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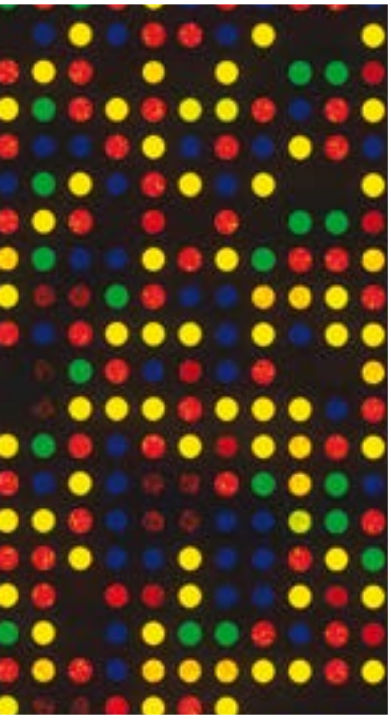
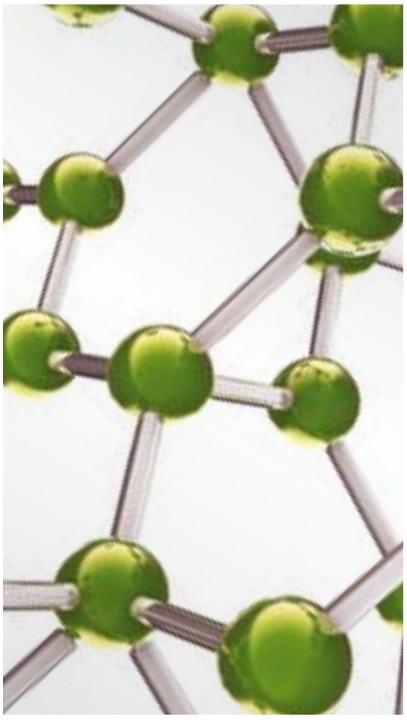
Auricular Acupuncture

Guest Editors: Gerhard Litscher and Pei-Jing Rong



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Editorial Board

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Editorial

Auricular Acupuncture

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This special issue includes six interesting manuscripts. Auricular acupuncture is a method which has been successfully used in various fields of medicine. Evidence-based results of this method are of special importance.

This special issue highlights the historical background, the development, and anatomical and neurological aspects of auricular acupuncture and related methods. In detail, the accepted manuscripts deal with the following interesting aspects.

D. H. Iunes et al. investigated the role of auriculotherapy with mustard seeds in the treatment of temporomandibular disorders (TMDs), anxiety, and electromyographic (EMG) activity in university students. The authors used the State Trait Anxiety Inventory (STAI), Research Diagnostic Criteria (RDC) for TMDs (RDC/TMDs), and electromyography in this study of 44 college students with high levels of anxiety and TMDs. The subjects were divided into two groups: an auriculotherapy (AA) group ($n = 31$) and an AA sham group ($n = 13$). The mustard seeds were applied to the shenmen, rim, sympathetic, brain stem, and temporomandibular joint (TMJ) points in the AA group and to sham points in the external ear and wrist in the AA sham group. The treatment protocol consisted of 10 sessions (two treatments per week). The results showed that anxiety ($p < 0.01$) was significantly reduced in the AA group. This group also showed a decrease in tender points in the mandibular posterior region ($p = 0.04$) and in the right side of the submandibular region ($p = 0.02$). Complaints of bilateral pain were reduced in the temporal tendon ($p \leq 0.01$) and in the left side of the TMJ ($p < 0.01$). In addition, electromyographic (EMG) activity was reduced during temporal muscle contraction ($p = 0.03$). The authors therefore concluded that auriculotherapy was effective in the treatment of students with anxiety and TMDs.

A randomized controlled trial on the effect of auricular acupressure on uremic pruritus in patients receiving hemodialysis treatment was described by C. Yan et al. Uremic pruritus (UP) is a common symptom in patients undergoing maintenance hemodialysis for end-stage renal disease (ESRD). Many nonpharmacological treatments, including acupressure, are currently used to relieve discomfort due to pruritus. The trial was designed to determine the clinical efficacy of auricular acupressure therapy on pruritus in hemodialysis patients and to explore possible underlying mechanisms. Patients receiving maintenance hemodialysis were recruited and assigned to intervention ($n = 32$) and control ($n = 30$) groups. The intervention group underwent auricular acupressure treatment three times a week for six weeks. The patients were asked to press their acupoints 5–8 times daily, with one mandatory press before going to sleep every night. Points on one side of the ear were chosen each time, with alternating bilateral treatment; the tape was replaced every other day and removed every Sunday as a break day. Pruritus scores were assessed using VAS scores, and enzyme-linked immunosorbent assays were used to measure levels of other possible contributory biochemical factors, including calcium, phosphorus, parathyroid hormone (PTH), histamine, substance P, protease activated receptor-2 (PAR-2), and tryptase. Auricular acupressure was not applied to patients in the control group; however, tape without vaccaria seeds was applied to the same six auricular acupoints as the intervention group, and patients were told that the tape contained traditional Chinese medicine that could reduce pruritus. There was a significant difference in mean VAS scores between the postintervention and control groups during follow-up (3.844 ± 1.687 versus 5.567 ± 2.285, $p < 0.0001$).

Compared to the control group, serum histamine levels in the postintervention group at the six-week follow-up had decreased significantly ($p = 0.0290$). However, there were no significant differences in serum levels of calcium, phosphorus, PTH, substance P, PAR-2, or tryptase. The findings suggest that auricular acupressure may be a useful treatment in the multidisciplinary management of UP in ESRD patients.

Y. Jiao et al. compared body, auricular, and abdominal acupuncture treatments for insomnia in order to identify the optimum treatment protocol. A three-factor (3 needling protocols) and three-level experimental scheme was designed based on orthogonal method. 54 patients suffering from insomnia, differentiated as internal harassment of phlegm-heat syndrome, were given two courses of acupuncture treatment, each consisting of 20 times of acupuncture. The therapeutic effects were evaluated by comparing the Pittsburgh sleep quality index (PSQI), Hamilton Depression Scale (HAMD) scores, and Hamilton Anxiety Scale (HAMA) scores of patients before treatment, after one course of treatment, after two courses of treatment, and one month after treatment. Body, auricular, and abdominal acupuncture treatments all alleviated symptoms of insomnia, depression, and anxiety, but body and auricular acupuncture had stronger therapeutic effects. The researchers concluded that body acupuncture at basic points should be given priority in protocol selection for insomnia. The second-best choice is auricular acupuncture with basic points combined with points based on traditional Chinese medicine (TCM) theories. Abdominal needling with very quick effects can be an alternative protocol with basic points combined with syndrome differentiation points.

In a review article, P.-W. Hou et al. examined the history, mechanism, and clinical application of auricular therapy in traditional Chinese medicine. Auricular therapy includes acupuncture, electroacupuncture, acupressure, lasering, cauterization, moxibustion, and bloodletting in the auricle. For 2500 years, people have employed auricular therapy for treating diseases, but the methods have been limited to bloodletting and cauterization. Only after 1957 did the international scientific community become aware that the map of the ear resembles an inverted fetus; its introduction has led to auricular acupuncture (AA) becoming a more systemic approach, and following the identification and standardization of more precise points, AA has been employed in clinical applications. The mechanisms of AA are considered to have a close relationship with the autonomic nervous system, the neuroendocrine system, neuroimmunological factors, neuroinflammation, and the neural reflex. The authors found that auricular therapy has been applied, for example, for pain relief, for the treatment of epilepsy, anxiety, and obesity, and for improving sleep quality. In conclusion, however, the mechanisms and evidence for auricular therapy still warrant further study.

An analysis of advantages and disadvantages of the location methods of international auricular acupuncture points (AAPs) was carried out by P.-J. Rong et al. The international standardization of AAPs is an important basis for auricular therapy or auricular diagnosis and treatment. The study on the international standardization of AAPs has gone through a long process, in which the location method is one of the key research projects. There are different points of view in the field of AAPs among experts from different countries or regions. By only analyzing the nine representative location methods, this article tried to offer a proper location method to locate AAPs. Through analysis of the pros and cons of each location method, the location method applied in the WFAS international standard of AAPs is thoroughly considered as an appropriate method by the authors. Yet they also stated that it is important to keep the right direction during developing an ISO international standard of AAPs and to improve the research quality of international standardization for AAPs.

Y. Bian et al. investigated functional connectivity modulation by acupuncture in patients with Bell's palsy (BP), an acute unilateral facial paralysis which is frequently treated with acupuncture in many countries. However, the mechanism of treatment is not clear so far. In order to explore the potential mechanism, 22 healthy volunteers and 17 BP patients with different clinical duration were recruited. The resting-state functional magnetic resonance imaging scans were conducted before and after acupuncture at LI4 (Hegu), respectively. By comparing BP-induced functional connectivity (FC) changes with acupuncture-induced FC changes in the patients, the abnormal increased FC that could be reduced by acupuncture was selected. The FC strength of the selected FC at various stages was analyzed subsequently. The results show that FC modulation of acupuncture is specific and consistent with the tendency of recovery. Therefore, the researchers propose that FC modulation by acupuncture may be beneficial to recovery from the disease.

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Research Article

Functional Connectivity Modulation by Acupuncture in Patients with Bell's Palsy

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Bell's palsy (BP), an acute unilateral facial paralysis, is frequently treated with acupuncture in many countries. However, the mechanism of treatment is not clear so far. In order to explore the potential mechanism, 22 healthy volunteers and 17 BP patients with different clinical duration were recruited. The resting-state functional magnetic resonance imaging scans were conducted before and after acupuncture at LI4 (Hegu), respectively. By comparing BP-induced functional connectivity (FC) changes with acupuncture-induced FC changes in the patients, the abnormal increased FC that could be reduced by acupuncture was selected. The FC strength of the selected FC at various stages was analyzed subsequently. Our results show that FC modulation of acupuncture is specific and consistent with the tendency of recovery. Therefore, we propose that FC modulation by acupuncture may be beneficial to recovery from the disease.

1. Introduction

Bell's palsy (BP), an acute unilateral facial paralysis, is a frequent facial movement dysfunction caused by the impaired facial nerve that controls movement of facial muscles [1–3]. Acupuncture, a traditional Chinese medicine [4, 5], has been considered to have a beneficial effect on the acute state of BP in the last few years [6]. Although acupuncture is used in treatment of BP in East Asia, the mechanism has not been completely elucidated so far [7].

Functional magnetic resonance imaging (fMRI), a non-invasive brain imaging technique, is widely used in the assessment of the effect of acupuncture [8, 9]. There are many fMRI investigations on how acupuncture affects healthy people, suggesting that acupuncture can adjust brain functional network [10–13]. In the meantime, more and more neuroimaging studies showed that acupuncture had the same effect on the brain functional network in patients with certain diseases [14]. For instance, acupuncture enhanced the hippocampal connectivity in patients with Alzheimer [15, 16]. Acupuncture also modulated endogenous pain regulation network, valued by analgesic effects in low-back and leg pain patients [17].

Our previous study has shown that functional connectivity (FC) in primary somatosensory area is modulated by acupuncture in BP patients [18]. Concomitantly, several studies on BP used fMRI to explore neuroplasticity, demonstrating that the altered FC occurred in the cortical facial motor network at early stage of the disease and gradually recovered during subsequent cortical reorganization [19–23]. However, it is unclear whether acupuncture could have any effect on the aforementioned altered FC in patients with BP, and whether such modulation would be beneficial to recovery. If these problems can be solved, it will be helpful to reveal the underlying mechanism of acupuncture treatment.

To explore the questions above, the regions of interest (ROIs) were firstly extracted from the activation mapping of BP patients undertaking acupuncture and the facial motor related regions. The intergroup analysis was conducted between healthy control and patients before acupuncture to extract the altered FC at the onset time. The intergroup analysis of post- and preacupuncture BP patients was then conducted to find out FC changes modulated by acupuncture. Thereafter, the overlapping regions in the two mappings were generated. FC intensity at various stages was also calculated to compare the tendency of recovery with modulation by acupuncture.

2. Materials and Methods

2.1. Subjects. This study was approved by the institutional review board of the First Affiliated Hospital of Anhui University of Chinese Medicine, and signed written informed consent was collected before the study. A total of 17 BP patients and 22 healthy volunteers were recruited, who were right handed and confirmed having no history of stroke, severe hypertension, drug abuse, psychiatric diseases, systematic diseases, or other serious diseases that might affect the study results. Both the healthy volunteers and the BP patients were acupuncture naïve before participating in the experiment. In the healthy group, all volunteers (13 males and 9 females, mean age 25.3 ± 3.4 years) were either students or staffs from the First Affiliated Hospital of Anhui University of Chinese Medicine. All BP patients (11 males and 6 females, mean age 33.5 ± 12.0 years) had right unilateral facial paresis and received acupuncture treatment three times a week till recovery. On the basis of House-Brackmann facial paresis (HBS scoring system of facial movement: 1 = normal facial movement, 6 = no movement [24]) and onset duration, all these patients were ranked as HBS ≥ III at the onset time of the disease and HBS = I when they got recovered. While healthy individuals undertook MRI examination only once, BP patients undertook the scanning at the onset time and after the recovery (due to loss of contact, one female did not receive scanning after the recovery), with the data used as the patient group and recovered group, respectively.

2.2. Data Acquisition of Acupuncture fMRI. The data acquisition was performed on a 1.5 T MRI whole body scanner (Symphony, Siemens Healthcare, Germany) with a standard head coil at the First Affiliated Hospital of Anhui University of Chinese Medicine. The experiment took about 60 minutes and a total of eight imaging sequences were scanned: (a) pilot images; (b) T2-weighted images, which could exclude any obvious diseases of the brain; (c) T1-weighted 2D anatomical images (SE sequence with TR/TE = 500/12 ms, field of view (FOV) = 230 × 230 mm, slice thickness/interval = 3.0/0.75 mm, resolution = 192 × 144, and a total of 36 slices) that covered the whole brain and paralleled to the anterior commissure-posterior commissure line; (d) resting-state fMRI images obtained before acupuncture using an echo-planar imaging (EPI) sequence (TR/TE/FA = 3000 ms/30 ms/90°); (e) resting-state fMRI images during acupuncture acquired with the same parameters; (f) resting-state fMRI images after acupuncture acquired with the same parameters; (g) task-state fMRI images acquired using EPI sequence (TR/TE/FA = 4000 ms/50 ms/90°); (h) T1-weighted 3D anatomical images, a total of 176 slices that covered the whole brain, using a spoiled gradient echo sequence (TR/TE/FA = 2100 ms/3.93 ms/13°, FOV = 250 mm × 250 mm, slice thickness/interval = 1.0/0.5 mm, and resolution = 256 × 256). All participants were trained to relax before the scanning and close their eyes, keep silent, and avoid psychological activity during the scanning. All the lights in the scanning room were turned off to reduce visual stimulation.

2.3. Functional MRI Paradigms. A 10-minute resting-state data was first acquired before acupuncture. Then, a stainless steel acupuncture needle was inserted into Hegu on the dorsum of left hand at 1 cm skin depth. LI4 or Hegu, located on the dorsum of the hand, is an important commonly used acupuncture point. When a de-qi sensation was obtained, the resting-state data was beginning to be acquired during acupuncture. This scan also lasted 10 minutes, and the needle was retained and rotated for 10 seconds every 2 minutes. Finally, the needle was pulled out and the third resting-state data was then acquired in the next 10 minutes.

Task-state data lasted 10 minutes and 40 seconds during acupuncture. There were 160 volumes (with TR 4 seconds) in this acquisition. As with the resting-state data acquisition, the needle was retained in the skin until de-qi before the acquisition began. In this paradigm, the needle retaining and twirling were conducted alternately, and the needle was rotated bidirectionally with an even motion at the rate of 1 Hz. The entire fMRI acquisition scheme was as follows: 32 volumes of retaining, 32 volumes of twirling, 48 volumes of retaining, 32 volumes of twirling, and finally 16 volumes of retaining (see Figure S2 in Supplementary Material available online at http://dx.doi.org/10.1155/2016/5928758).

2.4. Imaging Preprocessing. The imaging preprocessing as well as data analysis was performed using analysis of functional neuroimages (AFNI) software (http://afni.nimh.nih.gov/, Medical College of Wisconsin, Milwaukee, Wisconsin, USA). Considering the magnetic equilibrium, the first four images of each functional session were discarded. Thereafter, all the functional and anatomical images were preprocessed (reconstructed, corrected for slice acquisition time, corrected for motion, and skull stripped and smoothed with a Gaussian kernel of 6-mm full-width at half maximum). The head movements of all the data were less than 2 mm or 2°. All fMRI data was then filtered (0.007–0.1 Hz) to remove low-frequency drift and high-frequency noises. Then, the functional images were coregistered to the anatomical images and normalized to the MNI152 standard brain. All the normalized images were resliced by $3.0 \times 3.0 \times 3.0\ mm^3$ voxels. After preprocessing, the individual transformed 4D data was used for further analysis.

2.5. Extraction of the Region of Interest. The task-state fMRI data of the patient group was analyzed to produce the statistical activation map. The results of group analysis were

Table 1: All the overlapped regions were selected from two intergroup comparison functional connectivity results.

ROI	Common regions (BA)	Side	MNI coordinates			Voxel	Number
			X (mm)	Y (mm)	Z (mm)		
L MFG	Supplementary motor area	R	4	8	52	66	A1
	Supplementary motor area	L	−1	−23	53	66	A2
	Superior frontal gyrus (10)	R	32	50	31	48	A3
	Superior frontal gyrus	R	17	35	45	27	A4
L MI	Middle frontal gyrus (9)	L	−48	14	32	78	B1
	Precuneus	R	6	−67	53	76	B2
	Middle frontal gyrus	L	−35	19	26	32	B3
	Precuneus	L	−1	−62	39	29	B4
	Middle frontal gyrus	L	−37	9	52	20	B5
R CMA	Supplementary motor area	R	3	−12	54	123	C1
	Postcentral gyrus, SI	R	3	−49	67	82	C2

Note: ROI, region of interest; BA, Brodmann area; MFG, middle frontal gyrus; CMA, cingulate motor area; MI, primary motor cortex; SI, primary somatosensory cortex; R, right; L, left. The overlapped regions of less than 15 voxels were ignored. Coordinate point is the geometrical center of the overlapped region.

corrected with Monte Carlo method, in which the threshold of statistical significance was set to $p = 0.01$, $\alpha = 0.05$, and a minimum cluster size of 38 voxels (3dClustSim, AFNI). On the basis of the map, we extracted all the "peaks" of the activation areas as seed regions (Table S1).

In order to verify whether acupuncture could regulate the motor network in BP patients, we selected the motor areas activated by BP patient's mouth movement task. We selected 10 seed regions in the activation map of the nonaffected side motor task by Klingner's test [22] (Table S2). All the seed regions were extracted manually, with a diameter of 4 mm, containing 10 voxels (voxel size $3.0 \times 3.0 \times 3.0\ \text{mm}^3$).

2.6. Functional Connectivity Analyses. FC of each seed region was computed, respectively. First, the temporal signal series of white matter (WM), cerebrospinal fluid (CSF), and seed regions were extracted. Then, a linear regression analysis was conducted to remove the following confounding sources: (a) six motion parameters, (b) linear drift, (c) white matter signal, and (d) CSF signal. Thereafter, the individual statistical maps were obtained based on the general linear model for further group analysis.

2.7. Functional Connectivity Strength Analyses. We extracted the regions with abnormal FC where acupuncture modulated FC changes could also be observed in BP patients. In order to calculate the selected FC strength for all groups, we first obtained the mean time series of each of the selected regions (Figure S1, Table 1) by averaging the fMRI time series over all voxels in the region. Then, the Pearson correlation coefficients were computed between all pairs of the selected regions for each subject in all groups. In the end, Fisher's r-to-z transformation was applied to correlation coefficients in order to increase normality of the distribution.

2.8. Group Analysis. All the intergroup comparisons were performed through paired t-test between post- and preacupuncture statistical maps. All the intergroup comparisons of different groups before acupuncture were performed through two-sample t-tests. Monte Carlo correction was done to control the false discovery rate. The results of intergroup analysis were corrected with $p = 0.05$, $\alpha = 0.05$, and a minimum cluster size of 155 voxels (3dClustSim, AFNI). Two-sample t-tests were performed to compare the connectivity strength values in the intergroup analysis.

3. Results

Firstly, 17 ROIs were selected from acupuncture needling response (Table S1) and BP patients' motor task (Table S2), and the FC of each ROI in these cases was analyzed. Here, the seed point left middle frontal gyrus (MFG) was used as an example since all the FC analysis procedures for each ROI were the same. To investigate BP-induced changes in FC of left MFG, the preacupuncture FC of the healthy group was compared with that of the patient group. The significantly negative regions (blue areas, Figure S3A, Table S3) were found in the results that demonstrate the abnormal increased FC in the patient group. In order to explore acupuncture-induced changes in FC of left MFG in BP patients, we also compared FC between post- and preacupuncture in the patient group and found that acupuncture could reduce FC in patients with BP (Figure S3B, Table S4). We next set out to investigate whether acupuncture could reduce the abnormal increased FC in patients. The above-mentioned two intergroup results of left MFG were compared, and the overlapped areas were obtained in the bilateral supplementary motor area (SMA) and right superior frontal gyrus (SFG) of these results (Figure S3C). The overlapped regions were selected and demonstrated the abnormal increased FC that could be reduced by acupuncture in the patient group (Figure 1).

The same analysis method described above was applied to other selected seed points, respectively. Similarly, we compared those intergroup results of left primary motor cortex (MI) and determined overlapped areas in bilateral precuneus and left MFG (Figures 2 and S4). In right cingulate motor

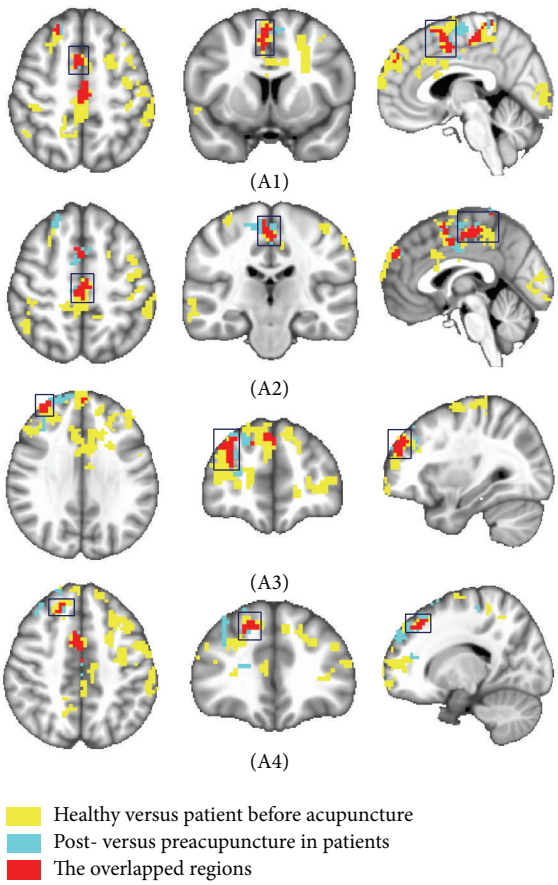

Figure 1: Demonstration of the overlapped regions which were selected from two intergroup comparison functional connectivity (FC) results of left middle frontal gyrus. The red areas represented the overlapped areas, which were detected from comparing BP-induced FC changes with acupuncture-induced FC changes in the patients. The overlapped areas were found in the bilateral supplementary motor area (A1, A2) and right superior frontal gyrus (A3, A4). The yellow areas represented the intergroup comparison FC results of areas between the healthy group and the patient group before acupuncture. The blue areas represented the intergroup comparison FC results of areas between post- and preacupuncture in the patient group. The threshold was set to $p \leq 0.05$, $\alpha \leq 0.05$, corrected using the Monte Carlo method.

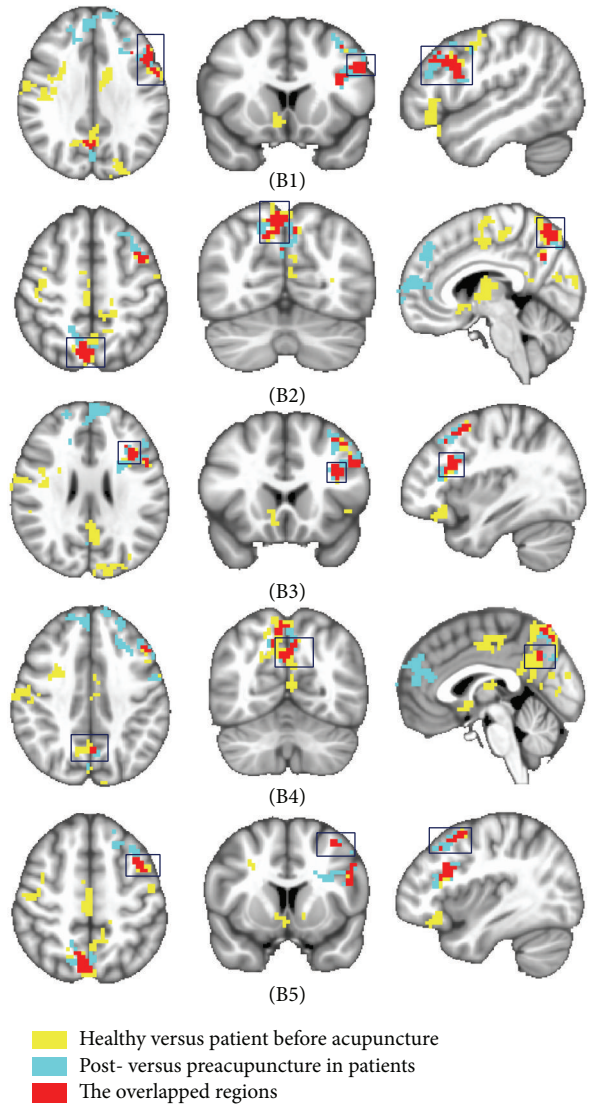

Figure 2: Demonstration of the overlapped regions which were selected from two intergroup comparison functional connectivity (FC) results of left primary motor cortex. The red areas represented the overlapped areas, which were detected from comparing BP-induced FC changes with acupuncture-induced FC changes in the patients. The overlapped areas were found in the left middle frontal gyrus (B1, B3, B5), left precuneus (B4), and right precuneus (B2). The yellow areas represented the intergroup comparison FC results of areas between the healthy group and the patient group before acupuncture. The blue areas represented the intergroup comparison FC results of areas between post- and preacupuncture in the patient group. The threshold was set to $p \leq 0.05$, $\alpha \leq 0.05$, corrected using the Monte Carlo method.

area (CMA), acupuncture could reduce abnormal FC in right SMA and primary somatosensory cortex (SI) (Figures 3 and S5). No other overlapped regions were found in comparison of these intergroup analysis results about the other remaining ROIs.

Then, the FC between ROIs (left MFG, MI, and right CMA) (Figure S1) and their overlapped regions were selected (Table 1). To investigate the changes of the selected FC when patients recovered, we computed their FC strength for all groups, respectively (Figure 4). Consistent with our previous discovery, significantly increased FC of three ROIs was observed in the patient group. After acupuncture, all the increased FC was significantly reduced, which also happened when patients recovered (Figure S6). In addition to a pair of FC between L MFG and R SFG (A4), there is no significant FC strength difference between healthy and recovered group (Figure 4).

Finally, in order to examine whether FC modulation by acupuncture was specific in the patient group, above-mentioned three seed points were chosen for further FC analysis. By comparing the FC between post- and preacupuncture

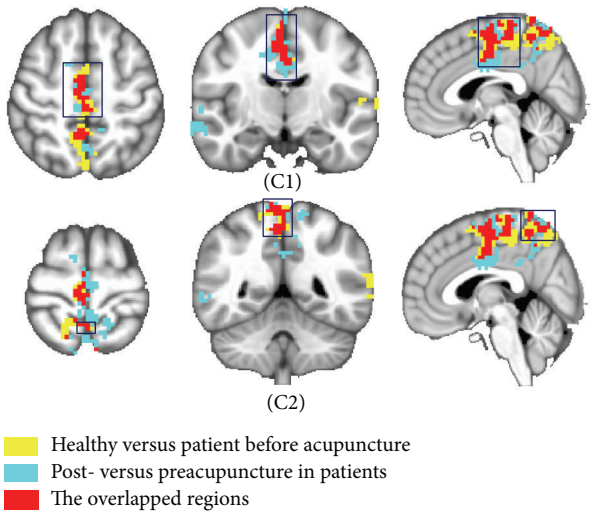

Figure 3: Demonstration of the overlapped regions which were selected from two intergroup comparison functional connectivity (FC) results of right cingulate motor area. The red areas represented the overlapped areas, which were detected from comparing BP-induced FC changes with acupuncture-induced FC changes in the patients. The overlapped areas were found in the right supplementary motor area (C1) and right primary somatosensory cortex (C2). The yellow areas represented the intergroup comparison FC results of areas between the healthy group and the patient group before acupuncture. The blue areas represented the intergroup comparison FC results of areas between post- and preacupuncture in the patient group. The threshold was set to $p \leq 0.05$, $\alpha \leq 0.05$, corrected using the Monte Carlo method.

in the healthy group, no significant changes in three ROIs were observed. By comparing the FC between post- and preacupuncture in the recovered group, no significant changes in three ROIs were observed. In the meantime, by comparing the FC between the recovered group and the healthy group in the resting-state data before acupuncture, no significant changes in three ROIs were observed.

4. Discussion

This study aimed to investigate FC modulation induced by acupuncture in patients with Bell's palsy, which might be helpful in exploring the mechanism of acupuncture treatment. With this objective, we first selected the abnormal increased FC that could be reduced by acupuncture in the patient group (Figures 1–3) and then investigated the FC strength of the selected FC changes with different stages. Most of the variation trends of the selected FC strength were roughly the same (Figure 4). The strength of FC reflected the degree of neuronal activity synchronization [25, 26] and also the strength of information transfer and collaboration between brain areas [23]. In this part, we discuss the selected ROIs firstly. Then, we focus on the regions in the selected FC and discuss the possible mechanism of the FC changes in patients during rehabilitation and acupuncture-induced changes in FC. Finally, we attempt to explain what these FC changes by acupuncture might imply in patients with BP.

4.1. Three Selected Regions of Interest. In this study, in order to examine the possible effect of acupuncture on the altered FC in patients with BP, 17 ROIs were extracted from acupuncture needling response (Table S1) and BP patients' motor task (Table S2). Many fMRI investigations about BP selected ROIs and explored the pathology in brain activation in BP patients while they were subjected to facial motor task of mouth [19–22]. Our previous study also extracted the ROIs from the acupuncture needling response to explore acupuncture-induced FC changes [18]. Thus, although these 17 seed points were from two different tasks, they were probably associated with the FC modulation by acupuncture in BP patients.

The overlapped regions were found only from three seed points (Figures 1–3). MI and CMA were selected as the ROIs from patients' mouth motor task (Figures S1B and S1C). The MI, located in the precentral gyrus, works in association with other related motor areas to plan and execute movements. There is a broadly somatotopic representation of different body parts in the primary motor cortex in an arrangement called a motor homunculus [27]. The CMA, which is buried in the cingulate sulcus and does not extend into the cingulate gyrus [28], participates in motor control by facilitating the execution of appropriate responses and/or suppressing the execution of inappropriate ones [29]. Many previous neuroimaging studies have shown that MI and CMA could be activated in the mouth movement of patients with BP [19, 20, 22]. In the meantime, the MI in this study corresponded to the somatotopic representation of the facial MI on the contralateral side of the facial palsy and was known to display the altered FC in patients with BP [23].

MFG was selected as one of the seed regions from the activation map of the acupuncture task in the patient group (Figure S1A). Other studies on acupoint-specific fMRI patterns showed that acupuncture at LI4 produced deactivation in frontal areas [30], which were consistent with our results. MFG belonged to the dorsolateral prefrontal cortex (DLPFC). The DLPFC is directly interconnected with the sensorimotor cortex and indirectly connected with limbic structures that process internal information and is critical for arbitrary associations between sensory cues, rewards, and voluntary actions [31, 32]. Other studies concerning acupuncture treatment for pain and diarrhea demonstrated that acupuncture could change the FC of DLPFC [33, 34]. Although this seed point was not extracted from the mouth movement task, it was closely linked with the traditional sensorimotor regions [35]. In the patient, the abnormal FC that could be changed by acupuncture was found from these three ROIs probably because of the important role of these ROIs in BP.

4.2. Changes in Functional Connectivity with Patients during Rehabilitation. Compared with the healthy group, the increased FC was found in the patient group (Figures S1–S3A). When the patients recovered, most of the selected FC was reduced to the levels that were not significantly different from those in the healthy group (Figure 4). In order to explore the mechanism of the changes, we first identified regions in the increased FC. In this paper, significant increased FC was found in the MI, CMA, and SMA (Table 1, Figure 4). In our study, MI and CMA were selected as the seed regions located

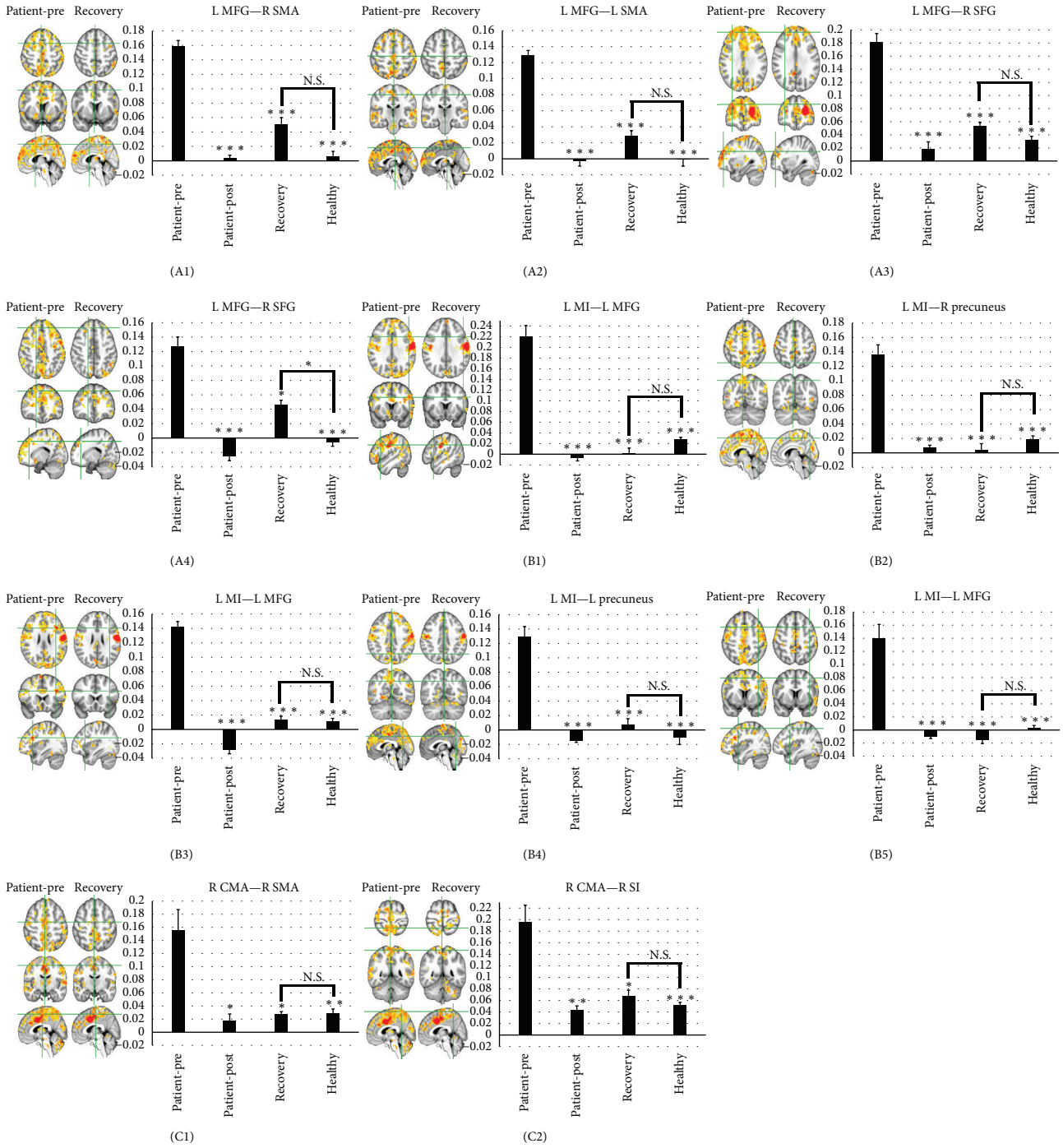

FIGURE 4: The histogram of functional connectivity strength and the resting fMRI maps of the selected ROIs and their overlapped regions for all groups. We found that the trend of functional connectivity changes induced by acupuncture was consistent with the changes induced by rehabilitation. Reduction of this functional connectivity was observed after acupuncture as well as during recovery process. The x-axis represents different groups and y-axis represents the functional connectivity strength. "Patient-pre" represents the patient group before acupuncture, "patient-post" represents the patient group after acupuncture, "recovery" represents the recovered group before acupuncture, and "healthy" represents the healthy group before acupuncture. Mean ± SEM, $^{***}p < 0.005$, $^{**}p < 0.01$, and $^{*}p < 0.05$ versus "patient-pre." NS, $p > 0.05$. ROI, region of interest; L, left; R, right; MFG, middle frontal gyrus; SMA, supplementary motor area; SFG, superior frontal gyrus; MI, primary motor cortex; CMA, cingulate motor area; SI, primary somatosensory cortex.

on facial motor areas. Previous investigations have reported that oral motor neurons received purely contralateral input from the cerebral cortex [36]. Other previous studies showed that FC of contralateral MI was altered in patients with BP [19, 20, 23]; our results supported their finding. The SMA is a part of the primate cerebral cortex that contributes to the control of movement. Many studies hypothesized that SMA had many functions including initiation of internally generated movement as opposed to stimulus driven movement [37] and coordinating temporal sequences of actions [38]. Both CMA and SMA are major contributors to early stage premovement activity and play an important role in the preparation and readiness for voluntary movement [39]. Therefore, considering that their FC had changed in patients with BP [19], such changes supported our results.

All of the above regions are components of the facial motor network [23, 40]. As is well known, the deafferentation (without afferent) is the most important characteristic of BP to account for the consequent impaired facial motor function of the affected side of the face. However, human brain is a complex integrative network of functionally linked brain regions, where multiple spatially distributed but functionally linked brain regions continuously share information with each other, together forming interconnected resting-state communities [41]. At the cortical level, a complex network of specialized motor areas supports voluntary facial movements [42], along with other areas especially the sensory areas playing an important role. Therefore, in healthy individuals, a balanced state is formed between the facial motor network and some other related regions, maintaining such synergies by ensuring that the facial muscles are working properly [18]. However, in patients with BP, impaired motor function initially leads to a disrupted connectivity within the cortical facial motor network and thus breaks the balance. The acute reduction of movement feedback leads to the cerebral cortical reorganization [19, 23], eventually accounting for the results that the FC between the motor association areas and other regions are changed in patients with BP. After the recovery from facial nerve palsy which is completed by cortical reorganization [23], the balance gets restored and may therefore be the reason for the increased FC changing back to a normal status. In the recovery group before acupuncture, only one pair of FC whose FC strength was different from the healthy group was found. We speculated that the reason might be that this pair of FC was not entirely restored. However, compared with the patient group, it was still reduced after the recovery.

4.3. Acupuncture-Induced Changes in Functional Connectivity with Patients. Compared with the preacupuncture, significant decreased FC was observed in sensorimotor related brain areas including MFG (BA9), SFG (BA10), SI, and SMA (Table 1, Figure 4). The SI is the main sensory receptive area for the sense of touch. In the neural network of facial movement, the motor command is transmitted from MI and its executive condition is fed back to SI. Previous studies of acupuncture demonstrated that the SI was activated in response to acupuncture at LI4 [43, 44]. Our previous studies have also shown that changes in FC of SI induced by acupuncture varied with onset duration of BP [18]. The other three areas were MFG (BA9), SFG (BA10), and SMA. BA9 is involved in verbal fluency [45], error detection [46], and auditory verbal attention [47]. BA10 is activated by tasks that require integration of multiple relations [48]. And it is involved in strategic processes in memory recall and various executive functions [49]. There were also many previous researches reporting that sensorimotor association areas could be affected by acupuncture [30, 34, 50, 51].

A significant decreased FC was observed in bilateral precuneus (Figures 2 and S4). The central role of this region is a wide spectrum of highly integrated tasks, including visuospatial imagery, episodic memory retrieval, and self-processing operations [52]. In Klingner et al.'s study [19], the stronger activation was observed in the precuneus during the movement of the paretic compared to those of the nonparetic side in the acute stage of BP. It demonstrated that the inability to perform the motor task led to the attempt to reactivate the image of the intended movement to support its execution; it might interpret our results in some way. In the meantime, the precuneus is known to be in the brain's default mode network (DMN), a set of areas that are spontaneously active during passive moments [53]. Recent investigations on DMN in patients demonstrated that the DMN could affect homeostasis regulation [54–56]. A lot of previous neuroimaging studies suggested that acupuncture stimulation could modulate the FC in the limbic system and DMN [34, 43, 44, 57, 58], and our results were consistent with these findings.

4.4. The Influence of Functional Connectivity Modulation Induced by Acupuncture. In patients with BP, we found the trend of FC changes induced by acupuncture was consistent with the changes induced by rehabilitation. As discussed above, impaired motor function might increase the FC between the motor association areas and other regions in patients. Thereafter, acupuncture could modulate the regions in the sensorimotor areas and the homeostatic related network to recover the increased FC. In the meantime, acupuncture-induced changes were only observed in the patient group, which demonstrated that acupuncture could specifically modulate the selected FC in patients with BP. This result was in accordance with our previous researches on effect of acupuncture on FC of ACC and SI for BP patients with different clinical duration [18, 59]. To some extent, our results supported the traditional Chinese medical theory that acupuncture could modulate homeostatic state of body [60]. In the end, importantly, all the selected FC returned to a normal state after the recovery, and all the patients only received acupuncture treatment in the course of rehabilitation. To account the sustained effect of acupuncture [51, 61], this demonstrated that FC modulation induced by acupuncture in patients with BP would possibly be beneficial to recovery from the disease.

BP is known as an acute idiopathic onset and self-limiting facial palsy [62]. Previous study suggests the recovery from facial nerve palsy is complemented by cortical reorganization [23]. The brain has an intrinsic capability to compensate for brain damage through reorganizing surviving networks [63].

There are many researches about cortical plasticity showing a functional plasticity in the brain of facial palsy patients in response to mere peripheral deafferentation [22, 64]. In fact, cortical reorganization is accompanied by changes of FC [21]. Our results showed that the abnormal FC could also be altered when BP patients recovered (Figures 4 and S6). Therefore, FC plays an important role in the rehabilitation of BP [19, 23]. To some extent, the above-mentioned conclusions could support our speculation that the regulation of acupuncture on the selected abnormal FC in BP patients was associated with rehabilitation.

In our previous studies on exploring the mechanism of acupuncture treatment for BP, we found that FC could be changed by acupuncture in BP patients [18, 59]. However, these preliminary findings cannot determine whether the effect of acupuncture on FC was associated with rehabilitation. In this paper, through a more in-depth research about FC modulation of acupuncture, we discovered that acupuncture could regulate some abnormal FC in BP patients and proved that the effort of acupuncture is consistent with the tendency of recovery.

5. Limitations and Conclusion

Although important discoveries were made by present studies, there were also limitations. First, the ROIs in this study were selected based on the activation mapping in the mouth movement task and acupuncture task sessions. Thus, only the regions where alterations were reduced by acupuncture were selected; although other ROIs and the altered FC might explain some of the problems about BP, they were ignored. Second, in this study, there was no sham acupuncture control group due to ethics restriction. Thus, the changes observed in this study may not be necessarily specific to acupuncture, which may be similarly observed in other somatic stimulations. Finally, a single acupoint (Hegu) was stimulated in the scanning process. In fact, when the patients were treated with acupuncture, multiple acupoints were stimulated at the same time. In the future, we may design the task to stimulate multiple acupoints to explore the mechanism of acupuncture for BP. In terms of these limitations, further investigations with stricter control of these relevant variables should be done to provide more convincing evidences to support our conclusion.

In summary, the present study suggests that acupuncture can specifically reduce some FC that may be increased by BP. Then, the results reflect that FC modulation induced by acupuncture in patients with BP is consistent with the tendency of recovery, which may be beneficial to recovery from the disease. Although further researches are still needed, the finding hopes to shed light on the clarification of the underlying mechanism of acupuncture on LI4 for BP.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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Research Article

Analysis of Advantages and Disadvantages of the Location Methods of International Auricular Acupuncture Points

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The international standardization of auricular acupuncture points (AAPs) is an important basis for auricular therapy or auricular diagnosis and treatment. The study on the international standardization of AAPs has gone through a long process, in which the location method is one of the key research projects. There are different points of view in the field of AAPs among experts from different countries or regions. By only analyzing the nine representative location methods, this paper tried to offer a proper location method to locate AAPs. Through analysis of the pros and cons of each location method, the location method applied in the WFAS international standard of AAPs is thoroughly considered as an appropriate method. It is important to keep the right direction during developing an International Organization for Standardization (ISO) international standard of auricular acupuncture points and to improve the research quality of international standardization for AAPs.

1. Introduction

The third regional conference of the working group of the standardization of acupuncture points was held in Seoul, South Korea, in 1987 [1]. In this conference, the China Association of Acupuncture-Moxibustion put forward a draft of international standard of auricular acupuncture points (AAPs) including ninety points. The draft was seriously discussed and the board set up three criteria of selection: (1) points which use international and common names; (2) points whose therapeutic values are well proven; (3) points whose location in the auricular area appears to be generally well-defined. Forty-three points that fulfilled all three criteria were classified with an alphanumeric code (a two-letter abbreviation and one number), pinyin, Han character, and English name. Thirty-six points that fulfilled the first and second criteria were not attributed a code, but only pinyin, Han character, and English nomenclature. Eleven points that failed to fulfill all three of the criteria were excluded. After a last inconclusive 1990 WHO meeting [2] in Lyon, Chinese researchers continued the standardization work and mainly continued due to the contribution of the publication of Chinese National Standard in 1993 [3]. This document was updated in 2008 [4] by a second document.

An international standard of AAPs is an inevitable requirement when the auricular diagnosis and treatment medicine develops for a long period and goes to a high level. Through more than 30 years of effort, great progress and achievements have been made in researches on the international standard of AAPs. Up to now, an international standard has been formulated and issued by the World Federation of Acupuncture-Moxibustion Societies. An International Organization for Standardization (ISO) international standard is also in development. Nevertheless, there are still debates on the location methods for locating AAPs, including location based on "points," "subzones," "coordinate," and other methods.

The corresponding author of this paper has been engaged in the study on the international standardization of AAPs since 1986 and had the honor to participate in the whole process of research work on the Chinese national standard of AAPs and international standard of AAPs. As the chief

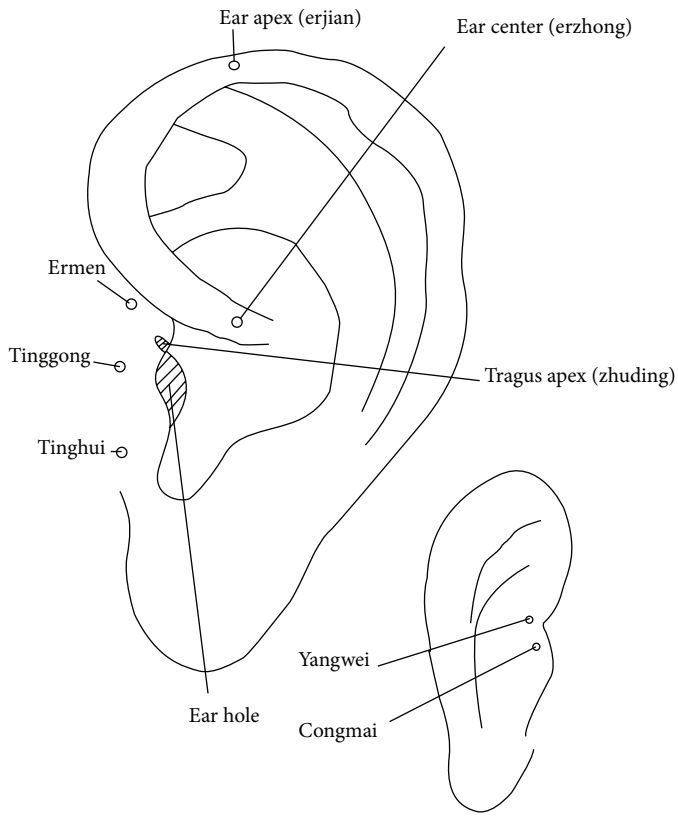


Figure 1: AAPs described by Chinese experts before the 18th century, recorded in Professor Huang Li-Chun's book, Auricular Diagnosis and Treatment.

expert of the project, he finished the international standard for auricular acupuncture point [5], which was issued by the World Federation of Acupuncture-Moxibustion Societies. Therefore, he had a comprehensive understanding on the background, content, advantages, and disadvantages of different location methods during developing this international standard. This paper aimed to analyze these location methods and provide a reference for the formulation of an ISO standard of AAPs in the future.

2. Methods

From perspectives of historical context of AAPs, clinical inheritance, and practice of AAPs, the understanding of the essence of points, advantages, and disadvantages of the following nine location methods for locating AAPs were analyzed, including (1) the location method based on points for the anterior of the auricle, (2) the location method based on subzones for the anterior of the auricle, (3) the location method based on the divided subzones according to anatomy of the anterior of the auricle, (4) the location method based on Nogier's Point Zero for the anterior of the auricle, (5) the location method based on the facial ties of the knee of the helix and lobe, (6) the location method based on both points and subzones of the anterior of the auricle, (7) the location method based on smaller subzones of the anterior of the auricle, (8) the location method based on subzones, points, and lines for the anterior and posterior of the auricle, and (9) the location method based on subzones, points, and lines for full cover of the anterior and posterior of the auricle. The analysis is described in detail with pictures so that readers can understand easily.

3. Results and Discussion

3.1. The Location Method Based on Points for the Anterior of the Auricle. No specific illustration of the location of AAPs can be found in Chinese ancient medical books [6] (Figure 1 [7]), except the posterior auricular map [8] (Figure 2) with the theory, where each of the five areas of the posterior of the auricle corresponded to each of the five Zang-organs, including heart, liver, spleen, lung, and kidney. Therefore, it is difficult to identify whether there was the thought of location of AAPs based on points at the old time. The ear reflex map of French physician, Paul Nogier, was introduced to China in 1958 by Dr. Ye Xiao-Lin. And this map was the earliest representative systematic auricular map in modern time [9–11] (Figure 3(a) [9] and Figure 3(b) [12]). The location method based on points and subzones is adopted in his two maps. The location method based on points is applied to represent the somatic structures of the body. Although the thought of location method of subzones to represent viscera and organs of the body was used, Figure 3(b) is only a sketch map. The location method based on points has three advantages. Firstly,

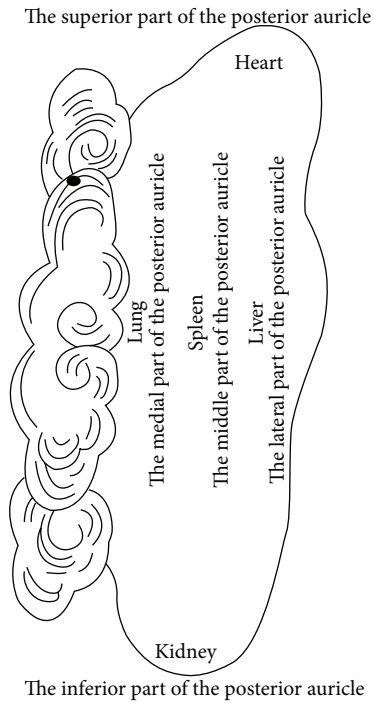


Figure 2: The posterior auricular map in 1888.

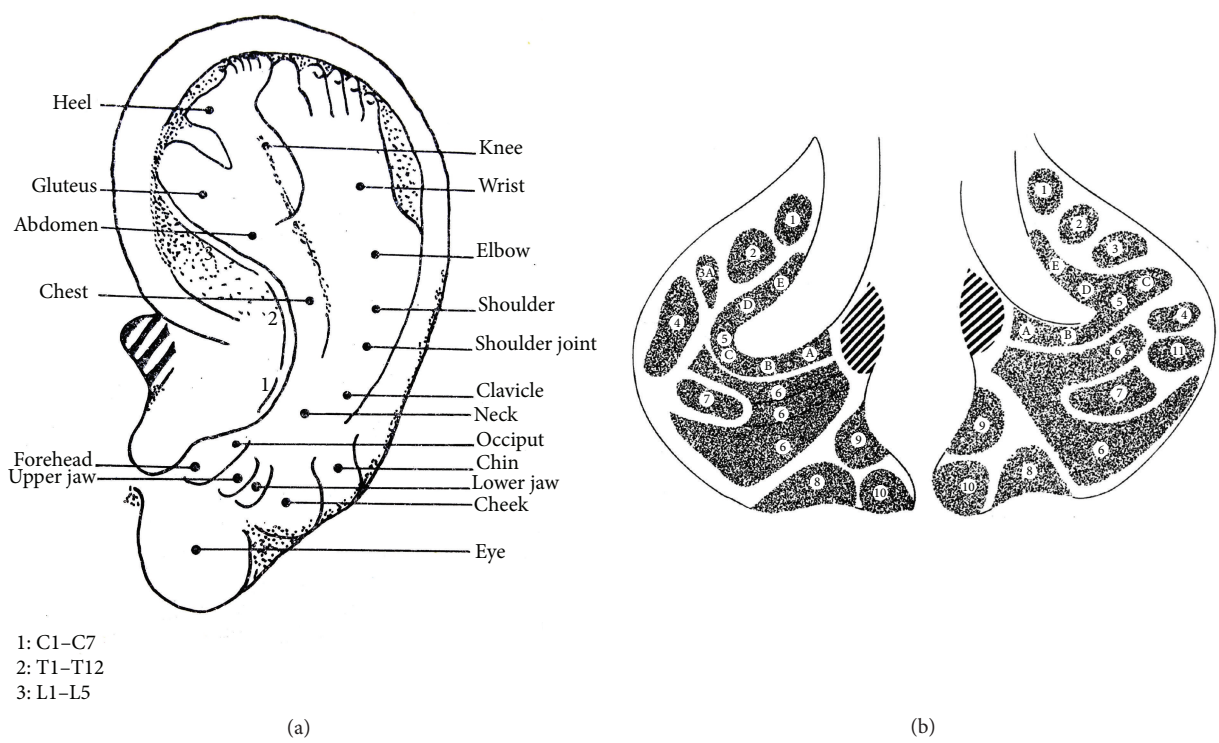


Figure 3: (a) Paul Nogier's findings of inverted fetus on the auricle representing the somatic structures in 1957. (b) Paul Nogier's findings of inverted fetus on the auricle representing viscera and organs in 1957. (1) Bladder; (2) kidney; (3) pancreas; (3A) gallbladder; (4) liver; (5A) oesophagus; (5B) cardia; (5C) stomach; (5D) small intestine; (5E) large intestine; (6) lung; (7) heart; (8) subcortex; (9) internal nose; (10) endocrine; (11) spleen.

the original is respected and it can comprehensively reflect the historic appearance of the development of auricular therapy in China and France. Secondly, it is visualized and it can effectively guide the clinical application of AAPs. Thirdly, those points which are marked at tips of the different zones of the auricle (e.g., the tip of the tragus) or notches (e.g., the intertragic notch) are easy to describe the location accurately with auricular anatomical terms. With the above advantages, this location method was adopted in the earliest draft of the international standard of AAPs. However, it has also some limitations. At first, it cannot accurately reflect the corresponding somatic structures, viscera, and organs reflexed on the auricle. Then, those points that are not located at the tips of the different zones of the auricle or notches cannot be accurately marked and described with auricular anatomical terms. Thirdly, it cannot cover the whole auricle. As a result, this location method was not the only location method in the later drafts.

Figure 2 is from Zhang Zhen-Jun's (Zhang Di-Shan's) book, *Essential Techniques for Massage*. The superior part of the posterior auricle corresponds to heart, the inferior part corresponds to kidney, the middle part corresponds to spleen, the lateral side corresponds to liver, and the medial side corresponds to lung.

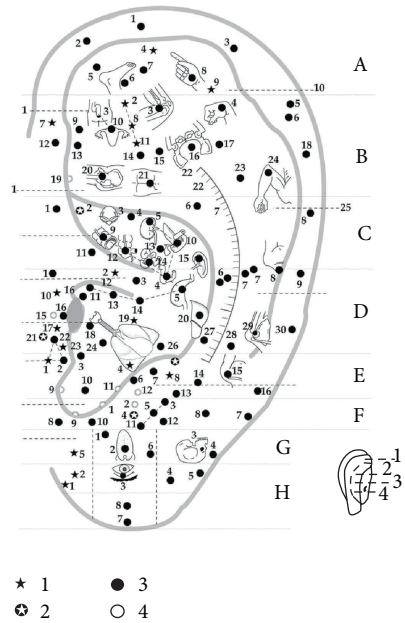


Figure 4: Dr. Jarricot's auricular map in 1973.

3.2. The Location Method Based on Subzones for the Anterior of the Auricle. With awareness of the limitations of the location method based purely on points, the Chinese academic circle in the late 1980s tried to locate AAPs according to the subzones. There were different zones on the auricle according to the anatomical structures of the auricle. Each zone was further divided into different subzones. The work began with the aim to locate AAPs at the ear lobe and concha where it was difficult to use points to locate these AAPs. The subdivision in vertical and horizontal lines of the ear lobe was published by Jarricot and Wong [13], who divided the whole outer auricle in horizontal stripes ((A) to (H), from top to bottom) which was called "the Great Ear of the School of Chen-Yang" (Figure 4). A Chinese physician, Dr. Wang, made also the exploration to locate AAPs by subzones in his book [14] (Figure 5), Auricular Acupuncture. According to the Chinese history of acupuncture, auricular acupuncture, and Nogier's auricular maps introduced into China in 1958, the location method based only on points is used to name acupuncture points, or AAPs. As a breakthrough of the thinking inertia, auricular point is just a point, and this location method based on subzones not only walked a significant step forward from perspectives of the clinical application of AAPs and description of the location of AAPs, but also provided an innovative idea for future study on the location of AAPs. The shortcoming of this method is that the division of zones is not comprehensive and standardized and lacks anatomical basis. Most of the AAPs are located by the location method based on points. The location method based on subzones is only applied to locate AAPs on the lobe, the inferior concha. There is not a general principle to specify the subzones, which makes it difficult to duplicate on different people. There is no description of anatomical borders, which can divide the auricle into zones and subzones.

3.3. The Location Method Based on the Divided Subzones according to Anatomy of the Anterior of the Auricle. In 1990, Oleson and Kroening, scholars from University of California, Los Angeles, the United States of America, first located all AAPs at the visible surface of the anterior auricle according to the anatomy of the auricle in his article [15] (Figure 6). Each subzone was coded by the initials of its corresponding anatomical structure and a number. For example, the first subzone of triangular fossa is short for TF1 and the second subzone of triangular fossa is short for TF2. His original intention was to ease the dispute over the problem-one name with different positions, or one auricular acupuncture point (AAP) with different names in Chinese and French auricular acupuncture systems, and to advocate neglecting the traditional names of AAPs but to name them with codes. Innovations of this location method are as follows. Firstly, location of AAPs is completely based on subzones instead of points, breaking through the limitations of the location method based on points. Secondly, the location method based on the divided subzones according to anatomy of the auricle has been proved to be the right direction to locate AAPs. Thirdly, the coding system, the name of the anatomical structure and a number, is simple and clear. Fourthly, according to the theory of bioholographic law, AAPs are the projections of the body parts on the auricle and therefore the location method based on the divided subzones can objectively reflect the correspondence between AAPs and the body parts. The shortcomings are as follows. Firstly, tips of the different zones of the auricle or notches are not proper to be marked as subzones. Secondly, the academic value of the historical evolution and clinical significance of AAPs are neglected. Thirdly, those AAPs at the junction of the neighboring anatomical structures of the auricle cannot be straight forwardly and accurately marked. Fourthly, the

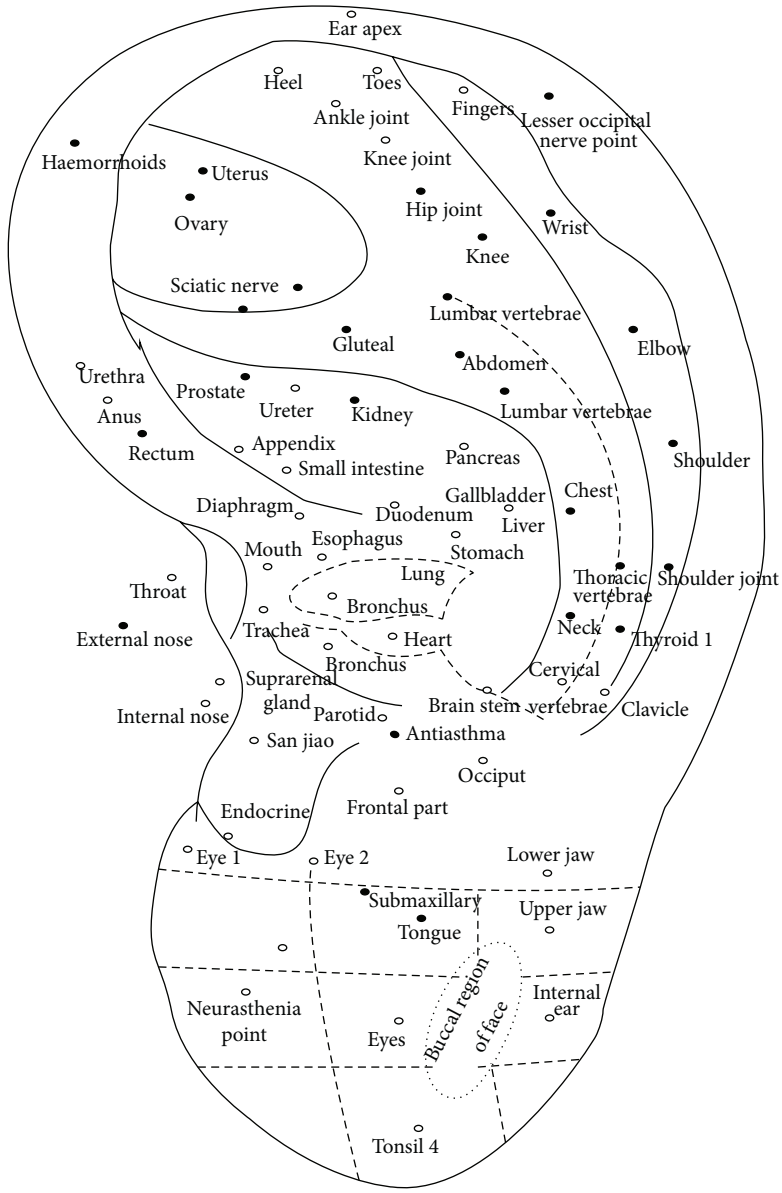


Figure 5: Dr. Wang Zhong's auricular map in 1984.

border of the neighboring anatomical structures of the auricle, such as scapha and antihelix, cannot be clarified and lacks detailed anatomical evidence. Finally, the posterior of the auricle is not divided into zones and further subzones.

3.4. The Location Method Based on Nogier's Point Zero for the Anterior of the Auricle. This method was proposed in 1990 by Dr. Bossy at the international conference on AAPs held by the WHO Regional Office for the Western Pacific in Lyon, France, to solve the long-troubling problem of international standardization of AAPs. The zero point was set at the helix crus notch and the auricle is divided into four quadrants by the horizontal and vertical axis. AAPs were marked by the intersections of the latitude and longitude lines in each quadrant. Dr. Rouxeville [16] further divided each quadrant into three equal sectors (Figure 7). Three other authors, the Russian Durinyan [17] and Romoli and Mazzoni [18] from Italy, also developed a grid with a variable number of sectors centered in Point Zero. The sectogram was obtained by subdividing the auricle into three semiaxes (A), (B), and (C) going, respectively, through the visual intersection point of the posterior edge of the raising branch of the helix with the lower branch of the antihelix (A) and through the antitragus-antihelix groove (B) and tangent to the posterior edge of the tragus (C). The resulting main sectors (A)-(B), (A)-(C), and (B)-(C) were subdivided, respectively, into 16 sectors, (A)-(B) and (A)-(C), and into 8 sectors, (B)-(C) (Figure 8). The location method based on Nogier's Point Zero for the anterior of the auricle has the thought of locating AAPs with subzones. The advantage of this method is that it could accurately locate every point with no controversy about the nomenclature and locations of AAPs. However, as the saying goes, "no leaves are

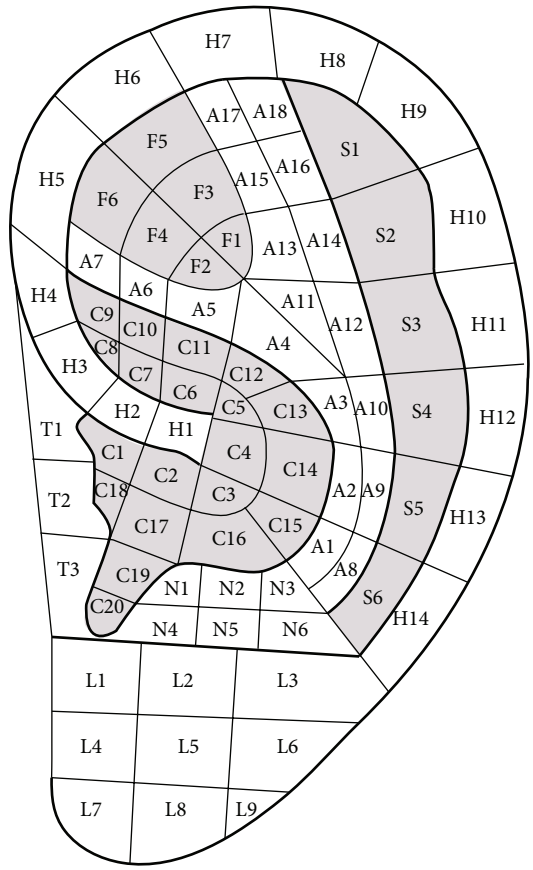


Figure 6: Oleson's nomenclature of subzones in 1983.

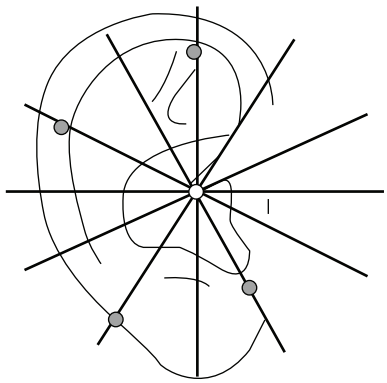


Figure 7: Dr. Rouxeville's location method of auricular acupuncture points in 1980.

exactly the same in the world," no ears have exactly the same shape. The latitude and longitude coordinates hardly match the actual positions of AAPs based on anatomical structures, which therefore is difficult to serve as a repeatable, standard location method. Up to now, this location method is not applied extensively enough.

3.5. The Location Method Based on the Facial Ties of the Knee of the Helix and Lobe. This location method (Figures 9(a) and 9(b)), proposed by Dr. David Alimi, took for base the anatomical structures of the ear as the ties which were constant at all humans: namely, the facial ties of the knee of the helix and lobule. These ties (their epicenter) were always aligned on a perfect right which always passed by the corpus callosum [19]. The corpus callosum connects the left and right cerebral hemispheres and facilitates interhemispheric communication. The point was considered to represent the corpus callosum, called 0 premium by the largest number, pulled tangents in these ties. A semicircle of an angular value of 180 degrees was divided into 20 equal angles, with 9 degrees for each sector. The group was a segmentogram recovering the totality of the anterior and posterior surfaces of the auricle. This location method is based on the division of subzones. However, this location method is not based on the anatomical structures of the auricle, and it is more complicated than Oleson's location method in 1983 and Chinese location method based on points and subzones when applied in clinical practice [20].

3.6. The Location Method Based on Both Points and Subzones of the Anterior of the Auricle. This method was proposed in 1988 by an article entitled "The Project of the Standardization of AAPs" by the China Association of Acupuncture-Moxibustion in the Journal of Traditional Chinese Medicine [21] (Figure 10). The article put forward for the first time a new location method, in which AAPs were named mainly by the divided auricular subzones and by supplementing

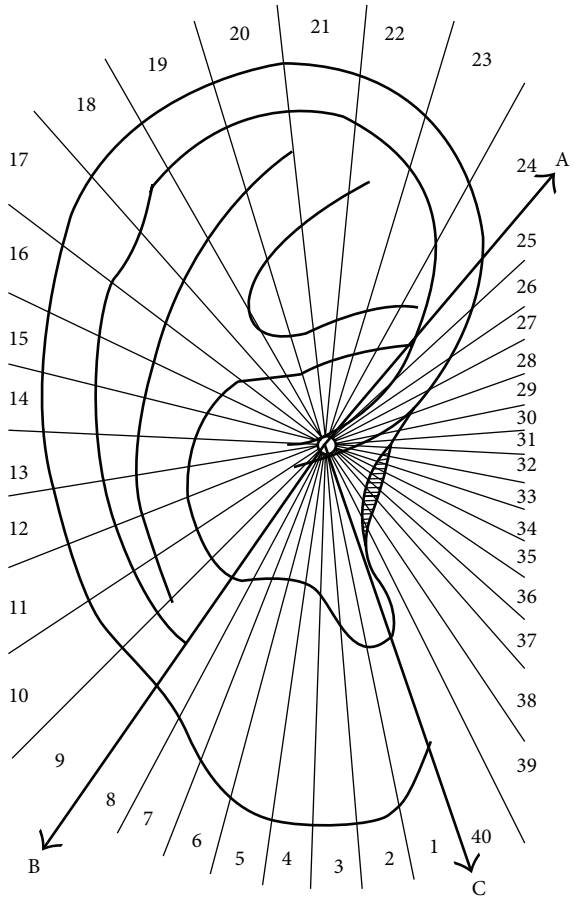
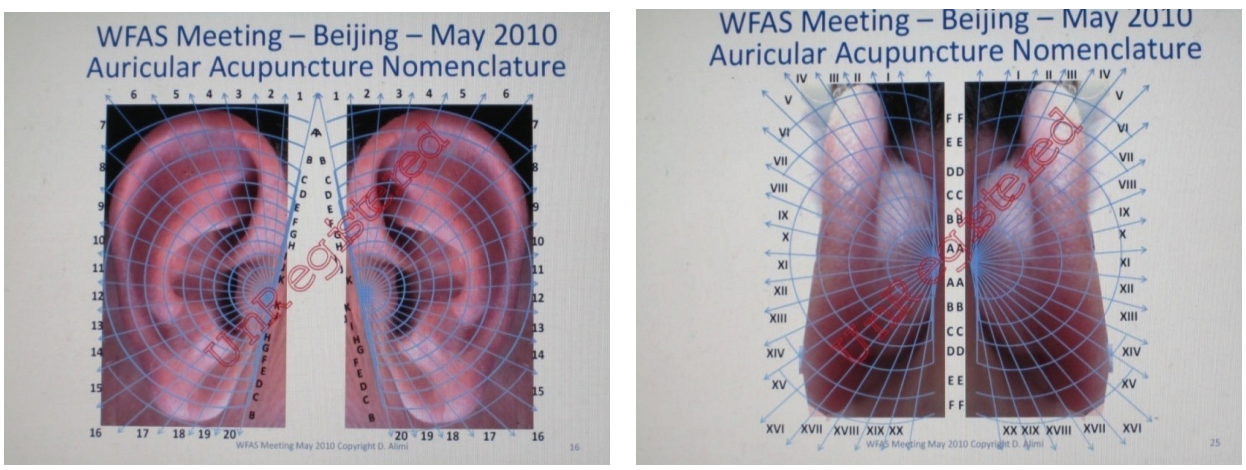


Figure 8: Professor Romoli's location method of auricular acupuncture points in 2009. Auricular sectogram, centered on Nogier's Point Zero, with the three half-lines (A), (B), and (C) subdividing the auricle.



(a) (b)

Figure 9: (a) Dr. Alimi's location method for the anterior of the auricle in 2010. (b) Dr. Alimi's location method for the posterior of the auricle in 2010.

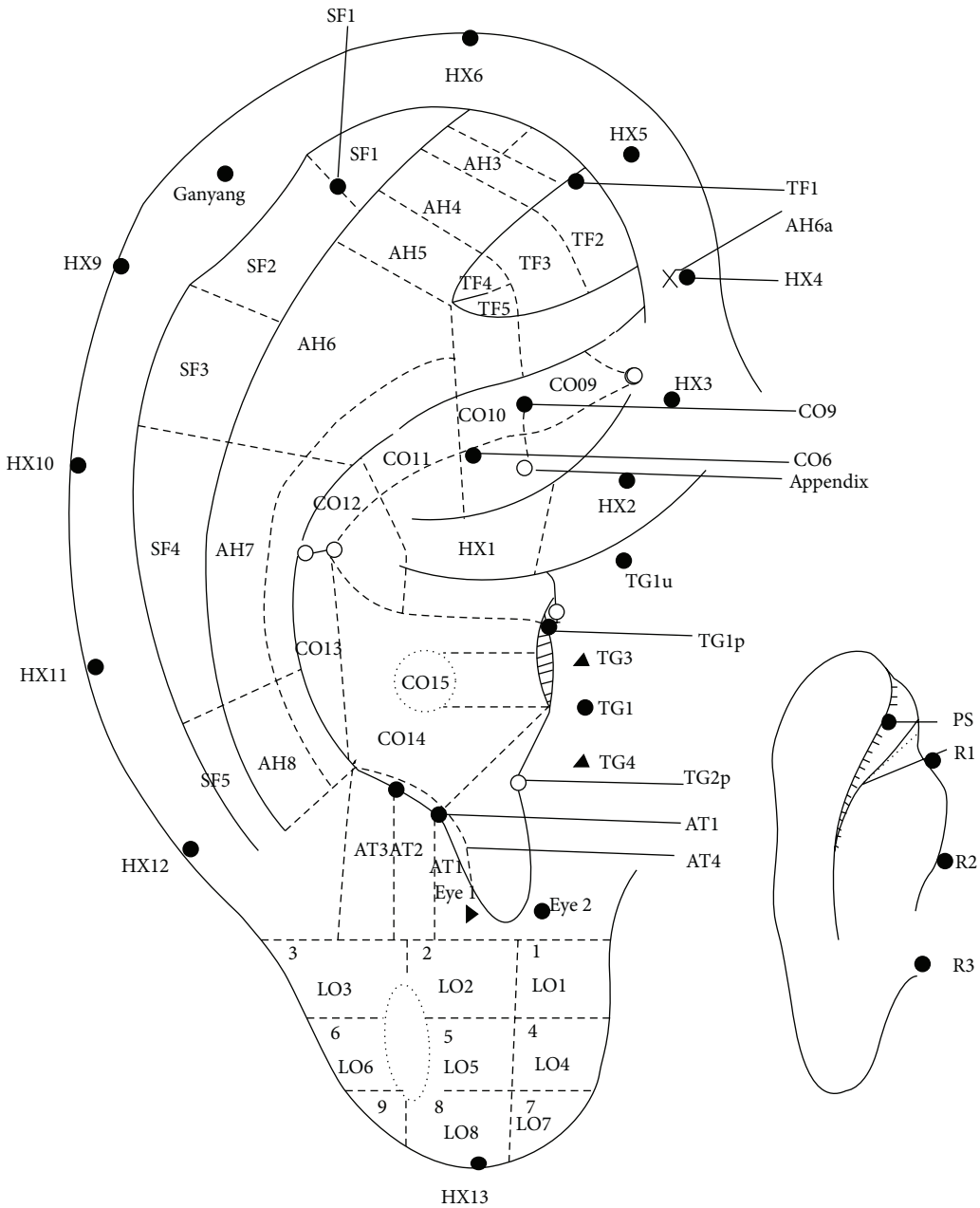


Figure 10: Standard project of auricular acupuncture points by the China Association of Acupuncture-Moxibustion in 1988.

with the location method based on points, and also basically covered the anterior of the auricle. Advantages of this method are as follows. Firstly, it is based on the anatomy of the auricle, taking into account the complicated structure of the surface of the auricle. For AAPs at relatively flat area, the location method is based on subzones. For AAPs at tips of the different zones of the auricle or notches, the location method is based on points. It opens up a new thought of locating AAPs by different location methods according to the actual situation. Secondly, it is of great importance to create the location method which integrates auxiliary lines to locate AAPs according to the anatomical structures of the auricle, for example, at the ear lobe. The disadvantages are as follows. Firstly, a complete location principle was not formed. The application of the location method based on both points and subzones of the anterior of the auricle is not normative enough. For example, the location method based on points is still used for AAPs at the flat helix. Secondly, a considerable part of the anterior of auricle is still unmarked. Thirdly, there was no specification on how to locate AAPs on the posterior of the auricle.

3.7. The Location Method Based on Smaller Subzones of the Anterior of the Auricle. The book, *Practical Auricular Acupuncture Therapy*, was published by Shanxi Science and Technology Press of China in 1988 which further divided the previous subzones into a number of even smaller subzones to improve the accuracy of the location of AAPs [22] (Figure 11).

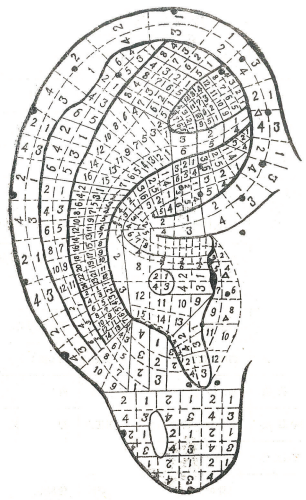


Figure 11: The location method based on smaller subzones of the anterior of the auricle in 1988.

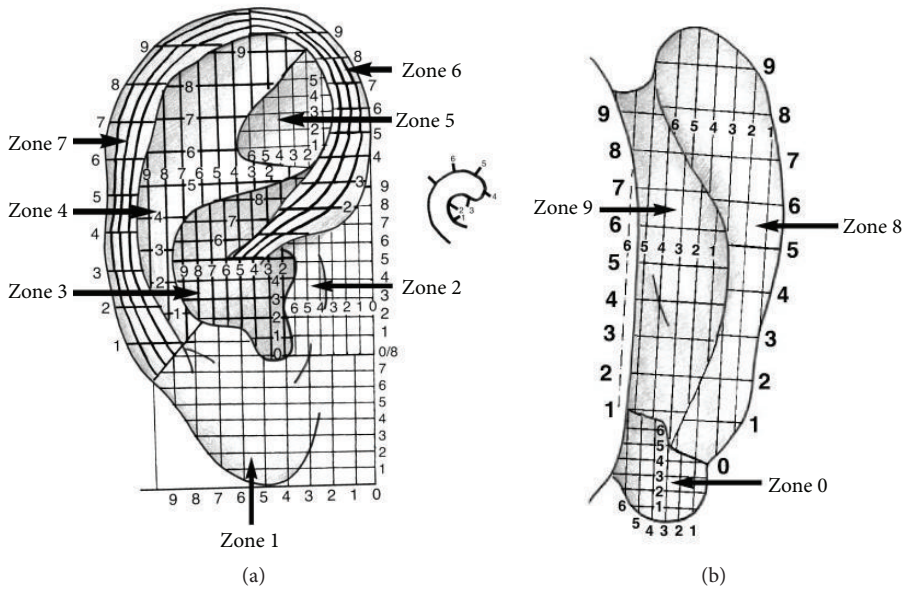
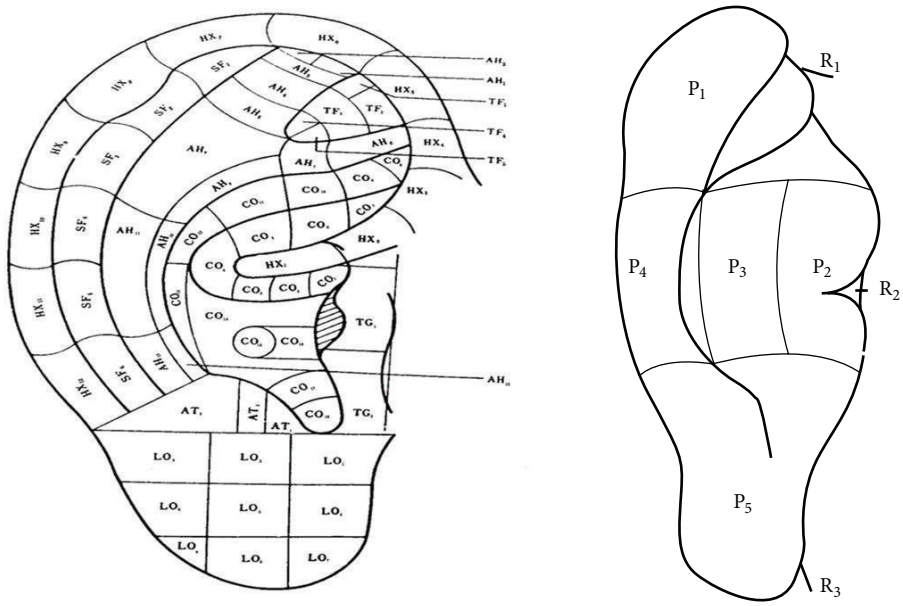


Figure 12: (a) Dr. Wojak's location method for the anterior of the auricle in 2010. (b) Dr. Wojak's location method for the posterior of the auricle in 2010.

One similar location method [19], proposed by Dr. Winfred Wojak from Germany, divided the anterior auricle into 7 zones/areas and the posterior auricle into three zones/areas (Figures 12(a) and 12(b)). The anterior 7 zones included Zone 1, Zone 2, Zone 3, Zone 4, Zone 5, Zone 6, and Zone 7. The posterior 3 zones included Zone 8, Zone 9, and Zone 0. Each zone/area, except the helix, was divided into 9 vertical lines and 9 or 6 horizontal lines, which depended on the sizes of the zones/areas. For example, Zone 5 (the triangular fossa) and Zone 0 (the posterior of the lobe) were divided into 6 horizontal lines. The advantages of this method are as follows. Firstly, the location method inherits the objectivity and normativeness of the previous location method based on the anatomical structures of the auricle. Secondly, it considers the demand for an accurate description of the location of the point where the needle is inserted in the clinical practice of AAPs. It is helpful to choose the right point under the condition of the application of the location method based on subzones. Thirdly, this location method encompasses the idea, and subzones can be further divided into smaller subzones, which can be also further divided into even points. This idea unifies the location method based on points and the location method based on subzones according to the clinical demand. The shortcomings of this method are as follows. Firstly, the divided smaller subzones are even more complicated than the previous location method based on subzones, which brings difficulty in getting popular. Secondly, due to the complexity of the structures of the



(a) (b)

Figure 13: (a) The subzones of the anterior of the auricle [3, 4] and the international standard of auricular acupuncture points, issued by the World Federation of Acupuncture-Moxibustion Societies in 2013. (b) The subzones of the posterior of the auricle [3, 4] and the international standard of auricular acupuncture points, issued by the World Federation of Acupuncture-Moxibustion Societies in 2013.

auricle, it is difficult to make further division of auricular zones according to the anatomical structures of the auricle. Therefore, this method does not become the mainstream location method for locating AAPs, though it is a helpful thought for the location of AAPs.

3.8. The Location Method Based on Subzones, Points, and Lines for the Anterior and Posterior of the Auricle. After retaining the advantages and discarding the disadvantages of the above location methods, a new location method based on subzones, points, and lines for the anterior and posterior of the auricle was formed and applied in the clinical practice of AAPs. The Chinese National Standard, The Nomenclature and Location of AAPs, was issued in 1993. This standard systematically adopted this location method for the first time [3] (Figures 13(a) and 13(b)). The advantages of this new location method are as follows. Firstly, it keeps as many traditional locations of AAPs whose clinical therapeutic effects are proved as possible, which ensures the consistency of the nomenclature and location of auricular points. Secondly, it absorbs the advantages of all of the above location methods and also integrates the location method based on the natural auricular groove at the posterior of the auricle, making the location of AAPs more systematic. Thirdly, the idea of imaginary marking points and lines (Figures 14 and 15) proposed by the corresponding author, Professor Zhou [23], is adopted in this standard. Imaginary Point (A) is located at the medial edge of the helix at the junction between the middle and upper one-third of the line from the notch of helix crus and the inferior edge of the inferior antihelix crus. Imaginary Point (D) is located where a level line drawn from the end of the helix crus crosses the concha edge of the antihelix. Imaginary Point (B) is located at the junction of the middle and posterior one-third of the line extending from the end of the helix crus to Point (D). Imaginary Point (C) is located at the junction of the upper one-quarter and lower three-quarters of the posterior edge of the orifices of the external auditory meatus. Line (AB) is a curved line that extends from Point (A) to Point (B) and mirrors the concha edge of the antihelix. Line (BC) is a curved line extending from Point (B) to Point (C) that mirrors the inferior edge of the helix crus. In this way Z. Liqun makes it possible to describe accurately the locations of all AAPs according to the anatomical structures of the auricle and thus promotes the development of the standardization of localization of AAPs. Finally, it is helpful for the publication, research, teaching, and clinical application of AAPs. The limitation of this method is that there are still a small number of subzones unnamed, such as the anterior part of the helix and the two subzones at the anterior and posterior of the ear apex.

3.9. The Location Method Based on Subzones, Points, and Lines for Full Cover of the Anterior and Posterior of the Auricle. The method based on subzones according to the anatomical structures of the auricle, points, and lines for full cover of the anterior and posterior of the auricle was adopted by the new Chinese National Standard, Nomenclature and Locations of AAPs (GB/T13734-2008) [4] (Figures 13(a) and 13(b)) and also by the International Standard, Auricular acupuncture point (Figures 13(a) and 13(b)), issued by the World Federation of Acupuncture-Moxibustion Societies [5]. This location method marks the increasing maturity of the

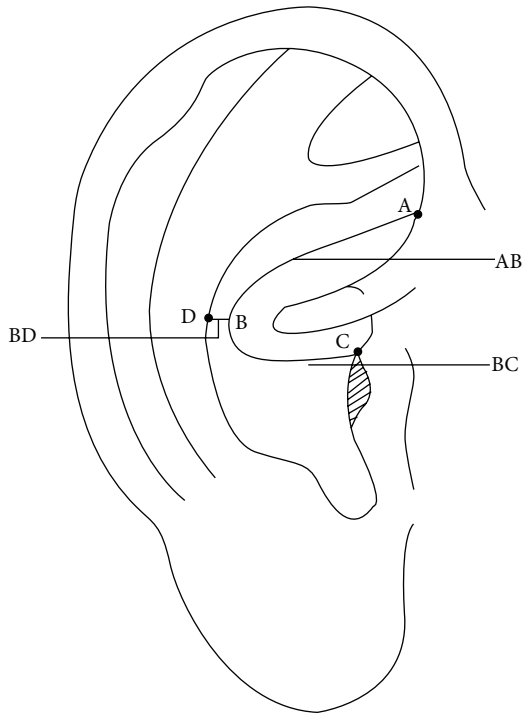


Figure 14: Marking points and lines in 1992.

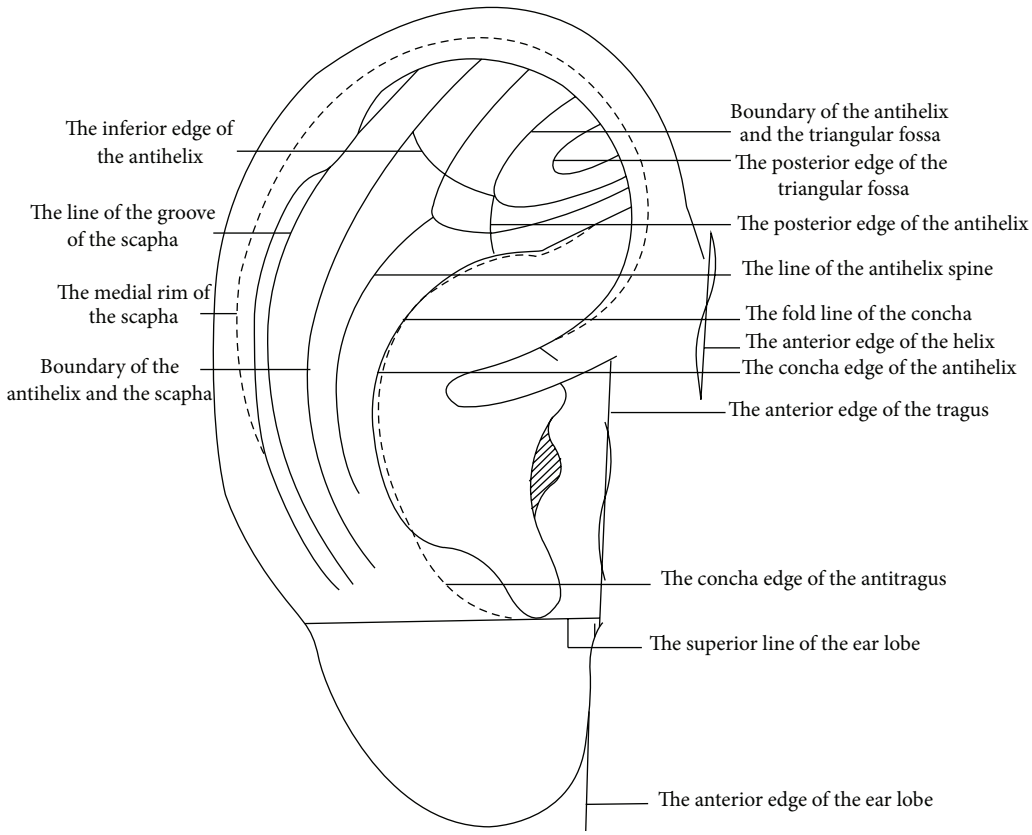


Figure 15: Marking lines in 1992.

location of international standard of AAPs. Firstly, it accumulates the successful experience from the research work on international standardization of AAPs in the past 20 years and avoids the disadvantages of the above-mentioned location methods. Secondly, it names the two unnamed subzones in the former Chinese national standard in 1993 so that all subzones, points, and lines can be matched to a name, covering all areas of the auricle. However, this method still has some limitations. Firstly, there are some disagreements on the names of certain subzones or points between China and Europe. Secondly, some zones or subzones, especially the zones of the posterior of the auricle, are too big to insert the needle on the posterior of the auricle. The location method for the posterior of the auricle needs to be further improved.

4. Conclusion

The research on history, mechanism, and clinical application of auricular therapy has experienced a long process [24]. The nomenclature, location method, and consistency between name and location are three topics in the research field of international standardization of AAPs. Through analyzing the advantages and disadvantages of these nine representative location methods, we tried to offer a proper location method to locate AAPs.

The location method based on subzones according to the anatomical structures of the auricle, points, and lines for full cover of the anterior and posterior of the auricle is an appropriate method and is adopted by the WFAS international standard of AAPs. It is important to keep the right direction during developing an ISO international standard of auricular acupuncture points and to improve the research quality of international standardization for AAPs and of auricular diagnosis and treatment.

Competing Interests

The authors declare that they have no competing interests.

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Review Article

The History, Mechanism, and Clinical Application of Auricular Therapy in Traditional Chinese Medicine

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Auricular therapy includes acupuncture, electroacupuncture, acupressure, lasering, cauterization, moxibustion, and bloodletting in the auricle. For 2500 years, people have employed auricular therapy for treating diseases, but the methods have been limited to bloodletting and cauterization. Only after 1957, the international scientific community became aware that the map of the ear resembles an inverted fetus, its introduction has led to auricular acupuncture (AA) becoming a more systemic approach, and, following the identification and standardization of more precise points, AA has been employed in clinical applications. The mechanisms of AA are considered to have a close relationship with the autonomic nervous system, the neuroendocrine system, neuroimmunological factors, neuroinflammation, and neural reflex, as well as antioxidation. Auricular therapy has been applied, for example, for pain relief, for the treatment of epilepsy, anxiety, and obesity, and for improving sleep quality. However, the mechanisms and evidence for auricular therapy warrant further study.

1. Introduction

Auricular acupuncture (AA) is a method for diagnosing and treating physical and psychosomatic dysfunctions by stimulating a specific point in the ear [1]. Ear stimulation involves the neurological reflex, neurotransmitters, cytokines, the immune system, and inflammation [1–3]. AA has been employed for approximately 2500 years, for which the oldest record is *Huang Di Nei Jing* (*The Yellow Emperor's Classic of Internal Medicine*), written in Chinese, and a report by Hippocrates is the oldest Western record [4]. In Traditional Chinese Medicine (TCM), the ear is directly or indirectly connected with 12 meridians, and stimulating the ear can restore the balance between Qi and blood [5]. In Europe, AA has been applied systematically and comprehensively since Doctor Nogier introduced the inverted fetus map in 1957 [6–9]. This article by Nogier was read by Russian, Japanese, and Chinese acupuncturists and was translated in 1958 and 1959 into Chinese, the latter reporting only Nogier's original image of the somatic parts of the body [10]. Information regarding the entire organism or body part can be retrieved from the ear (i.e., the holography rule of points) [11]. Various methods currently existing for ear stimulation are needles, seeds, magnetic stones, lasers, ultrasound, bloodletting, moxibustion, electric treatment, and pressure by hands [4, 12]. AA is a convenient and basic method used for treating many conditions (e.g., substance abuse, pain, obesity, anxiety, epilepsy, and sleep disorders), but the effectiveness of AA has been tested only in a relatively small number of evidence-based trials [5, 13]. Gueguen et al. (2013) reported a system review about 42 randomized control trials. AA has the effect to decrease the preoperative anxiety and peroperative pain but no effect in the prevention of withdrawal syndrome according to the poor methodological studies [14]. With technological advancements, increasingly more clinical trials conducted in the field of biochemistry are presenting evidence regarding

the detailed mechanisms of AA in the treatment of diseases. Therefore, this study traces and presents the history, mechanisms, and the clinical application of AA.

2. History of Auricular Acupuncture

2.1. In Europe and Surrounding Regions. In Europe and surrounding regions, AA has been applied for approximately 2500 years. Numerous historical records of AA are found worldwide. In Egypt, women can cauterize and stick a needle in the ear for sterilization. In Italy, the wounded of the auricle in war could occasionally heal their original ailments. In Saudi Arabia, certain tribes cauterize the ear to heal diseases [1]. The Mediterranean peoples wear an earring for improving their eyesight [4]. In Greece, the first record (ca. 460 BC) of AA is a report by Hippocrates, which stated that phlebotomy (i.e., applying a needle to the ear to create an incision in a vein) was conducted for treating impotence and facilitating ejaculation [4]. Another source indicated that phlebotomy can relieve leg pain [1]. The Roman Empire received medicine from Ancient Greece, present-day Egypt, Persia, and present-day Saudi Arabia, and they still use these methods for treating sciatica, hip pain, and sexual ailments [1]. In 1637, a physician named Zacatus Lusitanus cauterized the ear to treat sciatica after phlebotomy did not produce the desired effect. In 1717, the physician Antonio Maria Valsalva discovered a new point that can alleviate odontalgia after cauterization. In 1810, a professor named Ignazio Colla used a bee needle to stimulate the ear and relieved pain in the lower extremities. After 1850, numerous reports described major cases of ear cauterization conducted for tooth extraction. Journal des Connaissances Medico-Chirurgicales, a French journal, mentioned 13 cases of patients with sciatica treated with ear cauterization [1, 4]. In 1957, Doctor Paul Nogier reported the somatotopic correspondence in the ear, which marked the emergence of a new era for AA application.

2.2. In China. The oldest record on AA is from *Huang Di Nei Jing* (ca. 100 BC) [1]. Chapter 63 in the plain questions of *Huang Di Nei Jing* stated that a physician can employ a tube and blow air into the ear to save an unconscious patient. Chapter 20 in the miraculous pivot of *Huang Di Nei Jing* indicated that phlebotomy in the distended vein can relieve the tightness in the costal regions. *Zhou Hou Bei Ji Fang* (ca. 300 to 400 AD), emergency handbook, recorded that using aconite-derived oil, gladiolus, and sesame oil to irrigate the auditory meatus can treat ear pain. *Qian Jin Yao Fang* (652 AD), authored by Sun Si-Miao, stated that the point in the helix before the concha ridge can be targeted for treating jaundice. In *Wei Sheng Bao Jian* (1343 AD), Luo Tian-yi wrote that cauterizing a vein behind the ear can treat the infantile convulsion. In *Zhen Jiu Da Cheng* (1601 AD), an acupuncture text composed by Yang Ji-Zhou indicated that performing phlebotomy inside the tip of the ear can be effective for treating eye diseases. Concerning AA in the treatment of specific organs, *Essential Techniques of Massage* (Chinese name, *Li Zheng An Mo Yao Shu*, 1888 AD) written by Zhang Di-Shan divided the auricle into five regions, with each, respectively, targeting the heart, lung, liver, spleen, and kidney, and indicated that a functional organ can be identified by noting any changes in these respective regions (Figure 1) [15–17].

2.3. Modern Period. In 1956, Doctor Paul Nogier, the father of AA, presented his inverted fetus map at the congress of the *Société Mediterranéenne* in Marseille [4]. Nogier had found that sciatica could be healed by the cauterization in the inferior crus of the antihelix. He conducted repeated investigations into the conditions before introducing 37 AA points [1, 4, 18]. In 1966, he found that changes to the pulse rate in the radial artery were related to the stimulation of the auricle and coined this phenomenon "*Reflexe Auriculocardiaque*" (Vascular Autonomic Signal, VAS) [1, 4, 19]. After a journal published this finding, the Nanjing Army Ear Acupuncture research team recruited over 2,000 patients to establish an AA model, and their results ultimately confirmed Nogier's propositions from 1958 [1, 4, 5, 13, 20]. More than 1,000 AA acupoints have since been identified, and, in 1982, the Western-Pacific Regional Office, World Health Organization (WHO), convened a conference to discuss how to eliminate the confusion originating from duplicate names and regions. Finally, in 1987, the WHO released a report entitled "Scheme of Standardization of Auricular Acupoints" [1, 4, 5]. The standardization process was afterwards carried on only by Chinese researchers and the final document on nomenclature and location of ear acupuncture points was published in 1993 and confirmed in 2008 [17]. Actually, the use of acupoints in Europe still differs from Chinese practice, but it has to be pointed out that the current Chinese maps correspond faithfully to the historic maps of Nogier published in 1957 [18].

3. Mechanisms of Auricular Acupuncture

3.1. Anatomy of the Auricle. The basic terminology regarding the auricle concerns the prominent parts (i.e., the helix, antihelix [including the superior and inferior crus], and the tragus and antitragus); the concave parts (i.e., the scaphoid fossa, triangular fossa, and the superior and inferior concha); and a flat part (i.e., the lobe; Figure 2) [13, 21]. The ear is innervated by cranial and spinal nerves, which are separated into motor and sensory areas. The motor area concerns the motor branch of the facial nerve (CN VII), which controls the outer ear muscles. The sensory area is composed of auricular branches of the vagus nerve (ABVN), the auriculotemporal nerve (a branch of CN V), the sensory area of the facial nerve, the glossopharyngeal nerve, the lesser occipital nerve, and the greater auricle nerve. The most important nerve is ABVN because of its function in AA in affecting mainly the concha and most parts of the auditory canal [4, 9].

3.2. Theory of Auricular Acupuncture

3.2.1. Somatotopic Arrangement (Homuncular Theory). Nogier had devised the map of an inverted fetus by noting its resemblance to the ear, and this map is the most widely used reference for diagnosing and treating auricular diseases (Figure 3) [1, 4, 13]. The general arrangement is that the earlobe targets the head and brain, the antihelix represents the spine, the scaphoid fossa refers to the upper extremities,

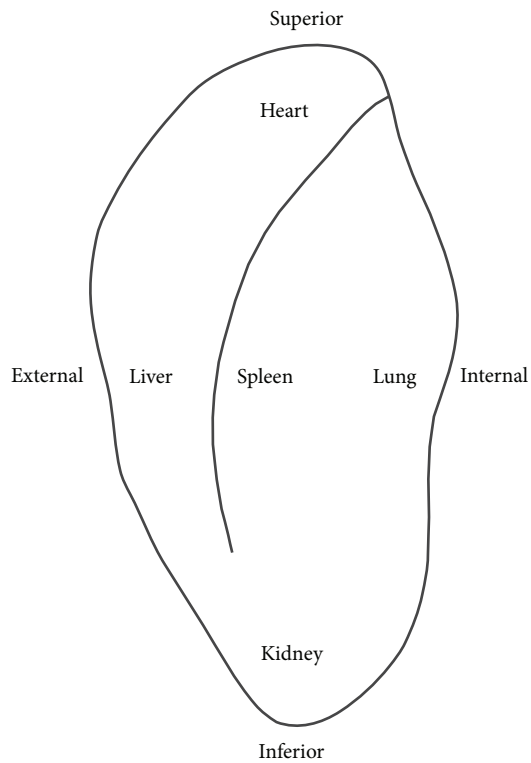

Figure 1: The five viscera distribution of ear in Traditional Chinese Medicine recording.

the superior and inferior crus target the lower extremities, and the concha represents the internal organs, but numerous differences still exist between the Europe and Chinese systems [1, 4, 13]. Nogier believed that the relationship between AA and the areas of the body is due to the vagus nerve-autonomic nervous system (ANS) [1, 4, 13]. Doctor Oleson, a US physician, used somatotopic arrangement of the auricle to diagnose the medical condition with a 75.2% accuracy rating [1]. Andersson et al. (2007) recruited 25 patients with chronic pain in a double-blind study to examine whether auricular maps correspond to parts of the body but they found that the AA map was not corresponding to the body parts [22]. Another blinded study was made by Romoli et al. on 506 patients employing 3 different diagnostic methods: inspection of the auricle, pain pressure test (PPT), and electrical skin resistance test (ESRT). Inspection was superior to PPT and ESRT and applying all three diagnostic methods together can achieve a success rate of 78.6% in identifying symptoms and syndromes related to somatic and mental disorders [23, 24].

3.2.2. Embryological Regions. Embryological organization is similar to somatotopic organization. The earlobe and tragus correspond to the ectoderm, the concha corresponds to the endoderm, and the remaining portion of the ear corresponds to the mesoderm. If an organ (e.g., the lungs) corresponds to the endoderm, we can use the concha to treat or diagnose the condition [4, 5, 25]. The distribution of embryological regions is based on the lower portion of the ear representing the head and the upper portion representing the foot [13].

3.2.3. Meridian Theory. According to meridian theory, the ear is connected directly or indirectly to 12 meridians. The *miraculous pivot* of *Huang Di Nei Jing* indicated that any channel and meridian converge in the ear [4, 15]. The application of AA in TCM is based on yin-yang theory and five-element theory, but most auricular treatments involve the acupoints of the four limbs and the visceral and endocrine related areas innervated by vagus nerve [26]. Regarding the application of AA in Ancient China, their traditional methods could not be devised into a theoretical framework and are akin to home remedies.

3.3. Mechanisms of Action

3.3.1. Connection between the Auricle and Autonomic Nervous System. In 1832, Friedrich Arnold, a German professor of anatomy, found that stimulating the external ear canal can induce a cough similar to the cough reflex induced by the vagal nerve. This reflex is called "Arnold's Reflex" and regards the ABVN as its afferent nerve [9]. Because ABVN stimulation can induce a response similar to that of the vagal nerve, the ABVN may have a relationship of the auricle and ANS [9].

The ABVN delivers fiber into the nucleus of the solitary tract (NTS). Nomura and Mizuno (1984) applied horseradish peroxide to the end of the ABVN in cats and found that the labeled nerve fibers of the ABVN surround the NTS [27]. The inputs of the NTS include fibers from the facial nerve (CN VII), the glossopharyngeal nerve (CN IX), the vagus nerve (CN X), and afferent nerves in the internal organs. By contrast, the NTS outputs include reticular formation,

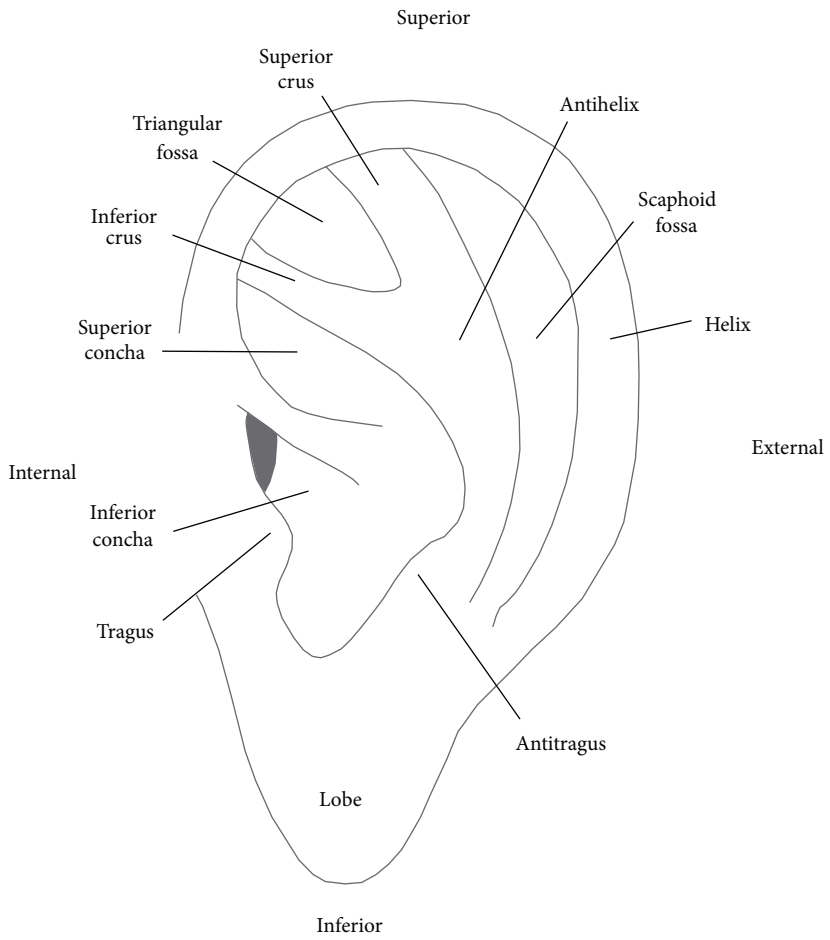

Figure 2: Anatomical structure of ear.

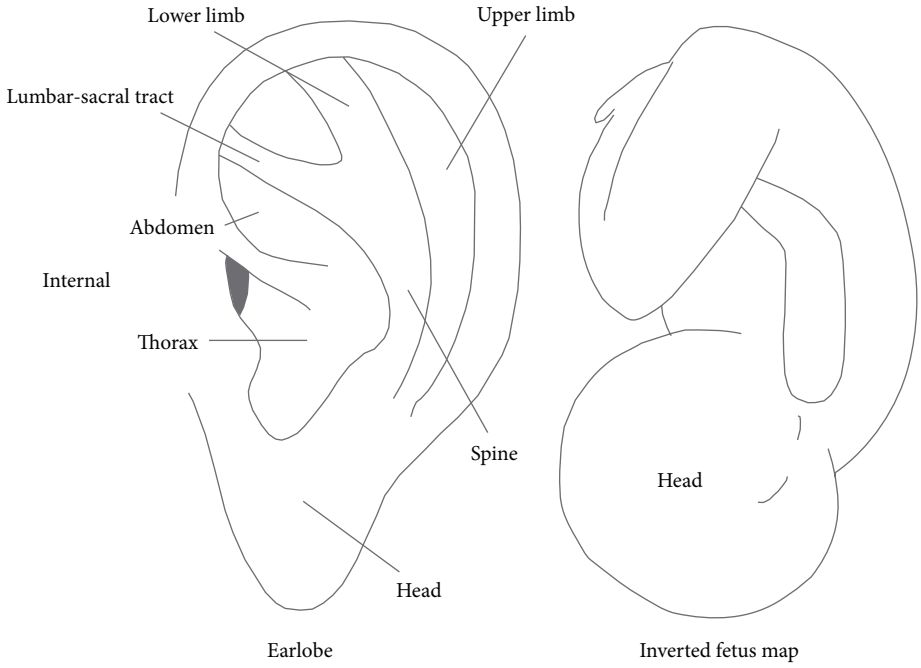

Figure 3: Ear map as like an inverted fetus.

parasympathetic preganglionic neurons to the viscera, the paraventricular nucleus of the hypothalamus, the thalamus (visceromotor center), and amygdala. The NTS mediates many reflexes, for instance, the carotid sinus reflex (chemoreceptor and mechanoreceptor), the aortic reflex (chemoreceptor and mechanoreceptor), the gag reflex, and the cough reflex, as well as several respiratory and gastrointestinal reflexes regulating organ function [28]. The concha of the auricle and the external auditory canal, especially the inner part of the tragus, is supplied mainly by the ABVN. Stimulation originates from the cutaneous concha through the auricular nerve (CN IIX) and travels to the jugular ganglion, and the branches of the vagus nerve start from this ganglion and end in the NTS of the medulla oblongata [29]. Based on the complex connections in the NTS between the brain and the viscera, ABVN stimulation can regulate the ANS.

The stimulus from AA raises the vagal tone and regulates the cardiovascular, respiratory, gastrointestinal, and endocrine systems [9]. Regarding the cardiovascular system, AA can lower the heart rate and blood pressure and accelerate blood flow and heart rate variability (HRV) [30]. Moreover, stimulating the heart acupoint of the ear in rats was found to lower arterial pressure and the heart rate significantly compared with the use of Zusnali (ST36) and Neiguan (PC6) [31]. Regarding the respiratory system, AA combined with electrical treatment had a positive effect on respiratory sinus arrhythmia by increasing vagal activity [32]. For the gastrointestinal system, the effects of AA on motility and the gastrointestinal tone were similar to those from medication [33].

3.3.2. Delta Reflex Theory. Delta reflex theory posits that cold or heat stimulation on parts of the body raises the temperature in the corresponding parts of the ear from 1.0°C to 5.5°C. Doctor Cho proposed this theory in the 1970s, which posits a relationship between parts of the body and the regions of the ear [5]. This reflex may be influenced in part by the vagal nerve.

3.3.3. Acupoints in the Ear: Experiences with Functional Magnetic Resonance Imaging (fMRI). Gao et al. (2008) proposed that stimulating different points in the ear can induce a similar response on the cardiovascular and gastrointestinal systems [34]. Alimi et al. (2002) demonstrate that acupuncture in the point of the ear for the hand leads to selectively altered fMRI changes in the somatosensory cortex for the hand of the postcentral gyrus [35]. Romoli et al. (2014) employed fMRI to detect the differences between two stimulated acupoints: Thumb Auricular Acupoint (TAA) to bilateral parietal operculum and the second somatosensory area and Brain Stem Auricular Acupoint (BSAA) to the limbic and cortical areas [36]. Alimi et al. (2014) used fMRI to prove the topography of the French-German auricular area better than the Chinese auricular area [37].

3.3.4. Anti-Inflammation. Ceccherelli et al. (1999) used carrageenan injection to make the inflammation of the rat's paw and the real electroacupuncture of AA has the anti-inflammatory effect [38]. Chung et al. (2011) found the same effect like above but the mechanism of action was blocked by methyl atropine which inhibits cholinergic muscarinic receptor—not naloxone, an inhibitor of the systemic opioid receptor [39]. Zhao et al. (2012) reported that transcutaneous auricular vagus nerve stimulation (ta-VAS) has an effect similar to that of vagus nerve stimulation (VNS). VNS regulates the immune system via the cholinergic anti-inflammatory pathway. The researchers administered rats with lipopolysaccharides through intravenous injection to induce inflammation. They found that VAS and ta-VNS reduced the serum levels of proinflammatory cytokines in lung tissue. The influence of ta-VNS can be suppressed by performing vagotomy or with the α7nAChR (nicotine acetylcholine receptor) antagonist [2]. Ceccherelli et al. suggest that superficial acupuncture is a real placebo method and the level of the pain threshold depends on the intensity of stimulation. They found that an "afferent" somatotopic representation is not equally an "efferent" somatotopy. The electrical stimulation of the ear decides the increased level of the pain threshold in the whole body and not only in the zone somatotopically according to the auricular acupoint [40].

3.3.5. Antioxidation. Liu et al. (2008) recruited 69 patients with high-risk diabetes mellitus and stimulated the shenmen as well as the kidney and endocrine acupoints for 20 days and found a significant reduction in serum superoxide dismutase (SOD) and catalase concentrations [41].

4. Clinical Application

4.1. Analgesia. AA is applied for managing various types of pain such as postoperative, dental, and musculoskeletal pain, as well as pain related to anesthesia [42]. The analgesic effects of AA are induced by activating the descending pain inhibitory pathway of the brainstem, thereby inhibiting the ascending pain pathway. AA application can activate the descending pain inhibitory pathway along the dorsal side of the spinal cord where the dorsal horn cells are located, which exert a pain-relieving effect. Thus, deep brain stimulation can produce analgesic effects by suppressing the dorsolateral funiculus in the spinal tract. Nociceptive pain can trigger activity in the hypothalamus, periaqueductal gray, somatosensory cortex, and prefrontal cortex, but deep brain stimulation can also activate the same regions in the subcortical thalamus to produce analgesic effects. This stimulation-induced analgesic effect increases the concentration of beta-endorphins and can be blocked by naloxone [43].

Simmons and Oleson (1993) conducted a study to measure changes in dental pain after treatment. The group of auricular electrical stimulation after saline injection had an elevated pain threshold of over 23% but the effect is reduced to less than 12% by naloxone. The analgesic effect from AES does not originate only from the endogenous opioid system [44]. Oliveri et al. (1986) used high-intensity transcutaneous electrical nerve stimulation (TENS) on the acupoints of the ear to increase pain threshold [45]. Woodward Krause et al. (1987) found that electrical stimulation (low frequency, 1 Hz, and high intensity, 1000 μA electrical stimulation) on one or two ears can elevate the pain threshold [46]. Noling

et al. (1988) found that a low frequency (1 Hz) with a high intensity (1000 μA) elevated the pain threshold, and this effect peaked 5 to 10 min after stimulation and lasted from several hours to a few days [47]. Lein et al. (1989) used TENS and also had the same result as above [48]. Sator-Katzenschlager et al. (2003) found that auricular electrical stimulation is better than auricular manual acupuncture when decreasing pain [49]. Sator-Katzenschlager et al. (2004) obtained similar findings for auricular EA [50]. Yeh et al. (2014) found an average reduction of 63% in pain intensity at Day 7 in the 27 participants who completed the 4-week treatment [51].

Taguchi et al. (2002) found that AA reduced the anesthetic (i.e., desflurane) requirement about 8.5% [52]. Greif et al. (2002) found that AES reduced the need about 11% [53]. Kindberg et al. (2009) reported that AA application led to greater pain relief compared with local anesthesia (53% versus 19%, resp.) after postpartum surgical repair [54]. Wetzel et al. found that AA reduced the requirement of fentanyl by 15% in 120 patients who underwent total hip arthroplasty [55]. He et al. (2013) employed the four acupoints of the ear (i.e., knee, shenmen, subcortex, and sympathesis) to reduce postoperative pain and the need of anesthesia after total knee arthroplasty [56].

About migraine, Romoli et al. used AA to treat migraine attacks and an innovative diagnostic test called needle-contact test (NCT) or use semipermanent needles to maintain the effect [57, 58]. Allais et al. (2011) found that using "appropriate" points is better than "inappropriate" points when improving migraine and the appropriate points are corresponding to the somatotopic representation of our body on the ear [59].

The application of ear acupuncture in treating postoperative pain remains controversial [60–65]. Usichenko et al. (2005, 2007) found that AA can reduce the consumption rate of ibuprofen in the 120 patients who underwent ambulatory knee surgery [60, 62]. Moreover, Usichenko et al. (2005) found a reduced consumption rate of piritramide in the patient who received total hip arthroplasty [61]. Michalek-Sauberer et al. (2007) found that the required acetaminophen dosage did not differ significantly among the 3 groups (auricular EA, AA, and sham auricular EA) [63]. Yeh et al. (2010) reported that auricular acupressure cannot relieve pain, reduce the dose of analgesics, or alleviate nausea and vomiting in the postoperative patient [65]. Regarding low back pain (LBP), AA has been found to be a beneficial and safe treatment [66–68]. Suen and Wong (2008) found that the longitudinal effects of AA in the elderly with LBP are improving the disability level, pain and sensation, and functional activity [66]. Wang et al. (2009) found that there are significant differences in pain relief of AA in 311 pregnant women with LBP [67]. Hunter et al. (2012) found that the patients in the exercise with AA group reported greater changes in the Oswestry Disability Questionnaire (of roughly 10.7% in points) compared with the exercise-only group at the end of the 6-month follow-up period [68]. Romoli et al. (2014) found that, after one session of ear acupuncture in a group of total knee replacement patients, AEA can reduce pain in sitting and standing position and improve sit-to-stand performance and these variations are still significantly maintained for six hours [69].

Regarding cancer pain, Dillon and Lucas (1999) found that AA led to rapid decreases in pain scores, and the treatment effect was sustained over a long period (i.e., 4 weeks) [70]. Alimi et al. (2003) found that the level of cancer pain decreased 36% in the auricular acupuncture group and auricular EA group but there was less change for patients in the placebo group [71]. Asher et al. (2010) collected 17 randomized control trials in their review and only included 12 studies in their meta-analysis. They found that AA is effective for pain relief but needed more accurate evaluations and a rigorous methodology [72]. Yeh et al. (2014) conducted a review and found that EA in the ear did not yield significant improvements in pain management [42]. Large-sample studies and a strong methodological design are required in order to discern the true efficacy of AA.

4.2. Epilepsy Treatment. Epilepsy is a disease inducing repeated seizures triggered by excessive and abnormal brain activity. The antiepileptic effect of AA is related to the vagus nerve and NTS. Auricular stimulation sends signals through the ABVN into the NTS and reaches other parts of the brainstem, hippocampus, thalamus, and amygdala. The signals from the NTS regulate inflammation by adjusting the levels of TNF-α and IL-1β in the brainstem and hippocampus, thereby preventing the thalamus and amygdala from inducing sleep as well as increasing kindling resistance [73]. He et al. (2013) found that ta-VNS significantly increased the first grand mal latency and the firing rates of the NTS that can suppress epileptiform activity; the reversible cold block of the NTS can inhibit the anticonvulsant effect [74]. Lin and Hsieh (2014) examined the effects of AA and somatic acupuncture in rats with kainic acid- (KA-) induced epilepsy. EA (ST36-ST37, 2 Hz) can decrease hyperexcitability in the brain of rats. Transient receptor potential ankyrin 1 (TRPA 1), which regulates inflammation resulting from environmental exposure, can be controlled by extracellular signal-regulated kinase (ERK), protein kinase A, and protein kinase C (PKC). Auricular EA can reduce epileptiform discharge and the levels of pPKCε, pPKCα, and pERK1/2 and prevent brain inflammation, which leads to epileptic seizures [3]. Liu et al. (2014) found the association between mossy fiber spouting which can be increased by KA contributing to epileptogenesis and auricular EA and ST36-ST37 and AA can reduce the formations of mossy fiber spouting in rats [75]. More randomized clinical and control trials are required to further our understanding regarding the exact effects of AA treatment in patients with epilepsy.

4.3. Substance Dependence. Regarding cocaine dependence, AA is an adjunct treatment combined with conventional approaches including relaxation, medication, and counseling. Wen and Cheung (1973) stated that auricular electrical acupuncture (AEA) in the patient with addiction can improve the withdrawal symptoms [76]. Ng et al. (1975) described that AEA can treat withdrawal syndrome but this effect was inhibited by naloxone. AEA treatment can produce significant decrease of certain naloxone-precipitated

morphine abstinence signs in rats [77, 78]. The National Acupuncture Detoxification Association (NADA) treatment protocol has been the most applied protocol since 1977 [79]. Cocaine can inhibit the reuptake of neurotransmitters in the brain, especially that of dopamine. AA can activate the neuronal release of serotonin in the hypothalamus via the ABVN. Serotonin can activate met-enkephalin, which can inhibit the release of γ-aminobutyric acid (GABA). GABA can inhibit dopamine output in the brain. Finally, AA can increase dopamine levels by inhibiting GABA [80]. Margolin et al. (1996) found that the preselection of acupoints in the ear is not an effective approach for treating subjects with cocaine dependence [81]. Bullock et al. (1999) revealed a nonsignificant difference among the groups as well as in the varied number of AA treatment sessions [82]. Margolin et al. (2002) found that there is a significant reduction in cocaine use but no differences among AA group, a needle-insertion control group, and a relaxation control group [83]. Killeen et al. (2002) found no differences in the psychological and physiological effects of AA between AA and sham AA groups [79]. D'Alberto (2004) conducted a review and found randomized control trials of adequate methodological quality but still could not support the NADA protocol in treating cocaine dependence [80]. Gates et al. conducted a Cochrane review and collected seven studies (comprising 1,443 participants) with low methodological quality, and the conclusions on this issue were inconsistent because of the small samples [84]. Janssen et al. (2012) evaluated the effect of AA (NADA protocol) in pregnant women with drug dependence and found that AA did not have benefit more than the control group. However, the use of methadone may induce an adverse event in the fetus, and AA may be a safe method [85].

Regarding smoking cessation, the mechanism of action of AA is related to the dopamine concentration in the brain. One study found a genetic variation between high and low responders after AA treatment; specifically, the detection frequency of the dopamine D2 receptor*A1 allele (DRD2 TaqI A) was lower in high responders. Detection of the DRD2*A1 allele is related to fewer dopamine receptors [86]. Waite and Clough (1998) recruited 78 smokers into the trial and only 5 participants in the AA group can keep cigarette away after 6 months [87]. Bier et al. (2002) combined AA and education on smoking cessation and cigarette consumption and revealed a significant reduction in smoking cessation and cigarette consumption in AA combined with education group. Moreover, the treatment effect had a negative correlation with the pack-year history [88]. Another study on AA with an Internet-assisted smoking cessation program also found a significant effect compared with AA only [89]. Wu et al. (2007) found a significant reduction in cigarette consumption in both groups (AA and sham group), and the AA group lowered nicotine withdrawal symptom scores. Moreover, no differences were found in the smoking cessation rate in both groups at the end of treatment as well as the follow-up [90]. Yeh et al. (2014) recruited 96 college students and assigned them to AA, interactive media (IM), and control groups. The authors evaluated FEV1, carbon monoxide (CO), and cotinine levels as well as nicotine dependence before and after the 10-week intervention period and found a significant reduction in CO levels and nicotine dependence in all 3 groups as well as lower cotinine levels in the AA and IM groups. However, no differences in FEV1 levels were found in all 3 groups before and after the intervention [91]. White and Moody (2006) investigated the effects of correct and incorrect acupoints on smoking cessation and identified 10 studies (four with high validity) indicating that the correct acupoints were more effective than the incorrect acupoints. Moreover, three high-quality studies reported no differences in the effect of AA between correct and incorrect acupoints, whereas two other studies indicated that incorrect acupoints had greater efficacy compared with correct acupoints. Based on these findings, they concluded that AA efficacy may not be correlated with the position of acupoints [92]. Di et al. (2014) evaluated two issues related to smoking cessation: (a) differences in efficacy between specific ear therapy (including acupuncture, acupressure, and auriculotherapy) and nonspecific control therapy and (b) differences in efficacy between specific ear therapy and specific treatments (i.e., behavioral therapy and body acupuncture). Their results showed that specific ear therapy was better than nonspecific control group and showed no differences between specific ear therapy and specific treatment [93]. The findings confirmed the efficacy of AA in smoking cessation, but the selected acupoints remained controversial.

For alcohol dependence, AA treatment has been found to be ineffective. Sapir-Weise et al. (1999) found no differences between correct and incorrect points in the drinking days and craving status. However, they noted a reduction in anxiety among women who received treatment with correct acupoints at 1-month follow-up [94]. Bullock et al. (2002) showed the significant improvements in the depression, anxiety, and functional status in all groups but no differences in the specific acupuncture, nonspecific acupuncture, and symptom-based acupuncture groups [95].

4.4. Antipsychogenic Effect. Patients may experience fear and anxiety before surgery, and this psychological state may complicate the induction of anesthesia, leading to a poor disease outcome [96]. Romoli and Giommi (1993) identified the Triple Heater (TH, *Sanjiao*) area of the Chinese map as the major area for diagnosing and treating a stress response related to important life events in order to reduce anxiety and depression [26]. Wang and Kain (2001) found that relaxation group is better than shenmen and sham groups in the State-Trait Anxiety Inventory State Scale (STAI) in the chronic disorder [97]. Wang et al. (2001) evaluated the changes in STAI scores in preoperative patients after receiving AA (based on TCM) relaxation, and control groups. The results revealed that the relaxation group had significantly lower STAI scores than the control group, but not the AA group [11]. Kober et al. (2003) evaluated the effect of AA (relaxation group) in alleviating anxiety in the ambulance. The relaxation group lowered the scores of the anxiety and anticipated pain measured by the Visual Analog Scale and improved the disease outcomes. The mechanism may induce the release of endorphins and neurotransmitters, serotonin, norepinephrine, and GABA in the brainstem, midbrain, and hypothalamus [98]. Wang et al. (2004) investigated the effect

of AA on mothers and their children scheduled for surgery. The mothers and their children in the AA group reported a significant reduction in STAI scores and on the modified Yale Preoperative Anxiety Scale compared with the control group. Moreover, children in the AA group reported higher scores in the Induction Compliance Checklist compared with the control group [96]. Mora et al. (2007) examined the effectiveness of AA in alleviating anxiety in patients before receiving extracorporeal shock wave lithotripsy. The results revealed a significant reduction in anxiety, reduction in pain, and improved treatment outcome in the AA group [99]. Karst et al. (2007) investigated the effectiveness of AA versus medication treatment on dental anxiety. The results revealed that AA and intranasal midazolam had similar effects in alleviating anxiety and raising compliance [100]. Black et al. (2011) examined the efficacy of AA in patients withdrawing from psychoactive drugs. The NADA protocol group did not report higher scores in reduced anxiety compared with the sham AA and control groups [101]. Michalek-Sauberer et al. (2012) examined AA efficacy in patients with dental diseases. The AA group reported lower anxiety scores compared with the sham group, whereas the control group reported increased anxiety [102]. Reilly et al. (2014) investigated the efficacy of AA on anxiety levels in caregiver. The results revealed a significant decrease in STAI scores and higher Caring Ability Inventory scores in the AA group [103]. Gagliardi et al. (2014) enrolled 20 health volunteers (divided into real and sham groups) and assessed the anxiolytic-sedative effect of AA on health person. There was a significant reduction of the numeric rating scale anxiety score ($p < 0.01$) and State-Trait Anxiety Inventory State anxiety score values ($p < 0.005$) in the real acupuncture group. The Bispectral Index System score did not change after 5 minutes, but a significant decrease in anxiety was noted in the real acupuncture group [104].

Regarding patients with depression, Nixon et al. (2003) examined the efficacy of AA in treating depression in adolescents with repetitive self-injurious behavior (SIB). The results revealed a significant decrease in SIB frequency 4 weeks after treatment, although the decrease in the urge to self-injure was nonsignificant [105]. Shi et al. (2013) examined the effects of continuous auricular EA in patients with depression. The results revealed a significant increase in HRV as well as lower scores on the Hamilton Anxiety Rating Scale (HAM-A), the Athens Insomnia Scale (AIS), and the Hamilton Rating Scale for Depression (HRSD), but the changes in heart rate and low frequency/high frequency ratio (LF/HF ratio) were nonsignificant [106]. Liu et al. (2013) investigated the efficacy of auricular EA in rat models. The findings revealed a significant reduction in blood pressure comparable to that achieved through VNS as well as a significant decrease in HRV in the EA in the auricular concha region (EA-ACR) group, but not in the other groups. EA-ACR groups experienced a significant reduction in plasma cortisol and adrenocorticotropic hormone (ACTH) levels. The effect of EA-ACR on depressed rats may be induced by the normalization of hypothalamic-pituitary-adrenal axis hyperactivity [107].

4.5. Insomnia. Insomnia affects many people of all ages and contributes to many disorders (e.g., fatigue, instability, depression, impaired daily function, anxiety, and substance abuse) [108]. Insomnia is diagnosed when the quality and amount of sleep are deemed unsatisfactory, and when people have difficulty falling asleep, staying asleep, and waking up too early [109]. The mechanism of AA in insomnia may involve the regulation of melatonin [110]. Suen et al. (2002) evaluated the effects of auricular therapy on sleep promotion. The results revealed significant improvements in nocturnal sleep time and sleep efficiency in all groups, but significant improvements in sleep behavior were found only in the magnetic pearl group [111]. One year later, Suen et al. (2003) reported long-term effects for magnetic pearl auricular therapy in treating insomnia in elderly people after identifying significant changes in nocturnal sleep time and improvements in sleep behavior in 15 elderly patients, and this effect was retained 6 months after treatment [112]. Kim and Sok (2007) examined the efficacy of AA in treating insomnia. The sleep state and sleep satisfaction improved significantly, and the effect lasted for 2 weeks [109]. Sjöling et al. (2008) examined the effects of AA on patients with insomnia. The results revealed nonsignificant differences in total sleep time in both groups, as well as in the frequency of waking up and ease in waking up in the AA group. However, the other sleep parameters improved substantially in both groups during treatment [113]. Wu et al. (2014) conducted a pilot study to evaluate the effects of AA on hemodialysis patients with insomnia. The results revealed significant decreases in the scores of the Pittsburgh Sleep Quality Index (PSQI) for sleep quality, sleep latency, sleep disturbance, daytime dysfunction, and reduced intake of medication [114]. Review articles were consistent in their conclusion that AA had an effect on insomnia, but the low methodological quality of these studies limited the validity of their findings [12, 108, 115, 116].

4.6. Obesity. Obesity was found to raise the risk of metabolic syndrome and cardiovascular and cerebrovascular diseases [117, 118]. The causes of obesity included an unbalanced diet, genetic heredity, socioeconomic factors, endocrine diseases, lack of exercise, and emotional issues [118]. Asamoto and Takeshige (1992) [119] stimulated the rat inner auricular areas that represent the human pylorus, lung, trachea, stomach, esophagus, and endocrine, and heart acupuncture points induced the action potentials in the hypothalamic ventromedial nucleus (HVM), the satiety center. Needle implantation into any of these points reduced the body weight of rats. Stimulation of other acupuncture points did not induce HVM action potentials. If the HVM was destroyed, the AA had no effect on body weight. There were no effects of the AA on the lateral hypothalamus (LHA). Shiraishi et al. (1995) investigated whether the electrical auricular stimulation affected the activities of the LHA and HVM in rats. The results revealed reduced activity in LHA neurons and increased activity in VMH neurons after electrical auricular stimulation. Even the nonobese rats still have the effects of the AA on reducing body weight [120–122]. Kim et al. (2001) found that AA treatment in unfed rats can lower neuropeptide Y (NPY), whereas in fed rats it can increase NPY [123]. Cabioğlu and Ergene (2006) investigated EA on the hunger and shenmen points of the auricle and found that the points LI4, LI11,

ST36, and ST44 can alter the levels of biochemistry in obese women. The results revealed increased serum insulin and C-peptide levels in the EA group compared with the placebo group. A higher C-peptide level is positively correlated with a higher body mass index (BMI) [124]. C.-H. Yeh and S.-C. J. Yeh (2008) investigated obesity-related parameters in nonobese and obese participants after AA treatment. The results revealed a significant reduction in waist circumference (WC) and hip circumference (HC) in nonobese subjects, but not in obese subjects [125]. Shen et al. (2009) described another mechanism, which differed from the involvement of NPY reduction. After 4 weeks of AA treatment, their body weight decreased in both the AA group and the control group. Sympathomimetic effects were noted in both groups and the effects are increasing the basal metabolism and reducing appetite temporarily [126]. Hsu et al. (2009) monitored the effects of AA on obesity-related parameters and hormone peptides. The findings indicated no change in body weight, BMI, and WC between both groups, but a significant increase in ghrelin and a decrease in leptin in the AA group [127]. Hsieh (2010) investigated the effectiveness of AA on body weight and serum lipid levels in obese adolescents. The BMI was significantly decreased in all groups but the total cholesterol, triglycerides, high density lipids, and low density lipids were all significantly increased [128]. Ching et al. (2012) recruited 86 obese patients with schizophrenia and randomly assigned them to an AA group and a control group. No differences were found between the AA group and the control group in body weight, WC, and body fat percentage after an 8-week intervention [129]. Abdi et al. (2012) hypothesized that the effects of AA on the reduction in body weight were related to the immune system or the inflammatory process. The results revealed a reduction in anthropometric factors and antiheat shock protein antibodies, but not in high-sensitivity C-reactive protein levels in the AA group, and indicated that the effects of AA are induced through immunomodulation [130]. Yeo et al. (2014) investigated the effect of different auricular acupoints in improving obesity. The results revealed significant differences in BMI, body weight, and body fat percentage between the treatment and control groups, but no differences between the five-point (i.e., shenmen, spleen, stomach, hunger, and endocrine) and one-point (hunger) groups [131]. Darbandi et al. (2014) examined the effects of different acupuncture methods on abdominal fat reduction. Body EA and AA were both found to have significantly reduced BMI, WC, HC, and trunk fat mass. Body EA was more effective in reducing WC compared with AA, whereas AA had a greater effect in reducing HC [132]. Kim et al. (2014) examined the effects of AA combined with *Sinapis alba* seeds in treating obesity. They found a significant decrease in body weight and BMI in the AA group, but the changes in body fat percentage and waist-to-hip ratio were nonsignificant [118]. Set et al. (2014) investigated the effects of AA in treating depression in obese women. The results revealed that the BMI and Beck Depression Inventory for Primary Care scores decreased following AA treatment [133]. He et al. (2012) designed a randomized controlled clinical trial to compare the effect between both auricular acupressure and exercise and exercise alone on obesity. They found that both auricular acupressure and exercise for 4 weeks may produce greater effect than exercise alone for body weight reduction in Chinese women with primary obesity [134].

5. Conclusion

Auricular therapy is a convenient approach for treating diseases in areas lacking medical resources. Evidence on auricular therapy supports its efficacy for pain relief, in treating epilepsy and anxiety, as well as obesity, and in improving sleep quality, but not for treating substance dependence. The mechanism of auricular therapy warrants further study.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Research Article

Comparison of Body, Auricular, and Abdominal Acupuncture Treatments for Insomnia Differentiated as Internal Harassment of Phlegm-Heat Syndrome: An Orthogonal Design

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Objective. To identify the optimum treatment protocol for insomnia among auricular, body, and abdominal needling methods. *Methods.* A three-factor (3 needling protocols) and three-level experimental scheme was designed based on orthogonal method. 54 patients of insomnia differentiated as internal harassment of phlegm-heat syndrome were given two courses of acupuncture treatment (each with 20 times of acupuncture). The therapeutic effects were evaluated by comparing the Pittsburgh sleep quality index (PSQI), Hamilton Depression Scale (HAMD) scores, and Hamilton Anxiety Scale (HAMA) scores of patients before treatment, after one course of treatment, and after two courses of treatment as well as one month after treatment. *Results.* Body, auricular, and abdominal acupuncture treatments all alleviated symptoms of insomnia, depression, and anxiety, but body and auricular acupuncture had stronger therapeutic effects. *Conclusions.* Body acupuncture at basic points shall be given priority in protocol selection for insomnia. The second-best choice is auricular acupuncture with basic points combined with points based on Traditional Chinese Medicine (TCM) theories. Abdominal needling with very quick effect can be an alternative protocol with basic points combined with syndrome differentiation points.

1. Introduction

Insomnia is a sleep disorder that includes trouble falling asleep, staying asleep, or waking too early, resulting in daytime impairment [1]. About 30% of adults report at least one of the symptoms of insomnia. When daytime impairment is added as a criterion, the prevalence is about 10% [2]. Long-term insomnia relates to body and mental health impairment, multivisceral dysfunction, and immune decline, as well as depression, anxiety, and other mental diseases [3]. Prevalence is higher among women [4], and, due to their physical and psychological peculiarity, women may easily get depression and anxiety as comorbidities of insomnia.

The sleep-wake cycle is a very complicated process, which involves central and peripheral nervous systems as well as the endocrine system [5, 6]. Modern medicine has not possessed a complete and clear understanding of the pathogenesis so far, whereas it is commonly accepted that pathological changes occur in the anatomical structure of the sleep-wake cycle, including inhibitory nucleus and arousal nucleus and the imbalance of corresponding neurotransmitters. In addition, endocrine regulation is in close relationship with the sleep-wake rhythm, for hormones like melatonin have been confirmed to have a curative effect on insomnia. To put it in a simple way, the pathogenesis manifests either as a weakening of the inhibitory function or as an enhancement of the arousal function.

From a Traditional Chinese Medicine (TCM) perspective, the pathogenesis of insomnia is intricate, involving disharmony of Zang and Fu organs (viscera) and disorder of Wei and Ying Qi (defensive qi and nutrient qi) as well as the Shen (spirit) disturbance of Zang organs. In brief, the pathogenesis

of insomnia is regarded as imbalance between Yin and Yang, particularly a result of excessive Yang and deficient Yin, which is quite similar to the general understanding of western medicine.

Acupuncture is a simple but useful treatment for insomnia, with a success rate of around 90% [7]. An explanation of modern medicine is that acupuncture can improve the neurotransmitter balance in the central nervous system. For instance, acupuncture increases the contents of γ-amino butyric acid (GABA) and Serotonin in the brain [8–10] and thus improves sleep quality. Improvement may be also due to the endocrine system, for example, the nocturnal increase in endogenous melatonin secretion [11]. Acupuncture treatment has several forms besides body needling, one group of which is micro needling system such as auricular and abdominal needling. Mechanisms underlying auricular and abdominal acupuncture are quite identical to the mechanism of body needling, which is characterized by dredging meridians and collaterals, building up body resistance to pathogenic factors, balancing Yin and Yang, and regulating the functions of Zang and Fu organs.

The study selected patients with phlegm-heat syndrome in TCM diagnosis based on references to traditional syndrome differentiation, clinical experiences, and literature review. As the life rhythm speeds up, more and more people suffer from inadequate sleep and improper diet. Their syndrome manifests as phlegm-heat. In the perspective of TCM, the pathogenesis of insomnia is "deficiency in origin and excess in symptom" (Ben Xu Biao Shi), and in most cases it cooccurs with phlegm and dampness as well as blood stasis [12]. The symptoms of phlegm-heat syndrome are as follows [13]: restless sleep, irritation and upset, suppression in the chest and gastric fullness, bitter taste in the mouth and profuse phlegm, dizziness, red tongue, yellow and thick tongue coating, and rapid pulse or rapid with slippery pulse.

Acupuncture is a complex therapy, including crucial factors such as syndrome differentiation, acupoint combination, and needling method as well as manipulation. Most clinical studies of insomnia treatments use single or combined protocols, whose therapeutic effects vary as different methods and indicators are used. Among Randomized Controlled Trials (RCTs) of acupuncture treatment for insomnia published in recent 10 years, the most commonly reported methods are body needling, auricular needling, abdominal needling, and their combinations. Although different influences are reported due to variances of methods and combination of acupoints, the effective rates in these studies are all highly or equally reported; moreover, there are various methods to form control groups, but the horizontal comparison and superiority trials are scanty. Aiming to identify an optimum protocol for insomnia, based on RCTs in China and abroad in recent ten years, this study chose the 3 highly evaluated protocols with different acupoints formula.

The orthogonal method is the best choice to design an experiment involving multivariate statistics. Its strengths lie in balanced distribution, calculation simplicity, and symmetrical comparability, so that it not only allows for effective experimental results with minimum time and cases of illness in clinical study, but also is capable of showing clearly interaction among factors and superiority among levels of each factor.

This study is designed as an orthogonal test to evaluate the effects of three acupuncture treatments on 54 patients with insomnia differentiated from internal harassment of phlegm-heat syndrome.

2. Materials and Methods

2.1. Data Collection. 54 patients (45 females and 9 males) suffering from primary insomnia diagnosed by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [1], and differentiated from phlegm-heat syndrome, all aged between 26 and 60 years (with the average age of 43.9 ± 9.9 years), were enrolled in the study and treated in the Acupuncture Hospital of China Academy of Chinese Medical Sciences from May 2012 to May 2013.

2.2. Inclusion and Exclusion Criteria. Inclusion criteria were as follows:

(1) Primary insomnia patients diagnosed in accordance with DSM-IV, as mentioned above.

(2) Patients with primary insomnia differentiated from phlegm-heat syndrome, diagnosed in accordance with Terminology of Clinical diagnosis and treatment of TCM as mentioned above.

(3) Patients aged between 20 and 60 years (including 20- and 60-year olds).

(4) The total score of Pittsburgh sleep quality index (PSQI) [14] > 7.

(5) The score of Hamilton Depression Scale (HAMD) [15] < 20.

(6) The score of Hamilton Anxiety Scale (HAMA) [16] < 14.

(7) Patients who signed the informed consent.

Exclusion criteria were as follows:

(1) Pregnancy and lactation.

(2) Patients with cardiovascular, lung, liver, kidney, or hemopoietic system diseases in late stages.

(3) Patients with mental diseases.

(4) Patients accepting related medication or other treatments.

(5) Severe adverse reactions to acupuncture (e.g., fainting during acupuncture).

2.3. Method

2.3.1. Grouping. The L_9 (3^4) orthogonal array (Table 1) was used in the study. Patients were randomly assigned to nine protocols in a single-blinded study. In Table 1, alphabets A, B, and C denote different treatment protocols and values 1, 2, and 3 indicate three different levels; alphabet D denotes the error term, which is excluded in the study. The details of protocols and levels employed in this paper are shown in Table 2.

Table 1: L_9 (3^4) orthogonal array.

Patient number	Column number			
	A	B	C	D
1	1	1	1	1
2	1	2	2	2
3	1	3	3	3
4	2	1	2	3
5	2	2	3	1
6	2	3	1	2
7	3	1	3	2
8	3	2	1	3
9	3	3	2	1

Table 2: Designs for protocols and levels.

Protocols	Levels
A: body acupuncture	Level 1: 0 (body acupuncture not applied)
	Level 2: basic acupoints
	Level 3: basic points + syndrome differentiation acupoints
B: auricular acupuncture	Level 1: basic acupoints
	Level 2: 0 (auricular acupuncture not applied)
	Level 3: basic points + acupoints based on TCM theories
C: abdominal acupuncture	Level 1: basic acupoints
	Level 2: basic points + syndrome differentiation acupoints
	Level 3: 0 (abdominal acupuncture not applied)

2.3.2. Treatment. Eight Chinese-trained and licensed acupuncturists with a median of 12 years of experience (range: 5 to 20 years) provided study treatments in the clinics. Before the study, all acupuncturists made consensus on the protocol of point selection and needle manipulations.

(1) Body Acupuncture. The acupuncture point selections were based on Traditional Chinese Medicine meridian theory to treat insomnia. The points were made references to the *evidence-based guidelines of clinical practice with acupuncture and moxibustion: insomnia* [17] and approved by committee of acupuncturists of the study.

Acupoints. The basic acupoints are Zhaohai (KI 6), Shenmai (BL 62), Shenmen (HT 7), Yintang (EX-HN 3), Sishencong (EX-HN 1), and Anmian (Ex-HN 22).

Acupoints selected on the basis of syndrome differentiation (hereafter referred to as syndrome differentiation acupoints) are Fenglong (ST 40), Neiting (ST 44), and Quchi (LI 11).

All acupoints were selected bilaterally except Yintang (EX-HN 3).

Operation. 1 cun (0.25 × 25 mm) and 1.5 cun (0.25 × 40 mm) disposable needles were used in the treatment. Patients laid in the supine position as the treatment proceeded. Needles were inserted with lifting and thrusting as well as rotating methods till qi sensation was felt. Among acupoints, Zhaohai (KI 6) was stimulated by the reinforcing technique, while Shenmai (BL 62) and syndrome differentiation acupoints were stimulated by the reducing technique. The rest of the acupoints were stimulated by the neutral reinforcing and reducing technique.

All points were stimulated for 1 minute in every 15 minutes. Needles were retained for 30 minutes.

Frequency and Courses of Treatment. Frequency and courses of treatment were as follows: once every other day, 3 times per week, 10 times in each course, and 2 consecutive courses in total.

(2) Auricular Acupuncture. The auricular point selections were based on TCM theory. The points were also made references to *evidence-based guidelines of clinical practice with acupuncture and moxibustion: insomnia* [17] and were approved by committee of acupuncturists of the study.

Acupoints. We used auricular acupoints as suggested in the *nomenclature and location of auricular points* [18].

The basic acupoints are Shenmen (TF4), Occiput (AT3), Chuiqian (LO4), and Subcortex (AT4).

Acupoints based on TCM theory were Spleen (CO13), Stomach (CO4), Heart (CO15), and Liver (CO12).

Acupoints were selected unilaterally at a time, and alternated every other day.

Operation. 1 cun (0.25 × 25 mm) disposable needles were used in the treatment. Patients took the supine position. After routine disinfection of acupoints, the needle was inserted and manipulated moderately without penetrating the skin.

The frequency and courses of treatment were the same as those of the body acupuncture.

(3) Abdominal Acupuncture. The abdominal acupuncture was guided by TCM theory and as one of holographic acupuncture methods. We used abdominal acupoints as suggested in the *Abdominal Acupuncture* [19].

Acupoints. Basic formula is as follows: Zhongwan (RN 12), Xiawan (RN10), Qihai (RN 6), and Guanyuan (RN 4); Shangqu (KI 17) (bilateral), Huaroumen (ST 24) (bilateral), Wailing (ST26) (bilateral), and Pinggan (extra point) (Bilateral).

Syndrome differentiation acupoints were Daheng (SP 15) (bilateral), Xiere (extra point) (bilateral).

Location of Pinggan was 0.7 cun outside and 0.3 cun above Huaroumen (ST 24); Xiere was 3 cun outside of Qihai (RN 6).

Operation. 1 cun (0.22 × 25 mm) and 1.5 cun (0.25 × 40 mm) disposable needles were used in the treatment. Patients took the supine position. After routine disinfection of acupoints, needles were vertically inserted into the skin according to the following sequence: from upward to downward, from inside to outside.

Table 3: Baseline data of patients with insomnia.

Group	Cases	M	F	Age (years)	Duration of disease (years)	PSQI	HAMD	HAMA
1	6	1	5	43.83 ± 11.05	3.42 ± 3.58	13.67 ± 3.01	10.67 ± 4.03	7.83 ± 4.17
2	6	1	5	44.17 ± 10.67	2.33 ± 3.12	11.67 ± 3.93	10.50 ± 2.43	7.83 ± 3.13
3	6	1	5	40.00 ± 15.87	1.58 ± 2.10	14.83 ± 1.60	12.00 ± 5.10	8.33 ± 3.50
4	6	1	5	44.00 ± 14.25	5.21 ± 7.46	13.33 ± 4.18	11.50 ± 6.63	8.50 ± 3.83
5	6	1	5	41.67 ± 7.76	4.25 ± 5.49	12.33 ± 3.14	13.50 ± 4.64	10.50 ± 5.21
6	6	1	5	43.83 ± 13.00	7.75 ± 7.07	12.00 ± 3.29	9.17 ± 2.32	8.33 ± 3.27
7	6	1	5	37.17 ± 10.98	2.58 ± 3.77	9.83 ± 2.86	10.67 ± 3.56	9.83 ± 3.25
8	6	1	5	41.50 ± 12.18	2.50 ± 2.56	11.50 ± 3.45	8.00 ± 4.90	6.67 ± 5.24
9	6	1	5	41.50 ± 10.41	1.19 ± 1.58	14.17 ± 3.43	11.50 ± 5.24	8.17 ± 3.66
Sum	54	9	45	41.96 ± 11.80	4.26 ± 5.34	12.59 ± 3.21	10.83 ± 4.32	8.44 ± 3.92

Needles were applied at Zhongwan (RN 12), Xiawan (RN10), Qihai (RN 6), and Guanyuan (RN 4), touching the linea alba of Ren meridian (fascia layer) and after needles were inserted at Zhongwan (RN 12), Xiawan (RN10), and Qihai (RN 6), the direction of needle tips was adjusted to be inserted obliquely at an angle of 45° along the Ren Meridian, while a needle was inserted vertically at Guanyuan (RN 4).

After a needle was applied at Shangqu (KI 17), the direction of the needle tip was adjusted to move obliquely downward at an angle of 45° along the kidney meridian to the depth of the fat layer.

Needles were inserted vertically at Huaroumen (ST 24), Wailing (ST26), Pinggan, Daheng (SP 15), and Xiere, to the fat layer at Huaroumen (ST 24), Wailing (ST 26), and Daheng (SP 15), to the muscle layer at Pinggan and Xier.

The frequency and courses of treatment were the same as those of the body acupuncture.

Patients were kept warm during treatment.

2.4. Clinical Outcomes. Sleep quality of patients was evaluated with PSQI scores before the treatment and after 1 course and 2 courses of treatment and 1 month after treatment. Similarly, depression was evaluated with HAMD scores and anxiety with HAMA scores.

2.5. Statistical Analysis. SPSS17.0 was used to analyze data. A descriptive analysis was performed first, and then was followed by a visual calculation in accordance with requests of orthogonal test. The R value indicated the influences of different protocols; that is to say, a higher score of R meant the protocol was more effective.

3. Results

3.1. General Data. There was no statistically significant difference between the groups in terms of age, duration of disease, and scores of PSQI, HAMD, and HAMA. The average age, duration of disease, and PSQI, HAMD, and HAMA scores were 41.96 ± 11.80 (years), 4.26 ± 5.3 (years), and 12.59 ± 3.21, 10.83 ± 4.32, and 8.44 ± 3.92, respectively (Table 3).

3.2. PSQI Scoring. The R values symbolizing the range of PSQI score in orthogonal test were shown in Figure 1. As time went by, auricular acupuncture demonstrated an accelerating trend on PSQI score reduction, while abdominal acupuncture showed a decelerating trend. Body acupuncture presented an impressive promotion after treatment rather than during the treatment (Figure 1).

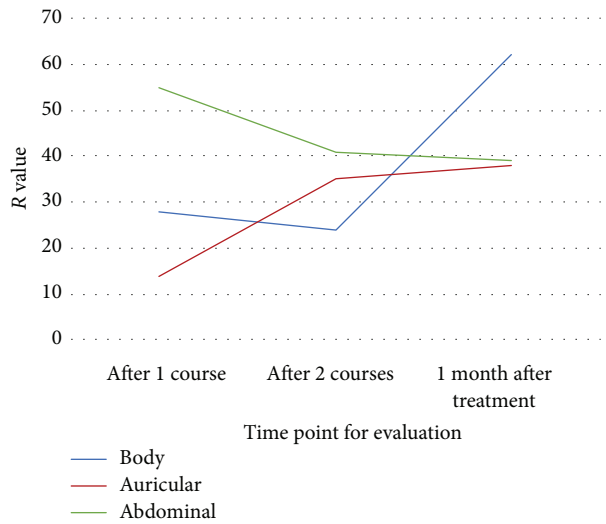

Figure 1: Influences on PSQI scores of different protocols at each time point.

Table 4 compares the PSQI score reduction from three levels of three protocols. It indicates that A2 basic acupoints, B3 basic points + acupoints based on TCM theories, and C2 basic + syndrome differentiation acupoints had stronger influences on the descending trend of PSQI scores, which meant continuous improvement of sleep quality (Table 4).

3.3. HAMD Scoring. The R values symbolizing the range of HAMD score in orthogonal test were shown in Figure 2. As time went by, auricular acupuncture demonstrated first a sharply decelerating and then accelerating trend on HAMD score reduction, while abdominal acupuncture showed an accelerating and then decelerating trend. Body acupuncture presented an impressive promotion especially after the treatment.

Table 4: PSQI comparison among three levels of each protocol (factor).

Group	After 1 course	After 2 courses	1 month after treatment
A1	79	116	111
A2	87	104	134
A3	75	115	81
B1	75	116	101
B2	81	104	92
B3	85	115	133
C1	52	98	91
C2	109	132	125
C3	80	105	110

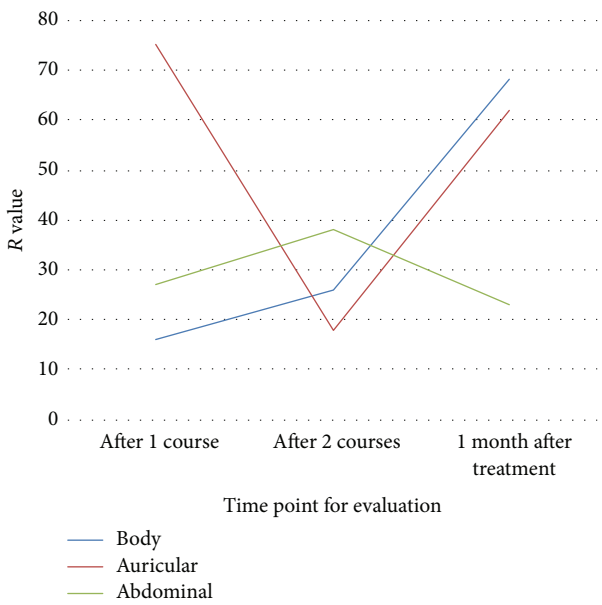

Figure 2: Influences on HAMD scores of different protocols at each time point.

Table 5 compares the HAMD score reduction from three levels of three protocols. It indicates that A2 basic acupoints, B3 basic points + acupoints based on TCM theories, and C2 basic + syndrome differentiation acupoints had stronger influences on the descending trend of HAMD score, which meant improvement in depression (Table 5).

3.4. HAMA Scoring. The *R* values symbolizing the range of HAMA score in orthogonal test were shown in Figure 3. As time went by, auricular acupuncture demonstrated a slightly decelerating and then accelerating trend on HAMD score reduction, while abdominal acupuncture showed a decelerating trend, whereas body acupuncture presented an accelerating trend.

Table 6 compares the HAMD score reduction from three levels of three protocols. It indicates that A2 basic acupoints, B1 basic acupoints, and C2 basic + syndrome differentiation acupoints had stronger influences on the descending trend of HAMA score, which meant improvement in anxiety (Table 5).

Table 5: HAMD comparison among three levels of each protocol (factor).

Group	After 1 course	After 2 courses	1 month after treatment
A1	57	90	85
A2	66	93	109
A3	50	67	41
B1	40	82	57
B2	29	75	59
B3	104	93	119
C1	45	92	66
C2	72	98	88
C3	56	60	81

Table 6: HAMA comparison among three levels of each protocol (factor).

Group	After 1 course	After 2 courses	1 month after treatment
A1	33	76	78
A2	48	72	95
A3	46	47	58
B1	36	73	94
B2	34	59	53
B3	57	63	84
C1	47	73	76
C2	49	67	79
C3	31	55	76

4. Discussion

The study used orthogonal design, an experimental design used to test the comparative effectiveness of 3 intervention components (protocols), each of which took on 3 variants (levels) in this study, because it allowed testing the effectiveness of body, auricular, and abdominal acupuncture simultaneously in a single study with far fewer experimental units than it would take to exhaust all possible intervention combinations [20]. To design and implement this technique, orthogonal array would first be chosen to fit the study purpose. Since 3 kinds of acupuncture were tested for interaction, and point selection was the second consideration, then it would be structured to the 3 factors (the number of columns in an array) and 3 levels (the maximum number of values that can be taken on by any single factor) of the array. With respect to suitable orthogonal array selection (orthogonal arrays are most often named following the pattern L_{Runs} ($Levels^{Factors}$)), the rule is to find one with the smallest number of runs (the number of test cases) [21]. Since there was no orthogonal array of 3 factors and 3 levels, then L_9 (3^4) orthogonal array was most suitable in the study.

Among the three protocols, body needling had steadily accelerating effectiveness on improvement of insomnia, depression, and anxiety in both the treatment and the follow-up period. Therefore it was the most recommended therapy and the best level was to use basic acupoints for treatment. The mechanism of body needling treatment for insomnia in TCM included regulating Yin Qiao and Yang Qiao meridians

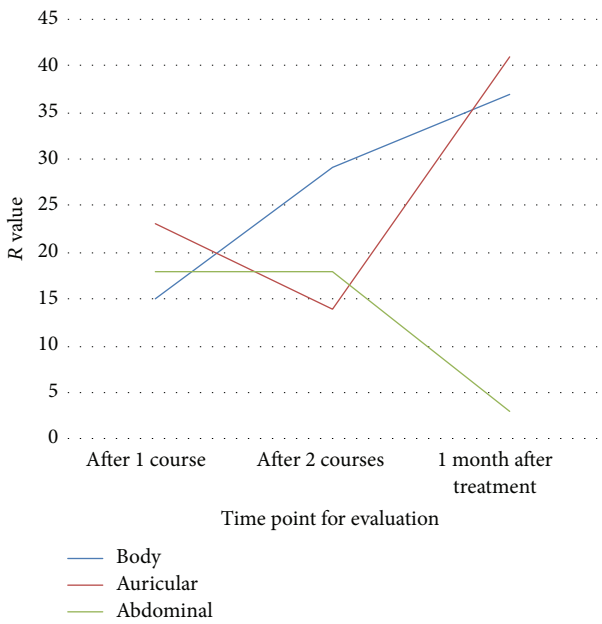

Figure 3: Influence on HAMA scores of different protocols at each time point.

with points of Zhaohai (KI 6) and Shenmai (BL 62) to balance Yin and Yang based on the Yin-yang theory and Ying-wei theory; tonifying the heart and calming the mind with Shenmen (HT 7), Yintang (EX-HN 3), Sishencong (EX-HN 1), and Anmian (Ex-HN 22) based on the shen- (spirit-) dominating-sleep theory. The basic points alone were able to adjust the function of the whole body, so that was enough to take effect on insomnia patients with internal harassment of phlegm-heat syndrome. However, further studies are needed to explore suitable protocols for insomnia patients with other syndromes.

In TCM, heart is the master of five viscera including heart, lung, spleen, liver, and kidney. "Shen of heart," dominating mental activity, is self-consciousness and unique human ability. Their function however quite resembles cerebrum. If shen calms down, humans fall asleep, while when shen activates, they wake up. Moreover, sleep follows daily biological rhythm and shows as a sign of balance of Yin and Yang. In TCM, if wei qi flourishes in Yang qiao meridian, eyes open and consciousness is regained, while if wei qi flourished in Yin qiao meridian, eyes close and sleep will come. According to meridian circulation, Yin qiao and Yang qiao meridians confluence at inner canthus and then enter the brain. In other words, they are both crucial routes related to sleep. Thus it can be seen that TCM theory considers the fact that sleep is closely linked with brain function, so that most of acupoints selected to treat insomnia locate on the head. In TCM, the insomnia treating principle lies in balancing Yin and Yang. And fMRI can be taken as one of parameters of insomnia regulations by acupuncture. Gao et al. [22] reported that, in sleep deprivation, an imbalance occurs; acupuncture stood for a homeostatic force to renormalize the Yin and Yang; biphasic regulation effects of acupuncture, the salience network, composed of the anterior insular cortex and anterior cingulate (ACC), a unique interoceptive autonomic circuit, might indicate the mechanism underlying acupuncture in restoring sleep deprivation. Effects of acupuncture were closing to launch homeostatic regulation [23, 24].

The auricular needling also had a clear therapeutic effect on insomnia, depression, and anxiety. Unlike body needling, its efficacy in treating insomnia increased continuously, while, in ameliorating depression and anxiety, the increase got decelerated in the treatment period while it was accelerated during follow-up period. From the respective of TCM, the auricle had close relationships with both meridians and viscera. Holographic medicine and modern medicine have also confirmed the somatotopic function of specific regions of the ear. Various nerves including the spinal and cranial nerves are distributed at the auricles, particularly in the triangular fossa and the concha region. Among those nerves, the vagus nerve is a mixed nerve composed of about 80% afferent fibers. The concha area has a rich distribution of the vagus nerve. Stimulating points in this region with needles can adjust functions of the viscera and the central nervous system, as well as the autonomous system [25–27]. It was speculated that the insomnia regulating effects of vagus nerve stimulation were partially attributed to the projection of afferent fibers to the nucleus tractus solitarius, which was further connected directly and indirectly with brain structures [28] including the locus coeruleus, cerebral cortex, hippocampus, thalamus, and cerebellum [29]. Just yet, some of these brain regions were also believed to be involved in the pathogenesis of sleep disorder [30–32], which built a basis for treatment with vagus nerve stimulation [29]. Moreover, excitation of the parasympathetic nerve, which was part of the vagus nerve, stimulated the pineal gland to secrete melatonin [33–37]. Insomnia closely related to functional decrease of central melatonin; mutual promotion between excitation of parasympathetic nerve and melatonin secretion became a basis of treating insomnia [38–41]. It might partly explain the therapeutic effect of auricular acupuncture. Furthermore, basic points like Occiput (AT3), Chuiqian (LO4), and Subcortex (AT4) were mainly used as corresponding points of the brain. Stimulation at these points and Shenmen (TF4) calms the mind. Points based on TCM theory such as spleen (CO13), stomach (CO4), heart (CO15), and liver (CO12) can regulate viscera functions to improve phlegm-heat symptoms, and since they are all located in the concha region, these points can improve sleep quality by stimulating the vagus nerve. Besides, the stimulation of auricular needling was stronger than the other two protocols, so it may take effect very quickly, especially for the treatment of anxiety and irritation, and it might explain why it had rapid and solid effect in depression and anxiety.

Brain imaging tools have been used to investigate the fMRI signal change evoked by transcutaneous vagus nerve stimulation recently [42]. Kraus et al. [42] found that robust tVNS can induce fMRI signal decreases in limbic brain areas, including the amygdala, hippocampus, parahippocampal gyrus, and middle and superior temporal gyrus, as well as an fMRI signal increase in the insula, precentral gyrus, and thalamus. As mentioned above, these were all important structures related to sleep-wake cycle. In recent study of tVNS

treating major depressive disorder, by the help of fMRI, Fang et al. [43] found that significant functional connectivity (FC) between default mode network (DMN) and brain regions such as the parahippocampus, ACC, and medial temporal areas. These results suggested that the modulation of tVNS was not targeted at one particular region but it rather influenced brain region networks associated with emotion/affect regulation. Since insomnia also related intimately to depression and anxiety, it might provide a reference approach for treatment and a mechanism explanation.

Abdominal needling could improve insomnia, depression, and anxiety with a gradually decelerated increase. The abdominal region is where the viscera and meridians are located, including the Ren, kidney, spleen, and stomach as well as gallbladder and branch meridian of Du meridians. The abdominal needling helped to harmonize Yin and Yang and regulate meridians and viscera, which corresponded to the pathogenesis of insomnia: imbalance of Yin-Yang and disorder of viscera function. Furthermore, the abdominal needling demanded slight and shallow stimulation, with finer needles, which minimized pain compared with traditional needling techniques, so it was easily accepted by patients, particularly at the initial stage of the treatment. That might explain its remarkable effect at the beginning of treatment. Basic formula combined with syndrome differentiation points produced a stable and better effect. Among the points, Daheng (SP 14) and Xiere are located on and near the spleen meridian, which might strengthen the spleen's function of dispersing phlegm. Wang [44] applied abdominal needling treatment for depression; the author observed that, by means of fMRI-ReHo, patients suffered abnormal changes in several brain regions in resting-state, especially limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit; however, after abdominal needling treatment, their function could be regulated through amelioration of blood oxygen and metabolism. The circuit and cortico-striato-thalamic-cortical loop (CSTC loop) overlapped quit a lot in the brain. The latter was known to regulate cortical arousal by controlling the effectiveness of the thalamic filter; this system regulated cortical arousal by filtering out sensory input for maintaining sleep or by allowing specific sensory input to the cortex for maintaining cortical arousal [30]. Therefore, one explanation for the fact that abdominal needling took effect on insomnia might lay in the circuit mentioned above.

It shall be noted that our study had several limitations. Firstly, the syndrome differentiation of patients in the study was internal harassment of phlegm-heat syndrome, so the conclusions shall not be applied to other syndromes. Secondly, though the study efficiently compared the therapeutic effects of three protocols and corresponding points selection with a L_9 (3^4) table of orthogonal design, it did not examine the interaction effects between them. Therefore, the conclusions did not address the question of whether the protocols shall be used together or separately. Thirdly, both the auricular and abdominal needling showed a significant therapeutic effect at the beginning of treatment, but the increasing effect of auricular needling was unsteady for depression and anxiety and so was the increasing effect of abdominal needling. Differences between body needling and micro-needling system, as well as between different micro-needling systems, need further studies. And finally, the sample in this study was relatively small. The mechanism needs to be researched with more diversified patients and sophisticated experimental designs from both the TCM and modern medicine perspectives.

5. Conclusions

The following conclusions can be drawn from this study:

(1) Body, auricular, and abdominal needling all improved insomnia and depression as well as anxiety for patients with internal harassment of phlegm-heat syndrome, with the first two protocols being more effective.

(2) Among the three protocols, body needling is firstly recommended for it consistently improved insomnia and depression as well as anxiety, and the therapeutic effect kept improving as time went by. The recommended points are basic ones.

(3) Auricular needling improved insomnia with a sustainably growing trend, but, for depression and anxiety, within the treatment period, the increasing is decelerated than that during follow-up period. The recommended points are basic points combined with points based on TCM theory.

(4) Abdominal needling improves insomnia with a decelerated increase, and, for depression and anxiety, the increase is first accelerated within treatment period, then decelerated during follow-up period. The recommended points are basic ones combined with syndrome differentiation points.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

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Research Article

Role of Auriculotherapy in the Treatment of Temporomandibular Disorders with Anxiety in University Students

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Introduction. The aim of this study was to evaluate the role of auriculotherapy with mustard seeds in the treatment of temporomandibular disorders (TMDs), anxiety, and electromyographic (EMG) activity in university students. *Methodology*. The State Trait Anxiety Inventory (STAI), Research Diagnostic Criteria (RDC) for TMDs (RDC/TMDs), and electromyography were used in this study of 44 college students with high levels of anxiety and TMDs. The subjects were divided into two groups: an auriculotherapy (AA) group ($n = 31$) and an AA sham group ($n = 13$). The mustard seeds were applied to the shenmen, rim, sympathetic, brain stem, and temporomandibular joint (TMJ) points in the AA group and to sham points in the external ear and wrist in the AA sham group. The treatment protocol was 10 sessions (two treatments per week). *Results*. Anxiety ($p < 0.01$) was significantly reduced in the AA group. This group also showed a decrease in tender points in the mandibular posterior region ($p = 0.04$) and in the right side of the submandibular region ($p = 0.02$). Complaints of bilateral pain were reduced in the temporal tendon ($p \leq 0.01$) and in the left side of the ATM ($p < 0.01$). In addition, electromyographic (EMG) activity was reduced during temporal muscle contraction ($p = 0.03$). *Conclusion*. Auriculotherapy was effective in the treatment of students with anxiety and TMDs.

1. Introduction

Temporomandibular disorders (TMDs) are one of the most common causes of orofacial complaints. They have multiple clinical manifestations, but the most frequent are pain in the region of the temporomandibular joint, pain and fatigue of the craniocervical muscles, especially those involved in mastication, limitation and deviations of mandibular movements, the presence of joint sounds [1], headaches, sensitivity to palpation of the masticatory muscles and temporomandibular joints [2], and tinnitus [3]. Given the variety of symptoms, TMDs have been attributed to multiple etiological factors [4], such as anatomical, functional, and psychosocial changes [4, 5]. There is a lack of consensus on whether there is a relationship between anxiety, depression, and TMDs [4].

Pain relief is the main objective of primary therapeutic treatment of patients with TMDs. Treatment strategies include drugs to control chronic pain, physical therapy, surgery, and arthroscopy [6]. Dental approaches include occlusal intraoral devices and occlusal adjustment [7]. Psychosocial interventions [8] and low-frequency laser therapy have also been applied [9]. According to the literature, complementary and integrative practices are often used, in conjunction with conventional treatment [6, 10].

Auriculotherapy or ear acupuncture is a therapeutic acupuncture technique [11] which is based on the idea that pluripotent cell groups contain information on the whole organism and create regional organization centers, which represent different parts of the body, and that stimulation of a reflection point in the auricle for a sufficient duration

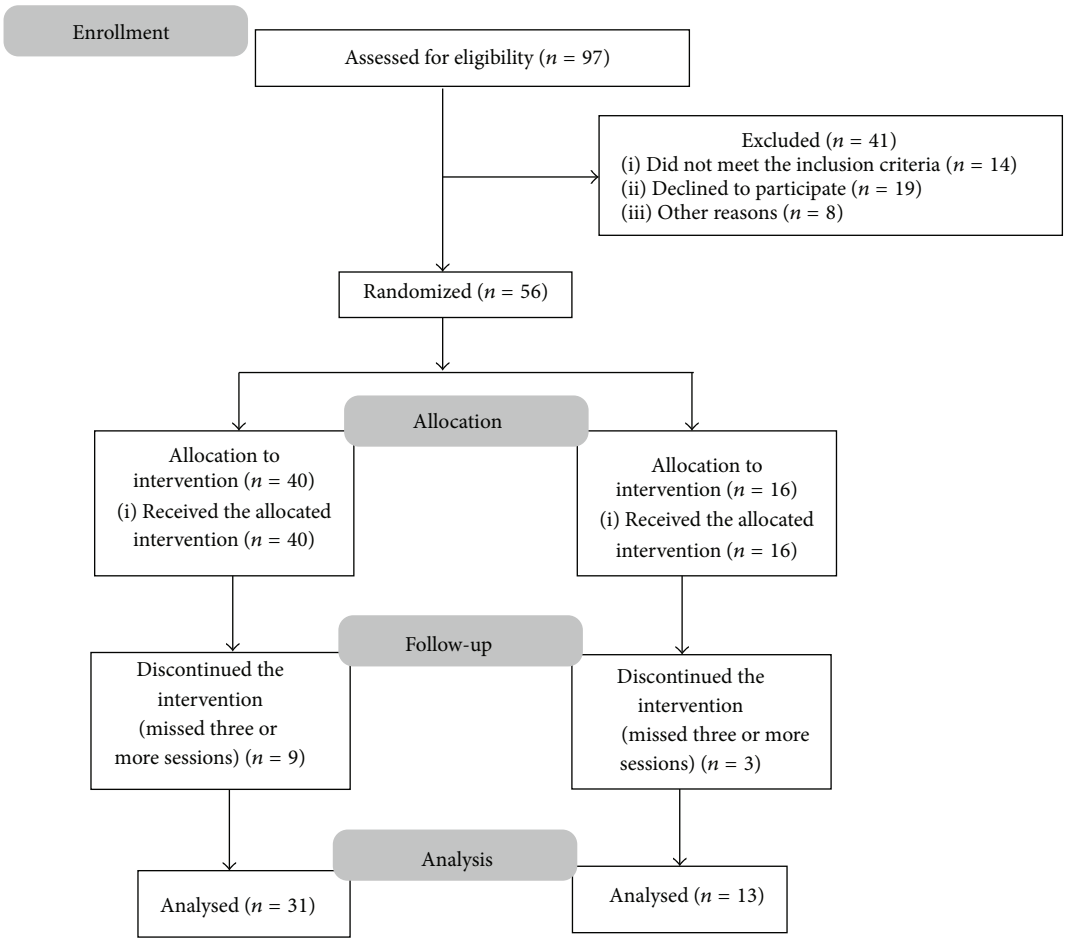

Figure 1: Flowchart of the participants.

Table 1: Pretreatment and posttreatment comparison of the mean anxiety profile according to the STAI-E in the AA group and sham AA group.

Groups	Pretreatment	Posttreatment	p^*	d
	95% CI			
AA	53.26	45.60	<0.01*	0.84**
(n = 31)	48.90–57.62	40.08–51.11		
Sham AA	48.20	47.00	0.58*	0.11
(n = 13)	43.71–52.68	40.45–53.54		

d: effect size; *paired t test; **power > 80%.

can relieve the symptoms of a disease [12]. Treatment with auriculotherapy is one of the most popular systemic microacupuncture techniques, with extensive applications [13].

Various studies have demonstrated the potential of auricular therapy in the treatment of a variety of conditions, such as its use in the treatment of TMDs [7] and its symptoms [14], especially pain [15]. Another study found that it improved the quality of life of individuals treated with traditional Chinese medicine (TCM), combined with conventional therapy [6].

Thus, the aim of this study was to evaluate the role of auricular acupuncture in the treatment of TMDs and anxiety in university students and the impact of the treatment on the electromyographic activity of various muscles.

2. Methodology

This controlled clinical, randomized, double-blind study was conducted with federal university students attending various health care courses (nursing, physiotherapy, pharmacy, and dentistry). A sociodemographic and clinical questionnaire was used to screen the students for major signs and symptoms of TMDs, such as headache, clicks, masticatory muscle pain, and TMJ pain. Ninety-seven students who reported signs and symptoms of TMDs were selected for the study.

The research was conducted over a 7-month period (October 2013 to May 2014). The inclusion criteria for this study were age being 18 years or over, availability for auriculotherapy sessions, and high levels of anxiety according to the State Trait Anxiety Inventory (STAI) [16]. The exclusion criteria were ear piercings (except a regular earring), inflammation, infection, or injury to the ear, receiving drug treatment for TMDs and anxiety, orofacial pain, or pregnancy.

Recruitment and enrollment of the participants is described in a trial flow diagram (Figure 1). Fifty-six volunteers fulfilled the eligibility criteria and were divided into two groups by simple randomization: an auriculotherapy

```
% Import data 'Data_matrix'
Data_matrix = dlmread ('RTSD2.txt');
% Storage of the original data 'Original_Data'
Original_Data = Data_matrix;
% Identifying the position of the data for time = 1 s and time = 4 s
one = find (Data_matrix == 1);
four = find (Data_matrix == 4);
% Excluding data when time ≤ 1 s and time ≥ 4 s
Data_matrix ([1: A four: end],:) = [];
Filtered_data = Data_matrix;
Number_lines = size (Filtered_data, 1);
% Normalization of the data
Data_RMS = Filtered_data;
mean = sqrt (mean (Data_RMS (:, 2)));
for counter = 1: Number_lines
Data_RMS (counter, 2) = ((Data_RMS (counter, 2))/mean);
end
% Mean
media_RMS = mean (Data_RMS (:, 2))
```

Algorithm 1: Algorithm used for normalization of the electromyography data.

group (AA) ($n = 40$) and a sham AA group ($n = 16$). During the intervention, some subjects dropped out. The postintervention reevaluation included 31 individuals in the AA group and 13 subjects in the sham AA group.

Fifty-six volunteers fulfilled the eligibility criteria and were evaluated at baseline and received a number. Then by a simple selection in a draw fewer volunteers were separated for the sham AA group ($n = 16$) and getting the other for the auriculotherapy group (AA) ($n = 40$).

The study subjects were evaluated before the first auriculotherapy session and after the 10th session by the same trained examiner who had no knowledge of the type of treatment applied. The instruments used in this evaluation were the STAI [16], I axis of the Research Diagnostic Criteria for TMDs (RDC/TMDs) [17], and surface electromyography (sEMG) measurements of the electrical activity of the bilateral trapezius, masseter, and temporal muscles.

The STAI was translated and adapted for the Portuguese language [18]. The STAI is composed of two parts, with 20 items for assessing trait anxiety and 20 for assessing state anxiety. The answers are scored on a Likert 4-point scale. The score ranges from 20 to 80 points, with 0–30 indicating a low level of anxiety, 31–49 denoting a medium level of anxiety, and 50 or more indicating a high level of anxiety [16].

The RDC/TMDs allowed standardized assessment [17]. This instrument is divided into two axes. Axis I is the physical examination for the classification of subtypes of TMDs into three groups: muscle disorders (group Ia and Ib myofascial pain and myofascial pain with limited opening), disk displacement dysfunction (group II), and joint disorders (IIIa, arthralgia; IIIb, TMJ; and IIIc, osteoarthritis). The reliability of the RDC/TMDs was previously tested [19, 20], and the instrument was translated and validated officially for the Portuguese language [21]. To measure the intensity of pain in the evaluated points, we used a visual analog scale (VAS), where 0 was no pain and 10 denoted severe pain [7].

The EMG signals of the masseter and anterior temporal muscles were collected by disposable bipolar surface electrodes (Hal and Hal, São Paulo, Brazil). The EMG signals of the trapezius and reference muscles were collected using Meditrace monopolar electrodes with an AgCl catchment surface and a diameter of 10 mm (Tyco/Kendall, Mansfield, Canada). The monopolar electrodes were positioned parallel to each other at a distance of 20 mm center to center, along the fibers of the muscles described above, as prescribed earlier [22].

All the electromyography signals were captured with the EMG-Brazil Model 800C. In this model, six channels are configured to receive the EMG signals with a digital band-pass filter, a cutoff frequency of 20–500 Hz, and final gain of 1000 times. Another channel is configured to receive signals from the load cell used for maximum voluntary isometric contraction. All the channels have a sampling frequency of 2000 Hz. The system features specific software for signal acquisition and storage in data files. The EMG signals of the trapezius muscle were collected at rest, during isometric contraction (bilateral and unilateral) against gravity, and during maximum voluntary isometric contraction [23] using a load cell of 200 kgf. For the masseter and temporal muscles, the EMG signals were collected in the mandibular rest position and during maximal voluntary isometric contraction [24]. All the data were collected in triplicate while the subjects contracted their muscles for 10 sec, at intervals of 60 sec. In the analysis, we used the data collected during 2–7 sec. During the collection of the EMG data, the volunteers sat on a chair, with their feet flat on the floor. They rested their hands on their legs, with their shoulders relaxed and their head parallel to the Frankfurt line. They were directed to look straight ahead.

The EMG signals were processed with a specific algorithm, using programmed routines in MatLab software (Algorithm 1). Quantification of the signal was performed

Table 2: Mobility evaluation of the mouth movements of the AA and sham AA groups pretreatment and posttreatment.

Mouth movements	AA (n = 31)				Sham AA (n = 13)			
	Pretreatment (95% CI)	Posttreatment (95% CI)	p^*	d	Pretreatment (95% CI)	Posttreatment (95% CI)	p^*	d
Passive opening	36.50 32.88–40.21	38.30 35.44–41.31	0.40	0.20	37.30 30.60–44.16	38.40 33.73–43.03	0.96	0.11
Maximum passive opening	50.90 47.59–54.34	51.00 48.73–54.02	0.80	0.01	49.00 45.01–53.13	52.50 48.29–56.62	0.04*	0.51
Maximum active opening	47.60 44.51–50.72	47.00 44.28–50.12	0.90	0.08	46.30 41.45–51.16	49.50 46.86–52.05	0.07	0.46
Overlap	3.50 2.81–4.21	3.40 2.51–4.37	0.60	0.05	5.40 4.11–6.80	4.20 2.51–5.94	0.19	0.47
Right lateral deviation	8.40 6.98–9.84	8.20 7.19–9.63	0.70	0.06	7.50 5.48–9.59	9.20 8.01–10.44	0.12	0.57
Left lateral deviation	8.70 7.71–9.73	7.86 6.99–8.80	0.10	0.34	7.40 5.41–9.50	8.50 7.34–9.58	0.30	0.37
Protrusion	5.40 4.37–6.59	4.80 3.76–5.95	0.20	0.21	6.40 5.31–7.60	6.20 5.44–7.01	0.70	0.12

d: effect size; *Wilcoxon test.

by RMS amplitude, as recommended to evaluate the level of muscle activity [25].

We established a protocol to determine the application of the points in the auriculotherapy. The protocol was based on personal clinical experience, the Standards for Reporting Interventions in Clinical Trials of Acupuncture [26], and the literature [27, 28]. The protocol was later submitted for refining to four judges with 2–10 years of accreditation and experience in auriculotherapy. Interventionists had training in auriculotherapy and at least two years of experience in the area.

The auriculotherapy used mustard seeds, which were attached to the skin with Micropore tape. Each volunteer underwent 10 sessions, twice a week (Monday and Thursday) for 6 weeks, with an alternate ear used each application. Prior to the placement of the mustard seeds, the subject's ear was cleaned with 70% ethyl alcohol. During the placement of the seeds, the volunteer remained sitting on a chair with a back support. As a constant pressure stimulus on the point is needed for the intervention to have the expected effect, the volunteer was instructed to press each auricular point at least 5 times a day, applying pressure for 1 min to every point [29] or until the pressure produced localized pain or discomfort [30]. The AA group received five points per subject per session being the shenmen, kidney, sympathetic, brain stem [27, 28], and TMJ [27]. These points have sedative and tranquilizer effects [11, 27, 31]. The sham AA group received two points per subject per session being the wrist and external ear [27, 28] (Figure 2). These points were chosen because they were far from the group of points the AA group.

The Statistical Package for the Social Sciences (SPSS), version 23.0, was used for the statistical analysis. The Shapiro-Wilk normality test was performed, followed by a t-test for data with a normal distribution and a Wilcoxon and Mann-Whitney test for data with a nonnormal distribution. The significance level was 5%. The effect size and the power effect of the sample were calculated with GPower 3.1.7 software (Franz Faut, Universität Kiel Germany, 2008). A small effect size (d) was considered $0.20 \leq d < 0.50$, a medium effect size was considered $0.50 \leq d < 0.80$, and a large effect size was considered $d \geq 0.80$. In the power analysis, more than 0.80 was needed to denote adequate power [32].

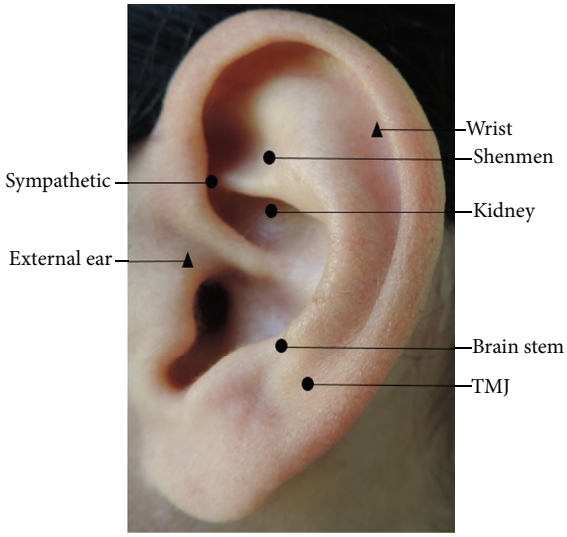

Figure 2: Auricular points used in the intervention: AA group (circle) and sham AA group (triangle). These points were used in the right and left ears alternately.

This study was approved by the Research Ethics Committee of the Federal University of Alfenas (Protocol number: 164 590), and it was registered with the Brazilian Registry of Clinical Trials Platform (Protocol number: U111-1147-3083). The volunteers received information regarding their participation in this research study and they signed free and informed consent documents.

3. Results

Forty-four college students participated in this study: 31 were assigned to the AA group and 13 were in the sham AA

Table 3: Pretreatment and posttreatment comparison of the tender points of the AA and sham AA groups based on the RDC/TMDs and the electromyographic activity of the trapezius muscle.

Points	AA (n = 31) Pretreatment (95% CI)	AA (n = 31) Posttreatment (95% CI)	p	d	Sham AA (n = 13) Pretreatment (95% CI)	Sham AA (n = 13) Posttreatment (95% CI)	p	d	Intergroup Before (p)	Intergroup After (p)
Right temporal										
A	1.20 0.47–1.93	0.93 0.24–1.62	0.45	0.15	1.34 0.04–2.72	1.77 0.98–2.55	0.51	0.22	0.64	0.01
M	1.00 0.20–1.79	0.86 0.17–1.54	0.57	0.67	0.85 −0.07–1.76	1.08 0.44–1.70	0.76	0.17	0.79	0.16
P	0.96 0.28–1.64	0.86 0.17–1.54	0.66	0.06	0.85 −0.07–1.76	0.77 0.15–1.38	0.74	0.06	0.95	0.60
Left temporal										
A	1.00 0.14–1.85	0.76 0.21–1.30	0.51	0.12	2.15 0.65–3.65	1.23 0.61–1.84	0.20	0.41	0.03	0.07
M	0.93 0.19–1.66	0.82 0.27–1.37	0.54	0.06	1.00 0.07–1.92	1.31 0.40–2.21	0.32	0.21	0.40	0.20
P	0.76 0.02–1.49	0.75 0.21–1.30	0.93	0.01	1.15 0.23–2.07	0.92 2.29–1.55	0.53	0.17	0.09	0.34
Right masseter										
O	2.96 1.99–3.93	1.69 0.90–2.47	0.06	0.54	2.38 0.99–3.77	1.85 0.83–2.85	0.32	0.26	0.50	0.48
B	2.58 1.73–3.43	1.62 0.85–2.38	0.10	0.45	3.08 1.48–4.66	2.23 1.15–3.31	0.37	0.37	0.60	0.20
I	1.58 0.68–2.48	1.00 0.44–1.55	0.29	0.23	4.08 2.52–5.62	1.70 0.63–2.75	**0.01***	**1.05**	<0.01	0.17
Left masseter										
O	3.10 2.01–4.19	1.96 1.16–2.76	0.08	0.44	1.92 0.51–3.32	2.31 1.06–3.55	0.51	0.18	0.22	0.55
B	2.72 1.77–3.67	2.10 1.26–2.93	0.25	0.26	2.31 1.06–3.55	2.08 0.96–3.19	0.68	0.12	0.71	0.95
I	1.58 0.63–2.53	1.76 0.78–2.73	0.82	0.07	3.54 2.10–4.96	2.61 1.52–3.70	0.17	0.43	<0.01	0.07
Posterior mandibular region										
R	5.00 4.00–5.99	3.44 2.54–4.35	**0.04***	**0.62**	4.84 3.21–6.47	7.08 6.20–7.94	**0.03***	**0.96**	0.85	0.00
L	4.69	4.34 3.15–5.53	0.33	0.11	3.85 2.15–5.53	6.38 5.40–7.32	**0.01***	**1.04**	0.37	0.05
Submandibular region										
R	5.07 3.87–6.26	3.07 2.14–3.99	**0.02***	**0.70**	5.38 3.70–7.06	5.77 4.20–7.33	0.72	0.14	0.90	<0.01
L	5.00 3.91–3.08	4.21 3.32–5.08	0.14	0.30	5.38 3.54–7.22	5.54 3.85–7.22	0.92	0.05	0.66	0.11
Lateral pterygoid										
R	3.65 2.64–4.66	2.45 1.47–3.42	0.09	0.46	2.08 0.25–3.89	1.23 0.09–2.36	0.18	0.32	0.06	0.09
L	2.00 1.01–2.98	2.51 1.51–3.51	0.42	0.20	2.69 0.80–4.57	1.85 0.45–3.23	0.45	0.30	0.55	0.44
Temporal tendon										
R	4.93 3.85–6.01	2.96 2.04–3.88	**0.01***	**0.74**	5.31 3.86–6.75	4.30 2.79–5.81	0.17	0.41	0.77	0.11
L	4.55 3.46–5.63	2.31 1.34–3.27	**<0.01***	**0.83**	5.46 4.21–6.71	3.67 2.00–5.53	0.06	0.69	0.38	0.10
Side portion TMJ										
R	3.52 2.53–4.50	3.17 2.10–4.24	0.48	0.13	3.08 1.86–5.97	2.92 3.20–6.33	0.79	0.06	0.79	0.06
L	3.34 0.96–1.86	1.41 0.68–2.21	**<0.01***	**0.80**	4.46 2.63–6.68	4.61 2.91–6.31	0.83	0.05	<0.01	0.17

Table 3: Continued.

Points	AA (n = 31) Pretreatment (95% CI)	AA (n = 31) Posttreatment (95% CI)	p	d	Sham AA (n = 13) Pretreatment (95% CI)	Sham AA (n = 13) Posttreatment (95% CI)	p	d	Intergroup Before (p)	Intergroup After (p)
Back of the TMJ										
R	1.83 1.05–2.59	1.45 2.29–4.39	0.70	0.19	3.92 1.22–4.93	4.77 1.43–4.41	0.44	0.28	0.26	0.04
L	0.62 0.34–0.89	0.93 0.31–1.54	0.64	0.22	3.00 1.23–4.76	1.77 0.32–3.21	0.07	0.46	<0.01	0.18
Trapezius										
R	5.03 3.85–6.21	4.17 3.09–5.25	0.16	0.29	5.00 3.08–6.91	6.23 4.61–7.85	0.22	0.42	0.88	0.03
L	4.03 2.93–5.30	3.89 2.74–5.04	0.78	0.05	3.23 1.30–5.16	5.77 4.03–7.49	**0.02***	**0.84**	0.38	0.06

A: anterior; M: middle; P: posterior; O: origin; B: belly; I: insertion; R: right; L: left; d: effect size; *Wilcoxon test; intergroup analysis: Mann-Whitney test.

group. In the AA group, 93.55% (n = 28) were women, and 9.67% (n = 3) were men. The mean ± SD age of the study participants was 21.61 ± 3.27 years. In the sham AA, 100% (n = 13) of the subjects were women, and the mean ± SD age of the study participants was 20.87 ± 1.50 years. According to the RDC/TMDs, all the participants were classified as category Ia. In the AA group and sham AA group, 33% and 15.38% of subjects, respectively, were also classified as having a category IIIa TMD. In the AA group, the anxiety state of the subjects was significantly reduced after the application of auriculotherapy (Table 1).

The results of the evaluation of the mobility of mouth movements using the RDC/TMD are shown in Table 2. No statistically significant changes were identified, even in the maximal passive opening movement in the sham AA group. Although the values of maximum passive mouth opening were significant, it exhibited a low power and a moderate effect size. In the initial assessment of both groups, none of the subjects had limitations in the evaluated movements.

The RDC/TMDs were used to evaluate the tender points of the masticatory muscles and TMJs and palpation of the trapezius muscle. The results are shown in Table 3. In the AA group, pain was significantly reduced in the five points assessed, together with a high power and medium to high effect size. The other points showed clinical improvement. In the sham AA group, 46% of those evaluated reported increased pain at the evaluated points, with statistical significance.

Table 4 shows the comparison of the intragroup and intergroup analyses of the EMG activity in the AA and sham AA groups. Only the bilateral contraction of the temporalis muscle in the AA group showed a significant difference between the pre- and postintervention, with a low power effect. However, in the posttreatment intergroup analysis, the EMG activity of the trapezius and temporalis muscles at rest and during contraction showed statistical significance.

4. Discussion

In TCM, disease is seen as an imbalance in the meridians. Therefore, the processing based on this analysis has the potential to provide a strategy for overall system management for TMDs [6], mainly with a view to reduce pain [33] and anxiety [11]. As noted previously, there is a need for different studies to find common auricular acupuncture points to create an international standard of clinical research that facilitates replication and dissemination of the results [13]. The establishment of the protocol for the treatment of TMDs in this study can aid this goal, although further multicenter, longitudinal studies with larger samples are needed in this area.

In the present study, auriculotherapy significantly reduced anxiety and provided pain relief. It also reduced the electrical activity of the trapezius and temporal muscles. Anxiety can contribute to the development of a TMD or be the result of this disorder and its perpetuation [34]. In this study, all the volunteers with high levels of anxiety had TMDs. Other researchers also observed a reduction in anxiety after auriculotherapy [11, 35, 36], pointing to the potential of this technique in the control of various clinical conditions.

Anxiety is an increasingly common disorder in people's lives today [37]. It is treated with anxiolytic psychotropic drugs, often at the request of the patient leading to unnecessary and inappropriate treatment [38]. The use of integrative/complementary treatments, including auriculotherapy, has been investigated to reduce the dependence on such drugs. The former can be integrated with traditional therapy or even replace it, as integrative/complementary treatments do not have side effects. They are also inexpensive and easy to administer.

TMD-related pain can be chronic, with the dysfunction affecting not only peripheral nervous system, but also the central nervous system, thereby producing a widespread perception of pain [39]. This type of pain is often difficult to treat and is accompanied by emotional components, such as anxiety and/or depression. The symptoms of anxiety are strongly related to muscle pain [40]. Joint symptoms were also observed in the present study.

The goal of all TMD treatment is to minimize pain. In the present study, the therapy was effective in reducing pain, with statistical significance for five of the points assessed. The findings corroborate those of an earlier study [7], which demonstrated the contribution of Eastern therapies in

Table 4: Results of the intragroup and intergroup analysis of the EMG activity of the AA group and sham AA group.

Muscles	AA (n = 31) Before (95% CI)	AA (n = 31) After (95% CI)	p^*	d	Sham AA (n = 13) Before (95% CI)	Sham AA (n = 13) After (95% CI)	p^*	d	Intergroup Before (p)	Intergroup After (p)
Bilateral trapezius rest										
R	3.33 3.27–3.39	3.34 3.28–3.41	0.43	0.06	3.21 3.00–3.42	3.21 3.04–3.38	1.00	0.00	0.267	**<0.01**[#]
L	3.64 3.55–3.73	3.66 3.56–3.75	0.12	0.08	3.49 3.19–3.79	3.50 3.25–3.75	0.46	0.19	0.899	**0.03**[#]
Bilateral masseter rest										
R	3.35 3.29–3.42	3.66 2.99–4.33	0.23	0.18	3.24 3.02–3.46	3.23 3.06–3.39	0.14	0.03	0.750	0.07
L	3.63 3.55–3.72	3.65 3.56–3.73	0.42	0.09	3.49 3.11–3.53	3.51 3.27–3.75	0.91	0.05	0.466	0.15
Bilateral temporalis rest										
R	3.41 3.35–3.47	3.40 3.37–3.43	0.23	0.07	3.32 3.11–3.53	3.29 3.14–3.45	0.05	0.08	0.841	0.21
L	3.58 3.51–3.66	3.55 3.47–3.62	0.12	0.14	3.44 3.21–3.67	3.43 3.24–3.61	0.11	0.02	0.236	**0.02**[#]
Bilateral trapezius contraction										
R	3.23 3.18–3.29	3.23 3.18–3.29	0.51	0.00	3.12 2.93–3.32	3.11 3.00–3.23	0.23	0.03	0.216	**<0.01**[#]
L	3.55 3.48–3.62	3.55 3.49–3.62	0.47	0.00	3.41 3.14–3.69	3.38 3.17–3.59	0.06	0.06	0.548	**<0.01**[#]
Unilateral trapezius contraction										
R	3.26 3.18–3.33	3.24 3.17–3.31	0.71	0.10	3.16 2.91–3.41	3.11 2.98–3.24	0.26	0.12	0.636	**<0.01**[#]
L	3.53 3.45–3.62	3.54 3.46–3.62	0.56	0.04	3.345 2.70–5.36	3.39 3.21–3.58	0.78	0.13	0.063	**<0.01**[#]
Bilateral masseter contraction										
R	3.23 3.18–3.27	3.20 3.16–3.24	0.09	0.25	3.15 2.99–3.30	3.10 2.99–3.21	0.09	0.19	0.675	0.23
L	3.51 3.43–3.59	3.51 3.44–3.58	0.29	0.00	3.39 3.15–3.62	3.39 3.19–3.59	0.50	0.00	0.455	0.88
Temporal bilateral contraction										
R	3.30 3.25–3.36	3.29 3.24–3.34	0.40	0.07	3.21 3.01–3.41	3.18 3.05–3.31	0.17	0.09	0.362	**<0.01**[#]
L	3.48 3.41–3.56	3.46 3.39–3.52	0.03*	0.10	3.35 3.13–3.56	3.34 3.17–3.50	0.14	0.03	0.209	**0.03**[#]

R: right; L: left; d: effect size; *Wilcoxon test; #Mann-Whitney test.

decreasing TMD-related pain. Treatments for TMDs must act in a holistic manner, both on the physical and emotional symptoms. In the current study, anxiety and pain were significantly reduced in the subjects who received auriculotherapy. In addition, the electrical activity of the muscles was significantly reduced in the intergroup analysis.

The anxiety and pain associated with TMDs can trigger hyperactivity and altered muscle mechanics, which can perpetuate the muscle pain [41]. Therefore, a muscle evaluation is important to establish the diagnosis and treatment of TMDs. In many cases, TMDs may cause inflammation of the joints, followed by biomechanical changes, which give

rise to pain in the affected region. A previous study found that TMDs may be related to abnormal processing of pain in the trigeminal system [41]. Other studies pointed to the relationship between mastigatory and cervical muscle tenderness associated emotional changes [42, 43]. They found that this resulted in emotional changes, which predisposed individuals to orofacial pain and TMDs [42, 43]. In the current study, the efficacy of the treatment was assessed by evaluating the presence of pain in both groups and the EMG activity. The treatment was effective, as shown by the improvement in tender points and the electrical activity of the trapezius muscle over time in the intergroup analysis. Therefore, it is believed that the auriculotherapy may have served as a mechanism of muscle modulatory activity, as reported previously [34].

A previous study reported that anxiety and stress contributed to the development of TMDs and that it increased the recruitment of the anterior temporal muscle, sternocleidomastoid, and upper trapezius, in addition to the excitability of the trigeminal-neck reflex, causing pain and trigger points in the muscles, leading to a vicious cycle [44]. In the present study, after the intervention, the EMG activity of the descending trapezius and anterior temporal decreased during maximal muscle contraction. The reduction in the EMG activity of the temporal muscle was significant in the AA group but not in the sham AA group. No changes in EMG activity were observed in the masseter muscle. A previous study reported that the EMG activity of the descending fibers of the trapezius did not change in individuals without a history of masticatory system dysfunction during maximal effort centric occlusion of the jaw [23]. The lack of EMG activity reported in the previous study explains why anxiety and stress can lead to the development of a vicious cycle that contributes to hyperactivity of the masticatory muscles in adolescents with severe TMD symptoms [24].

The between-group comparison revealed a reduction in EMG activity at rest and during muscle contraction. This reduction in EMG activity may be related to the effect of the auriculotherapy that was observed after the intervention, as auriculotherapy stimulates the peripheral nervous system by promoting local and systemic reflex responses [45, 46]. These responses are mediated by the release of endorphins, serotonin, and noradrenaline released from the endocrine system, immune system, and higher centers in the central control of pain [45, 46].

Study Limitation. The limitations of this study were the small sample size, absence of follow-up, and absence of a control group.

5. Conclusion

Auriculotherapy helped to reduce anxiety and tender points in the posterior region right mandibular and submandibular, tendon bilateral temporalis, and left TMJ. It also reduced EMG activity during temporal muscle contraction.

Conflict of Interests

The authors declare no conflict of interests.

Acknowledgment

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Research Article

Effect of Auricular Acupressure on Uremic Pruritus in Patients Receiving Hemodialysis Treatment: A Randomized Controlled Trial

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Background. Uremic pruritus (UP) is a common symptom in patients undergoing maintenance hemodialysis for end-stage renal disease (ESRD). *Objective*. To determine the clinical efficacy of auricular acupressure therapy on pruritus in hemodialysis patients and to explore possible underlying mechanisms. *Methods*. Patients receiving maintenance hemodialysis at a referral medical center were recruited and assigned to intervention ($n = 32$) and control ($n = 30$) groups. The intervention group underwent auricular acupressure treatment three times a week for six weeks. Auricular acupressure was not applied to patients in the control group. However, tape without *Vaccaria* seeds was applied to the same six auricular acupoints as the intervention group. Pruritus scores were assessed using VAS scores, and enzyme-linked immunosorbent assays (ELISA) were used to measure levels of other possible contributory biochemical factors. *Results*. There was a significant difference in mean VAS scores between the postintervention and control groups during follow-up (3.844 ± 1.687 versus 5.567 ± 2.285, $F = 22.32$, $P < 0.0001$). Compared to the control group, serum histamine levels in the postintervention group at the six-week follow-up had decreased significantly ($F = 5.01$, $P = 0.0290$). *Conclusion*. Our findings suggest that auricular acupressure may be a useful treatment in the multidisciplinary management of UP in ESRD patients.

1. Introduction

Uremic pruritus (UP) is a common symptom in patients with end-stage renal disease undergoing maintenance hemodialysis (HD) [1]. UP or itching affects about 20 to 50 percent of patients with ESRD [2–4] with no other primary skin diseases or systemic or psychological dysfunctions that might cause pruritus. Moreover, while the distribution of pruritus between patients is highly variable, its symmetrical manifestation is a common feature [1].

The pathogenic molecular basis of pruritus in chronic renal failure remains elusive, which limits options for effective treatment. Previous studies showed that, besides metabolic factors and dialysis clearance, inflammation is the factor mainly associated with UP in patients receiving hemodialysis [5]. Aoki et al. reported that the skin of patients with ESRD and UP had increased numbers of mast cells; these cells release a variety of substances including histamine, tumor necrosis factor (TNF-a), and interleukin-6 (IL-6), which are common inflammatory markers [6]. Unfortunately, the results of different studies are inconsistent, and most of the described treatments have had limited success [7].

Pruritus is frequently refractory to treatment and is associated with substantial medical, psychological, and social disturbances in patients receiving hemodialysis [8]. Current UP treatments include oral antihistamines, gabapentin, ondansetron, thalidomide, naltrexone/nalbuphine, ultraviolet (UV) light, and topical tacrolimus [9]. However, many nonpharmacological treatment methods such as acupressure are also used to relieve UP discomfort [10].

In traditional Chinese medicine, ear acupoints correspond to body organs and meridians, as well as the four limbs and skeleton; they serve both as a disease reaction point and treatment trigger. Auricular acupressure is the combination of visceral state doctrine and meridian theory; it can be used to adjust different parts of the human body by reconditioning the meridians, conductivity of senses, and energy deficiency and excess to achieve a relative balance

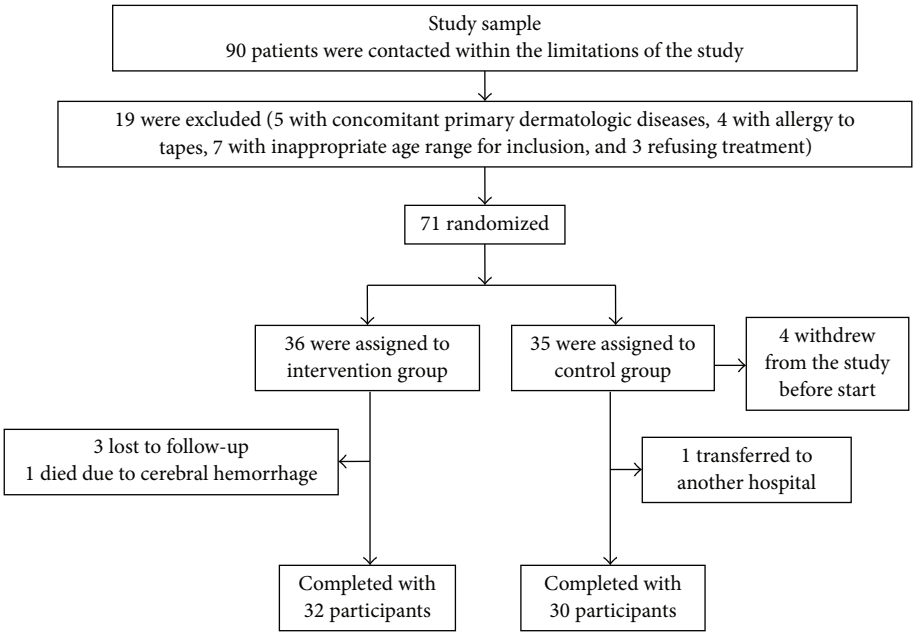

Figure 1: Participant screening, randomization, and completion in the six-week intervention study.

and facilitate therapeutic modalities that target disease [11]. Auricular acupressure therapy combines a treatment modality with traditional Chinese medicine. It is safe and effective, with fewer side effects, and is more easily accepted by patients. The present study evaluated the efficacy of auricular acupressure in patients receiving hemodialysis treatment for UP. We hypothesized that at the end of the six-week intervention period patients in the auricular acupressure group would have a greater reduction in UP scores and more improvements in health-related quality of life than those measures in the control group.

2. Materials and Methods

2.1. Patients. Patients were referred by doctors and acupuncturists in the Department of Hemodialysis in Putuo Hospital, part of the Shanghai University of Traditional Chinese Medicine. The current study took place between April and October 2014 and included 32 and 30 participants in the intervention and control groups, respectively (Figure 1). The study procedures, risks, benefits, and data management were clarified in detail before the patients were asked to provide their informed consent.

All participants enrolled in this study were undergoing hemodialysis three times per week for 3-4 hours each visit, with a blood flow rate maintained above 200–250 mL/min to guarantee sufficient dialysis. Participants met the following inclusion criteria [10]: (1) between 20 and 65 years of age; (2) undergoing dialysis at HD units for 6 months; (3) having had pruritus for at least 3 months; (4) having at least 3 or more points on the visual analogue scale (VAS) for pruritus; (5) having sufficient cognitive ability to answer questions regarding outcome measures; (6) not having previously been diagnosed with skin disease involving pruritus; (7) not having previously been diagnosed with liver disease, psychiatric disorder, or cancer; (8) not having had any nervous, vascular, or soft-tissue disorders in their extremities; (9) having no visible infection or having undergone surgical operations on their extremities; and (10) having provided informed consent. Participants were permitted to continue their routine medications and maintain their usual visits to their primary care physicians or nephrologists throughout the study. No other nonpharmacological treatments were permitted at the pruritus sites for participants in both groups during the study period.

2.2. Procedure. The intervention group underwent *Vaccaria* seed alignment (Runshi Trading, China). Six auricular acupoints were selected for their potential effects on pruritus, including the "kidney" (CO10), the "lung" (CO14), the "heart" (CO15), "Shenmen" (TF4), the "endocrine" (CO18), and the "subcortical" (AT4); these organs are identified in traditional Chinese medicine and are distinct from organ sites in Western medicine (Figure 2).

The auricular acupressure protocol was as follows: the ear point was disinfected with 75% alcohol, the most sensitive point was identified, and pressure was applied at the point to mark the skin surface. A *Vaccaria* seed was attached and pressure was applied to each ear point for 1-2 min with appropriate finger force until the patients felt a tolerable soreness, numbness, and heat. All auricular acupressure operators were medical staffs with professional backgrounds; they were also responsible for collecting subjective and objective data and outcomes before and after the intervention.

2.3. Intervention Group. The auricular acupressure intervention occurred three times weekly for six weeks. The patients were asked to press their acupoints 5–8 times a day, with one mandatory press before going to sleep every night. One side of

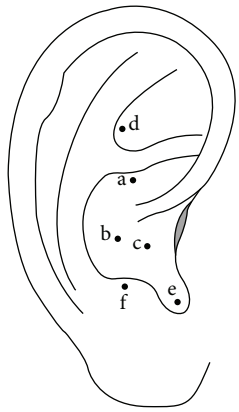

Figure 2: Location of auricular acupoints used in the auricular acupressure treatment group; a: the "kidney": the back of the bottom ear helix (i.e., the concha 10 region, CO10); b: the "lung": adjacent to the area of the "heart" and the "trachea" (i.e., the concha 14 region, CO14); c: the "heart": in the middle ear cavity depression (i.e., the concha 15 region, CO15); d: the "Shenmen": in the upper part of the posterior 1/3 of the triangular fossa (i.e., the triangular fossa 4 region, TF4); e: the "endocrine": within the intertragic notch in the lower front concha (i.e., the concha 18 region, CO18); f: the "subcortical": within the inner side of the tragus (i.e., the tragus 4 region, AT4).

the ear acupoint was chosen each time, alternating bilaterally. The tape was replaced every other day and removed every Sunday as a break day. The patients were informed that the tape should be protected against moisture and contamination in order to avoid loss of tape or auricular skin inflammation and that the tape should not be attached to damaged skin or skin with frostbite or other lesions in order to prevent infection. The baseline was defined as the VAS score collected during the face-to-face interview at week 0. The research team collected additional data from participants by repeating the VAS testing after participants had completed the full course of treatment.

2.4. Control Group. The control group did not undergo auricular acupressure treatment; there was no *Vaccaria* seed in the tape placed on the same six auricular acupoints as the intervention group, and the patients were told that the tape contained a traditional Chinese medicine that could reduce pruritus. The tape was replaced every other day and removed every Sunday as a break day. Participant information was collected identically to the intervention group, and VAS scores were determined through face-to-face interviews.

2.5. Outcome Measures and Follow-Up

2.5.1. VAS. VAS scores [12] indicated the intensity and severity of pruritus experienced by the study participants: 0 meant no pruritus, while 10 indicated very intense pruritus. The scale, which has been used to assess pain intensity in many studies, has been shown to be a valid and reliable tool. It has also been used to assess the intensity and severity of pruritus, which is a subjective sensation like pain [13, 14].

2.5.2. Blood Sample Collection. A 5-mL disposable vacuum syringe was used to sample 3 mL of blood. After 1 hour of standing and 15 min high-speed centrifuge at 3,000 rpm/min, the sample supernatant was stored at −80°C for enzyme-linked immunosorbent assay (ELISA) analysis. Samples were collected before hemodialysis was performed.

2.6. Biochemical Parameters. Serum concentrations of histamine, substance P, protease activated receptor-2 (PAR-2), and tryptase were measured by ELISA; all standards and samples were run in duplicate, following the manufacturer's instructions for commercial histamine (HA) (CEA927Ge, cloud-clone), substance P enzyme immunoassay (EIA) (583751, Cayman Chemical), PAR-2 (SEA852Hu, cloud-clone), and tryptase (TPS) (SEB070Hu, cloud-clone) kits. Serum calcium, phosphorus, and PTH concentrations were measured in the clinical laboratory of our hospital using standard techniques.

2.7. Ethics. This clinical study received formal approval from the ethics committee of Putuo Hospital, part of the Shanghai University of Traditional Chinese Medicine. The primary researcher explained the purpose of the study, data collection procedures, information confidentiality, and the right to withdraw from the study to prospective participants. Patients signed consent form if they agreed to participate in the study.

2.8. Randomizations and Procedures for Setting. In order to achieve comparable groups for known and unknown risk factors, a random allocation sequence was generated using randomized block methods in SAS 9.1.3 statistical software in a 1 : 1 allocation ratio and with block size = 4. The eligible participants were divided into control and intervention groups. The practitioners participating in the study did not take part in the randomization process, and the evaluation and analysis of results was performed by professionals blinded to the treatment assignments. These blinded professionals performed outcome assessments and checked for missing data. Except for the practitioners, all individuals involved in the outcome assessment were blinded to participant allocation.

2.9. Statistical Analysis. All tests were performed using GraphPad Prism Software 5.0 (GraphPad Software, La Jolla, CA) and SAS software, version 9.1.3 (SAS Institute Inc., Cary, NC, USA). The data were expressed as mean ± standard deviation (SD) and median (interquartile range). t-tests were used for comparison of independent groups involving normally distributed data, and Wilcoxon tests were used for comparison of independent nonnormally distributed groups. VAS scores and biochemical parameters in the intervention and control groups were compared separately according to their follow-up weeks with ANCOVA. $P < 0.025$ was considered statistically significant for the primary outcome (VAS score), while $P < 0.05$ was considered statistically significant for secondary outcomes.

3. Results

3.1. Patient Baseline Characteristics. Table 1 shows that the baseline data of the 62 participants were reasonably well balanced between the two groups. Age, gender, duration

Table 1: Baseline participant characteristics.

Variable	Control group (n = 30)		Intervention group (n = 32)	
Gender				
Female, n (%)	11 (36.7)		13 (40.6)	
Age, mean (SD)	54.00 ± 8.690		56.63 ± 7.088	
Duration of hemodialysis, months, Md (Q1, Q3)	48.00 (20.50, 72.50)		27.50 (13.00, 75.00)	
BMI	23.08 ± 1.286		22.96 ± 1.300	
Kt/V	1.842 ± 0.02394		1.835 ± 0.02258	
URR	71.44 ± 2.356		72.83 ± 3.304	
Primary disease diagnosis				
Chronic glomerulonephritis	15	50	17	53.1
Diabetic nephropathy	7	23.3	8	25
Hypertensive nephropathy	5	16.7	5	15.6
Other primary diseases	3	10	2	6.3
Visual analogue scale	5.600 ± 2.127		5.750 ± 2.032	
Calcium (mmol/L)	2.386 ± 0.3083		2.479 ± 0.3523	
Phosphorus (mmol/L)	2.246 ± 0.6625		2.134 ± 0.5149	
PTH (pg/L) Md (Q1, Q3)	239.0 (98.90, 435.5)		189.0 (92.90, 339.0)	
Histamine (ng/mL) Md (Q1, Q3)	1.363 (0.524, 2.457)		0.897 (0.250, 2.349)	
Substance P (pg/mL) Md (Q1, Q3)	10.81 (4.336, 22.59)		10.79 (5.094, 16.23)	
PAR-2 (ng/mL) Md (Q1, Q3)	1.748 (0.828, 3.638)		1.927 (0.860, 3.884)	
Tryptase (pg/mL) Md (Q1, Q3)	306.2 (148.7, 442.5)		371.1 (204.8, 524.0)	

Md: median, Q1: 25% percentile, and Q3: 75% percentile.
$P > 0.05$.

of dialysis, dialysis efficiency (Kt/V), urea reduction ratio (URR), body mass index (BMI), primary disease diagnosis, and VAS score were similar among participants in the intervention and control groups. The levels of calcium, phosphorus, PTH, histamine, substance P, PAR-2, and tryptase were also measured as biochemical factors that might contribute to pruritus. However, no significant differences in these baseline biochemical parameters were detected between the groups ($P > 0.05$).

3.2. Primary Outcome. As shown in Table 1, the mean baseline VAS scores of the intervention and control groups were 5.750 ± 2.032 and 5.600 ± 2.127, respectively. These scores did not differ significantly between these groups ($P > 0.05$). There was a significant difference between the mean VAS scores of participants in the postintervention and control groups in their follow-up assessment (3.844 ± 1.687 versus 5.567 ± 2.285, $F = 22.32$, $P < 0.0001$) (Figure 3).

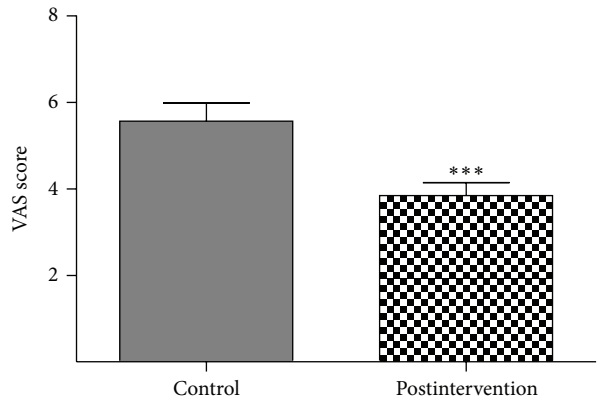

Figure 3: Mean change in visual analog scale (VAS) scores after six weeks, according to the postintervention group. Participant visual analog scale (VAS) scores indicate pruritus intensity and severity: 0 means no pruritus and 10 means very intense pruritus. $^{***}P < 0.001$ versus control group.

3.3. Mean Changes in Seven Secondary Outcomes after Six Weeks. Baseline serum histamine levels (Table 1) did not differ significantly between the intervention and control groups ($P > 0.05$). However, comparison of the serum histamine levels at the six-week follow-up revealed a significantly greater decrease in the postintervention group (Figure 4) than the control group ($F = 5.01$, $P = 0.0290$).

The levels of biochemical factors associated with pruritus, including calcium, phosphorus, PTH, substance P, PAR-2, and tryptase, did not differ significantly between groups (Figure 5). The six-week calcium serum levels for the postintervention and control groups were 2.532 ± 0.3651 mmol/L and 2.419 ± 0.2823 mmol/L, respectively ($F = 1.68$, $P = 0.2001$), and 2.038 ± 0.4012 mmol/L and 2.206 ± 0.6785 mmol/L for serum phosphorus levels, respectively ($F = 1.57$, $P = 0.2145$). The serum PTH levels were 119.5 (29.83, 268.3) pg/L and 234.0 (98.90, 435.5) pg/L, respectively ($F = 2.02$, $P = 0.1609$). Serum levels of substance P were 10.81 (4.336, 22.59) pg/mL and 9.332 (4.099, 14.50) pg/mL, respectively ($F = 3.89$, $P = 0.0533$). PAR-2 serum levels were 1.695 (1.010, 3.403) ng/mL and 1.713 (0.8283, 3.683) ng/mL, respectively ($F = 0.16$, $P = 0.6925$), and serum tryptase

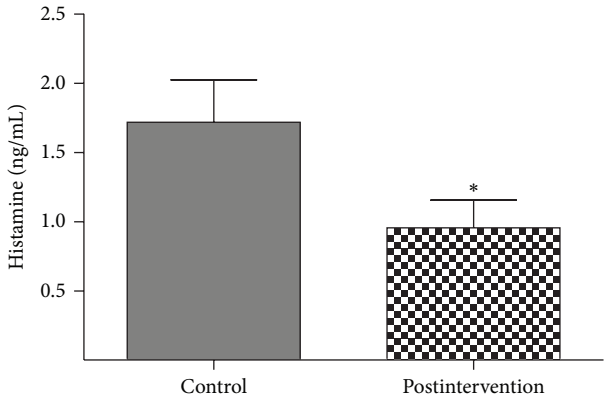

Figure 4: Mean change of serum histamine levels after six weeks, according to the postintervention group. $^{*}P < 0.05$ versus control group.

levels were 363.9 (205.0, 437.4) pg/mL and 305.2 (148.7, 447.0) pg/mL, respectively ($F = 0.41$, $P = 0.5261$).

No adverse events were noted during the study interventions.

4. Discussion

This experimental study was performed with 62 participants undergoing hemodialysis. As the primary outcome, the VAS scores of individuals in the postintervention group decreased over time compared to VAS scores in the control group ($P < 0.001$). Furthermore, serum levels of histamine in the postintervention group declined more significantly than those in the control group. These results of this study show that auricular acupressure is effective in reducing the frequency and severity of UP associated with hemodialysis, as well as improving quality of life.

Acupuncture is effective for other types of pruritus, including atopic dermatitis and asteatotic eczema; acupuncture has also been shown to have significant beneficial effects on histamine-induced itch in healthy volunteers. Pfab et al. [15] investigated the effect of acupuncture on type I hypersensitivity itch and skin reaction in a double-blind randomized placebo-controlled crossover trial, reporting that acupuncture resulted in a significant reduction in type I hypersensitivity itch in patients with atopic eczema.

Auricular acupressure therapy, a traditional Chinese medicine treatment modality, has the same purpose as acupuncture: simple, convenient, and cost-effective method widely used for clinical management of diseases [16–18]. The VAS scores of individuals in the postintervention group in our study decreased over time compared to scores in the control group ($P < 0.001$). Similarly, Akça et al. [10] showed that acupressure applied on acupuncture points using a transcutaneous electrical nerve stimulation (TENS) acupuncture apparatus was effective in reducing the frequency and severity of UP associated with hemodialysis. Meanwhile, Che-Yi et al. [19] reported lower mean posttrial pruritus in the group of participants who received acupuncture on the LI 11 acupuncture point, compared to both pretrial and control group scores. The treatment was reported to be successful after a 3-month follow-up period. Auricular acupressure for treatment of insomnia, hypertension, and depression in uremic patients has also been reported, which provides new insights for management of ESRD patients with UP.

UP develops for various reasons at any stage of treatment in patients receiving hemodialysis due to ESRD. Xerosis and hypohidrosis, the presence of pruritogenic cytokines (histamine, kallikrein, interleukin- (IL-) 2, acetylcholine, and other substances released by histamine-mediated mast cell stimulation), as well as secondary hyperparathyroidism, and immune-inflammatory reactions, have been proposed as reasons for the occurrence of UP [20, 21]. Multiple hypotheses and parameters have been put forth to explain the pathophysiology of UP; however, a consensus has not yet been reached in the literature [22].

The association of mast cells and UP in patients with ESRD has been extensively studied, which could possibly serve as one of the major pathogenic factors. Studies have shown that the skin of ESRD patients with UP has increased numbers of mast cells; these cells can release a variety of substances, including histamine, TNF, and IL, which are also common inflammatory markers [6]. The number of mast cells and histamine levels are reportedly higher in hemodialytic patients with pruritus compared to those in patients without pruritus symptoms [23]. Mast cells are an important class of immune cells that participate in a variety of biological responses through the release of particulate mediators in the body. They are involved in immune defense, endocrine regulation, and axonal reflex. In addition to hypersensitivity, mast cells also play a role in various immune functions, including innate and adaptive immunity. The major component of skin keratinocytes also plays an important role in pruritus pathogenesis, during which histamine released from mast cells serves as the major mediator [24].

For example, Kremer et al. [25] reported that intradermal application of histamine by iontophoresis or intradermal injection causes itching after a characteristic latency of up to 1 min, which is accompanied by a wheal and surrounding flare. Abundant mast cell clusters were found within acupoints in previous studies [26]. Our study also observed significantly reduced serum histamine levels in the postintervention group compared to the control group at the six-week follow-up (Figure 4) ($F = 5.01$, $P = 0.0290$). We believe that auricular acupressure decreases pruritus symptoms in patients undergoing sustained hemodialysis by reducing histamine levels.

However, histamine is present in both bound and inactive forms within tissue mast cell particles and basophils. When the body is subjected to physical and chemical irritation or allergic reactions, cell degranulation occurs, resulting in the release of histamine and subsequent biological effects. Acupuncture has a biphasic regulatory role for physiological and pathological conditions, and studies have shown that activation of acupuncture points can induce mast cell degranulation in localized connective tissue [27], and electric acupuncture can cause mast cells to gather at these points [28]. For example, auricular acupuncture on "stomach,"

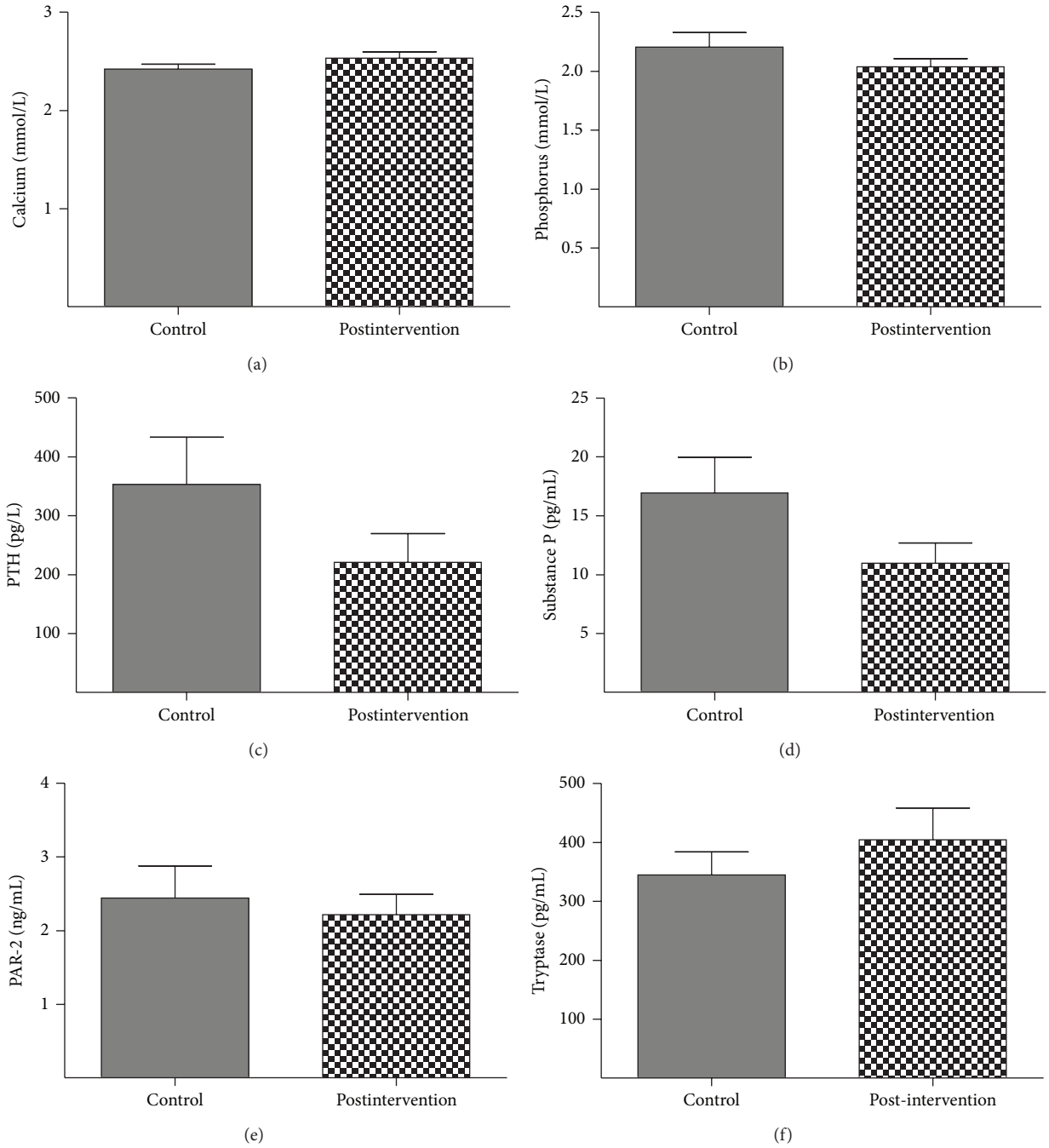

Figure 5: Mean changes in six secondary outcomes after six weeks, according to the postintervention group; $P > 0.05$ for postintervention group versus control group.

"Zusanli," and other points can reduce visceral inflammation and ultimately suppress mast cell degranulation, which may play a therapeutic role in treatment of gastric ulcers [29]. Based on our data, the effect of auricular pressure in decreasing pruritus in hemodialysis patients is associated with reduced histamine levels (Figure 4). Auricular acupressure may control mast cell degranulation and consequently reduce the histamine release.

Analysis of mediators closely associated with mast cells revealed no significant differences in levels of substance P, PAR-2, and tryptase between the postintervention and control groups. This finding might be due to insufficient acupressure therapy duration or follow-up period. There were also no significant differences in calcium, phosphorus, and PTH levels between the groups; future multicenter randomized trials with larger sample sizes and longer treatment durations

are necessary to verify the long-term efficacy of auricular acupressure among hemodialysis patients with pruritus.

The patients in the control group were informed that the tape contained a traditional Chinese medicine that could reduce pruritus. The tape was replaced every other day and removed every Sunday as a break day. This procedure was meant to eliminate the potential placebo response during the VAS interview and to prevent patients from identifying the control and intervention groups. The practitioners participating in this study did not take part in the randomization process, and evaluation and analysis of results was performed by professionals blinded to the assignation of treatment options; therefore, we consider the results of this study to be objective and reliable.

5. Conclusion

Our preliminary findings indicate that auricular acupressure may be a useful treatment in the multidisciplinary management of UP in patients with ESRD. Longer-term studies involving larger clinical samples are warranted to assess the generalizability of our findings and to deepen our understanding of this promising therapeutic approach.

Conflict of Interests

The authors have no conflict of interests to declare regarding this study.

Authors' Contribution

Cui-na Yan and Wei-guo Yao contributed equally to this work.

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