR corrected $P<.05$ was significant).

3.4. The cost efficiency of brain functional networks

As shown in Fig. 4, the cost efficiencies of brain networks with beforeTEAS, afterTEAS, beforeMTEAS and afterMTEAS were all greater than zero over the whole range of cost threshold, indicating economical properties in the brain networks of these groups [22]. The networks of these four conditions showed also relatively higher local efficiencies and nearly equivalent global efficiencies as compared to the random networks [22].

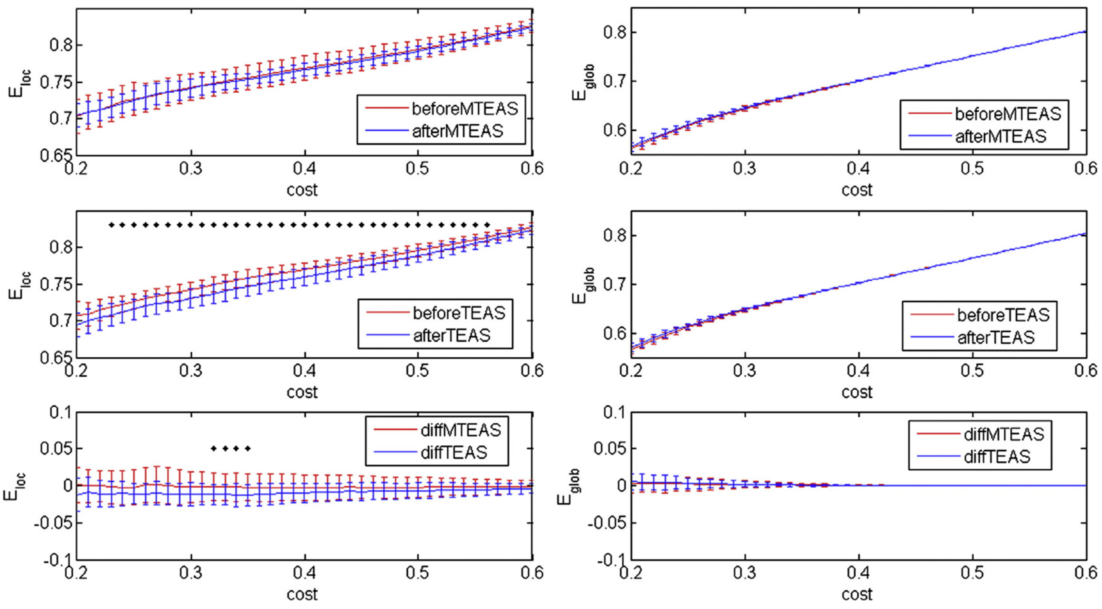

Fig. 3. The E_{loc} and E_{glob} for the beforeTEAS, afterTEAS, beforeMTEAS, afterMTEAS, diffTEAS and diffMTEAS brain networks as a function of the cost, with the cost values ranging from 0.2 to 0.6 to reveal the results more clearly. Error bars correspond to standard error of the mean. Black asterisks indicate where the difference between the two groups was significant (paired two-tailed t test, FDR corrected, $P<.05$).

4. Discussion

This study investigated the effects of long-duration TEAS on the small-world properties of brain functional networks. The alteration of the functional networks by TEAS was seen as lower local efficiency, while no significant change was induced by MTEAS. Moreover, the reduction of local efficiency induced by TEAS was more than that by MTEAS. Our study also revealed that the nodal efficiencies were profoundly affected in several regions, regardless of stimulation types. All these results indicated that small-world properties of brain functional networks were altered by long-duration TEAS.

4.1. Efficient small-world brain network

The human brain has an economical and small-world architecture with densely local connections and few long connections as a large, dynamic functional network [22,37]. Functional segregation and integration are two major organizational properties of the human brain. That means a suitable balance between local specialization and global integration of brain functional activity is required for an optimal brain [38]. In this study, it was demonstrated that the resting brain functional networks of the healthy subjects before/after TEAS/MTEAS presented salient economical small-world properties (Fig 4), which were consistent with the findings from previous brain network studies [20,39].

Table 2
The regions whose integrated nodal efficiency showed significant difference (paired two-tailed t test, FDR corrected, $P<.05$) between afterMTEAS and beforeMTEAS.

Region	Hemisphere	*P* value	Nodal efficiency of before MTEAS	Nodal efficiency of after MTEAS
Middle frontal gyrus	Right	<1e-4	0.7215	0.6813
Rolandic operculum	Left	.0026	0.7016	0.7253
Supramarginal gyrus	right	<1e-4	0.7238	0.6899
Heschl gyrus	left	.0012	0.6835	0.7108
Superior temporal gyrus	left	.0023	0.7037	0.7295

4.2. Altered small-world topology of brain functional networks by TEAS/MTEAS

In this study, a significant decrease of local efficiency (also integrated local efficiency) together with no significant difference of global efficiency (also integrated global efficiency) was found in the brain networks after TEAS, while no significant difference was observed after MTEAS. Global efficiency is predominantly associated with long-range connections to ensure effective interactions or rapid transfer of information across remote cortical regions that are involved in many cognitive processes. Local efficiency is mainly combined to short-range connections among neighboring regions to mediate modularized information processing or fault tolerance of a network [33]. The reduction of local efficiency might be related to the decreased mean global CBF after TEAS (the mean CBF of beforeTEAS and afterTEAS was 68.3383 and 66.2605 ml/100 g/min in this study, two-tailed paired t test, $P=.0468$) [2]. The results here indicate that long-duration TEAS had more influence on the short-range connections (mainly related to local efficiency) than the long-range connections (mainly related to global efficiency).

To remove the baseline and possible psychological impact, we compared the local and global efficiency between diffTEAS and

Table 3
The regions whose integrated nodal efficiency showed significant difference (paired two-tailed t test, FDR corrected, $P<.05$) between afterTEAS and beforeTEAS.

Region	Hemisphere	*P* value	Nodal efficiency of before TEAS	Nodal efficiency of after TEAS
Middle OFC	right	.0028	0.7218	0.6977
Rectus gyrus	right	.0009	0.7211	0.6844
Anterior cingulate gyrus	left	.0041	0.7314	0.7148
Hippocampus	left	.0008	0.7056	0.7334
Parahippocampal gyrus	left	.0031	0.7169	0.7435
Superior temporal gyrus	left	.0022	0.711	0.7355
Superior temporal pole	left	.0024	0.7144	0.7356
Inferior temporal gyrus	right	.0025	0.698	0.6693

Table 4
The nodes whose integrated efficiency revealed significant difference (paired two-tailed *t* test, FDR corrected, $P<.05$) between diffTEAS and diffMTEAS.

Region	Hemisphere	P value	Nodal efficiency of diffMTEAS	Nodal efficiency of diffTEAS
Middle frontal gyrus	Right	.0249	−0.0402	−0.0148
Middle OFC	Right	.0029	0.0085	−0.0241
Rectus gyrus	Right	.0083	0.0135	−0.0366
Anterior cingulate gyrus	Left	.0066	0.0122	−0.0166
Hippocampus	Left	.0158	0.0028	0.0277
Supramarginal gyrus	Right	.018	−0.0339	−0.0093

diffMTEAS. The comparison showed that diffTEAS had lower E_{loc} but no significant change of E_{glob}, compared to diffMTEAS (although no significantly changed integrated local efficiency with the cost value ranging from 0 to 1 was found between these two groups, the mean value of diffTEAS was still lower than that of diffMTEAS; Table 1). E_{glob} and E_{loc} measure the capability of the network with regard to information transmission at the global and local levels, respectively [33]. With this, we conclude that acupuncture may have more influence on information transmission at the local level than that at the global level.

4.3. Altered nodal efficiency of brain functional networks by TEAS/MTEAS

The nodal efficiency measures the extent of connectivity of a node to all other nodes, likely indicating the importance of a nodal region in the whole brain network [22]. A significant decrease of nodal efficiency after MTEAS was found in the middle frontal gyrus (part of the frontal cortex). Since the frontal cortex is related to many higher cognitive functions and has links to the limbic system, it may have an important role in modulating affection and pain processing [40]. Also, the significantly changed nodal efficiency found in other regions likely indicates that MTEAS did induce brain activity as a control (Table 2).

It was also found that the nodal efficiencies in several brain regions were altered by TEAS (Table 3), including the middle OFC, anterior cingulate gyrus, hippocampus and parahippocampal gyrus. The anterior cingulate gyrus, connecting with the amygdala and periaqueductal gray, plays a complex pivotal role in the affective–motivational component of pain [41,42] and was shown to be deactivated in previous acupuncture studies [6,43–45]. The OFC is a paralimbic region receiving inputs from the areas of different sensory modalities and has extensive connections with anterior cingulate cortex, brainstem, amygdala and hippocampal gyrus [46]. Previous studies indicated that the OFC was involved in sensory integration, decision making, expectation and reward-related behaviors [47,48]. Previous positron emission tomographic studies indicated that the OFC was involved in driving pain modulation cognitively with increasing regional CBF [49]. The OFC also seems to be important for drug-associated cues to elicit cocaine seeking according to strong activation of the OFC by drug-associated cues [50]. The parahippocampal/hippocampal gyrus, which is a part of the limbic system, links affective states with memory processing and is believed to process the affective and cognitive signals of pain [51]. The altered nodal efficiencies in these regions indicate that the limbic system was modulated by long-duration TEAS, which was in accordance with previous studies on acupuncture [6,7,43–45].

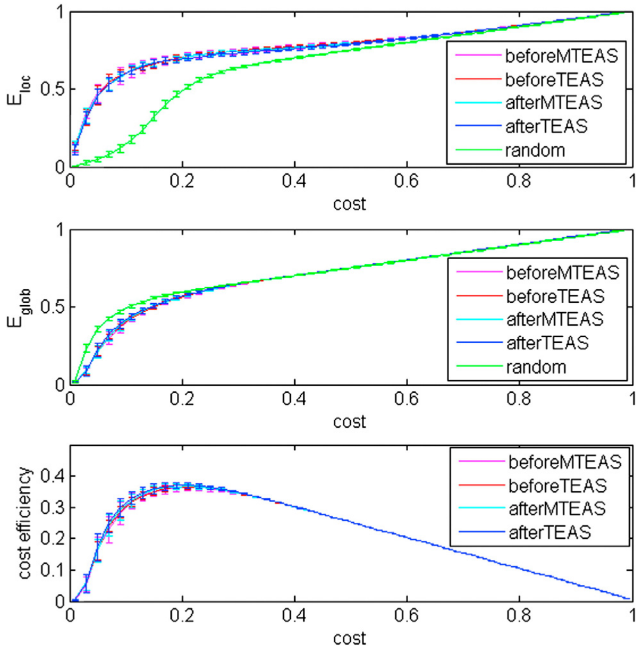

Fig. 4. The cost efficiency for the beforeTEAS, afterTEAS, before MTEAS and afterMTEAS brain networks, and the E_{loc} and E_{glob} for the above groups and random network as a function of the cost. Error bars correspond to standard error of the mean.

To examine the central effects of long-duration TEAS, the comparison of nodal efficiency between diffTEAS and diffMTEAS was obtained (Table 4). The regions whose nodal efficiencies were significantly changed included frontal gyrus, OFC, anterior cingulate gyrus and hippocampus gyrus, which was in accordance with the modulation of the limbic–paralimbic–neocortical network by acupuncture [44]. The decreased nodal efficiencies in OFC and anterior cingulate gyrus were compatible with the deactivation in these two regions by acupuncture [6,43–45], while the increased nodal efficiencies in frontal gyrus and hippocampus gyrus (deactivated by acupuncture [6,43–45]) may reflect greater effort in modulating affect and pain processing with long-duration TEAS.

4.4. Limitations

There are some limitations in the present study. First, the slice thickness was 8 mm (with a gap of 2 mm) in the MR scanning, causing several brain regions, such as the Heschl gyrus, to be comprised of only several voxels (mean 8.7 voxels included). Also, the large slice thickness resulted in signal loss in some regions, such as the rectus gyrus and the middle OFC (the mean intensities of these two regions were about one third and two thirds of the mean intensity of the whole brain). The conclusions made in these regions may need to be interpreted cautiously, and further study with thinner slices is needed to address this concern. Second, other acupuncture points are needed for long-duration TEAS/MTEAS to investigate the specificity of the acupuncture points. Third, healthy subjects with quantifiable noxious stimulus or patients with acupuncture treatable diseases need to be included to explore the mechanisms of acupuncture treatment. Fourth, the studies using MTEAS as a control for acupuncture [2,3] are still limited. Further research is needed to strengthen the physiological effect of MTEAS on the brain function. Finally, the regional network changes after TEAS may not be specific to TEAS as functional activation evoked in other tasks can have similar effects on the same brain network. More studies on TEAS are needed to consolidate these findings in this study.

5. Conclusion

In summary, this is the first study, to our knowledge, that revealed the small-world properties of brain functional networks altered by long-duration TEAS. Decreased local efficiency of the whole-brain functional networks and changed nodal efficiencies in several paralimbic/limbic regions were found for TEAS, while only regional nodal properties in frontal gyrus and other regions were altered by MTEAS. To remove the baseline and possible psychological influence, comparison was obtained between diffTEAS and diffMTEAS. It was demonstrated that long-duration TEAS resulted in decreased local efficiency of the network, as well as changed nodal efficiency in the frontal gyrus, OFC, anterior cingulate gyrus and hippocampal gyrus. These results indicate that long-duration TEAS modulates the short-range connections in brain functional networks and the limbic system.

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