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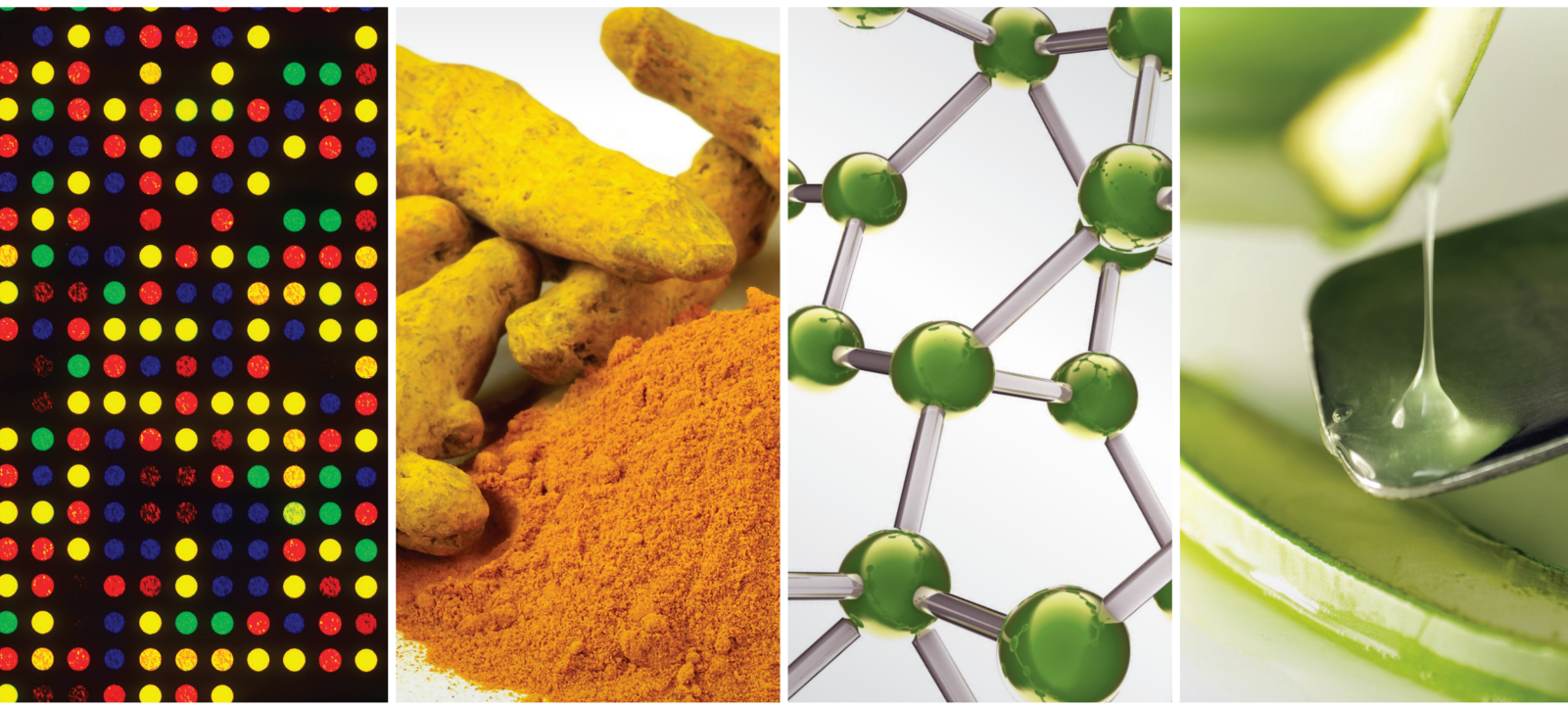
Deqi Sensation in Different Kinds of Acupuncture 2014

Guest Editors: Cun-Zhi Liu, Gerhard Litscher, Fan-Rong Liang, Jian Kong, Lin-Peng Wang, and Lu Wang



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Editorial Board

Contents

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Editorial

Deqi Sensation in Different Kinds of Acupuncture 2014

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This is an annual special issue published in this journal. The current issue is the 2014 issue which includes 7 interesting papers.

Acupuncture stimulation elicits Deqi, a composite of unique sensations that is essential for clinical efficacy according to traditional Chinese medicine. In recent years, clinical trials of acupuncture have paid increasing attention to the evocation of Deqi. The physiological mechanism that produces the effect of Deqi has also been explored in several studies but is not well understood.

This special issue contains 12 papers, of which 7 were published. Five papers are related to the characterization of the Deqi during acupuncture treatment. Y. Ren et al. conducted survey to determine acupuncturists' perspectives about Deqi. Deqi not only refers to needling sensations but also involves the changes of qi induced by needle insertion into the acupoint. Another 4 papers of clinical trials in patients with chronic fatigue syndrome, primary dysmenorrhea, depression, and motility of esophagus introduced the proper way to induce Deqi. These results may provide some evidences to the qualitative and quantitative research of Deqi.

Y.-S. Su et al. suggested somatosensory nerve fibers mediated generation of Deqi in manual acupuncture and local moxibustion-like stimuli-modulated gastric motility in rats. It is related to the physiological mechanism of Deqi. D.-S. Tian et al.'s paper is neuroimaging study on the interaction between Deqi and acupuncture. They revealed that acupuncture treatment with Deqi apparently increased acupoint blood flow, tissue displacement, and amplitude of myoelectricity and induced fMRI signal increase/decrease in different brain regions although no significant change was found in electroencephalography. This study provides evidence to understand neural mechanism underlying acupuncture.

Deqi should be taken into account in clinical trials, and more researches are required to understand the underlying mechanisms, as described in this special issue.

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Research Article

A Survey of the Practice and Perspectives of Chinese Acupuncturists on *Deqi*

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Deqi refers to the special sensation and reaction sensed mainly by both acupuncturist and patient when a needle was inserted into the acupoints and is considered to be vital to achieve acupuncture effect. For acupuncturist, it is important to judge and control *Deqi* in clinical practice. However, enough attention is paid to patients' feelings rather than acupuncturists' nowadays. We thus conducted this survey to determine acupuncturists' perspectives about *Deqi* and to further find the proper way to induce *Deqi*. A total of 250 questionnaires were sent out to acupuncturists and 202 (80.8%) were returned. According to the results, most acupuncturists believe that *Deqi* is vital to obtain preferable clinical effects. The reliability of acupuncturists' *Deqi* sensation ranks as sinking> tightening> astringent. The reliability of patients' *Deqi* sensations ranks as sourness> numbness> distention> heaviness> pain. The reliability of influential factors ranks as manipulation> specificity of acupoint> TCM constitution> disease status> patient's psychological condition> acupuncturists' psychological guidance> clinical environment. This study is believed to provide additional evidence to the qualitative and quantitative research of *Deqi* in the future.

1. Introduction

Acupuncture is one of the major treatment modalities in traditional Chinese medicine (TCM). For more than 2500 years of practice, it has been widely accepted by general population in China for its curative effect, wide range of indication, simplicity, and safety in practice. It has gradually become a global therapeutic method in recent decades. According to the theory of traditional acupuncture, the effect of acupuncture is achieved by regulating the channel *Qi*. Therefore, *Qi* arrival (*Deqi*), also known as needling sensation, is considered to be closely related to the acupuncture efficacy [1]. In clinical practice, *Deqi* is measured by the sensation of acupuncturists' finger and patient's reaction. Generally speaking, when *Deqi* occurs, an acupuncturist may feel sinking (*Chen*), astringent (*Se*), and tightness (*Jin*) around the needle by his/her fingers. Meanwhile, the patient may sense soreness (*Suan*), numbness (*Ma*), distention (*Zhang*), and heaviness (*Zhong*) around the acupoint; sometimes, *Deqi* sensation could be different like coldness, warmness, pain electric-shock feeling, and so forth. However, the intensity and property of acupuncture *Deqi* may differ as a result of the different physical and psychological conditions of individuals, which made it difficult to be comprehensively applied in clinics.

Deqi sensation scale, as an important qualitative and quantitative measuring tool for *Deqi*, was applied to acupuncture clinical trials and mechanism studies recently [2–5]. In 1989, the Vincent *Deqi* scale was invented with 20 adjectives based on the McGill pain questionnaire. And then there were the Park *Deqi* scale and the MacPherson *Deqi* scale followed by [6, 7]. However, these scales had mainly focused on the patients' sensations but no attention had been paid to the *Deqi* sensation of acupuncturist. Further, the Southampton *Deqi* scale was drafted based on the suggestions of both patients and acupuncturists but failed to discriminate the noxious pain sensation from *Deqi* sensations according to a German trial [8, 9]. The Massachusetts general hospital acupuncture sensation scale (MASS), which was modified based on the subjective acupuncture sensation scale (SASS) [10], was composed of various needling sensations and had a measurement of the spreading of *Deqi* and patient's anxiety during needling. It has already been validated as a reliable and valid tool to measure *Deqi* in healthy young Chinese people [11]. However, till now no standardized, valid, and reliable *Deqi* scale has been formed due to the lack of sufficient evidence.

In TCM classics, the process to achieve *Deqi* is also called "*Qizhi,*" which means *Qi* arrival or *Qi* obtained through acupuncturist's manipulations after needle insertion. One of the chief indicators of achieving *Deqi* is the sensation change felt by acupuncturist's fingers. The activation, retention, and spreading of *Deqi* are closely and directly related to acupuncture manipulation techniques, while recent literature indicates that research attention has been merely paid to the patients' or healthy subjects' needle sensations, with ignorance of the *Deqi* sensation felt by acupuncturists. Therefore, we conducted this survey by consulting acupuncturists, who are engaging in clinical practice in Chinese hospitals, to explore acupuncturist's perspectives on *Deqi* and to further understand if there are different views among acupuncturists with different levels of experience.

2. Methods

The questionnaire for measuring acupuncture *Deqi* in acupuncturist was initially designed by 2 senior acupuncture experts, together with 2 clinical acupuncturists and 2 doctoral candidates. All participants of questionnaire design embrace rich experiences in acupuncture treatment with skillful acupuncture manipulation techniques. The current questionnaire we presented in this paper is an autonym questionnaire in Chinese that is finally completed after 5 times revisions according to acupuncture experts suggestions and comments. It contains three parts with 16 items relating to acupuncture *Deqi*. Part 1 includes 2 single choice questions and 1 open-ended question regarding the acupuncturist's thoughts on the relationship between *Deqi* and acupuncture efficacy. The questions in part 2 include 2 single choice questions, 3 multiple choice questions, and 2 questions for multiple choices, aimed to identify the proper way to judge *Deqi* in clinical practice. The questions in part 3 include 4 single choice questions, 2 multiple choice questions, and 1 question for multiple choices, aiming to find the proper manipulation for a better control and guidance of *Deqi* in clinical practice.

According to the latest literature [12], 90% acupuncturists thought *Deqi* was related to clinical efficacy. Based on assumption that it reached 96% in this study, a sample size of 200 at least is needed to achieve 90% power to detect a statistical significance by using a two-sided binomial test. The target significance level was 0.05. Thus, 250 acupuncturists were needed assuming a 25% dropout rate. A total of 250 questionnaires were sent out to 250 acupuncturists regardless of age or gender in 44 hospitals with express delivery. The included hospitals were geographically distributed in *Zhejiang, Jiangxi, Hunan, Shanxi, Qinghai, Sichuan, Yunnan, and Guizhou* province and *Beijing, Tianjin, and Chongqing* municipal city. The rationale for choosing these hospitals in different areas of different directions of China is aiming to avoid deviations caused by the dominance of a specific acupuncture theory or schools in one region. Among them, there were 34 top grade hospitals (77.2%), and most of them are TCM hospitals, 7 second grade hospitals (16%), and 3 community hospitals (6.8%). All questionnaires were completed by included acupuncturists independently.

The data of questionnaire was collected back-to-back by two researchers. Then, the data was completely and accurately transferred to computerized database for data processing including double data entry, edit checks, data cleaning, coding, and reconciliation. Continuous variables were summarized as means (SDs) and discrete data as frequency and percentage.

3. Results

3.1. Participants. 250 questionnaires were sent out, and 202 (80.8%) were returned. 49.5% of the respondents were male. The participants were aged from 19 to 59 years (mean, 33.5), with working years ranging from 1 to 45 years (mean, 9.0 years) (1–5-year experience, $N = 96$; 6–10-year experience, $N = 49$; 10+ years of experience, $N = 57$). Regarding the education level, there are 8 with associate degree, 93 participants with bachelor's degree, 73 with master degree, and 18 with Ph.D. degree. Regarding technical title, there were 7 physician assistants, 98 resident doctors, 43 attending physicians, 41 associate physicians, and 13 chief physicians.

3.2. Perspectives on the Relationship between Deqi and Acupuncture Efficacy. As shown in Table 1, regarding the question "whether the *Deqi* was crucial to clinical efficacy," 194 acupuncturists responded, and 85.57% of them thought that in most cases *Deqi* was crucial to clinical efficacy, and 8.76% thought it was absolutely crucial, while 2.06% of them stated that in most cases *Deqi* is not vital to therapy, and 3.61% of them were not sure. No one chose that *Deqi* was not related to treatment at all. Regarding the question "whether a higher intensity of *Deqi* resulted in a more preferable efficacy," most acupuncturists (65.80%) did not think so, while 34.20% of the participants agreed. For the reason why the higher *Deqi* intensity did not yield better efficacy, some

Table 1: Perspectives on the relationship between *Deqi* and acupuncture efficacy.

Questions	Views	Respondents (n)/all respondents (n), %
(1) Do you think *Deqi* is crucial to acupuncture clinical efficacy?	① Yes, totally	17/194, 8.76%
	② Yes, mostly	166/194, 85.57%
	③ No, mostly not	4/194, 2.06%
	④ No, totally not	0
	⑤ Uncertainty	7/194, 3.61%
(2) Do you think a higher intensity of *Deqi* results in a more preferable efficacy?	① Yes	66/193, 34.20%
	② No	127/193, 65.80%

Table 2: The way to judge *Deqi*.

Questions	Views	Respondents (n)/all respondents (n), %
(3) Which way(s) do you prefer to judge the occurrence of *Deqi*? (multiple choices)	① According to sensation of patient's reaction.	169/193, 87.56%
	② According to sensation of your fingers	157/193,81.35%
	③ According to facial expression of patient	66/193, 36.27%
(4) What is the probability of the case that *Deqi* has been felt by your fingers but the patient reported not?	① Less than 5%	50/192, 26.04%
	② 5%–10%	97/192, 50.52%
	③ 10%–15%	26/192, 13.54%
	④ 15–20%	13/192, 6.77%
	⑤ More than 20%	6/192, 3.13%
(5) Can you recognize whether the *Deqi* has appeared just by your fingers' sensations during manipulations?	① Yes	171/194, 88.14%
	② No	23/194, 11.86%
(6) What sensations have been felt by your fingers when *Deqi* has emerged? (multiple choice)	① Sinking	176/185, 95.14%
	② Astringent	141/185, 76.22%
	③Tightening	180/185, 97.30%
	④ Others	7/185, 3.78%
(7) Please rank the acupuncturists' *Deqi* sensations (those you chose in Question (6) in the order of their reliability for telling the arrival of *Qi*.	/	Shown in Figure 1
(8) When *Deqi* occurred, what are the sensations reported by patients? (multiple choices)	① Sourness	182/196, 92.86%
	② Numbness	170/196, 86.73%
	③ Distention	189/196, 96.43%
	④ Heaviness	139/196, 70.92%
	⑤ Pain	104/196, 53.06%
	⑥ Others	7/196, 3.57%
(9) Please rank the patients' *Deqi* sensations (those you chose in Question (8)) in the order of their reliability for telling the arrival of *Qi*.	/	Shown in Figure 2

acupuncturists (45.67%) thought it was related to patients' acceptance and tolerability to acupuncture, because a higher intensity possibley resulted in harm of healthy *qi* or even noxious stimulation. 26.77% thought it was attributed to individual difference. 3.94% thought it was complicated. And 23.62% did not give any answers.

3.3. The Way to Judge Deqi. As shown in Table 2, Question (3) is a multiple choice question, and acupuncturist could make one or more choices. 87.56% of the acupuncturists said they jndged the occurrence of *Deqi* according to patient's sensation, 81.35% based on their personal sensation felt by fingers, and 36.27% according to the facial expression of patient. Question (4) demonstrated that there is only a small chance when *Deqi* was felt by acupuncturist but not by patient. The results showed that 50.52% of acupuncturists thought the probability was 5%–10%, and 26.04% thought it is less than 5%. Regarding Question (5), 88.14% of the acupuncturists could tell whether the *Deqi* was achieved just by their manipulating fingers' sensation regardless of patient's sensation.

Question (6) was also a multiple choice question. The highest frequency of any sensation felt by the acupuncturists during *Deqi* was tightening (97.30%), followed by

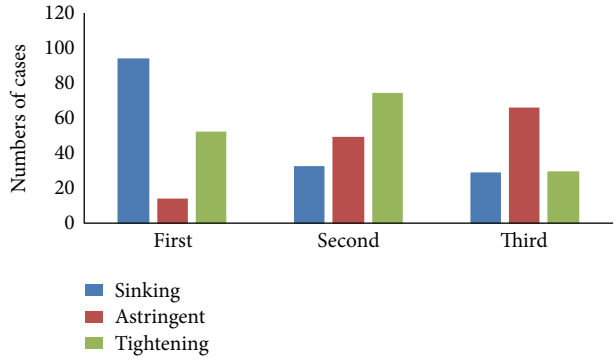

Figure 1: The reliability order of acupuncturists' *Deqi* sensations in Question (6).

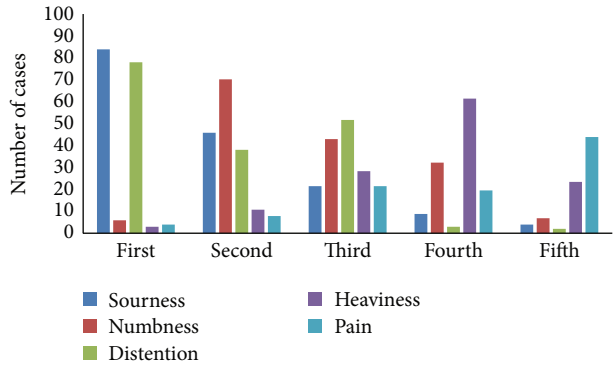

Figure 2: The reliability order of patients' *Deqi* sensations in Question (8).

sinking (95.14%), astringent (76.22%), and others (3.78%). In Question (7), acupuncturists ranked the reliability of telling *Deqi* according to their sensations shown in Question (6) in sequence. Figure 1 demonstrated that acupuncturist believed that sinking was ranked at the first place, while tightening the second, and astringent the third, in the reliability of telling *Deqi* based on their personal sensations.

Answers to Question (8) demonstrated that main sensations of *Deqi* reported by patients were distention (96.43%), soreness (92.86%), numbness (86.73%), heaviness (70.92%), and pain (53.06%). In order to determine the reliability of telling *Deqi* by patient's subjective sensation, acupuncturists were required to answer Question (9). The result in Figure 2 showed that acupuncturist believed that soreness was ranked at the first place, while numbness the second, and distention the third, followed by heaviness and pain, in the reliability of telling *Deqi* based on patients' subjective sensations.

3.4. The Way to Control Deqi. As shown in Table 3, Question (10), regarding the influential factors of *Deqi* during clinical practices, was a multiple choice question. The main influential factors of *Deqi* were manipulation (98.43%), patient's body constitution (95.29%), acupoint (87.43%), the state of illness (80.10%), and psychological condition of patient (68.06%). The importance and reliability of *Deqi*'s influential factors to *Deqi* was ranked in the order as manipulation

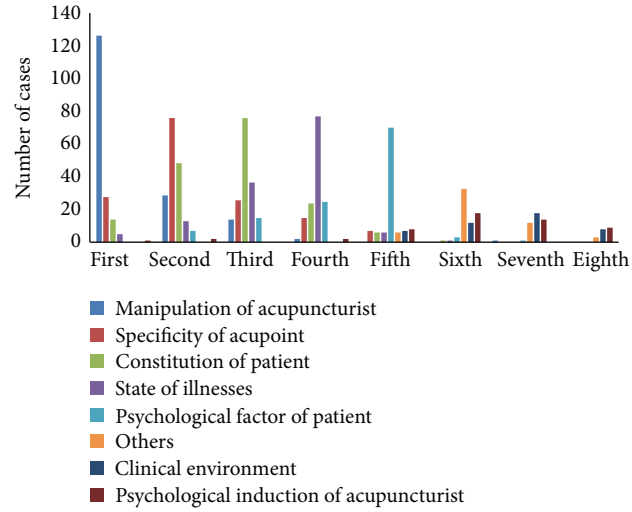

Figure 3: The order of influencing factors of *Deqi* in Question (16).

of acupuncturist> specificity of acupoints> constitution of patient> status of illness> pathogenetic condition of patient, as shown in Figure 3.

Regarding Question (12), the most frequently used manipulation to promote *Deqi* sensations was the combination of rotating, lifting, and thrusting (72.54%), and supplementary manipulations such as scrape, shake, and press were also used by some acupuncturists (17.62%), while just one kind of manipulation was seldom applied. The questions (13) showed that most acupuncturists (74.21%) believed that the depth of insertion to elicit *Deqi* sensation should be based on the patient's conditions, and 25.79% thought that deep insertion was easier, but few chose shallow insertion. In response to the question of whether the strong sensation produced by rotating the needle in single direction was true *Deqi* or not, 46.87% acupuncturists agreed with this point. According to Question (15), the majorities of acupuncturists (98.45%) are able to induce *Deqi* right at the moment of needle insertion, even without needle manipulation. But the possibility was not high for 21.05% of acupuncturists thought it <20% and 38.42% of acupuncturists thought 20%–40%, indicated in Question (16).

4. Discussions

4.1. Deqi Is Crucial to Acupuncture Efficacy. In our study, 94.33% acupuncturists stated *Deqi* was crucial to clinical efficacy. Of these, 85.57% thought it was crucial in most cases while 8.76% thought it was always crucial. No one denied its importance completely. A recently randomized controlled trial (RCT) of Bell's palsy demonstrated that the strong *Deqi* could result in better outcomes [2], while another study stated no pain relief in osteoarthritis patients [13]. Regarding the intensity, the majority of acupuncturists did not believe that a stronger intensity would increase the benefits while 34.20% agreed. This result was similar to the results reported by Han [14], who showed that a low frequency (2 Hz) had better effects on easing pain than a high frequency (100 Hz). There

Table 3: The way to control *Deqi*.

Questions	Views	Respondents (*n*)/all respondents (*n*), %
(10) What is the influential factors of *Deqi* during your clinical practices? (multiple choices)	① Manipulation of acupuncturist	188/191, 98.43%
	② Specificity of acupoint	167/191, 87.43%
	③ Constitution of patient	182/191, 95.29%
	④ State of illnesses	153/191, 80.10%
	⑤ Psychological factor of patient	130/191, 68.06%
	⑥ Clinical environment	53/191, 27.75%
	⑦ Psychological induction of acupuncturist	54/191, 28.27%
(11) Please rank *Deqi*'s influential factors (those you chose in Question (10)) in order according to their reliability and importance.	/	Showed in Figure 3
(12) Which manipulation is the most commonly used to promote the arrival of *Deqi* sensations?	① Lifting and thrusting	12/193, 6.22%
	② Rotating	2/193, 1.04%
	③ Combination of rotating, lifting, and thrusting	140/193, 72.54%
	④ Supplementary manipulations like scrape, shake, and so forth.	4/193, 1.04%
	⑤ Combination of ③ and ④	34/193, 17.62%
	⑥ Others	1/193, 0.52%
(13) For deep or shallow insertion, which one more easily elicits *Deqi* sensation according to your experiences?	① Deep	49/190, 25.79%
	② Shallow	0/190, 0%
	③ Depending on patients' conditions	141/190, 74.21%
(14) For the strong sensations caused by rotating with one single direction, does this feeling belong to *Deqi*?	① Yes	90/192, 46.87%
	② No	102/192, 53.13%
(15) Have *Deqi* ever occurred as soon as the needle was inserted without any manipulations?	① Yes	190/193, 98.45%
	② No	3/193, 1.55%
(16) If (15) has occurred, what is the approximate occurrence rate?	① Less than 20%	40/190, 21.05%
	② 20%–40%	73/190, 38.42%
	③ 40%–60%	55/190, 28.95%
	④ 40–80%	19/190, 10%
	⑤ More than 80%	3/190, 1.58%

is no doubt that *Deqi* is crucial to clinical efficacy in our study. However, future clinical trials are required to confirm this.

4.2. Deqi and Acupuncture Manipulations. Our investigation showed that the most significant influencing factors of *Deqi* were the acupuncturist's manipulation. Acupuncturists' manipulation was also reported to be the most important influencing factor in clinical studies. It is accepted that manipulation could induce the release of *Deqi* and promote the degree of *Deqi* or alleviate the strong *Deqi* sensation. It is also known that different types of manipulation can result in different *Deqi* sensations. For promoting or controlling *Deqi*, acupuncturists preferred to use the combined manipulations of rotating, lifting, and thrusting and also used the supplemental manipulations such as scraping and shaking. As the issue of whether the strong feeling caused by rotating with one single direction was due to *Deqi*, acupuncturists themselves did not come to an agreement. Sometimes, nearly all acupuncturists have experienced that *Deqi* occurred just as the needle was inserted without any other manipulations, but the probability was very low.

Different depth of insertion has aroused considerable debate, and more researchers favor the idea that with deep insertion it is easier to produce *Deqi* sensations. Functional magnetic resonance imaging (fMRI) has shown that deep electroacupuncture on GB34 and GB35 could generate stronger *Deqi* sensations and more effectively modulate the pain-related neuromatrix than shallow electroacupuncture [15]. Other studies also proved that deep acupuncture could result in higher *Deqi* sensations scores [16] and increase the skin and muscle blood flow [17] in healthy subjects. However, some studies report the opposite views. A fMRI research declared no significant differences in the blood oxygen level dependent (BOLD) responses by the deep and shallow stimulations [18]. RCT also showed that the same effects were achieved by both deep and superficial acupuncture in

idiopathic anterior knee pain patients [19]. Our questionnaire results demonstrated that no one thought the shallow insertion made it easier to produce *Deqi* sensations, and 25.79% of the acupuncturists stated that deep insertion made it easier, while the majority of the acupuncturists (74.21%) explained that it depended on the patients' conditions and was not relevant to the depth of insertion. The shallow stimulation usually means that the needle tip reaches the subcutaneous tissue, while the deep stimulation may arrive at the muscular or nervous tissues. *Deqi* sensation may not be completely relevant to the deep tissues. One study provided evidence that *Deqi* was not relevant to the deep median nerve contact nor median nerve penetration during needling in P6 point with ultrasound measurement [20]. Another study also explained that it depended on the patients' conditions and no relevance was attributed to the depth of insertion because in healthy subjects the skin and muscle blood flow increased with no significance comparing deep and shallow stimulation, but in fibromyalgia patients there were significant differences [5].

4.3. The Deqi Sensation of Acupuncturists and Patients. It seems that the feelings of patient and acupuncturist are often used to judge whether *Deqi* has been generated or not, but few researches have demonstrated the real details of judgment. The results of this study showed that the majority of acupuncturists recognized whether the *Deqi* had been achieved just by their fingers' sensations during manipulations. These sensations were mostly tightening, sinking, and astringent, which were similar as those described in textbooks [1]. Interestingly, the *Deqi* sensations experienced by fingers were ranked as sinking, tightening, and astringent according to the reliability. In our survey, the patients' sensations were mainly described as soreness (*Suan*), numbness (*Ma*), distention (*Zhang*), heaviness (*Zhong*), and pain (*Tong*). The results showed the order of frequency as distention, soreness, numbness, heaviness, and pain, and the orders of its reliability level scores ranked as soreness>numbness>distention>heaviness>pain. For the top three sensations, although there were different words and expressions to describe Zhang, Suan, and Ma, some previous researchers also demonstrated similar results [21–24]. So, *Deqi* sensation in both acupuncturist and patient, occurrence probability, and the order of reliability were revealed. These results may provide some advice for further quantification studies for *Deqi*.

4.4. Influencing Factors of Deqi. Except for acupuncturist's manipulation, the common influencing factors of *Deqi* included the specificity of acupoint, the constitution of patient, and the patients'psychological factor as shown in our study. For the specificity of the acupoint, studies had shown that it existed and was related to clinical effects closely [25], but it needs further clinical study to determine its direct relationship with *Deqi*. Yet for all that, according to common sense, the feeling of pain is evident with needling the terminal points on the four limbs, while the soreness and distention are noted in thick muscle points. Meanwhile, the conditions of patient such as constitution, illness state, and psychology were considered as the important factors to *Deqi* in Chinese ancient and modern literatures [26–28]. As noted in "*Ling* Shu *Jing,*" the speed of *Deqi* emergence is faster in patient with *yang* excess constitution than the one with *yin* excess. Compared with healthy volunteers, patients suffering chronic pain tended to acquire a much stronger *Deqi* sensation [29]. Some researchers believe that *Deqi* is the brain awareness and consciousness because the sensations of the subjects were the same between sham laser acupuncture and true laser [30]. However, in the classical literature such as the "*Huangdi Neijing*" and the "*Zhenjiu Dacheng,*" psychological factors are important with *Deqi*, not only in the process of acupuncture but also in influencing the clinical outcomes. Clinical trials revealed that Bell's palsy patients with the personality factors of excitability, sociability, braveness, and intellectuality had an easier time to gain *Deqi* [31], and the anxiety and dominance were correlated with the treatment effects of primary dysmenorrhea [32]. In addition, the anxiety also affected the heart rate variability in healthy subjects [33].

4.5. Limitations. The main limitation of this survey is that the contents are designed according to Chinese acupuncturist's customs, including manipulations, acupuncturist's needling sensations, patient's sensations, and the factors of *Deqi*, and some items may be difficult to understand and do not conform with international conventions. Most of the acupuncturists came from the grade-three general province hospitals, and opinions from lower grade hospitals were insufficient. The results are from acupuncturists' general perspectives; a supplementary survey of the patients' views is necessary.

5. Conclusions

Our survey demonstrates that *Deqi* is important to clinical effects according to the acupuncturist's views. The integrated manipulations are the most common way to promote *Deqi* sensation. The reliability of primary acupuncturist fingers' *Deqi* sensations ranks as sinking> tightening >astringent. The reliability of primary patients' *Deqi* sensations ranks as sourness>numbness>distention>heaviness>pain as reported by patients. The reliability of primary patient's *Deqi* sensation factors ranks as manipulation>specificity of acupoint>TCM constitution>disease status>patient's psychology>acupuncturist's psychological hint>clinical environment.

In short, this paper shows the perspectives of Chinese acupuncturists on *Deqi*. The results may provide some evidences to the qualitative and quantitative research of *Deqi*. To formulate and evaluate a *Deqi* sensation scale, it may be better to include both of the sensations of acupuncturist and patient on the basis of the credible rank. In clinical research and practice, the influential factors of *Deqi* should be considered.

Conflict of Interests

The authors declare that there is no conflict of interests in this paper.

Authors' Contribution

Yu-lan Ren and Tai-pin Guo contributed equally to this paper.

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Review Article

Application of Acupoints and Meridians for the Treatment of Primary Dysmenorrhea: A Data Mining-Based Literature Study

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Background. Dysmenorrhea is a common problem for which acupuncture provides effective analgesia. Although acupoint selection affects the effectiveness of acupuncture, the basic rules of acupoint selection are little understood. This study aims to investigate the principles of acupoint selection and characteristics of acupoints used for primary dysmenorrhea. *Methods.* PubMed, China National Knowledge Infrastructure, and Chinese Biomedical Database were searched for clinical trials published in English or Chinese from January 1978 to April 2014 evaluating the effect of acupuncture on primary dysmenorrhea, with or without methods of randomization and/or control. Three authors extracted information and two reviewers inputted information on titles, journals, interventions, main acupoints, and outcomes using the self-established Data Excavation Platform of Acupoint Specificity for data mining. *Results. Sanyinjiao* (SP06), *Guanyuan* (CV04), and *Qihai* (CV06) were used most frequently. The most frequently used meridians were Conception Vessel, Spleen Meridian of Foot *Taiyin*, and Bladder Meridian of Foot *Taiyang*. 67.24% of acupoints used were specific acupoints. Acupoints on lower limbs were most frequently used. *Conclusion.* Data mining is a feasible approach to identify the characteristics of acupoint selection. Our study indicated that modern acupuncture treatment for primary dysmenorrhea is based on selection of specific acupoints according to traditional acupuncture theory.

1. Introduction

Dysmenorrhea is a common problem for adolescent girls and women of reproductive age [1]. Primary dysmenorrhea (PD) is medically defined as those menstrual periods when females feel pain without any organic change in the uterus. The typical symptom is a pain that originates in the lower abdomen and spreads to the inner thighs; this can cause agony for a couple of days every month [2]. The prevalence of dysmenorrhea appears different across the world, ranging from 80% in Western Australia [3] to 60% in Canada [4], 48.4% in Mexico [5], and 79.9% in Iran [6]. One estimate depicted that 51% of young women reported limited activities and another 17% had sick leave from either school or work because of severe menstrual pain [4]. Hence, the burden of dysmenorrhea is greater than any other gynecological complaint and has a significant impact [7].

Common treatments for dysmenorrhea include rest (58%), medications (52%), heating pads (26%), tea (20%), exercise (15%), and herbal medicine (only 14%) [8]. The most frequently applied therapy to treat PD is nonsteroidal anti-inflammatory drugs (NSAIDs) [9]. However, there are often unpleasant adverse events associated with NSAID use, including stomachache, diarrhea, and nausea [9]. This has led to increasing numbers of patients seeking complementary and alternative techniques such as acupressure and moxibustion to treat symptoms of PD [10].

Acupuncture is an important technique in the field of Traditional Chinese medicine (TCM), used for both disease prevention and therapy. However, evaluation of acupuncture

in clinical trials that could accelerate TCM modernization has not been possible until the past few years. With the introduction of evidence-based medicine (EBM), domestic and foreign scholars have carried out a lot of scientific research into acupuncture. It is now well known that the randomized controlled trial (RCT) is the gold standard for efficacy and safety assessment. Through the comprehensive collation of relevant RCTs, one systematic review found that acupuncture was associated with a significant reduction in pain compared with pharmacological treatment or herbal medicine for PD [11]. Another systematic review indicated that acupuncture was superior to both no-acupuncture control and sham acupuncture for the treatment of chronic pain, suggesting that factors in addition to the specific effects of needling are important contributors to therapeutic effects [12].

The development of EBM has caused acupoint specificity to become the research focus. Acupoint specificity is of prime importance in point selection, and it involves specificity in terms of clinical effect, biological structure, and biophysics. According to the principles of TCM, the selection of acupoints plays a vital role in the therapeutic effectiveness of acupuncture.

The selection of acupoints is changeable according to the different ideas and experience of the acupuncturists. There is a vast volume of literature related to acupuncture and moxibustion; however, as the diversity between different schools is huge, determination of the most effective selection and application of treatment is very difficult. Thus precise information describing the optimal selection and combination of acupoints for the treatment of PD is not presently available.

Fortunately, the emergence of data mining techniques allows new ways of analyzing acupuncture and moxibustion information. Data mining, which is also referred to as knowledge discovery in databases, is the nontrivial extraction of implicit, previously unknown, and potentially useful information from data [13]. To date, our team has fundamentally researched the application of meridian points for the treatment of poststroke disorder [14], migraine [15], and functional dyspepsia (FD) [16] based on data mining technology. Proper use of data mining can acquire new knowledge hidden in vast amounts of TCM information, enabling the design of more rigorous RCTs to validate results. For example, one study analyzed the application characteristics and laws of acupoints in the treatment of FD and found that *Zusanli* (ST36) was the most frequently used acupoint [16]. Another study also found that acupuncture on *Zusanli* (ST36) of the Stomach Meridian group is effective in the treatment of FD and is superior to the Gallbladder Meridian group [17]. This trial may provide evidence for the existence of specificity between acupoints on different meridians and that the benefit of acupuncture relies on acupoint specificity. Therefore determining the characteristics and rules of acupoint selection for PD is important for future research and in clinical practice.

The aims of this study were to (1) discover the basic rules of acupoint selection in meridians and specify acupoints in different body parts used for treating PD in modern literature and (2) investigate the association rule of acupoints based on data mining, so as to provide relatively standard treatment guidelines in the application of meridian points for PD.

2. Methods

2.1. Search Methods. PubMed (http://www.pubmed.com/), China National Knowledge Infrastructure (CNKI) (http://www.cnki.net/), and Chinese Biomedicine Database (CBM) (http://www.sinomed.ac.cn/) were searched for literature on acupuncture treatments for PD from January 1978 to April 2014.

The search strategy combined the key words (i) "acupuncture" or "electroacupuncture" or "moxibustion" or "meridian" or "acupoint"; and (ii) "primary dysmenorrhea" or "dysmenorrhea" or "menstrual pain." The search included the literature on acupuncture treatment for secondary dysmenorrhea. Only electronic databases were searched for eligible studies. Language was restricted to English and Chinese.

2.2. Review Process

2.2.1. Data Screening

(1) Types of Studies. Inclusion criteria included clinical trials evaluating the effect of acupuncture, with or without methods of randomization and/or control. The number of participants had to be more than ten in each group/trial. The final publication was used in the case of duplicate publications.

Exclusion criteria included reviews, animal trials, case reports, systematic reviews, and meta-analyses.

(2) Types of Participants. Inclusion criteria included clinical trials involving participants diagnosed with PD.

Exclusion criteria included trials evaluating the therapeutic effect of acupuncture for secondary dysmenorrhea caused by endometriosis, uterine myoma, endometrial polyps, pelvic inflammatory disease, and other gynecological problems.

(3) Types of Intervention. Inclusion criteria were as follows. The treatments for PD had to involve needle insertion and/or moxibustion at either traditional meridian acupoints or extraordinary acupoints. Electrical stimulation of needles was included. Acupuncture and/or moxibustion was either used alone or in addition to other interventions (e.g., Chinese herbs). Trials that compared different forms of acupuncture for PD were included.

Exclusion criteria included studies investigating modern methods of stimulating acupuncture points without needle insertion (e.g., laser stimulation or transcutaneous electrical stimulation). Trials of microacupuncture systems were also excluded, as the theoretical basis of microacupuncture has no relevance to traditional acupoints. Trials evaluating acupressure and trials stimulating pain points or trigger points alone for PD were excluded.

(4) Types of Outcome Measurements. Inclusion criteria were as follows. Studies were included if they reported at least one clinical outcome related to dysmenorrhea (e.g., response,

frequency, pain intensity, menstrual symptom scale, or analgesic use). In the case of controlled trials, studies included were those in which patients treated with acupuncture alone or in combination showed more benefits than patients who did not get acupuncture therapy. If a study compared the therapeutic effects of different acupoint prescriptions, the most effective acupoint prescription was included.

Exclusion criteria were as follows. Trials reporting only physiological or laboratory parameters were excluded. In the case of controlled trials, studies were excluded if patients treated with acupuncture alone or in combination showed fewer benefits than patients who did not get acupuncture therapy. If a study compared the therapeutic effects of different acupoint prescriptions, acupoint prescriptions other than the most effective one were excluded.

2.2.2. Data Collection. All abstracts identified by the literature search were screened by Siyi Yu, who excluded those that were clearly irrelevant (e.g., studies focusing on reviews, animal trials, case reports, and so on). Full texts of all remaining references were obtained and again screened to exclude irrelevant papers. The eligibility of all other articles was then formally checked by Jie Yang and Mingxiao Yang according to the abovementioned selection criteria. Disagreements were resolved by discussion.

2.2.3. Data Preprocessing. Information on titles, journals, interventions, main acupoints, and outcomes was inputted independently by Yan Gao and Jiao Chen using the self-established Data Excavation Platform of Acupoint Specificity (Copyright Registration number 2009SR014647) for data mining. As many acupoints have aliases, the names of acupoints were standardized according to *Fundamentals of Acupuncture*.

2.2.4. Data Processing. Based on the data mining algorithm of multihierarchy rules, related knowledge of selection and combination of acupoints can be acquired by calculating the frequency, support degree, confidence, and list level of acupoint item sets. Support degree is an index to describe the probability that events A and B synchronize under specific conditions; this was used to measure the statistical significance of association rules within the entire dataset. The coverage of an association rule is the number of instances for which it predicts correctly; this is often called its support. Its confidence or accuracy is the number of instances that it predicts correctly, expressed as a proportion of all instances to which it applies [18]. Support displays antecedent support, that is, the proportion of instances for which the antecedents are true, based on the training data. Confidence displays the ratio of rule support to antecedent support. Lift displays the ratio of confidence for the rule to the prior probability of having the consequent. In general, rules with lift different from 1 will be more interesting than rules with lift close to 1. Association rules are useful only when the support degree and confidence level meet the minimum requirements. See Figure 1 for a flow diagram of data processing steps taken.

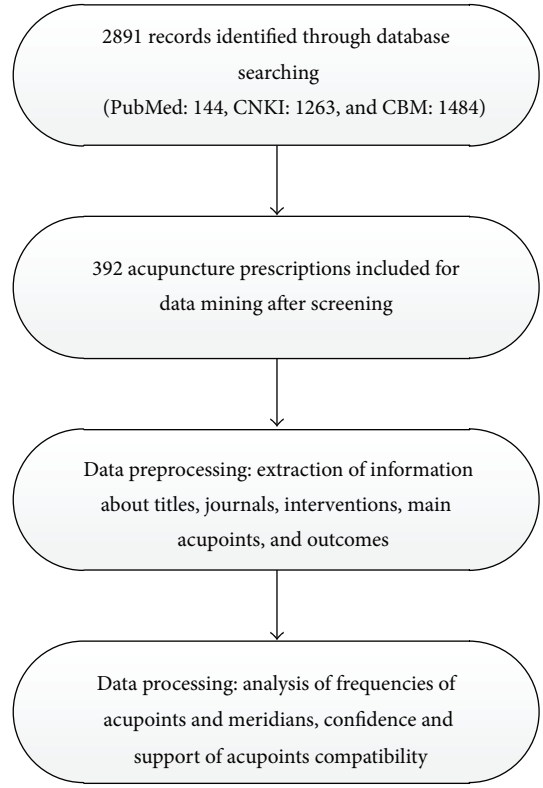

Figure 1: Flow of information through the different phases of data mining.

3. Results

3.1. Overall Profile of Acupuncture Prescriptions. Database searching identified 144 records in PubMed, 1263 records in CNKI, and 1484 records in CBM. After filtering, a total of 392 acupuncture prescriptions were included in this study (see Figure 1).

3.2. Application of Acupoints. This analysis aimed to provide the acupoint selections and their frequencies when curing certain diseases. The most frequently used acupoints for PD in descending order were *Sanyinjiao* (SP06), *Guanyuan* (CV04), *Qihai* (CV06), *Diji* (SP08), *Ciliao* (BL32), *Zusanli* (ST36), *Taichong* (LR03), *Xuehai* (SP10), and *Shenshu* (BL23) (see Table 1).

3.3. Application of Meridians. Meridian application analysis demonstrated how the selected acupoints in the prescription were distributed in the 14 channels, including the frequency and percentage of the acupoints on each meridian, the number and percentage of acupoints used, and the name and frequency of each acupoint. The selected acupoints were distributed among 13 meridians, including 11 regular meridians, Governor Vessel, and Conception Vessel. The most frequently used meridian was Conception Vessel, with Spleen Meridian of Foot *Taiyin* and Bladder Meridian of Foot *Taiyang* also frequently used. Extraordinary acupoints were

Table 1: 20 most frequently used acupoints identified by data mining.

Number	Acupoint	Frequency	Support (%)
1	*Sanyinjiao* (SP06)	257	65.56
2	*Guanyuan* (CV04)	234	59.69
3	*Qihai* (CV06)	142	36.22
4	*Diji* (SP08)	126	32.14
5	*Ciliao* (BL32)	126	32.14
6	*Zusanli* (ST36)	123	31.38
7	*Zhongji* (CV03)	120	30.61
8	*Taichong* (LR03)	114	29.08
9	*Xuehai* (SP10)	77	19.64
10	*Shenshu* (BL23)	73	18.62
11	*Shenque* (CV08)	70	17.86
12	*Hegu* (LI04)	58	14.80
13	*Zigong* (EX-CA1)	49	12.50
14	*Guilai* (ST29)	43	10.97
15	*Mingmen* (GV04)	42	10.71
16	*Shuidao* (ST28)	40	10.20
17	*Ganshu* (BL18)	36	9.18
18	*Yinlingquan* (SP09)	32	8.16
19	*Shiqizhui* (EX-B7)	30	7.65
20	*Pishu* (BL20)	27	6.89

also frequently used. The frequencies for each meridian and acupoint are shown in Table 2.

3.4. Application of Special Acupoints. The results of the analysis depicted how certain acupoints are used in acupuncture prescriptions, including the frequency of the main categories, the numbers, and the type of acupoint used. Seventy-eight of the 116 acupoints used were specific acupoints, accounting for 67.24% of the total number of acupoints. The majority of the special acupoints used were Crossing acupoints, with meridian qi passing through and crossing in the abdomen; Front-*Mu* acupoints, Five *Shu* acupoints, Yuan-Source acupoints, and Back-*Shu* acupoints were also frequently used (see Table 3).

3.5. Application of Acupoints on Different Body Parts. The results of the analysis displayed the frequency and percentage of the distribution of acupoint selections in the prescriptions, the numbers and percentages of acupoints used, and the names and frequencies of particular acupoints. Acupoints on lower limbs were most frequently used, with 33 acupoints used a total of 839 times. This was followed by acupoints on the chest and abdomen (used 752 times), back and lumbar acupoints (used 409 times), acupoints on the upper limbs (used 93 times), and acupoints on the head, face, and neck (used five times) (see Table 4).

3.6. Association of Acupoint Compatibilities. The aim of the analysis was to indicate the compatibility of acupoints where the number of selected acupoints in the prescription was equal to or more than two, with the effectiveness of the compatibility measured by support degree and confidence level. The top acupoint pairing was *Guanyuan* (CV04) and *Sanyinjiao* (SP06). The support degree indicates that *Guanyuan* and *Sanyinjiao* appeared together in the 392 prescriptions 60.97% of the time, while the confidence level suggests that *Guanyuan* and *Sanyinjiao* appeared together in the related prescriptions 60.70% of the time. Lift was different from 1 in all results, indicating that the results predicted by the rules were reliable. The combination of the acupoints *Sanyinjiao* (SP06), *Guanyuan* (CV04), *Qihai* (CV06), *Ciliao* (BL32), *Zhongji* (CV03), and *Diji* (SP08) was used most frequently, as indicated by the support degree and confidence level meeting the minimum requirements. The 10 most frequently used acupoint compatibilities and their support, confidence, and lift are shown in Table 5.

4. Discussion

4.1. The Characteristics of Data Mining Applied to Acupuncture and Moxibustion. In data mining, the databases used for acupuncture and moxibustion have many unique attributes compared to those of other types. The purpose of data collection is to enhance patient treatment as well as making the information available source for research purposes. The difficulties associated with data mining for acupuncture and moxibustion treatments are as follows.

4.1.1. Ambiguity. TCM therapy involves the physician choosing a treatment based on syndrome differentiation after acquiring pertinent information. The ambiguity of data refers to not only the treatment forms but also the fact that many symptoms are not individually named or one name is not solely related with a single symptom. Consequently, physicians may use different terms to describe the same symptom.

4.1.2. Privacy. The data relating to acupuncture and moxibustion inevitably involves some private patient information. It is the obligation and responsibility of researchers mining data to conduct scientific research based on protecting the privacy of the patients and ensuring data security and confidentiality.

4.1.3. Redundancy. There can be a lot of entirely or partially repeated information in the huge data source relating to acupuncture and moxibustion, some of which may be immaterial or contradictory.

4.1.4. Complexity. In the field of acupuncture and moxibustion the data can be discrete, continuous, or hybrid, making noise processing rather complicated. The mining process needs human-computer interaction and multiple replications, with professional expertise required at every step.

To summarize, the data mining of acupuncture and moxibustion treatments is an interdisciplinary subject fraught with difficulty. There must be cooperation between acupuncture scholars and information technology professionals for success. The aim is to make some breakthroughs in coalescing

Table 2: Meridians and acupoints used in acupuncture therapy for PD.

Number	Meridian	Frequencies	PCT (%)	Acupoints		
				Number	PCT (%)	Selected acupoints and their frequencies
1	CV	608	27.92	11	10.47	*Guanyuan* (CV04) 234, *Qihai* (CV06) 142, *Zhongji* (CV03) 120, *Shenque* (CV08) 70, *Zhongwan* (CV12) 16, *Qugu* (CV02) 8, *Yinjiao* (CV07) 5, *Danzhong* (CV17) 4, *Shimen* (CV05) 3, *Xiawan* (CV10) 3, and *Shuifen* (CV09) 3
2	SP	501	23.01	9	8.57	*Sanyinjiao* (SP06) 257, *Diji* (SP08) 126, *Xuehai* (SP10) 77, *Yinlingquan* (SP09) 32, *Gongsun* (SP04) 4, *Daheng* (SP15) 2, *Fujie* (SP14) 1, *Yinbai* (SP01) 1, and *Taibai* (SP03) 1
3	BL	365	16.77	23	21.90	*Ciliao* (BL32) 126, *Shenshu* (BL23) 73, *Ganshu* (BL18) 36, *Pishu* (BL20) 27, *Geshu* (BL17) 19, *Shangliao* (BL31) 17, *Zhongliao* (BL33) 14, *Xialiao* (BL34) 12, *Weishu* (BL21) 7, *Chengshan* (BL57) 5, *Zhiyin* (BL67) 5, *Guanyuanshu* (BL26) 4, *Weizhong* (BL40) 3, *Qihaishu* (BL24) 3, *Jueyinshu* (BL14) 3, *Dachangshu* (BL25) 2, *Zhibian* (BL54) 2, *Heyang* (BL55) 2, *Kunlun* (BL60) 1, *Baihuanshu* (BL30) 1, *Feishu* (BL13) 1, *Zhishi* (BL52) 1, and *Sanjiaoshu* (BL22) 1
4	ST	243	11.16	11	10.47	*Zusanli* (ST36) 123, *Guilai* (ST29) 43, *Shuidao* (ST28) 40, *Tianshu* (ST25) 22, *Fenglong* (ST40) 7, *Wailing* (ST26) 1, *Shangjuxu* (ST37) 1, *Neiting* (ST44) 2, *Daju* (ST27) 1, *Dubi* (ST35) 1, and *Qichong* (ST30) 2
5	LR	139	6.38	8	7.62	*Taichong* (LR03) 114, *Xingjian* (LR02) 8, *Ququan* (LR08) 6, *Zhangmen* (LRl3) 3, *Qimen* (LR14) 3, *Ligou* (LR05) 2, *Zhongdu* (LR06) 2, and *Zhongfeng* (LR04) 1
6	EX-HN	79	3.63	2	1.90	*Zigong* (EX-CA1) 49, *Shiqizhui* (EX-B7) 30
7	GV	63	2.89	10	9.52	*Mingmen* (GV04) 42, *Yaoyangguan* (GV03) 10, *Dazhui* (GV14) 3, *Baihui* (GV20) 2, *Zhongshu* (GV07) 1, *Jinsuo* (GV08) 1, *Yaoshu* (GV02) 1, *Xuanshu* (GV05) 1, *Jizhong* (GV06) 1, and *Shuigou* (GV26) 1
8	LI	63	2.89	3	2.86	*Hegu* (LI04) 58, *Quchi* (LI11) 4, and *Shangyang* (LI01) 1
9	KI	60	2.75	12	11.42	*Taixi* (KI03) 24, *Yindu* (KI19) 17, *Zhaohai* (KI06) 8, *Dahe* (KI12) 3, *Yongquan* (KI01) 1, *Youmen* (KI21) 1, *Huangshu* (KI16) 1, *Siman* (KI14) 1, *Yingu* (KI10) 1, *Shuiquan* (KI05) 1, *Fuliu* (KI07) 1, and *Qixue* (KI13) 1
10	GB	26	1.19	8	7.62	*Yanglingquan* (GB34) 16, *Xuanzhong* (GB39) 4, *Xiaxi* (GB43) 1, *Fengchi* (GB20) 1, *Tinghui* (GB02) 1, *Daimai* (GB26) 1, *Zulinqi* (GB41) 1, and *Jingmen* (GB25) 1
11	PC	19	0.87	2	1.90	*Neiguan* (PC6) 18, *Zhongchong* (PC9) 1
12	LU	5	0.23	2	1.90	*Lieque* (LU07) 4, *Kongzui* (LU06) 1
13	HT	4	0.18	2	1.90	*Shenmen* (HT07) 3, *Shaofu* (HT08) 1
14	TE	2	0.09	2	1.90	*Zhongzhu* (TE03) 1, *Waiguan* (TE05) 1

Note. CV stands for Conception Vessel, SP stands for Spleen Meridian of Foot *Taiyin*, BL stands for Bladder Meridian of foot *Taiyang*, ST stands for Stomach Meridian of Foot Yangming, LR stands for Liver Meridian of Foot *Jueyin*, EX-HN stands for extraordinary point, GV stands for Governor Meridian, LI stands for Large Intestine Meridian of Hand Yangming, KI stands for Kidney Meridian of Foot Shaoyin, GB stands for Gallbladder Meridian of Foot Shaoyang, PC stands for Pericardium Meridian of Hand *Jueyin*, LU stands for Lung Meridian of Hand *Taiyin*, HT stands for Heart Meridian of Hand Shaoyin, and TE stands for Triple Energizer of Hand Shaoyang. Frequencies of meridians mean that the total frequency is of acupoints on the same meridian. PCT means the percentage of a specific meridian frequency accounting for the total frequency of all meridians. The number of acupoints means the total number of selected acupoints on the same meridian. PCT of acupoints means the percentage of number of acupoints accounting for the total number of selected acupoints in all meridians.

Table 3: Frequencies and numbers of different types of acupoints.

Number	Special point	Frequencies	Number
1	Crossing point	783	29
2	Front-*mu* point	406	9
3	Five-*mu* point	353	25
4	Yuan-source point	200	5
5	Back-*shu* point	150	8
6	Lower *he*-sea point	143	4
7	*Xi*-cleft point	130	4
8	Eight confluent points	62	6
9	*Luo*-connecting point	36	6
10	Eight convergent points	36	6

Table 4: The frequencies and numbers of acupoints on different body parts.

Number	Body part	Frequencies	Number
1	Lower limbs	839	33
2	Chest and abdomen	782	30
3	Back and lumbar	439	27
4	Upper limbs	93	11
5	Head, face, and neck	5	4

related information in multidimensional attributes, increasing the efficiency and accuracy of mining algorithms.

4.2. Application Characteristics of Meridian Points for PD. The selection and combination of acupoints plays an important role in the effectiveness of PD treatments. The therapeutic effect of acupuncture is dependent on appropriate acupoint selection and combination.

4.2.1. Great Importance Attached to Yin Acupoints and Meridians. The three most frequently used acupoints were *Sanyinjiao* (SP06), *Guanyuan* (CV04), and *Qihai* (CV06), all of which belong to *yin* meridians. *Sanyinjiao* (SP06) belongs to the collection of distal acupoints, which are located below the elbows and knees. As the junction point of three *yin* meridians of the foot, *Sanyinjiao* is heavily related to the Thoroughfare Vessel, Conception Vessel, and uterus. Needling *Sanyinjiao* can affect and promote the flow of qi and blood so as to improve the nourishment of the Thoroughfare Vessel, Conception Vessel, and the uterus and can relieve menstrual pain. *Sanyinjiao* is commonly used for gynecologic indications in clinical practice, especially for alleviating dysmenorrhea [19–21]. *Guanyuan* (CV04) and *Qihai* (CV06) are local acupoints, which means that they are acupoints located in the affected area. The three *yin* meridians of the foot meet the Conception Vessel at *Guanyuan* and the Thoroughfare Vessel comes into confluence with the Kidney Meridian in the abdomen.

According to modern literature on the acupuncture treatment of PD, acupoints on the Conception Meridian were most frequently used. The Conception Meridian is a *yin* meridian; it is also one of the eight extra meridians, which act as reservoirs of Qi and blood for the 12 regular channels, filling and emptying as required, and provide further connections between the twelve regular channels. Furthermore, the Conception Vessel starts from the uterus and emerges from the perineum. The acupoints on this particular meridian have specific therapeutic effects on the body parts that the meridian runs along and connects with.

4.2.2. Emphasis on the Specific Points. Specific acupoints recorded for the treatment of PD exceeded nonspecific acupoints in both number and frequency. Crossing acupoints, Front-*Mu* acupoints, Five *Shu* acupoints, Source-Yuan acupoints, and Back-*Shu* acupoints were the most frequently used acupoint types. The larger number and higher frequency of specific acupoints are in accordance with their specific therapeutic effects. The Crossing acupoints refer to those located at the intersection of two or more meridians. Since meridians converge at Crossing acupoints, the Crossing acupoints can be used to treat disorders of multiple meridians. Front-*Mu* acupoints are located on the chest and abdomen, while Back-*Shu* acupoints are located on the back. Each zang organ and fu organ are associated with one Front-*Mu* and one Back-*Shu* acupoint, respectively. These Front-*Mu* and Back-*Shu* acupoints are the areas where visceral qi infuses. Five *Shu* acupoints are used to treat diseases located on the regions over which the meridians run along the surface of the body. Additionally, source points are closely related to the zang-fu organs and are the points where visceral qi is infused via the Triple Energizer. Therefore, disorders of zang-fu organs can be treated by needling source points.

4.2.3. Priority Given to Distal Acupoint Selection. Acupoints on the lower limbs were much more frequently used than acupoints on other parts of the body. The frequent use of distal acupoints is consistent with the principle of distal acupoint selection. Distal curative effect is a feature of the acupoints on the fourteen meridians. These distal acupoints can not only be needled to treat disorders of the regional tissues but also can be used to treat viscera, tissues, and organs associated with the meridians they are located on. Some of the distal meridian acupoints can even be needled to treat disorders of the whole body, thus explaining the saying that "the indication extends to where the meridian reaches."

4.3. Acupoint Compatibility in Treatment of PD. Categories of acupoint combinations include local acupoint combinations, distal-proximal acupoint combinations, exterior-interior acupoint combinations, and anterior-posterior point combinations. These results from modern literature discovered via data mining might shed some light on the selection of acupoints and meridians for PD in clinical practice and scientific research.

However, needling compatible acupoint combinations can increase treatment effectiveness. The combination of such

Table 5: Statistics of the 10 most frequently used acupoint combinations.

Number	Combination of acupoints	Support (%)	Confidence (%)	Lift
1	*Guanyuan* (CV04) → *Sanyinjiao* (SP06)	60.97	60.70	1.12
2	*Sanyinjiao* (SP06) → *Guanyuan* (CV04)	54.08	68.40	1.12
3	*Sanyinjiao* (SP06) → *Qihai* (CV06)	28.06	81.82	1.34
4	*Guanyuan* (CV04) → *Qihai* (CV06)	28.06	80.00	1.48
5	*Sanyinjiao* (SP06) → *Ciliao* (BL32)	27.04	71.70	1.18
6	*Guanyuan* (CV04) → *Zhongji* (CV03)	26.53	65.39	1.21
7	*Sanyinjiao* (SP06) → *Zhongji* (CV03)	26.53	65.39	1.07
8	*Sanyinjiao* (SP06) → *Diji* (SP08)	25.77	82.18	1.35
9	*Guanyuan* (CV04) → *Diji* (SP08)	25.77	59.41	1.10
10	*Guanyuan* (CV04) → *Qihai* (CV06), *Sanyinjiao* (SP06)	22.96	76.67	1.42

acupoints as *Sanyinjiao* (SP06), *Guanyuan* (CV04), *Qihai* (CV06), *Ciliao* (BL32), *Zhongji* (CV03), and *Diji* (SP08) was most frequently used in modern literature and might have better therapeutic effects than other less frequently used or unused acupoint combinations for PD. Compatibility of acupoints is considered to have a synergistic effect, which can enhance the therapeutic effect of acupuncture. For instance, one study showed that the therapeutic effect of needling *Shiqizhui* (EX-B8), *Sanyinjiao* (SP06), *Ciliao* (BL32), and *Diji* (SP08) in combination provided superior analgesia 10 min after needle insertion compared with needling *Shiqizhui* (EX-B8) alone [22].

Conversely, an antagonistic effect of acupoints might exist, as with TCM herbs. Although no evidence supporting acupuncture therapy for PD being effective has been found in related literature, an animal trial indicating that electroacupuncture can improve gastrointestinal movement in rats found that the effect of needling *Pishu* (BL20) alone was better than the effect of needling *Pishu* (BL20) and *Zusanli* (ST36) at the same time [23]. A lot of acupuncturists adopt the principle that the more acupoints needled the better curative effect can be achieved. However therapeutic effect is not always synchronized with a high number of acupoints needled, of which some may be unnecessary. Unfortunately, the use of a complicated acupuncture combination without self-limitation may hinder the synergistic effect and may cause an antagonistic effect that could worsen the clinical symptoms.

4.4. Limitations. Although the results of data mining can be useful to acquire new knowledge, there are still limitations.

First, in the modern acupuncture literature with randomized controlled evidence, those involved evidence-based medicine methodologies are lacking. Hence in this study the quality of the included studies was not evaluated. This may affect the scientific quality and objectivity of the results owing to the inconsistent quality of the literature.

Second, since the study information was not standardized, some studies failed to report the specific treatment time, treatment frequency, and amount of stimulation. Some descriptions of the outcome measurements were also unclear or confusing in the classification of syndromes.

5. Conclusions

In this study, data mining was applied to identify the most frequently used acupoints, meridians, special points, and the distribution of acupoints, as well as the correlating rules for selecting acupoints in practice for treating PD. The most frequently used acupoints were *Sanyinjiao* (SP06), *Guanyuan* (CV04), and *Qihai* (CV06). The most frequently used meridians were Conception Vessel, Spleen Meridian of Foot *Taiyin*, and Bladder Meridian of Foot *Taiyang*. The majority of acupoints used were specific acupoints (67.24%), with acupoints on the lower limbs being most frequently used. Our findings indicate that *Sanyinjiao* (SP06), *Guanyuan* (CV04), *Qihai* (CV06), *Ciliao* (BL32), *Zhongji* (CV03), and *Diji* (SP08) should be investigated further in forthcoming trials or used in clinical practice for PD.

Data mining is a feasible and applicable approach for researchers to identify the characteristics of acupoint selection. Our study indicated that selection of specific acupoints according to traditional acupuncture theory serves as the basis of modern acupuncture treatments for primary dysmenorrhea.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Siyi Yu and Jie Yang contributed equally to the work.

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Review Article

Gray Matter Volumes in Patients with Chronic Fatigue Syndrome

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Chronic fatigue syndrome (CFS) is a debilitating and complex disorder characterized by profound fatigue with uncertain pathologic mechanism. Neuroimage may be an important key to unveil the central nervous system (CNS) mechanism in CFS. Although most of the studies found gray matter (GM) volumes reduced in some brain regions in CFS, there are many factors that could affect GM volumes in CFS, including chronic pain, stress, psychiatric disorder, physical activity, and insomnia, which may bias the results. In this paper, through reviewing recent literatures, we discussed these interferential factors, which overlap with the symptoms of CFS.

1. Background

Chronic fatigue syndrome (CFS) is an illness which can cause severe impairment in daily functioning, bringing heavy social and economic burden [1, 2]. In Japan, a total economic burden of CFS was estimated to be $4.0 billion per year [3]. The prevalence of CFS ranges from 0.007% to 2.8% in the general adult population [4–6], depending on the different definition [7], the varied target population, and the diverse study methods [8]. After all, most persons diagnosed as CFS are 30–40 years old, and most surveys demonstrate female preponderance [4, 6]. CFS also occurs in children and adolescents but at a lower rate [9].

CFS is a syndrome whose diagnosis is based on the clinical manifestation of the patients. There are a number of diagnostic criteria for CFS, and most of the researches apply the one given by the Centers for Disease Control and Prevention [10]. Owing to the causes of CFS that have not been identified, the treatment is also limited. The most popular therapeutical method is cognitive behavior treatment (CBT) [11]. However, a review of 14 studies of CFS reported that only 5% of patients fully recover after conventional treatment [12]. As an ancient traditional therapy, acupuncture got satisfied efficacy for CFS. Much research reported that acupuncture could relieve fatigue syndrome obviously, and the total effective rates are mostly over 85% [13, 14].

Meanwhile the pathological mechanism of CFS is still uncertain, major findings in etiology of recent studies include cerebral blood flow reduced in some brain regions [15–18], ventricular cerebrospinal fluid lactate increased [19], concentrations of corticosteroid declined combined with feedback of the hypothalamic-pituitary-adrenal (HPA) axis enhanced [20–22], brain-derived neurotrophic factor (BDNF) decreased [23, 24], serotonergic neurotransmitter system altered [25–27], and brain cytokines system activated [28, 29]. Although there are various findings, none of them can explain the mechanism and clinical symptoms in CFS comprehensively. In recent years, many studies on CFS focusing on the brain structures/systems benefit from rapid progress in neuroimaging techniques. The researchers wish that new findings could help to elucidate the central nervous system (CNS) pathologic mechanism of CFS.

Early findings of brain abnormalities in CFS were mostly focused on white matter hyperintensities (WMH). However, the inconsistent results [30–33] of WMH did not provide solid evidences to explain the pathologic changes in CNS of

Table 1: The gray matter volumes change in different researches.

Year	Title	Authors	Results			
			Gray matter	Regions	White matter	Regions
2004	Mechanisms underlying fatigue, a voxel-based morphometric study of chronic fatigue syndrome	Okada et al. [34]	Reduction	Bilateral prefrontal	No significance	
2005	Gray matter volume reduction in the chronic fatigue syndrome	de Lange et al. [36]	Reduction	Globe, no special regions	No significance	
2008	Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome	de Lange et al. [37]	Increased	Lateral prefrontal	No significance	
2011	A brain MRI study of chronic fatigue syndrome evidence of brainstem dysfunction and altered homeostasis	Barnden et al. [43]	No significance		No significance	
2012	Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome), a voxel-based morphometry 3-T MRI study	Puri et al. [35]	Reduction	Occipital lobes, the right angular gyrus and the posterior division of the left parahippocampal gyrus	Reduction	Left occipital lobe

CFS. Then, it is a primary transfer to focus on the changes of gray matter (GM) volumes in CFS. We found 6 studies focusing on the change of GM volumes. Okada et al. [34] found in a voxel-based morphometric study of CFS that GM volumes reduced in bilateral prefrontal and that the affected areas extended from Brodmann area (BA) 8 to 9 in right cerebral hemisphere and from BA 9 to 11 in left. Puri et al. [35] also found that GM declined in occipital lobe, right angular gyrus, and posterior division of the left parahippocampal gyrus in a voxel-based morphometric 3-T MRI study. de Lange et al. [36] found that global GM volumes reduced by 8% compared to healthy controls and the rate of decline is 2.2 mL/year in a cohort study; moreover, the GM volumes could increase after cognitive behavioral therapy [37].

The occipital lobe, right angular gyrus, parahippocampal gyrus, and lateral prefrontal cortex in CFS showed abnormal activities in functional studies compared with healthy people [38, 39]. These changes consisted of the symptoms of cognition dysfunction, short memory loss, and so forth. The occipital lobe is an important part of visual processing in the brain. The right angular gyrus plays a critical role in perceptual sequence learning [40]. It also computes action awareness representations; in particular, it is involved in both awareness of discrepancy between intended and movement consequences and awareness of action authorship [41]. The parahippocampal gyrus is important in mnemonic functions such as encoding and retrieval. The lateral prefrontal cortex is an essential node of the network promoting executive functions [42]. Therefore, observing GM volumes provides an important method to interpret the CNS mechanism in CFS. However, not all the researches got positive results. Barnden et al. [43] reported their results: the total GM, WM, and cerebrospinal fluid (CSF) volumes from voxel-based morphometry (VBM) analysis showed no significant difference statistically and did not correlate with fatigue duration either.

Most of the results showed reductions of GM volumes, but the reductions were not involved in the same brain regions (Table 1). These inconsistent results made it difficult to draw a conclusion on CNS mechanism of CFS. This could be related to inconsistent design of studies such as sample size, age, proportion of genders, diagnosis criteria, CFS duration, and different accompanied symptoms. Although most researchers considered age as the confounding covariate when they did statistical analysis [36, 37] and some only recruited female patients or reconciled the proportion of the male versus the female between CFS and healthy controls so as to remove the influence of gender discrepancies [36, 37, 43], there are still some important factors related to the changes of GM volumes in CFS patients that are not taken into account. So in this paper, we review recent literatures and sum up the important aspects that are related to GM volumes and that coexist in CFS patients including chronic pain, personality, stress, psychiatric disorders, physical activity, and sleep (Table 2).

2. Chronic Pain

In CFS patients, 5 out of all 8 concomitant symptoms are pain related, including sore throat, tender glands, aching or

Table 2: The regions of gray matter volumes change with different factors.

Factors	Regions
Chronic pain	Cingulate cortex, prefrontal cortex, insula, and dorsal pons [55]
Personality	Orbitofrontal, occipital, and parietal structures; anterior prefrontal cortex (negatively related to women) [63]
Stress	Right orbitofrontal area of the prefrontal cortex [66–68]
Psychiatric disorder	Amygdala, hippocampal and parahippocampal, the ventral, medial temporal lobes, insular cortex [80]
Physical activity	Right prefrontal and cingulate cortex, left prefrontal cortex, cingulate cortex, bilateral occipitotemporal regions, and cerebellum, right anterior frontal cortex, middle prefrontal gyrus, anterior cingulate cortex, and supplementary motor area [83, 84]
Insomnia	Left orbitofrontal cortex, bilateral anterior precuneus of the parietal cortex, and bilateral posterior precuneus in the occipitoparietal cortex [85]

stiff muscles, multijoint pain, and new headaches. According to the diagnosis criteria [10], CFS patient must have 4 concomitant symptoms, which means that the patients must have one pain symptom at least. However, current studies on CFS hardly have considered the role of pain. So further researches should elucidate the effect of chronic pain on pathologic progress of CFS, whether and how chronic pain changes the GM volumes in CFS patients.

Chronic pain is considered to be induced partly by maladaptive functional or structural plasticity of the nociceptive system that can occur at various sites from the spinal cord to the cerebral cortex [44]. MRI-based volumetric studies repeatedly found that patients with chronic pain show GM reductions in several brain areas belonging to the nociceptive system. Altered brain morphology has been described in several types of pain, such as chronic back pain [45–47], chronic tension-type headache [48], fibromyalgia [49, 50], migraine [51–53], and somatoform pain disorder [54]. The so-called "brain signature" of chronic pain has been suggested in cingulate cortex, prefrontal cortex, insula, and dorsal pons because different types of pain show GM alterations in these regions [55].

Different pain locations may have their specific brain regions. Some results suggest that GM reductions in the low back pain and headache groups are located on frontal regions, while GM reductions in the joint pain group may be more concentrated on parietal regions and the posterior cingulate cortex (PCC) [56]. Some evidences suggested that GM changes are neither preexisting nor due to irreversible cell damage [57, 58].

Whether direct correlation existed between GM volumes reduction and pain duration, frequency or intensity is still controversial. Previous studies reported positive correlations between GM volumes decrease and pain duration [59, 60], while the others did not [61].

Prefrontal cortex is the only region that changed in CFS overlapped with "brain signature." Whether other regions in "brain signature" have changes in CFS and whether CFS pain has its specific brain regions are questions that need further studies to clear.

3. Personality

Harm avoidance (HA) is one of the three main dimensions of personality [62], which refers to an individual's tendency to inhibit behaviors and is expressed as an innate tendency to caution, apprehensiveness, and pessimism. It manifests as pessimistic worry in anticipation of future problems, passive avoidant behavior, fear of uncertainty, shyness of strangers, and rapid fatigability. HA is usually measured as an anxiety-related personality trait. CFS is also thought to be anxiety-related, in accordance with several features of HA personality trait, such as rapid fatigability. So we can presume that HA could contribute to most percentages of personality traits among CFS patients.

There is a hypothesis that individual differences in personality traits might be biologically determined and associated with volumetric variability in specific regions of the brain. Recently, several researches support this notion shown below.

A large sample of eighty-five young adult participants completed the Three-dimensional Personality Questionnaire (TPQ) in which their brains were imaged with MRI. A voxel-based correlation analysis was carried out between individuals' personality trait scores and GM volumes value extracted from 3D brain scans. HA showed a negative correlation with GM volumes in orbitofrontal, occipital, and parietal structures. And only in females there was a negative correlation between HA scores and GM volumes in the anterior prefrontal cortex [63].

Another study demonstrated that smaller right hippocampus was correlated with higher anxiety-related traits in both genders. Correlational analyses showed a significant negative correlation between the scores of HA and the regional GM volumes in left anterior prefrontal cortex in female but not in male subjects [64].

Interestingly, GM volumes in occipital and prefrontal cortex structures are also found decreasing in CFS patients. Because personalities are said to be heritable, stable across time, and dependent on genetic and neurobiological factors, whether CFS has the same characters is still unknown. In further studies, we should survey the HA prevalence rate in CFS patients and unveil the interaction between them.

4. Stress

The CFS patients are usually at the age of 30s to 40s, during which they endure more work and life stress [4, 6]. A case-control study suggested that stressful events and difficulties preceded the onset of CFS [65]. So stress is an important

pathogenic factor of CFS. A longitudinal study on healthy postmenopausal women who had suffered from chronic stress over approximate 20 years reported decreased GM volumes in the right hippocampus which were consistent with previous human clinical MRI studies [66–68]. A secondary finding of the study was that chronic perceived stress predicted decreased GM volumes in the right orbitofrontal area of the prefrontal cortex.

5. Psychiatric Disorders

Anxiety is a major comorbidity in CFS [69] and a high proportion of patients with anxiety disorders complain of fatigue [70]. Indeed, patients with CFS have increased prevalence of temporary or lifetime mood disorders, primarily major depression, compared to other chronically ill subjects or healthy comparison subjects; 25% and 50%–75% of patients have a temporary or a lifetime history of major depression [71–73]. Generalized anxiety disorder and somatoform disorder also occur at a higher rate in chronic fatigue syndrome subjects than in the general population [69, 74]. In most [75, 76], but not all cases [77, 78], the mood or anxiety disorder precedes the onset of chronic fatigue syndrome. Although the major depression patients were excluded in most of the study, their anxiety and depression scores were still higher than those of healthy controls [43].

Recently, a large sample investigation including 640 subjects was administrated to measure the prevalence of specific cognition and behaviors in patients with CFS and to determine their association with comorbid anxiety or depression disorders. The results showed that 54% of the total sample had a diagnosis of CFS and no depression or anxiety disorder, 14% had CFS and one anxiety disorder, 14% had CFS and depressive disorder, and 18% had CFS and both depression and anxiety disorders [79].

A recent study also found that, compared to healthy controls, participants with major depression disease showed significant decreases of regional GM volumes in the amygdala, hippocampal, parahippocampal regions, ventral and medial temporal lobes, and insular cortex [80].

The changes in prefrontal cortex and parahippocampal are consistent with the known GM volumes reduction areas in CFS. We need to design a strict study to unveil whether CFS contributes to these changes either dependently or with coeffect with psychiatric disorders.

6. Physical Activity

Like chronic pain sufferers, CFS patients have been shown to avoid or fear physical activities [81]. van der Werf and his colleagues [82] conducted a long-term case-control study of daytime physical activity in 277 patients with CFS. The CFS patients in general were less active than healthy controls, with less intensity and shorter activity peaks that were in turn followed by longer rest periods.

The significantly positive correlations were found between local GM volumes and physical activity levels in parts of right prefrontal and cingulate cortex, as well as left prefrontal cortex, cingulate cortex, bilateral occipitotemporal regions, and cerebellum. The highest association was found in the right anterior frontal cortex. The present studies were partly overlapping with areas implicated in previous studies about the impact of physical activity on local GM volumes, including middle prefrontal gyrus, anterior cingulate cortex, and supplementary motor area [83, 84].

Healthy people take more physical activities than the patients of CFS, so they seem to have larger GM volumes naturally [34, 36]. Thus, the physical activity discrepancy should be considered when we design the neuroimaging research.

7. Insomnia

Unrefreshing sleep is the most prevalent of the 8 CFS case-defining symptoms, being endorsed by 87.5% of cases identified in population-based studies [6]. Reports showed that poor sleep or insomnia can also correlate with GM volumes. Altena et al. [85] found that insomnia patients had a smaller volume of GM than control subjects do in left orbitofrontal cortex (OFC), bilateral anterior precuneus of the parietal cortex, and bilateral posterior precuneus in the occipitoparietal cortex. No areas of higher GM volumes were found in the insomnia patients, compared with control participants [85]. One of the mechanisms in CFS is sleep architecture disorder [86]. So the effect of sleep on CFS should be researched deeply in neuroimage study.

8. Conclusion

Currently, acupuncture demonstrates more advantages than the other therapies, though this result should be further proved by more convincible evidences. Because of vague pathologic mechanism, it is urgent to develop robust diagnosis and evaluation methods. Neuroimage methods may provide a new angle to probe CFS. Although most studies found GM volumes reduced in some brain regions in CFS, as we discussed above, there are so many factors that could affect brain structure should have been considered. So far, no study has controlled all these factors. Thus, in further studies, we should improve research quality from the following points: (1) exclude factors which should be controlled, such as stress, psychiatric disorders, and physical activity; (2) study the effects of some important accompany symptoms on the occurrence and development of CFS, such as chronic pain and insomnia; (3) we need more large scale, perspective studies to prove our findings; (4) apply new imaging techniques and analyze methods, like diffusion tensor imaging, magnetic resonance spectroscopy, connectomics, and so forth to investigate CNS alterations of the disease and find specific pathological mechanism of CFS through which we could well understand and treat this disease in the future.

Abbreviations

BA: Brodmann area
BDNF: Brain-derived neurotrophic factor

CFS: Chronic fatigue syndrome
CNS: Central nervous system
CSF: Cerebrospinal fluid
GM: Gray matter
HA: Harm avoidance
HPA: Hypothalamic-pituitary-adrenal
OFC: Orbitofrontal cortex
PCC: Posterior cingulate cortex
TPQ: Three-dimensional Personality Questionnaire
VBM: Voxel-based morphometry
WMH: White matter hyperintensities.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

De Qi, a Threshold of the Stimulus Intensity, Elicits the Specific Response of Acupoints and Intrinsic Change of Human Brain to Acupuncture

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Objectives. De qi is the subjective constellation of sensations perceived by the acupuncturists and patients as described in several literatures, but the absence of quantitative evaluation methods in *de qi* restricts the use of acupuncture treatment widely in the world. In the present study, we tried to investigate the intrinsic property of *de qi* is and how evaluate it quantitatively. *Methods.* 30 healthy adult volunteers were determined to investigate intrinsic changes in the human body after acupuncture with *de qi*. *Results.* Acupuncture treatment with *de qi* apparently increased acupoint blood flow, tissue displacement, and the amplitude of myoelectricity after *de qi* on acupoints. Furthermore, acupuncture treatment induced fMRI signal increase/decrease in different brain regions although no significant change in electroencephalography. *Interpretation.* The intrinsic change of the subjects representing the specific response of acupoints and human brain to acupuncture indicated that *de qi* might be evaluated quantitatively by those above aspects, which facilitated the confirmation in validity and propagation of this treatment modality widely in the world.

1. Introduction

Now, acupuncture is becoming increasingly popular in the world and is routinely recommended for the treatment of pain and for relief of many other symptoms such as nausea and vomiting associated with chemotherapy, substance dependency, and chronic disorders difficult to manage with conventional treatment [1]. In women's health, acupuncture has been found to be beneficial for patients with premenstrual syndrome, dysmenorrhea, and several pregnancy-related conditions [2]. Whatever the exact pathway may have been, by the time traditional Chinese medicine was codified at some time in the first century BC (in a canonical text known as the *Inner Classic of the Yellow Emperor*), acupuncture was already a signature therapy of Chinese medicine. *De qi*, achieving *qi*, which is interpreted as the flow of "vital energy," is the resultant effect of characteristic needle manipulation, sensations perceived by the patients, which manifests as numbness, heaviness, distention, and soreness, with spreading sensation; and it is also perceived by the acupuncturists, which manifests as heavy and tight sensation coming from beneath the needle [3]. Although the underlying therapeutic mechanism remains unclear, it is generally accepted that "*de qi*" is the sign of optimal effect of needle manipulation, and more importantly, *de qi* is considered as the sine qua non of acupuncture for the achievement of a clinical therapeutic effect according to traditional Chinese medicine (TCM) [4–8]. There is a long-held belief in the traditional theory and clinical practice of acupuncture that the intensity of the stimulus must reach a threshold to elicit *de qi*, which plays a pivotal role in achieving the best therapeutic effects. Recently, our study was published

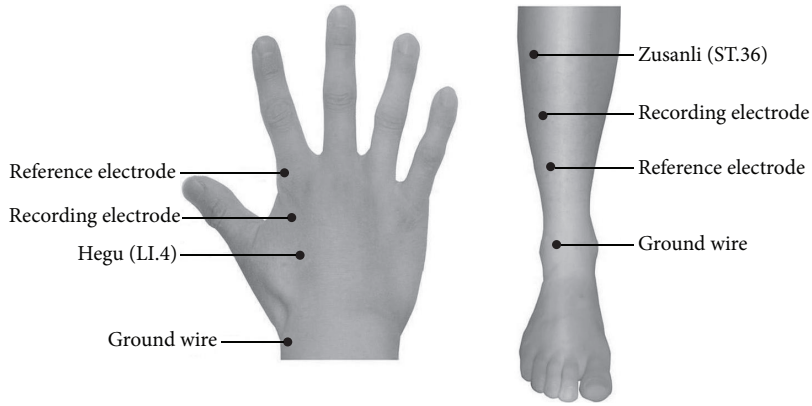


Figure 1: Acupoints schematic diagram. Acupuncture was performed using sterile disposable stainless steel needles at two acupuncture points on the right extremity in separate runs: ST.36 (traditionally known as the Zusanli acupoint) on the leg and LI.4 (traditionally, the Hegu acupoint) on the hand. The acupuncture point ST.36 is located in the tibialis anterior muscle, 4 fingerbreadths below the kneecap and 1 fingerbreadth lateral from the anterior crest of the tibia. The acupoint LI.4 is located in the dorsal surface of the web between the thumb and the index finger. Recording electrode and reference electrode are placed on the distal end of acupoints in the right limbs. Ground wires were placed on the dorsal surface to avoid electrical disturbance.

in CMAJ and found evidence that acupuncture with *de qi* improved facial muscle recovery, disability, and quality of life among patients with Bell palsy. Stronger intensity of *de qi* was associated with better therapeutic effects [9]. However, the absence of quantitative evaluation methods in *de qi* restricts the use of acupuncture treatment widely in the world. And the fundamental aspects behind its therapeutic benefits are very poorly understood, and progress in this regard has been further hindered by a consistent discrepancy between traditional theory and scientific explanations. There is no an ideal evaluation criteria and standards for the optimal effect and intensity of stimulation of acupuncture till now, thus many acupuncturists only settle for inserting the needle into the acupoints but ignore the essentiality of achieving a certain intensity of stimulation and optimal effect of needle manipulation in the course of acupuncture treatment, leading to suboptimal or no therapeutic effect of acupuncture. Therefore, an understanding of the therapeutic mechanism of acupuncture and establishing methods and criteria for quantitative evaluation of *de qi* and the intensity and threshold of acupuncture could play an important role in the demonstration of validity and the wider use of this treatment modality in the world.

In the present study, 30 healthy adult volunteers were recruited to investigate intrinsic change in the body after *de qi* during acupuncture, such as change in local region of acupoints including acupoint blood flow, tissue displacement, electromyography, electroencephalography, and brain functional magnetic resonance imaging (fMRI).

2. Materials and Methods

2.1. Subjects and Procedures. The study was performed on 30 right-handed, 20–47 years old (29.0 ± 7.8), acupuncture naive healthy adult volunteers, 12 male and 18 female. The study was approved by the Ethics Committee of Tongji Medical College, HUST. For the quantitative evaluation of *de qi* during acupuncture, healthy adult volunteers (not patients) were recruited. The participants provide verbal but not written informed consent to participate in this study. The subjects were screened and those who had major medical illnesses, history of head trauma, neuropsychiatric disorders, use of medications within one week, and contraindications for exposure to high magnetic fields were excluded.

2.2. Procedures of Acupuncture. The subjects were instructed to lie still and keep their eyes closed during the procedure. Acupuncture was performed using sterile disposable stainless steel needles at different acupoints. The two acupuncture points on the right extremity in separate runs: ST.36 (traditionally known as the Zusanli acupoint) on the leg and LI.4 (traditionally, the Hegu acupoint) on the hand (seen in Figure 1). The acupoint ST.36 is located in the tibialis anterior muscle, 4 fingerbreadths below the kneecap and 1 fingerbreadth lateral from the anterior crest of the tibia. The acupoint LI.4 is located in the dorsal surface of the web between the thumb and the index finger. These two acupoints were chosen because of their easy accessibility of *de qi* sensation and were most frequently used in acupuncture. Although several reports indicated that there was a difference in acupoints and nonacupoints when acupuncture was administrated, in the present study we only focus on the quantitative evaluation of *de qi* and the relationship between *de qi* degree and the clinical therapeutic effects.

Disposable sterile stainless steel needles (KINGLI Medical Appliance Co., Ltd., Wuxi, China) of 0.22 mm in diameter and 40 mm in length were used. The needle was inserted vertically to a depth of 2-3 cm. The sensitivity of the subject to needle manipulation was tested and adjusted to tolerance prior to procedure, aiming to elicit *de qi* sensation without noxious pain. In the event of a sharp painful sensation, the needle position should be readjusted and the pain would disappear within a few seconds. During the acupuncture procedure, the subjects were questioned about the sensations

that they had felt and whether the *de qi* sensations (aching, pressure, soreness, heaviness, fullness, warmth, cooling, numbness, tingling, and dull pain), sharp pain or any other sensations, occurred. The stimulation paradigm is depicted in Figure 2. The needle was kept in place for 2 min prior to needle manipulation and then was rotated approximately 180° in each direction with even motion at the rate of one cycle per second, which is a technique used in clinical practice. The two stimulation blocks, for example, S1 and S2, were separated by an interval of 30 s as a break period with needle remaining in place.

2.3. Tissue Displacement. In vivo ultrasonic imaging using a System FiVe (GE-Vingmed) at 7.5 MHz was performed on the healthy subjects at different stages of acupuncture needle stimulation including before *de qi* and during *de qi*. Displacements were estimated using the ultrasonic radio-frequency (RF) data, with a 2 mm window and a window overlap of 60%. Seventy RF scans were acquired continuously during each experiment at the rate of 13.2 frames per second. Ciné-loop displacement images were generated off line during and between the different stages of acupuncture stimulation.

2.4. Laser Doppler Perfusion Imaging (LDPI). A PeriScan PIM II LDPI (made by Perimed Company, Sweden) was used in this study with a scanning laser wavelength of 670 nm and a maximum output power of 1 mW. An NR scanning pattern was used, of minimum scanning accuracy, with usual sampling points at 35 (width) × 40 (height) and an image with a pixel size of $0.5 \times 0.5\,\text{mm}^2$ [2]. LDPI 2.5 imaging software was used for recording, storage, analysis, and processing of the acupoint blood perfusion image.

2.5. Electromyography (EMG). The electromyography system (Viking Quest, NICOLET, USA) was used to perform nerve stimulation and reflex recording, before and after *de qi* induced by acupuncture treatment at Hegu and Zusanli acupoints. The skin resistance overlying acupoints was made as minimal as possible by shaving the area and brushing it with alcohol. After skin preparation with 70% alcohol, disposable silver-silver chloride pregelled snap on electrodes (9 mm diameter recording surface) were placed 15 mm proximal and distal to acupuncture point, in parallel with the muscle fibers, for maximum selectivity and sensitivity. The stimulator was placed over the distal to the peroneal nerve and median nerve. A reference ground electrode was placed over the medial epicondyle or phalange of index finger, respectively, as recommended by EMG protocol. The EMG machine worked in conjunction with a Pico Technology Limited ADC-100 dual channel oscilloscope, which connected the EMG machine to a laptop computer. Pico Log data logging software was used to collect and analyze the EMG data. The program was set at a sampling rate of 1000 Hz over the 10 seconds testing time. The volunteers were instructed to keep the arm resting on the couch throughout.

2.6. Electroencephalography (EEG). EEGs constitute an objective, continuous, noninvasive, and simple method for evaluating cerebral functions. In the present study, the EEG system, manufactured by Biopac Systems, Inc., was used on EEGs during acupuncture stimulation. EEGs were collected from 12 channels, and frequency bands with α-waves (8–13 Hz), β-waves (13–30 Hz), θ-waves (4–8 Hz), and δ-waves (0.5–4 Hz) as standards were used. EEGs consist mainly of α-waves and β-waves. It is abnormal if EEG exhibits slow waves in the waking stage. The region of the brain per electrode was marked as frontal, parietal, temporal, and occipital. The experimental subjects' EEGs were measured through the electrodes via the 10–20 electrode placement method. Electrodes were attached to both ears as reference electrodes.

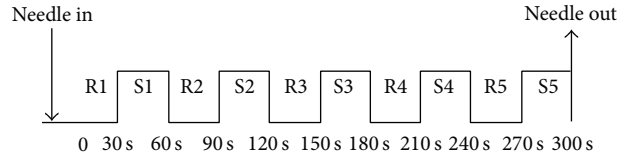


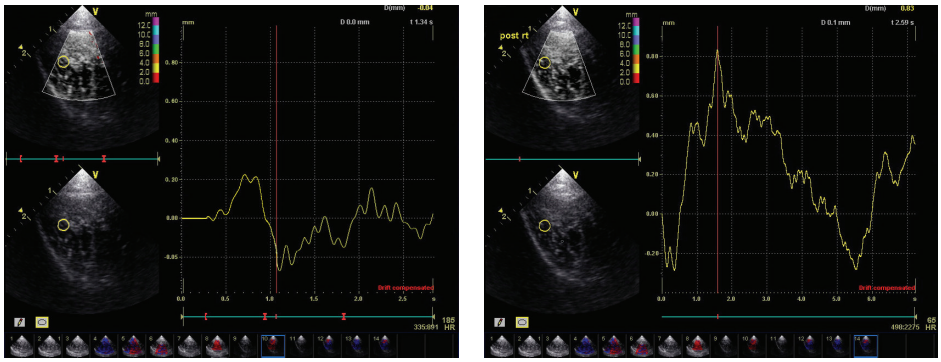
Figure 2: Acupuncture manipulation paradigm. Manual acupuncture was administered to LI4 and ST36 on the right. The subject's sensitivity to needling was pretested and adjusted to tolerance prior to scanning. After remaining in place for 30 s (R1), the needle was rotated forward and backward with stimulation for 30 s at the rate of 60 times per minute with an amplitude of approximately 180° in each direction (S1). After a rest period of 30 s (R2), needle manipulation was repeated in the same manner (S2). The needle was withdrawn after completion of 5 cycles of R-S acupuncture.

2.7. Functional Magnetic Resonance Imaging (fMRI). Brain imaging was conducted on a 1.5-T Siemens Sonata MRI system equipped for echo planar imaging (EPI) with a standard head coil. Functional scans were collected with sagittal sections parallel to the AC-PC plane, slice thickness 3.0 mm with 20% gap. Imaging encompassed the entire brain, including the cerebellum and brainstem. The functional data were acquired by a $T2^*$-weighted gradient echo sequence (TE 30 ms, TR 4 s, matrix 64 × 64, FOV 200 mm, flip angle 90°, in-plane resolution 3.125 × 3.125 mm). A set of 3D MPRAGE (magnetization-prepared rapid acquisition gradient echo) images, voxel size of $1\,\text{mm}^3$, 128 images per set, and a set of T1-weighted high-resolution structural images (TE 3.39 ms, TR 2.73 s, matrix 192 × 256, FOV 256 mm, flip angle 7°, in-plane resolution 1 × 1 mm, slice thickness 1.33 mm) were acquired prior to functional scans.

2.8. Statistical Analysis. SPSS 13.0 software for Windows (SPSS Inc., USA) was used for statistical analysis. Continuous variables were expressed as mean ± S.D. The group comparison was performed with two-tailed t-test and SNK method (ANOVA). The P values of less than 0.05 were considered to be statistically significant.

3. Results

Acupuncture increased tissue displacement and skin blood flow on acupoints after *de qi*.



(a) (b)

Figure 3: Tissue displacement on acupoints following needle stimulation before and after *de qi*. In vivo ultrasonic imaging using a System FiVe (Vingmed) at 7.5 MHz was performed on the healthy subjects at different stages of acupuncture needle stimulation including before *de qi* and during *de qi*. Displacements were estimated using the ultrasonic radio-frequency (RF) data. Seventy RF scans were acquired continuously during each experiment at the rate of 13.2 frames per second.

It was found that soft-tissue displacement could be estimated using only the stimulus caused by the movement of the needle. In the present study, the amount of tissue displacements, induced by acupuncture treatment, was measured by in vivo ultrasonic imaging before *de qi* and during *de qi* stage. As shown in Figure 3, the distance of tissue displacements in Zusanli was found to increase in amplitude by up to 0.167 ± 0.047 mm during *de qi* stage (Figure 3(b)), compared with 0.105 ± 0.027 mm, the distance before *de qi* (Figure 3(a), $P < 0.01$).

In addition, change of blood flow in Hegu and Zusanli acupoints was determined by the LDPI technology. We found that blood flow increased transiently when the acupuncture needle was inserted into the acupoint Hegu and then reverted to baseline before *de qi*. When the volunteers felt the sensations of numbness, heaviness, distention, and soreness, representing *de qi*, the skin blood flow increased significantly and was maintained at a relatively high level for up to 6 min (D1–D6, Figures 4(a1) and 4(a2)). Similar results were also found in Zusanli acupoint (see Figures 4(b1) and 4(b2)).

Acupuncture increased amplitude of myoelectricity after *de qi*, although no remarkable change was seen in EEG.

The Viking Quest portable EMG/evoked potential systems were used in this study for analysis of the myoelectricity and deep resistance. The deep resistance before *de qi* in Hegu acupoint of the healthy subjects was 34.85 ± 12.43 uV, which was increased to 51.98 ± 11.84 uV after *de qi* ($P < 0.01$). The similar results were seen in Zusanli acupoint, which were 39.38 ± 9.07 uV before *de qi* and 55.18 ± 6.19 uV after *de qi* ($P < 0.01$). Figures 5(a1), 5(a2), 5(b1), and 5(b2) are the representative image of myoelectricity in Hegu acupoint following acupuncture before and after *de qi*. The amplitude of myoelectricity after *de qi* in Hegu was significantly increased than that measured before *de qi*.

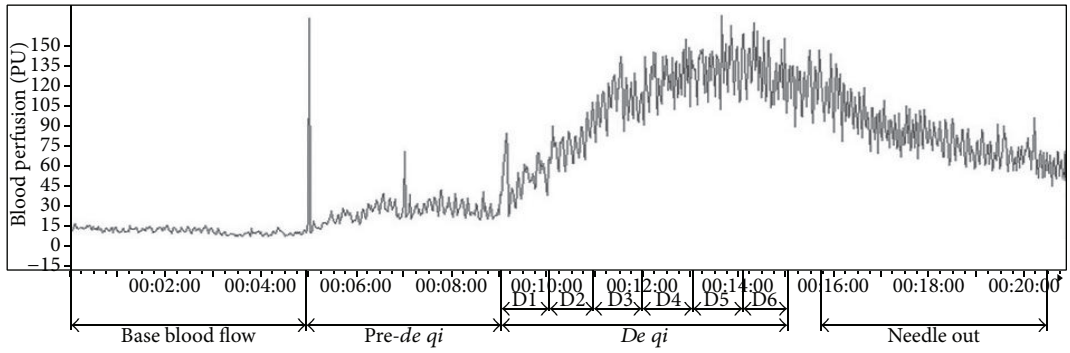
In addition, the change of electroencephalogram in Hegu acupoint following acupuncture before and after *de qi* was determined. In Figure 6, O-A, T-O, and C-O represented the electrodes placed in the different brain regions. We found that in different brain regions, the change of electroencephalogram before and after *de qi* was not evident.

Acupuncture treatment induced fMRI signal increase/decrease in different brain regions on Zusanli acupoint before and after *de qi*.

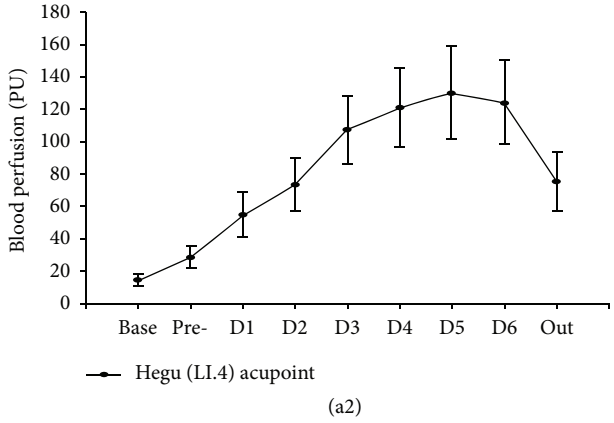
The results for fMRI (Figure 7; Tables 1 and 2) during acupuncture at ST.36 showed an activation/deactivation pattern in the different brain regions. Representative color-coded statistical maps derived from data obtained during the four stimulations paradigms (overlaid on morphologic MR images) showed the distribution of foci with significant increases (shown in the spectrum from red to yellow) and decreases (shown in the spectrum from blue to green) in signal intensity, relative to that of the respective states.

Multiple regions of signal increase were observed during acupuncture needle manipulation. Acupuncture-induced activation over the ipsilateral inferior parietal lobule (Brodmann areas 40), ipsilateral subcortex white matter, ipsilateral superior temporal gyrus (Brodmann areas 22), ipsilateral gyrus frontalis medius (Brodmann areas 47), ipsilateral prefrontal lobe (Brodmann areas 46), ipsilateral cuneate lobe (Brodmann areas 19), ipsilateral posterior central gyrus (Brodmann areas 3), the contralateral precuneus (Brodmann areas 7), the contralateral inferior parietal lobule (Brodmann areas 40), the contralateral central occipital gyrus (Brodmann areas 19), the contralateral frontal lobe frame gyrus (Brodmann areas 10), and the contralateral supramarginal gyrus (Brodmann areas 40). In addition, there was activation in the ipsilateral ventriculus dexter cerebri and mesencephalon.

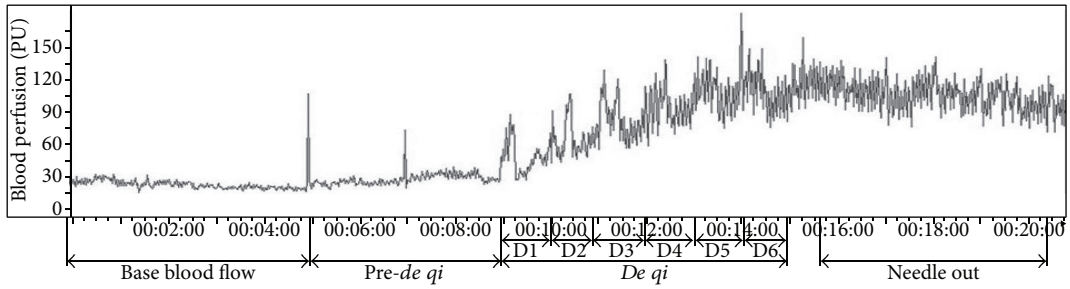
Acupuncture needle manipulation related deactivation (signal intensity decreased during *de qi* stage as compared with that before *de qi*) was found bilaterally in the majority of structures including posterior central gyrus (Brodmann areas 2 and 3), putamen, inferior parietal lobule (Brodmann areas 40), culmen cerebelli, intercerebral fissure, clivas, thalamus, cingulate gyrus (Brodmann areas 24), and occipital lobe (Brodmann areas 18 and 19). In addition, deactivation also occurred in the contralateral insular lobe, the contralateral mesencephalon, the contralateral subthalamic nucleus, the ipsilateral superior temporal gyrus (Brodmann areas 22 and 52), the ipsilateral gyrus frontalis medius (Brodmann areas 6, 9, and 45), the ipsilateral dentate body of cerebellum, the



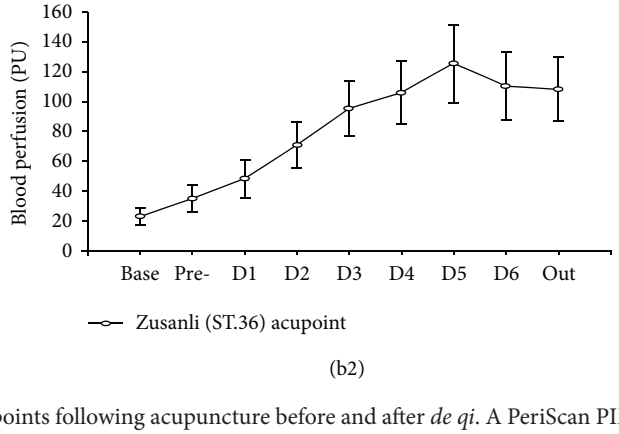
(a1)



(a2)



(b1)



(b2)

Figure 4: Blood flow changes at acupoints following acupuncture before and after *de qi*. A PeriScan PIM II laser Doppler perfusion imaging (LDPI) was used in this study for analysis and processing of the acupoint blood perfusion image. Before the acupuncture needle stimulation, the basal blood flow of the healthy subjects was low and then significantly increased when deep-punctured but without *De qi* ($P < 0.05$). When the healthy subject felt *de qi* sensation, the skin blood flows at the acupoints were more evident than those before *de qi* ($P < 0.01$) and these changes were time-dependent (Figures 4(a1) and 4(a2) for Hegu and Figures 4(b1) and 4(b2) for Zusanli).

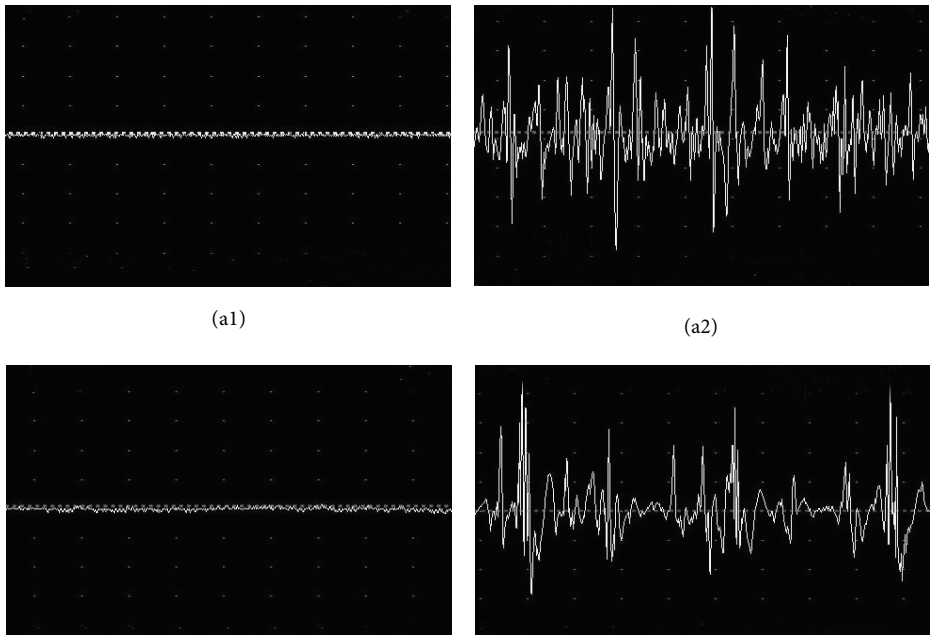


Figure 5: Myoelectricity and deep resistance at acupoints following acupuncture before and after *de qi*. The Viking Quest portable EMG/evoked potential systems were used in this study for analysis of the myoelectricity and deep resistance. The deep resistance before *de qi* in Hegu acupoint of the healthy subjects was 34.85 ± 12.43, which was increased to 51.98 ± 11.84 uV after *de qi* ($P < 0.01$). The similar results were seen for Zusanli acupoint which was 39.38 ± 9.07 uV before *de qi* and 55.18 ± 6.19 uV after *de qi* ($P < 0.01$). Figure 5 is the representative image of myoelectricity at acupoints following acupuncture before and after *de qi* ((a1) and (a2) for Hegu; (b1) and (b2) for Zusanli). The amplitudes of myoelectricity after *de qi* in Hegu and Zusanli were significantly increased than those before *de qi*.

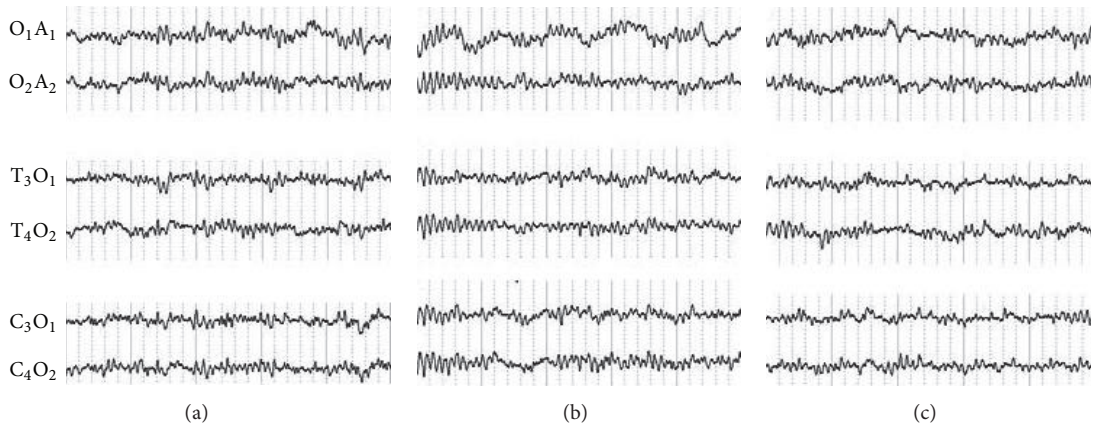


Figure 6: Change of electroencephalogram in Hegu acupoint following acupuncture before and after *de qi*. O-A, T-O, and C-O represent the electrodes placed for the different brain regions. We found that in different brain regions, the change of electroencephalogram before and after *de qi* was not evident.

ipsilateral corpus callosum, and the ipsilateral midtemporal gyrus (Brodmann areas 21).

4. Discussion

Acupuncture has been widely used for a range of acute and chronic disorders in China, and during recent decades acupuncture has been used in many countries around the world. In spite of popular clinical applications, there are no objective evaluation criteria for optimal effect of needle manipulation, the intensity of stimulation during acupuncture. And evidence to support the use of acupuncture needs to be established. In fact, it has been accepted that induction and occurrence of *de qi* are a prerequisite for acupuncture and often an indicator of a clinical acupuncture effect [4, 6, 7, 9]. *De qi*, which manifests as numbness, heaviness, distention, and soreness, with spreading sensation and manifests as heavy and tight sensation coming from beneath the needle,

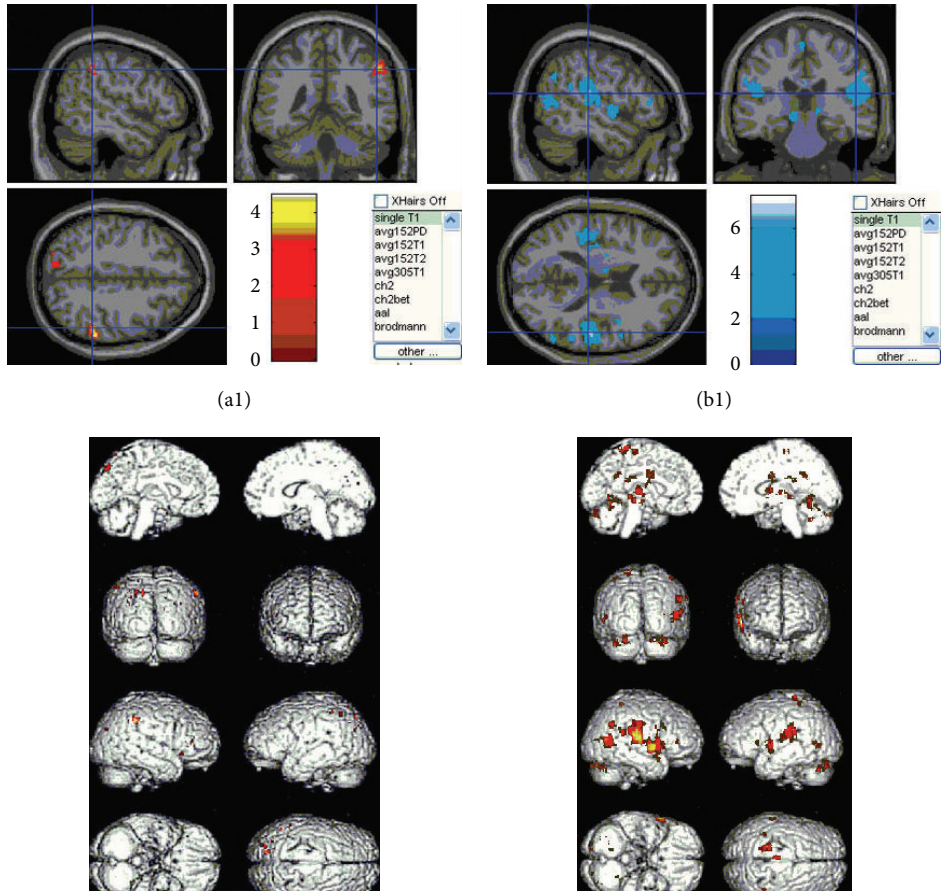


Figure 7: Change of functional magnetic resonance imaging (fMRI) in Zusanli acupoint following acupuncture before and after *de qi*. Mean results of functional MR images of brain activation/deactivation of nine subjects in each stimulation paradigm. Representative color-coded statistical maps derived from data obtained during the four stimulations paradigms (overlaid on morphologic MR images) show the distribution of foci with significant increases (shown in the spectrum from red to yellow) and decreases (shown in the spectrum from blue to green) in signal intensity, relative to that of the respective states.

is the sine qua non of acupuncture for the achievement of a clinical therapeutic effect according to traditional Chinese medicine. And most of the experts in acupuncture consider that *de qi* is the intensity threshold of acupuncture treatment by means of needle rotation, upright and down, and acupuncture exerts its clinical therapeutic effects only under the certain condition of achieving *qi* (*de qi*). In spite of the importance and necessity of *de qi*, there is a lack of adequate experimental data to indicate what the intrinsic property of *de qi* is and how to evaluate it quantitatively. Till now, there are no ideal objective evaluation methods and criteria for optimal effect of the needle manipulation and for the intensity of stimulation. Many acupuncturists only acquire acupuncture needle to stick into the acupoints but ignore the essentiality of acupuncture intensity and threshold in the course of acupuncture treatment, leading to the impairment of the therapeutic effect of acupuncture.

In our study, it was a surprise to find that *de qi* induced intrinsic change in the human body during acupuncture treatment, including changes in acupoint blood perfusion, tissue displacement, electromyography, electroencephalography of local region at acupoints, and brain fMRI signals. The results showed that needle stimulation after *de qi* significantly increased blood perfusion, tissue displacement, and the amplitude of myoelectricity in the acupoints. Furthermore, acupuncture treatment induced brain fMRI signal increase/decrease in different brain regions although no significant change was seen in electroencephalogram. The intrinsic changes indicated that *de qi* elicited intense response of human body to acupuncture, especially at the location of acupoints and even in the brain, and it could be evaluated quantitatively, which might shed light on the therapeutic mechanism of acupuncture and facilitate the wider use of this treatment modality in the world.

In our report, the amount of tissue displacements, induced by acupuncture treatment, was measured by in vivo ultrasonic imaging before *de qi* and during *de qi*. Tissue displacements were found to significantly increase in amplitude after *de qi* compared to those before *de qi*. Tissue displacement caused by acupuncture needle manipulation

Table 1: Activated regions in fMRI after *de qi* in Zusanli acupoint following acupuncture.

Anatomy	BA	Side	Talairach			Z score
			X (mm)	Y (mm)	Z (mm)	
Inferior parietal lobule	40	R	60	−38	42	3.93
Subcortex white matter		R	22	−66	28	3.71
			32	−52	38	3.02
Precuneus	7	L	−24	−80	44	3.22
			−12	−76	46	3.06
Superior temporal gyrus	22	R	30	12	−22	2.91
Inferior parietal lobule	40	L	−46	−58	52	2.86
			−52	46	54	2.57
Gyrus frontalis medius	47	R	36	22	−6	2.37
			48	36	10	2.74
Central occipital gyrus	19	L	−30	−76	48	2.74
Prefrontal lobe	46	R	44	38	18	2.68
Cuneate lobe	19	R	16	−80	20	2.62
Frontal lobe frame gyrus	10	L	−40	40	24	2.59
Posterior central gyrus	3	R	18	68	60	2.55
Ventriculus dexter cerebri		R	2	8	14	2.46
Mesencephalon		R	4	−38	−20	2.44
Supramarginal gyrus	40	L	−38	−52	34	2.42

Table 1 lists the Talairach coordinates. Numbers in cortical areas of the images correspond to Brodmann areas. Multiple regions of signal increase were observed during acupuncture needle manipulation of the right leg at ST.36. Acupuncture induced activation over the ipsilateral inferior parietal lobule (Brodmann areas 40), ipsilateral subcortex white matter, ipsilateral superior temporal gyrus (Brodmann areas 22), ipsilateral gyrus frontalis medius (Brodmann areas 47), ipsilateral prefrontal lobe (Brodmann areas 46), ipsilateral cuneate lobe (Brodmann areas 19), ipsilateral posterior central gyrus (Brodmann areas 3), the contralateral precuneus (Brodmann areas 7), the contralateral inferior parietal lobule (Brodmann areas 40), the contralateral central occipital gyrus (Brodmann areas 19), the contralateral frontal lobe frame gyrus (Brodmann areas 10), and the contralateral supramarginal gyrus (Brodmann areas 40). In addition, there was activation in the ipsilateral ventriculus dexter cerebri and mesencephalon.

following needle rotation may deliver a mechanical signal into the subcutaneous tissue and consequently generate important effects on cellular elements (fibroblasts, blood vessels, and sensory nerves) present within this tissue [1]. This may prove to be the key to acupuncture's therapeutic mechanism and the proposed imaging technique, the key method for monitoring this effect.

In addition, changes of blood flow at acupoints Hegu and Zusanli were determined by the LDPI technology. In our study, the local response could be seen clearly around the acupoint; the increment of blood perfusion was higher (about 10%) around Hegu and Zusanli after *de qi* than that measured before *de qi*, and the increase of blood perfusion was maintained at a relatively high level. The local increase of blood flow may be caused by axon reflection. An acupuncture-induced neural signal can be reflected along the branch of the same axon to the skin surface and can cause the release of substance *P*, which further evokes the release of histamine from nearby mast cells and causes vasodilatation and increase of blood perfusion [10]. The increase of blood perfusion and vasodilatation might be explained by the finding that several volunteers felt the sensation of heat and perspiration during acupuncture manipulation, which indicated *de qi*.

Furthermore, electrophysiological changes induced by *de qi* of acupuncture were also determined in this study. We found that acupuncture after *de qi* significantly decreased the deep electrical resistance at the acupoints and increased the amplitude of myoelectricity, suggesting that the local tissue of acupoints responded to the needle acupuncture. However, the change of electroencephalogram in different brain regions before and after *de qi* was not evident. The EEG results were consistent with those of Starr et al. [11] but appear to be contradictory with other reports in the literature [12–15]. Indeed, this is not entirely surprising in view of the difficulties in the measurements being attempted and the techniques adopted. During the recording of a normal EEG the signal may vary considerably and the effect of acupuncture has to be found within these variations [16]. In addition, the magnitude of the changes brought about by acupuncture may be small and conventional paper recording of the EEG is unlikely to be sufficiently sensitive to demonstrate changes [16]. Digital EEG recordings and brain mapping techniques which allow more quantitative data analysis offer better prospects in this regard.

Finally, we investigated the fMRI signal change induced by the acupuncture treatment and found that different brain regions were activated or deactivated in response to the needle stimuli. Acupuncture with *de qi* resulted in a marked predominance of signal attenuation or deactivation in the posterior central gyrus, putamen, inferior parietal lobule, thalamus, cingulate gyrus, occipital lobe, insular lobe, subthalamic nucleus, superior temporal gyrus, gyrus frontalis medius, midtemporal gyrus, and cerebellum. On the other hand, clusters of activated regions were seen in the inferior

Table 2: Deactivated regions in fMRI after *de qi* in Zusanli acupoint following acupuncture.

Anatomy	BA	Side	Talairach			Z score
			X (mm)	Y (mm)	Z (mm)	
Posterior central gyrus	2/3	L/R	−16	−42	68	5.63
			52	−24	18	5.33
Superior temporal gyrus	22/52	R	58	2	0	5.29
			58	10	−4	4.78
Putamen		L/R	−28	2	6	5.26
			−26	−8	8	5.04
			22	2	−2	3.99
Insular lobe		L	−45	22	18	4.55
			−36	−18	12	4.06
Inferior parietal lobule	40	L/R	−50	−34	22	5.14
			58	−42	22	4.03
			50	−44	24	4.00
Culmen cerebelli		L/R	8	−56	−8	4.72
			−2	−46	−10	4.27
Intercerebral fissure		L/R	−2	−62	0	4.21
			2	−34	22	3.36
Clivas		L/R	−2	−60	−18	3.51
			36	−70	−28	4.51
			26	−82	−28	4.06
			16	−86	−28	3.85
Gyrus frontalis medius	6	R	−2	−24	64	4.57
	9/45	R	48	6	30	3.99
			56	18	26	3.56
Dentate body of cerebellum		R	14	−58	−34	4.56
Mesencephalon		L	−10	−26	−8	4.45
Thalamus		L/R	−4	−12	2	3.63
			14	−28	0	3.32
Cingulate gyrus	24	L/R	4	0	28	4.08
			−12	0	34	3.86
Corpus callosum		R	2	−4	20	4.27
Midtemporal gyrus	21	R	54	−60	6	4.10
Occipital lobe	18/19	L/R	−52	−70	4	3.78
			34	−82	12	3.50
Subthalamic nucleus		L	−8	−14	−8	3.44

Table 2 shows the Talairach coordinates. Numbers in cortical areas of the images correspond to Brodmann areas. Deactivation was noted bilaterally in posterior central gyrus (Brodmann areas 2 and 3), putamen, inferior parietal lobule (Brodmann areas 40), culmen cerebelli, intercerebral fissure, clivas, thalamus, cingulate gyrus (Brodmann areas 24), and occipital lobe (Brodmann areas 18 and 19). In addition, deactivation also occurred in the contralateral insular lobe, the contralateral mesencephalon, the contralateral subthalamic nucleus, the ipsilateral superior temporal gyrus (Brodmann areas 22 and 52), the ipsilateral gyrus frontalis medius (Brodmann areas 6, 9, and 45), the ipsilateral dentate body of cerebellum, the ipsilateral corpus callosum, and the ipsilateral midtemporal gyrus (Brodmann areas 21).

parietal lobule, subcortex white matter, superior temporal gyrus, ipsilateral gyrus frontalis medius, prefrontal lobe, ipsilateral cuneate lobe, ipsilateral posterior central gyrus, contralateral precuneus, inferior parietal lobule, central occipital gyrus, frontal lobe frame gyrus, and supramarginal gyrus. During acupuncture manipulation, several cortical and subcortical areas of human brains responded, according to the previous studies of acupuncture at ST36, which were localized at thalamus, insula, cingulategyrus, temporal gyrus, and cerebellum [17–21]. However, there are some different activated areas, such as basal ganglia and PAVN. Our results further validated findings of those previous studies. Acupuncture at analgesic acupoints, such as LI4 (*Hegu*) and ST36 (*Zusanli*), can modulate the hypothalamus and limbic system, which are pain-related neuromatrices [2, 17, 20, 22–24]. According to TCM, all acupoints are located along the meridians. ST36 is a commonly used acupoint on the stomach meridian of foot-*Yangming,* which starts from the lateral side of the ala nasi, ascends to the ipsilateral forehead, and descends to the dorsum of the foot, with a branch extending to the tip of the great toe [25]. The activation of the ipsilateral middle frontal gyrus is in accordance with the TCM theory. This area

of the brain includes the pathway of *qi* along the stomach meridian of foot-*Yangming*. In the aspect of curative effects, the stomach meridian of foot-*Yangming* has a therapeutic effect for mental problems, gastralgia, and intestinal pain [25]. Our preliminary study demonstrated that *de qi* elicited significant response to acupuncture in the specific brain regions, but the mechanisms whether different acupoints are coupled with specific brain regions are not clear, and the reasons that the specific brain regions responded to *de qi* intensively also remain to be elucidated.

5. Interpretation

In summary, we have shown that acupuncture with *de qi* elicited the intrinsic change of human body. These recordings of all the aspects above may be taken as an indicator of *de qi* sensation. Biochemical effects shown by tissue displacement and blood flow change after acupuncture manipulation were derived from mechanical stimulation of connective tissue and potential spreading of these effects along connective tissue planes, which might deliver a mechanical signal into the subcutaneous tissue, induce the release of several pain-related substances, and then extend the communicated signal spreading. These processes might consequently enhance the response of specific brain regions and trigger the nerve-immune-secretion network to alleviate pain. Ongoing investigations over a larger pool of human subjects correlating with biochemical and neurological as well as morphological effects are expected to shed important light on the therapeutic mechanism of acupuncture and facilitate the intensive propagation of this treatment modality in the world.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Somatosensory Nerve Fibers Mediated Generation of De-qi in Manual Acupuncture and Local Moxibustion-Like Stimuli-Modulated Gastric Motility in Rats

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The aim of this study was to reveal the somatosensory nerve fibers mediated generation of De-qi in manual acupuncture stimuli (MAS) and local moxibustion-like stimuli (LMS). The effects of strong and slight MAS, as well as 41°C, 43°C, and 45°C LMS at ST36 and CV12 on gastric motility were observed in rats. Gastric motility was continuously measured by an intrapyloric balloon, and the average amplitude, integral, and frequency of gastric motility during LMS were compared with those of background activity. Gastric motility was facilitated by MAS and LMS at ST36 and inhibited at CV12. The modulatory effects induced by strong MA with potent De-qi (needle grasp feeling) were markedly higher than those by slight MA with mild De-qi sensation ($P < 0.05$). The nociceptive 43°C and 45°C LMS, rather than nonnociceptive 41°C LMS, produced significant regulatory effects on gastric motility. Based on the afferent fibers activated in the present study, these results support the hypothesis that Aδ- and C-afferent fibers were more likely to be involved in the generation of De-qi sensation.

1. Introduction

Manual acupuncture and moxibustion, as two traditional Chinese medicinal techniques, have been widely used to treat a wide range of diseases in clinical practice in China. During the past decades, the therapeutic effects of manual acupuncture and moxibustion on digestive disorders have been investigated and partially confirmed [1, 2]. Some regular responses of gastrointestinal tract contraction induced by acupuncture and moxibustion stimulation have been observed in previous studies [3, 4]. Additionally, it is suggested that acupuncture and moxibustion stimuli with different intensities are more likely to activate distinct afferent fibers to achieve their therapeutic effects [5, 6].

Among factors contributing to the effectiveness of manual acupuncture and moxibustion treatment, De-qi feeling is considered the most critical one [7]. For manual acupuncture stimulation, De-qi is elicited by rotating, lifting, and thrusting the inserted needle and perceived by the patient as "distention," "heaviness," or "soreness." "Needle grasp" sensation perceived by acupuncturist during manual manipulation is also an important indicator of De-qi, which is also classically described as "like a fish biting on a fishing line." Unlike manual acupuncture, De-qi sensation elicited by moxibustion stimulation is described as heat-sensitive moxibustion sensation, including penetrating heat, expanding heat, and transmitting heat [8]. Although De-qi sensations induced by manual acupuncture and moxibustion are different, both are closely related to the function of afferent terminals innervating muscles and connective tissues beneath acupoints [9].

Based on the possible correlation between intensity of stimulation, distinct afferent fibers, and generation of De-qi, we hypothesized that manual acupuncture or moxibustion stimuli with certain intensities could elicit De-qi feeling via activating specific afferent fibers. In order to reveal the correlation further, the effects of strong and slight manual acupuncture stimuli (MAS) as well as nonnociceptive (41°C) and nociceptive (43°C, 45°C) local moxibustion-like stimuli

(LMS) on gastric motility in rats were investigated in the present study.

2. Materials and Methods

2.1. Animal Preparation. Male Sprague-Dawley (SD) rats (n = 36), weighing 250–300 g, were purchased from Institute of Animal, Academy of Chinese Medical Sciences. The animals were housed under a 12 h light/dark with free access to food and water. All animals were treated according to the Guide for Use and Care of Medical Laboratory Animals from the Ministry of Public Health of People's Republic of China.

2.2. Gastric Motility Recording. The animals were fasted overnight with free access to water. For anesthesia, 10% urethane (1.0–1.2 g/kg, via intraperitoneal route) was administered. Gastric motility was recorded by inserting a small balloon via an incision of duodenum into the pyloric area as described previously [10]. In order to detect the gastric contraction, 0.2-0.3 mL warm water was injected into the balloon to keep the basal pressure at about 100 mm H_2O.

Changes in pressure of the balloon were measured continuously by a transducer and then input into a polygraph amplifier (NeuroLog, NL900D). The signal was captured online and analyzed offline using a data acquisition system (Power-Lab/4s, AD Instruments) and Chart 5.2 software. Gastric contraction was recorded as a control for at least 30 min before any stimulation. Responses induced by MAS or LMS were compared with the background activity in terms of average amplitude (the average difference between the cyclic maxima and minima in the selected cycles), integral (calculated as the sum of the data points multiplied by the sample interval), and frequency (per minute) of gastric contraction waves. Systemic blood pressure and heart rate were monitored by using Biopac data acquisition system (MP150, USA), and rectal temperature was kept constantly around 37°C by a feedback-controlled heating blanket (DC, USA).

2.3. Manual Acupuncture Stimuli (MAS) and Local Moxibustion-Like Stimuli (LMS) of CV12 and ST36. MAS and LMS were performed at ST36 (Zusanli) or CV12 (Zhongwan). ST36 is located 5 mm below the head of the fibula under the knee joint and 2 mm lateral to the anterior tubercle of the tibia. CV12 is located 4 cm below the processus xiphoideus, in the middle line of the abdomen. Rats were randomly divided into four groups: MAS + ST36 group, MAS + CV12 group, LMS + ST36 group, and LMS + CV12 group (n = 9, in each group). To minimize mutual interference, the noninvasive LMS was applied prior to MAS. Hair located around the acupoints was cut off to expose the local skin before LMS application. The LMS was performed by application of a heat generator (Physitemp Controller NTE-2A, Physitemp Instruments INC, USA) connected with a probe (2 cm in diameter) to avoid burning by real moxibustion. The contact area between the probe and skin (acupoints) is about 1 cm in diameter. The stimulation parameters of the instrument were set at 41°C, 43°C, and 45°C, respectively. When the temperature was stable, the LMS would be given by attaching the probe to the skin area (acupoints) for 180 s. Rats were allowed to stabilize for at least 30 min after the LMS.

When the gastric contraction wave recovers to control level, MAS with a needle of 0.3 mm in diameter was inserted about 5 mm into the skin and its underlying muscles at ST36 or CV12. The needle was rotated clockwise and anticlockwise for 60 s at 1 Hz and 2 Hz in slight MAS and strong MAS, respectively [11]. During each strong MAS, the "needle grasp" sensation can be perceived obviously by the acupuncturist, which is more stronger than that induced by slight MAS.

Both LMS and MAS were applied at ST36 or CV12 in an ascending order. The latter stimulus can only be applied when the gastric motility recovered to control level. The background gastric activity and gastric activity during and after LMS and MAS were recorded continuously, 60 s for each session.

2.4. Statistical Analysis. Changes in the average amplitude and integral were calculated according to (the value during stimulation − the value before stimulation) ÷ the value before stimulation × 100%. The data obtained before and after treatment in the same group or different group was compared statistically by a paired t-test or unpaired t-test. $P < 0.05$ was considered as a statistical significance. All data are expressed as mean ± SE.

3. Results

3.1. Facilitatory Effects on Gastric Motility Induced by Different LMS at ST36. LMS at ST36 induced facilitatory effects which were dependent on the intensity. Figure 1(a) showed typical responses of gastric motility following LMS with three different temperature stimulations for 180 s. Figures 1(b), 1(c), and 1(d) summarized the responses obtained from all 9 tested rats. It should be noted that 41°C LMS had no significant impact on the amplitude and integral of gastric motility. In addition, both 43°C and 45°C at ST36 failed to produce any marked changes during the first 60 s of LMS. However, 43°C and 45°C LMS at ST36 elicited a significant enhancement on the amplitude and integral of gastric contraction in the last 120 s compared with the background activities (amplitude changes in the second and third 60 s: 43°C: 15.0 ± 3.6%, 16.7 ± 4.8%, $P < 0.01$, $P < 0.05$; 45°C: 26.3 ± 3.1%, 32.5 ± 3.1%, $P < 0.001$) (integral changes in the second and third 60 s: 43°C: 16.5 ± 4.2%, 17.7 ± 5.5%, $P < 0.05$; 45°C: 25.6 ± 2.1%, 33.4 ± 1.9%, $P < 0.001$). A 60-second latency was also observed before the emergence of the LMS-modulated gastric motility. In addition, the facilitatory effects induced by 45°C LMS at ST36 were significantly higher than those by 43°C LMS in terms of the amplitude and integral of gastric motility ($P < 0.05$).

Figure 1(d) illustrated the impact of LMS at ST36 on the frequency of gastric motility. 41°C and 43°C LMS failed to bring about any significant response, while 45°C LMS at ST36 induced significant enhancement on the frequency of gastric motility compared with the background activities, which also appeared in the last 120 s of stimulation (frequency changes

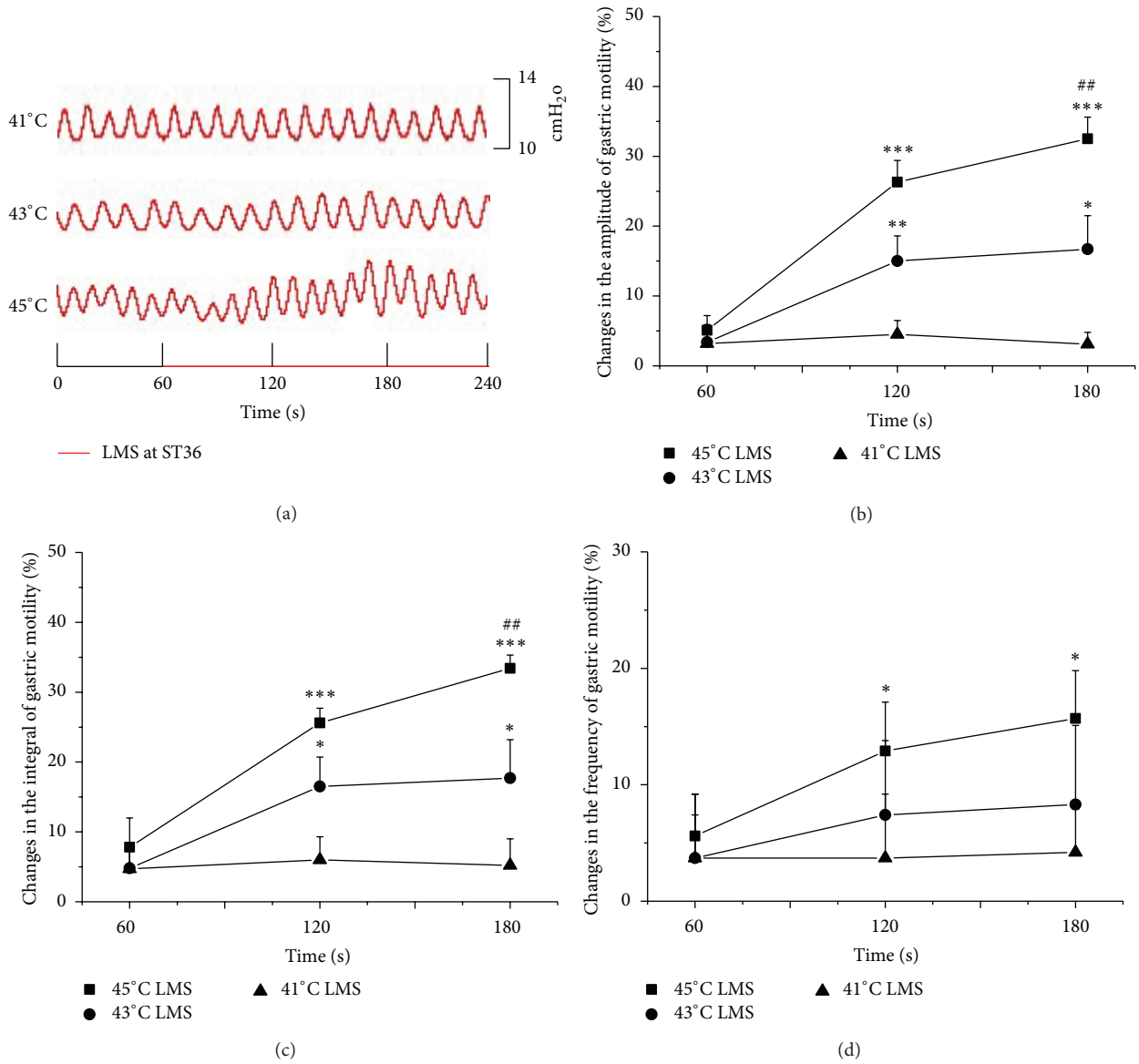

Figure 1: Gastric motility in response to LMS at ST36 with different intensities in rats. (a) Examples of the alterations of gastric contraction wave induced by different intensities of LMS at ST36. (b, c, and d) The changes of the amplitude, integral, and frequency of gastric motility induced by LMS at ST36 in total 180 s, respectively ($n = 9$; $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$, versus background activities; $^{\#\#}P < 0.01$, as compared with the facilitatory effects in the same time course of 43°C LMS at ST36).

in the second and third 60 s of 45°C LMS: 12.9 ± 4.2%, 15.7 ± 4.1%, $P < 0.05$).

3.2. Inhibitory Effects on Gastric Motility Induced by LMS at CV12. LSTS at CV12 induced inhibitory effects which were also dependent on the intensity. Figure 2(a) showed typical responses of gastric motility following LMS with three different intensities for 180 s, and Figures 2(b), 2(c), and 2(d) summarized the responses obtained from all 9 tested rats. There was no significant change of gastric motility during 41°C LMS. During the second and third 60 s of 43°C and 45°C LMS, the gastric motility was markedly inhibited by CV12 (amplitude changes: 43°C: −18.2 ± 4.2%, −20.5 ± 4.9%, $P < 0.01$; 45°C: −31.5 ± 2.5%, −39.9 ± 2.3%, $P < 0.001$) (integral changes: 43°C: −20.7 ± 4.5%, −21.0 ± 5.4%, $P < 0.05$; 45°C: −28.2 ± 3.7%, −38.6 ± 3.5%, $P < 0.001$) (frequency changes: 43°C: −12.9±4.2%, −12.4±4.1%, $P < 0.05$; 45°C: −17.6±4.5%, $P < 0.01$; −18.5 ± 4.3%, $P < 0.05$). Similarly, the inhibitory effects of 45°C LMS at ST36 on the amplitude and integral of gastric motility were significantly higher than those by 43°C LMS ($P < 0.05$). Besides the existence of the short latency, the temperature-specific (43°C) manner was quite obvious in the responses of gastric motility to LMS at ST36 and CV12.

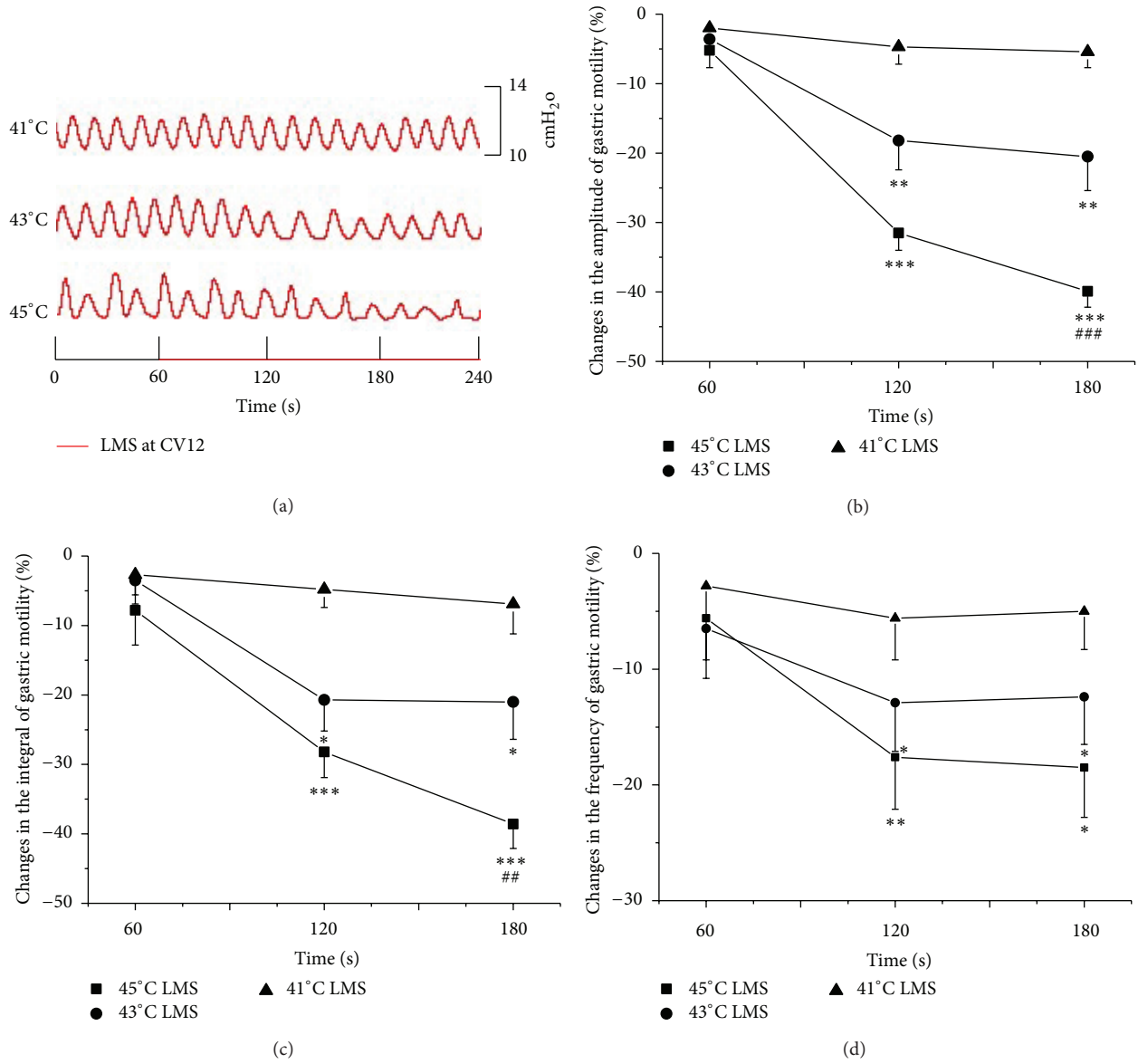

Figure 2: Gastric motility in response to LMS at CV12 with different intensities in rats. (a) Examples of the alterations of gastric contraction wave induced by different intensities of LMS at CV12. (b, c, and d) Changes of the amplitude, integral, and frequency of gastric motility induced by LMS at CV12 in total 180 s, respectively ($n = 9$; $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$, versus background activities; $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$, as compared with the inhibitory effects in the same time course of 43°C LMS at CV12).

3.3. Modulation on Gastric Motility Induced by Different MAS at ST36 or CV12. The modulatory effects of strong and slight MAS at ST36 or CV12 were investigated in the present study. As illustrated with an individual example in Figure 3(a) and with pooled data in Figures 3(b), 3(c), and 3(d), gastric motility was significantly facilitated by both strong and slight MAS at ST36 (amplitude changes: strong MAS: 46.9 ± 4.4%, $P < 0.01$; slight MAS: 23.5±4.6%, $P < 0.05$) (integral changes: strong MAS: 50.4 ± 4.7%, $P < 0.001$; slight MAS: 34.5% ± 5.7%, $P < 0.01$) (frequency changes: strong MAS: 21.8±4.9%, $P < 0.01$; slight MAS: 14.6±4.6%, $P < 0.05$). On the contrary, as shown in Figure 4, strong and slight MA at CV12 produced significant inhibition on gastric motility (amplitude changes: strong MAS: −55.7±8.2%, $P < 0.01$; slight MAS: −36.9±6.4%, $P < 0.01$) (integral changes: strong MAS: −67.4 ± 3.4%, $P < 0.001$; slight MAS: −41.2% ± 1.5%,, $P < 0.01$) (frequency changes: strong MAS: −51.2 ± 3.4%, $P < 0.001$; slight MAS: −36.3 ± 3.7%, $P < 0.01$). Notably, the modulatory effects induced by strong MAS with potent De-qi (needle grasp feeling) were markedly higher than those by slight MAS with mild De-qi sensation ($P < 0.05$, Figures 3(d) and 4(d)). In addition, the effectiveness of strong MAS in gastric motility was significantly higher than that of the last 60 s of 45°C LMS ($P < 0.05$, $P < 0.01$, and $P < 0.001$, Figure 5).

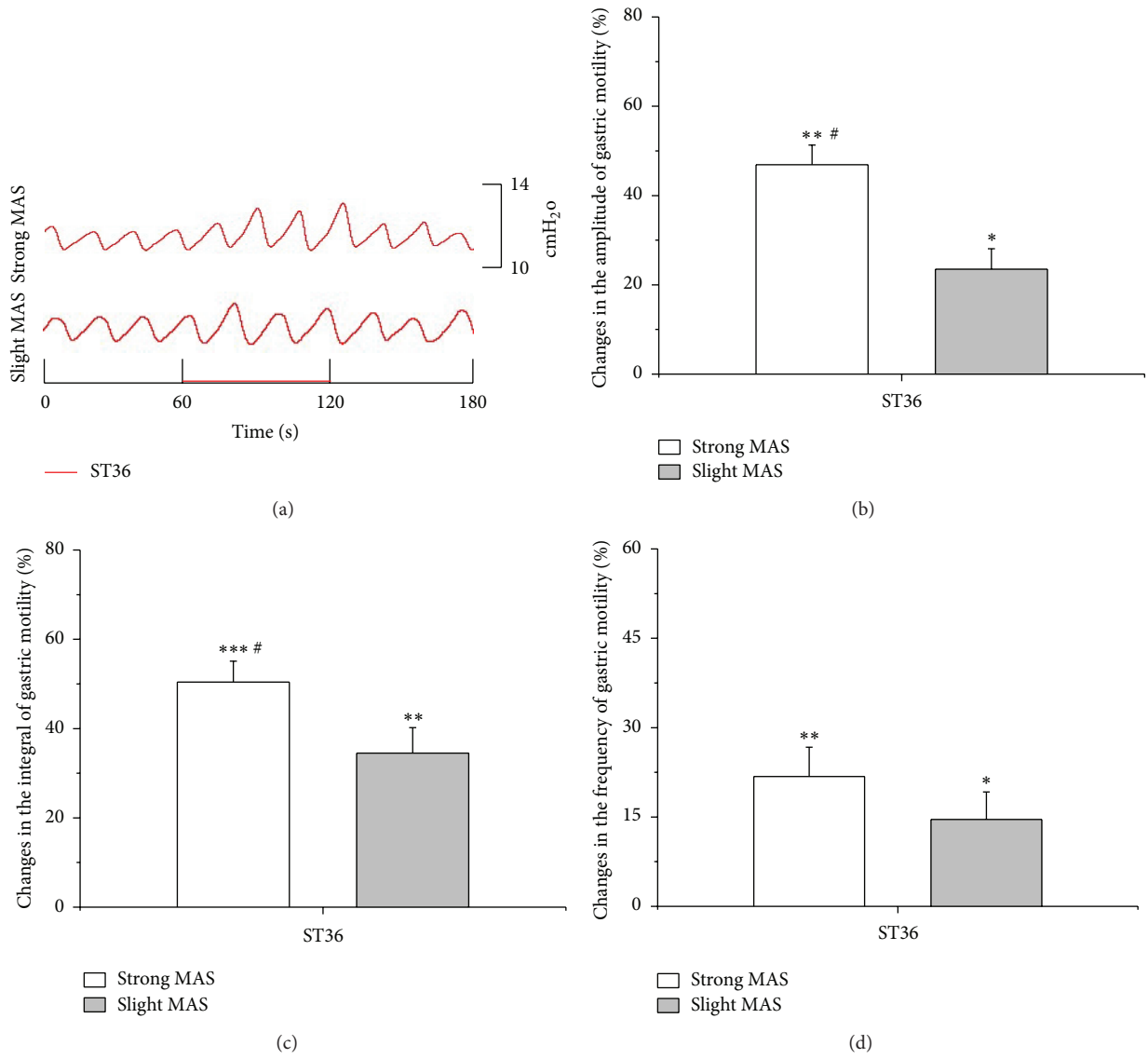

FIGURE 3: Gastric motility in response to MAS at ST36 with different intensities in rats. (a) Examples of the alterations of gastric contraction wave induced by different intensities of MAS at ST36. (b, c, and d) Changes of the amplitude, integral, and frequency of gastric motility induced by MAS at ST36 in 60 s, respectively ($n = 9$; $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$, versus background activities; $^{\#}P < 0.05$, as compared with the facilitatory effects of slight MAS at ST36).

4. Discussion

In the present study, we investigated the possible correlation between intensity of stimulation, distinct afferent fibers, and generation of De-qi sensation. Through observation on the effects of nonnociceptive (41°C) and nociceptive (43°C, 45°C) LMS on gastric motility in rats, our results strongly indicated that both the facilitatory effect of ST36 and inhibitive effect of CV12 induced by LMS were closely related to the temperature intensity by which afferent fibers were activated. 43°C and 45°C LMS, rather than 41°C, produced significant regulatory effects on gastric motility. These results suggested that the nociceptive (>42°C) heat-activated Aδ-/C- fibers were essential to the generation of De-qi and LMS-modulated gastric motility, whereas the nonnociceptive warm stimulus can hardly trigger De-qi sensation and the somatovisceral reflex. Additionally, the excitatory effect of ST36 and inhibitory effect of CV12 on gastric motility by MAS have also been demonstrated in this study. Notably, the regulatory effects of strong MAS were significantly higher than those of slight MAS, which might be contributed to the stronger De-qi sensation (needle grasp) induced by the former.

Increasing evidence showed that acupoints located in different parts of body produce different effects through specific somatoautonomic reflexes; for example, the facilitatory effect of ST36 at hindlimb on gastric motility was mediated via the parasympathetic pathway, whereas the inhibitory effect of acupuncture on abdomen was reasoned to be attributed

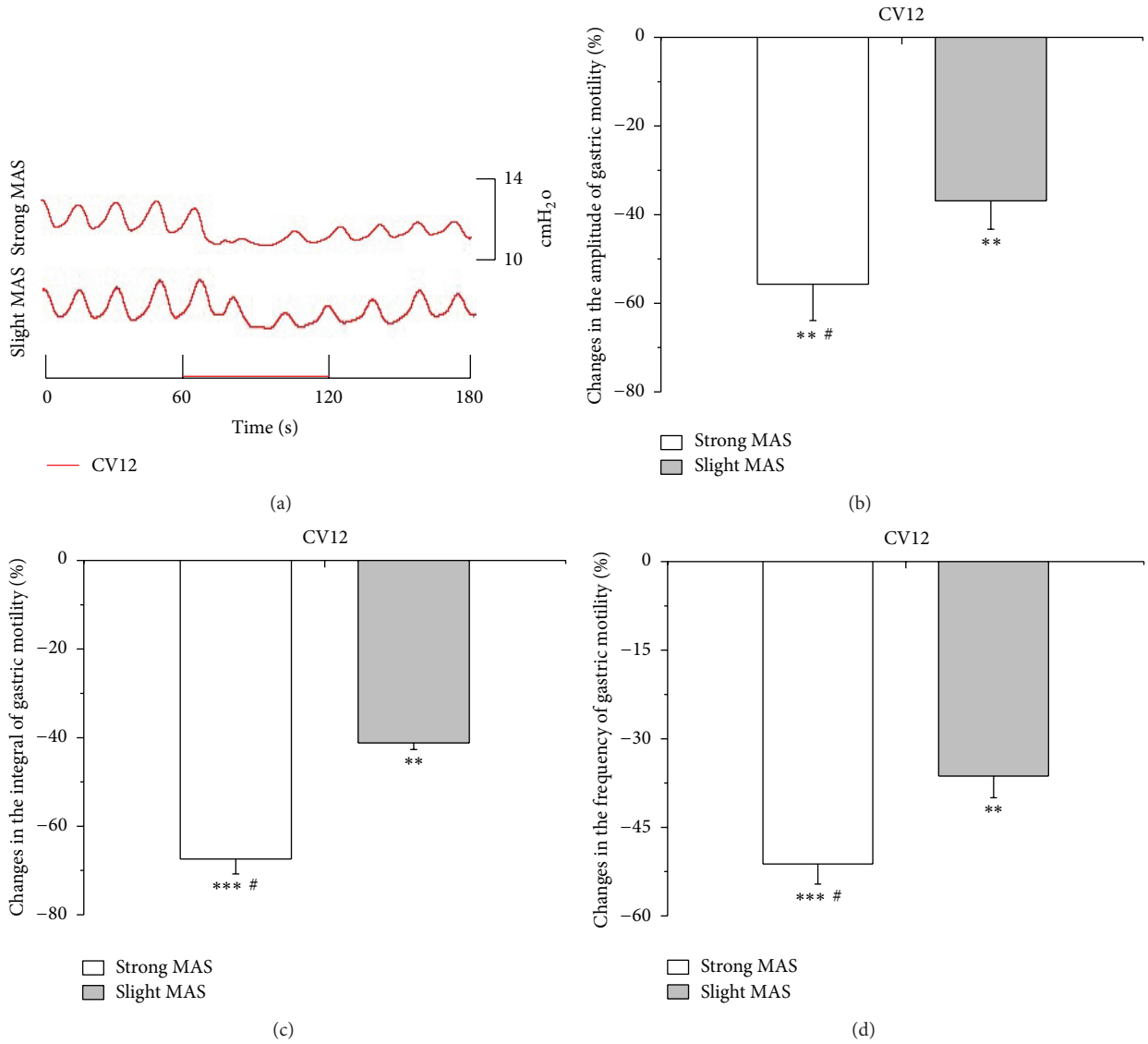

FIGURE 4: Gastric motility in response to MAS at CV12 with different intensities in rats. (a) Examples of the alterations of gastric contraction wave induced by different intensities of MAS at CV12. (b, c, and d) Changes of the amplitude, integral, and frequency of gastric motility induced by MAS at CV12 in 60 s, respectively ($n = 9$; $^{**}P < 0.01$ and $^{***}P < 0.001$, versus background activities; $^{\#}P < 0.05$, as compared with the inhibitory effects of slight MAS at CV12).

to the sympathetic pathway [12, 13]. Using recording method of unitary discharge of nerve fibers, some studies showed that Aδ- and C-afferent fibers were activated during MAS in humans and rats [14, 15]. Moreover, it is suggested that A-type fibers are activated when gentle MAS induces De-qi, whereas C-afferent fibers are involved in the enhancement of De-qi feeling when the needle is rotated and twisted repetitively [16]. It has been showed that rotation is the most commonly used manipulation for acupuncture to produce De-qi [17–19]. Consequently, it is conceivable that the De-qi feelings (needle grasp) elicited slight and strong MAS were more likely to be mediated by the activation of Aδ- and C-afferent fibers.

The effects of moxibustion on various gastrointestinal diseases have been observed in humans and animals and it was showed that moxibustion has beneficial effects on improving gastrointestinal motility, protecting gastric mucosa, and relieving visceral hyperalgesia [20–22]. Temperature-related (local moxibustion-like stimulation, LMS) and nontemperature-related factors (smoke, odor, and herbs) are likely to be involved in the mechanism underlying the effectiveness of moxibustion [23]. Actually, the temperature was even emphasized and had been used as an alternative method of moxibustion in a lot of experimental studies [24, 25]. Previous studies proved that the mean heat-evoked responses of Aδ- and C-afferent fibers were about 43°C [26–28]. Given the results in the present study, as a nociceptive heat, 43°C was essential to the effective regulation of gastric motility by LMS, which implied that Aδ- and C-afferent fibers play critical roles in the generation of De-qi.

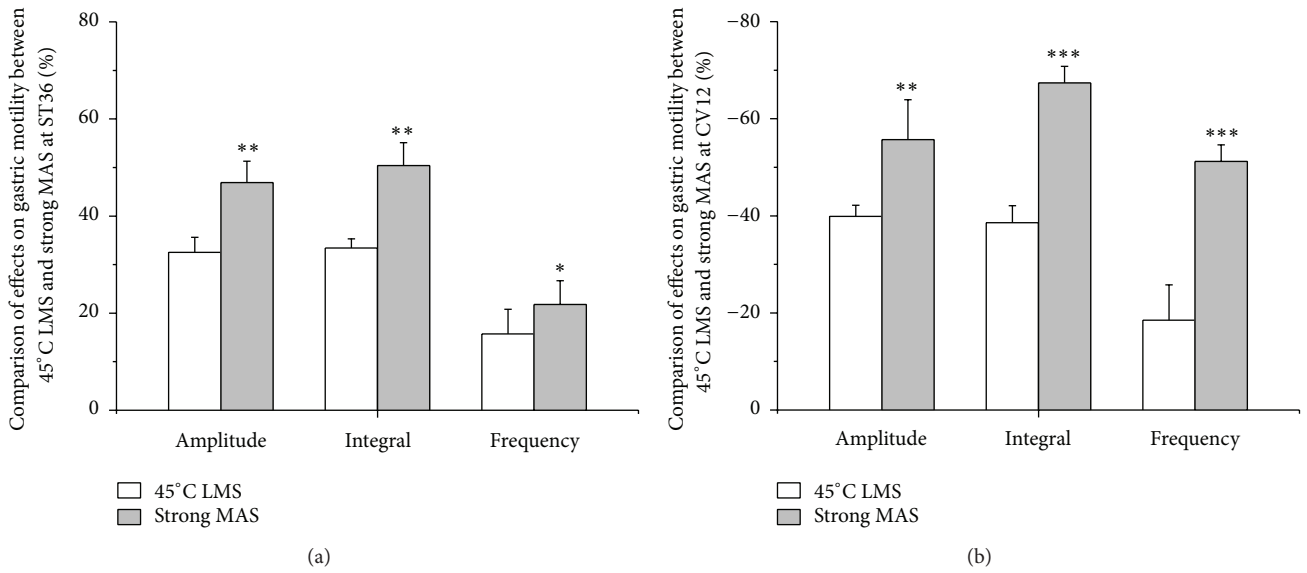

Figure 5: Comparison of the regulatory effects on gastric motility between the last 60 s of 45°C LMS and strong MAS. (a) Comparison of the facilitatory effects on gastric motility between the last 60 s of 45°C LMS and strong MAS at ST36. (b) Comparison of the inhibitory effects on gastric motility between the last 60 s of 45°C LMS and strong MAS at CV12 ($n = 9$; $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$).

5. Conclusion

Taken together, the correlation between intensity of stimulation, afferent fibers, and the generation of De-qi feeling has been preliminarily demonstrated in the present study. Our results indicated that the generation of De-qi sensation induced by MAS and LMS was more likely to be mediated by Aδ- and C-afferent fibers.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

The experiments were done by Yang-Shuai Su. Zhao-Kun Yang, Juan-Juan Xin, Hong Shi, Xiao-Yu Wang, and Ling Hu provided advice on the statistical analyses and data interpretation. Yang-Shuai Su, Xiang-Hong Jing, and Wei He drafted and finalized the paper. Xiang-Hong Jing and Bing Zhu were responsible for the conception, design, and overseeing of the implementation of the study.

Acknowledgments

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Research Article

Electroacupuncture at PC6 or ST36 Influences the Effect of Tacrine on the Motility of Esophagus

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Aim. To investigate the mechanisms of gastrointestinal side effects of tacrine, and find treatment methods with electroacupuncture (EA). *Methods*. Twenty-five healthy cats were randomly divided into 5 groups: gastric-distention group (model group), tacrine group (cholinesterase inhibitor), tacrine + sham acupoint group (control group), tacrine + PC6 (neiguan) group, and tacrine + ST36 (zusanli) group, with 5 cats in each group. Saline 2 mL i.p. was given 30 min before gastric distention in model group. Tacrine 5.6 mg/kg i.p. was given 30 minutes before gastric distention in the other groups. Tacrine + sham acupoint group (control group), tacrine + PC6 group, and tacrine + ST36 group received EA at corresponding acupoints during gastric distention. The frequency of TLESRs and LESP were recorded by using a perfused sleeve assembly. *Results*. Compared with the model group, tacrine significantly increased the frequency of gastric distention-induced TLESR ($P < 0.05$) but did not influence the rate of common cavity during TLESR. Tacrine significantly increased the LESP, which could not remain during gastric distention. EA at PC6 could decrease the frequency of TLESR and maintain the increase of LESP, but EA at ST36 did not have these effects. *Conclusion*. Tacrine can significantly increase the gastric distention-induced transient lower esophageal sphincter relaxations (TLESRs). Electroacupuncture (EA) at PC6 may reverse the above side effect.

1. Introduction

Tacrine was the first acetylcholinesterase inhibitor (AChEI) introduced in therapy for the treatment of Alzheimer's disease (AD) [1], which was used to increase the levels of acetylcholine, a neurotransmitter in the brain that was involved in learning and memory [2]. However, tacrine was limited in clinic because of the side effects in gastrointestinal tract such as nausea, vomiting, and regurgitation [3].

Transient lower esophageal sphincter relaxations (TLESRs) are the most important mechanism of gastroesophageal reflux (GER) either in the patients of gastroesophageal reflux disease (GERD) or in normal subjects [4]. Acupuncture has been used to treat functional gastrointestinal disorders in Eastern countries for centuries. It can modulate visceral sensation as well as function through stimulation at selected acupoints along the meridians (channels of acupoints). Our previous studies have suggested that electroacupuncture (EA) at Neiguan (PC6) [5] and Zusanli (ST-36) [6] can inhibit the frequency of TLESR triggered by gastric distention. But the effects of EA on the side effects of tacrine by EA have not been investigated. The aim of our research is to investigate the mechanisms of gastrointestinal side effects of tacrine and evaluate the efficacy of EA at ST-36 or PC6.

2. Materials and Methods

2.1. Materials. The experiments were performed on 25 adult cats, weighing 3.6 ± 0.2 kg (M/F : 15/10). Cats were provided by the Animal Center of the First Hospital of Peking University. They were kept in individual cages in a controlled environment with a temperature of 22–26°C, 12/12-h light/dark cycles, and fed with standard cat diet. The animals were deprived of food 10 h before each experiment. All procedures

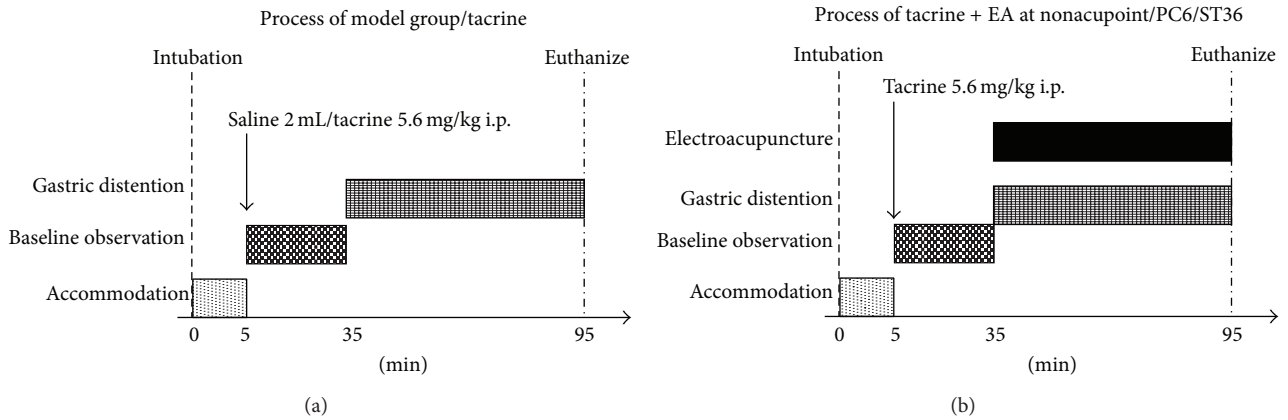

Figure 1: After manometry catheter intubation, the cat accommodated it for 5 min. Then the esophageal manometry was performed for 30 min at the baseline and for 60 min during gastric distention or gastric distention + EA. The model group only received saline 2 mL i.p. and the other groups received tacrine 5.6 mg/kg i.p., 30 min before gastric distention.

were approved by the Committee for Animal Care and Usage for Research and Education of the Peking University. Anesthesia was initially induced with ketamine hydrochloride (30 mg/kg i.m.). Supplementary doses of ketamine hydrochloride (15 mg/kg i.p.) were given whenever necessary to maintain an appropriate depth of anesthesia, as assessed them remained motionless yet still had cornea reflex. They were euthanized with pentobarbital sodium (0.5 mL/kg i.p.) at the end of the protocol.

Tacrine was obtained from Sigma Chemical Co. (St. Louis, MO, USA). Saline was provided from Beijing Shuanghe Chemical Company.

2.2. Experimental Groups (Figure 1). After manometry catheter intubation, the cat accommodated it for 5 min. Then the esophageal manometry was performed for 30 minutes at the baseline and for 60 minutes during gastric distention/gastric distention + EA. The model group only received saline 2 mL i.p. and the other groups received tacrine 5.6 mg/kg i.p. 30 min before gastric distention.

(i) Gastric-distention group (model group, $n = 5$): received saline 2 mL i.p. 30 minutes before gastric distention.

(ii) Tacrine group ($n = 5$): received tacrine 5.6 mg/kg i.p. 30 minutes before gastric distention.

(iii) Tacrine + sham acupoint (control group, $n = 5$): received tacrine 5.6 mg/kg i.p. 30 minutes before gastric distention and received EA at sham acupoint during gastric distention for 60 minutes.

(iv) Tacrine + PC6 group ($n = 5$): received tacrine 5.6 mg/kg i.p. 30 minutes before gastric distention and received EA at PC6 during gastric distention for 60 minutes.

(v) Tacrine + ST36 group ($n = 5$): received tacrine 5.6 mg/kg i.p. 30 minutes before gastric distention and received EA at ST36 during gastric distention for 60 minutes.

2.3. Recording Methods. The manometry catheter (outer diameter 0.5 cm) consisted of a multilumen silicone tube with five side holes located at 9, 6, 3, 0, and −6 cm from the upper margin of the 6 cm long Dent sleeve sensor (Dentsleeve, Belair, Australia). The catheter was continuously perfused with distilled water by a low compliance pneumohydraulic capillary infusion system (UPS-2020, Holland) at a rate of 0.2 mL/min. The external pressures transducers were connected via an analog/digital converter to a personal computer system. The data were displayed continuously on a monitor and stored on the personal computer system (MMS B.V., The Netherlands). After anesthesia the cat was set in a supine position. A manometry catheter was placed through the mouth into esophagus and positioned so that the sleeve sensor straddled the LES to register LES pressure. The distal side hole was used as a reference point for intragastric pressure. And the upper LES side holes were used to measure esophageal body pressure. A mylohyoid electromyography (MMS B.V., The Netherlands) was used to record swallowing. The pinhead electrode was inserted in the mylohyoid muscle, and the reference electrode was fixed to the interscapular region of the back.

2.4. Electroacupuncture. Two acupuncture needles of 0.22 mm in diameter (Suzhou Global Acupuncture Instrument Co., Ltd., Suzhou, China) were inserted perpendicularly at the bilateral Neiguan acupoint (PC6, located 1.5–2.0 cm above the wrist between the ligaments of the flexor carpi radialis and the palmaris longus overlying the median nerve [5]) or Zusanli acupoint (ST36, located at the proximal one-fifth of the craniolateral surface of the rear leg, distal to the head of the tibia in a depression between the muscles of the cranial tibia and the long digital extensor [6]) to a depth of 5 mm. After the needle was inserted, we manipulated with uniform reducing-reinforcing methods to induce the deqi sensations of acupuncturist, such as heavy, tight or even vibration of the needle, and then electrostimulation was introduced. An electrical stimulator (Model LH202H Hans, Beijing Huawei Medical Instrument

Co., Ltd., Beijing, China) provided current to the needles. Wave patterns were sparse with dense pulse intervals ranging from 2 to 100 Hz (2/100 Hz), with constant amplitude and current flow (3-4 mA). The duration was 60 min and correct positioning was confirmed by observing slight repetitive paw flexion during stimulation. Control stimulation on a sham acupoint was conducted at the hip, a point away from the traditional meridians and dermatomes.

2.5. Gastric Distention. Air was insufflated (at a rate of 15 mL/s) into stomach through a 2.0 mm diameter tube intubated through mouth to stomach. Its depth equals to 5 cm plus the esophageal body length. 30 mL air into stomach every 6 min amount to to 300 mL was insufflated in the 1 h period of gastric distention.

2.6. Data Analysis. TLESRs were defined according to established methods [7]. Basal LES pressure was measured at end expiration relative to gastric pressure. The LES pressure during gastric distention was measured for 1 min every 6 min, and an overall mean for each period of the study was calculated. Common cavities were defined as abrupt simultaneous and sustained rises of basal esophageal pressure to intragastric pressure in at least the two lower esophageal body manometry recording sites [8]. Common cavities are considered as markers of gas or liquid reflux from the stomach into the esophagus.

2.7. Statistical Analysis. The number of TLESRs was compared using Wilcoxon signed rank test and expressed as median (interquartile range). Basal LESP, postmedicine LESP, and gastric distension LESP were presented as means ± SD and were compared using ANOVA. The rate of common cavity was compared using paired sample χ^2. SPSS 17.0 was used for statistical analysis, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Transient LES Relaxations

3.1.1. Effect of Tacrine on TLESR. Tacrine [32/hour (range: 15–47)] significantly increased the frequency of gastric distention-induced TLESRs compared with model group [7/hour (range: 4–19)], $P < 0.05$. (Figure 2).

3.1.2. Effect of Tacrine + EA on TLESR. After the use of tacrine, EA at PC6 [10/hour (range: 7–21)], the frequency of gastric distention-induced TLESR, was significantly inhibited than that of the control group [32/hour (range: 14–47)], $P < 0.05$. (This result was consistent with our former research [5].) EA at ST36 [26/hour (range: 14–32)] could not change the frequency of gastric distention-induced TLESR compared with the control group [32/hour (range: 14–47)], $P = 0.388$. (Figure 2)

3.2. Effect of Tacrine on Common Cavity. Tacrine had no effect on common cavity rate during TLESR. In model group, a total of 51 TLESRs were induced by gastric distention, among them there were 37 associated with common cavity, and the ratio was 72.5%. In tacrine group, there were 156 gastric distention-induced TLESRs in all, from which 98 were associated with common cavity, and its ratio was 62.8%. (72.5% versus 62.8%, $P = 0.238$).

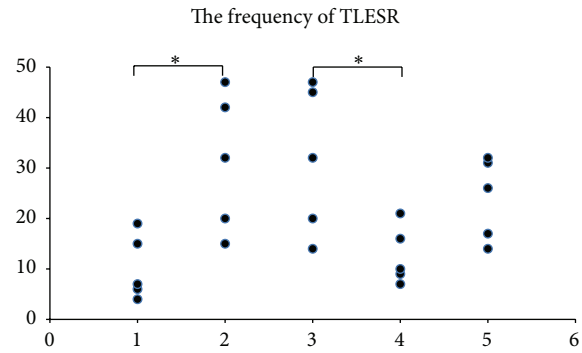

Figure 2: Tacrine significantly increased the frequency of TLESRs compared with model group ($P < 0.05$). EA at PC6 significantly inhibited the frequency of TLESRs than control group ($P < 0.05$). EA at ST36 could not change the frequency of TLESRs compared with control group ($P = 0.388$). $^*P < 0.05$: (1) gastric distention group (model group); (2) tacrine group; (3) tacrine + non-acupoint (control group); (4) tacrine + PC6; and (5) tacrine + ST36.

3.3. Lower Esophageal Sphincter Pressure (LESP). There were three parts of LESP in the whole protocol: baseline LESP, postmedicine (tacrine/saline) LESP, and gastric distention LESP.

3.3.1. Effect of Tacrine on LESP. In model group, there was no significant difference between baseline LESP and postmedicine LESP (33.6 ± 7.1 mmHg versus 33.2 ± 6.9 mmHg, $P = 0.374$). The gastric distention LESP was significantly lower than baseline LESP (24.2 ± 6.1 mmHg versus 33.6 ± 7.1 mmHg, $P < 0.05$) and postmedicine LESP (24.2 ± 6.1 mmHg versus 33.2 ± 6.9 mmHg, $P < 0.05$). In tacrine group, the postmedicine LESP (78.4 ± 10.2 mmHg) was significantly higher than baseline LESP (39.2 ± 7.4 mmHg) and gastric distention LESP (45.4 ± 14.3 mmHg) $P < 0.05$, and there was no significant difference between baseline LESP and gastric distention LESP (39.2 ± 7.4 mmHg versus 45.4 ± 14.3 mmHg, $P = 0.651$) (Table 1, Figure 3).

3.3.2. Effect of Tacrine + EA on LESP. In control group and tacrine + ST36 group, the postmedicine LESP was significantly higher than baseline LESP ($P < 0.05$) and the gastric distention LESP was falling to the baseline level (gastric distention LESP versus postmedicine LESP, $P < 0.05$ and gastric distention LESP versus baseline LESP, $P > 0.05$) (Figure 3). In tacrine + PC6 group, the postmedicine LESP was significantly higher than that of baseline (56.0 ± 4.1 mmHg versus 34.2 ± 4.5 mmHg, $P < 0.05$) and the gastric distention LESP did not decline and even had ascending trend (gastric distention LESP 76.2 ± 6.6 mmHg

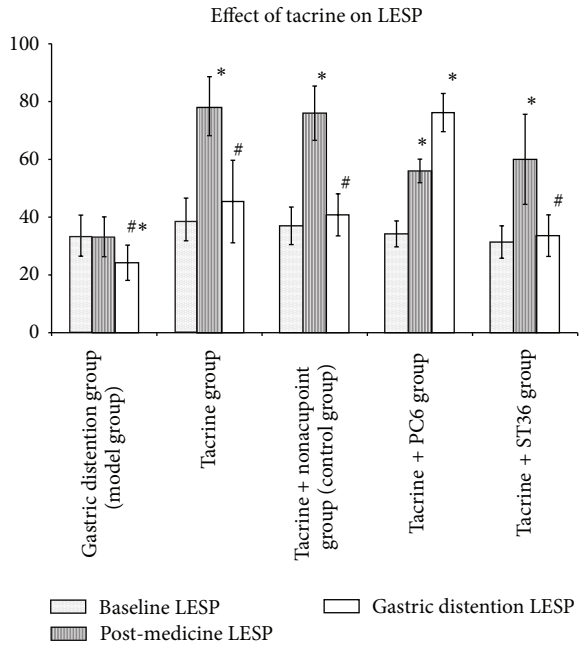

Figure 3: (a) In model group, there was no significant difference between baseline LESP and postmedicine LESP. The gastric distention LESP was significantly lower than baseline LESP and postmedicine LESP. In tacrine group, the postmedicine LESP was significantly higher than baseline LESP and gastric distention LESP; there was no significant difference between baseline LESP and gastric distention LESP. (b) In control group and tacrine + ST36 group, the postmedicine LESP was significantly higher than baseline LESP. And the gastric distention LESP was falling to the baseline level. In tacrine + PC6 group, the postmedicine LESP was significantly higher than baseline LESP. And the gastric distention LESP did not decline and even had ascending trend ($P = 0.086$). $^{*}P < 0.05$ versus baseline LESP. $^{\#}P < 0.05$ versus postmedicine LESP.

versus postmedicine LESP 56.0 ± 4.1 mmHg, $P = 0.086$) (Table 1, Figure 3).

4. Discussion

4.1. Effects of Tacrine. Tacrine is the first acetylcholinesterase inhibitor (AChEI) introduced in therapy for the treatment of Alzheimer's disease (AD) [1], but its clinical application is limited because of the side effects in gastrointestinal tract such as nausea, vomiting, and regurgitation [3]. In this study, we investigated the mechanisms of gastrointestinal side effects induced by tacrine. Acetylcholine is not only a neurotransmitter involved in learning and memory [2], but also an important neurotransmitter in esophageal-gastric motility, especially in regulating TLESR. As we know, atropine, an anticholinergic agent with central and peripheral actions, can inhibit the frequency of TLESR and some selective peripheral cholinergic blockade did not reduce it, so a central cholinergic pathway may be involved in regulation of TLESR. Tacrine is a kind of acetylcholinesterase inhibitor (AChEI), which works through increasing the level of acetylcholine in brain.

In this study, the relationship between tacrine and esophageal motility was investigated. We firstly observed that tacrine significantly increased the frequency of gastric distention-induced TLESR compared with model group, but tacrine did not change the common cavity rate during TLESR. TLESR was the most important mechanism of gastroesophageal reflux [4]. The effect of tacrine to increase the frequency of gastric distention-induced TLESRs may be the most important reason for nausea, vomiting, and regurgitation.

At the same time, tacrine significantly increased the LESP compared with baseline LESP. Although tacrine may increase LESP, this increase could not maintain during gastric distention, so it could not inhibit the gastroesophageal reflux during gastric distension.

4.2. Effects of Tacrine + EA. Acupuncture has been used to treat functional gastrointestinal disorders in Eastern countries for centuries. A large amount of clinical evidence supports the effectiveness of acupuncture for treating functional disorders of the gastrointestinal tract, and the most commonly used acupoints in treating gastrointestinal symptoms are Neiguan (PC6) and Zusanli (ST-36). Based on another experiment in our research group, electroacupuncture (EA) at PC6 [5] and ST-36 [6] could inhibit the frequency of TLESR triggered by gastric distention.

Our previous research showed that after using tacrine and EA at PC6, the frequency of gastric distention-induced TLESR was significantly decreased compared with control group [5]. In this study, it was further demonstrated that EA at PC6 could also inhibit the decrease of LESP due to gastric distention and even had ascending trend ($P = 0.086$). In the present study, EA at PC6 may increase the LESP after increase the level of acetylcholine in brain and peripheral tissue, however, in our previous research only EA at PC6 had no effect on LESP [5]. It indicated that EA at PC6 was an attractive therapeutic option to treat the gastrointestinal side effects of tacrine. Further study needed to be done about the mechanism about the EA at PC6 treating the gastrointestinal side effects due to tacrine.

Previous study also showed that EA at ST36 increased LESP and decreased the frequency of TLESR [6]. While in this study, after the level of acetylcholine was increased, EA at ST36 did not have these effects. The results suggested that the effects of EA at ST36 were through acetylcholine pathway.

4.3. Deqi Sensation in Animal Experiment. The term of "Deqi" was first found in "Huang Di Neijing" [9]. It plays an important role in the process of acupuncture and it is closely related to the treatment efficacy. Deqi does not only refer to needling sensations, but also involves the changes of qi induced by needle insertion into the acupoint. Some research has found that EA at acupoint (deep needling) induces significant stronger deqi sensation than EA at acupoint (subcutaneous needling) or at nonacupoint [10]. In our research, we use deep needling at PC6 or ST36. After inserting the needle, we manipulated with uniform reducing-reinforcing methods to induce the deqi sensations of acupuncturist, such

Table 1: The effects of tacrine and tacrine + EA on LESP.

Group	Baseline LESP	Postmedicine LESP	Gastric distention/gastric distention + EA LESP
Model group	33.6 ± 7.1 mmHg	33.2 ± 6.9 mmHg	24.2 ± 6.1 mmHg$^{*\#}$
Tacrine group	39.2 ± 7.4 mmHg	78.4 ± 10.2 mmHg*	45.4 ± 14.3 mmHg$^{\#}$
Tacrine + nonacupoint	37.0 ± 6.5 mmHg	76.0 ± 9.4 mmHg*	40.8 ± 7.3 mmHg$^{\#}$
Tacrine + PC6	34.2 ± 4.5 mmHg	56.0 ± 4.1 mmHg*	76.2 ± 6.6 mmHg*
Tacrine + ST 36	31.4 ± 5.6 mmHg	60.0 ± 15.6 mmHg*	33.6 ± 7.2 mmHg$^{\#}$

$^{*}P < 0.05$ versus baseline LESP. $^{\#}P < 0.05$ versus postmedicine LESP.

as heavy, tight or even vibration of the needle, and then electrostimulation was introduced. By this method we may induce deqi sensation and obtain better results. But this still needs further research.

5. Conclusion

Tacrine may have some effects on esophageal motility, such as increasing the frequency of gastric distention-induced TLESR and elevating LESP. And this LESP elevation may not persist during gastric distention. EA at PC6 can decrease the frequency of TLESR and maintain the increase of LESP, but EA at ST36 does not have these effects.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Can Tongue Acupuncture Enhance Body Acupuncture? First Results from Heart Rate Variability and Clinical Scores in Patients with Depression

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Tongue acupuncture (TA) is a method which is not used in western medicine and even in China it is applied very rarely in clinical practice. This study aimed at investigating whether additional TA can improve the efficacy of body acupuncture (BA) in patients with depression. Twenty patients with a mean age of ± SD of 42.9 ± 11.2 years were randomly divided into two groups ($n = 10$ patients each), one group receiving BA (Zusanli, Sanyinjiao, Neiguan, Shenting, Yintang, and Baihui) and the other receiving BA and TA (Liver, Heart, and Brain). The quantitative and qualitative outcome measures were heart rate (HR), heart rate variability (HRV), and different clinical scores. We found that in both groups all scores and HR improved significantly, whereas HRV increased partly significantly. It seems that TA can enhance acute and treatment effects of BA in patients with depression. The investigation of de qi sensation in TA needs further attention.

1. Introduction

Tongue acupuncture (TA) is a unique natural therapy. Specific tongue acupoints are supposed to be related to various functional domains of the body. It is claimed that TA can stimulate different meridians associated with different organs' functions in order to adjust blood circulation and energy-flow in the body [1].

De qi sensation evoked by TA is essential to its clinical effectiveness. One purpose of TA is restoring consciousness and brain resuscitation. In China, it is used as a complementary method to treat not only several diseases, like stroke [2], but also children with visual impairment [3].

In contrast to TA, there are a lot of clinical investigations concerning body acupuncture (BA) and major depressive disorders [4].

Figures 1(a) and 1(b) summarize the number of publications concerning different terms related to TA and BA.

Our research group recently found acute stimulation effects on neurovegetative parameters like heart rate (HR) and heart rate variability (HRV) in patients with depression [5] and insomnia [6].

The present clinical study was performed at the Military Acupuncture Centre at the People's Liberation Army General Hospital, Beijing, in cooperation with the Traditional Chinese Medicine (TCM) Research Center Graz, Austria (http://litscher.info/ and http://tcm-graz.at/). This paper compares results from BA and BA + TA measurements in depression patients with regard to neurophysiological parameters like HR and HRV.

2. Materials and Methods

2.1. Patients. Twenty patients (all females; mean age ± SD 42.9 ± 11.2 years; range 20–65 years) suffering from depression (Chinese diagnosis "Yu Zheng") received acupuncture

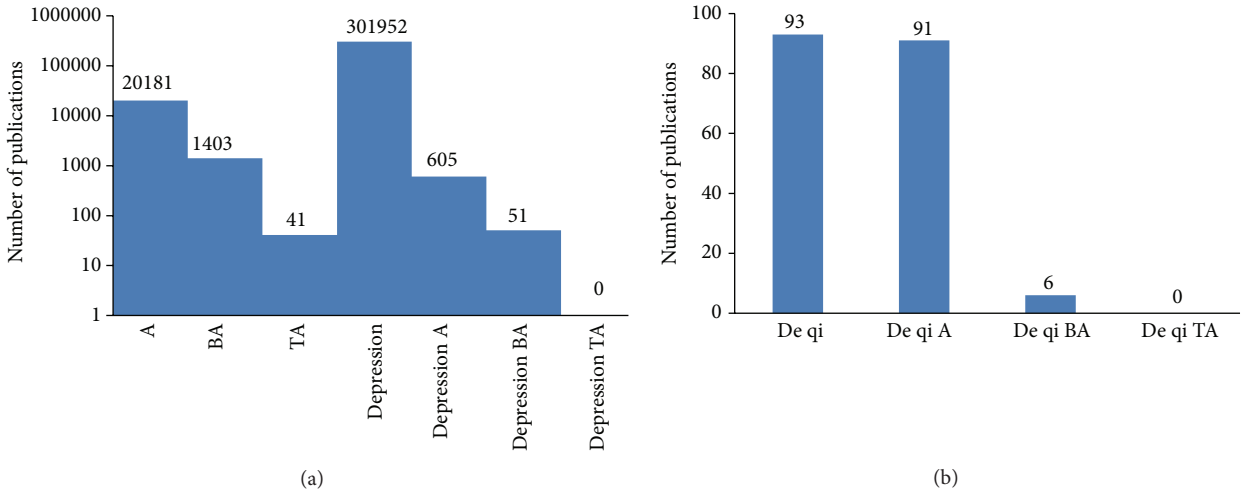

Figure 1: Use of different acupuncture approaches (http://www.pubmed.gov/): A ... acupuncture; BA ... body acupuncture; and TA ... tongue acupuncture.

treatment at the Chinese People's Liberation Army Hospital, Beijing. The clinical evaluation of the patients, performed before the first and after the last acupuncture session, used three main scales: the Hamilton Anxiety Rating Scale (HAM-A) [7], the Athens Insomnia Scale (AIS) [8], and the Hamilton Rating Scale for Depression (HRSD) [9]. No patient was under the influence of centrally active medication or had a history of heart or cerebrovascular disease, respiratory or neurological problems, or hypertension. The study was approved by the Ethics Committee of the Chinese People's Liberation Army Hospital and carried out in compliance with the Declaration of Helsinki. All patients gave oral informed consent.

2.2. Teleacupuncture. Electrocardiographic (ECG) biosignal recording was performed in China, and data analysis took place in Europe. For ECG registration three adhesive electrodes (Skintact Premier F-55, Leonhard Lang GmbH, Innsbruck, Austria) were used which were applied to the chest.

The research team in China used a medilog AR12 HRV (Huntleigh Healthcare, Cardiff, United Kingdom) system from the TCM Research Center at the Medical University in Graz. The system has a sampling rate of 4096 Hz; the raw data are stored digitally and transferred to the TCM Research Center Graz via the Internet. The biosignals were analyzed and HRV was calculated.

Like in previous studies [5, 6, 10], mean HR, total HRV, and the LF (low frequency)/HF (high frequency) ratio of HRV were chosen as evaluation parameters, as such being recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [11].

2.3. Body Acupuncture, Tongue Acupuncture, and Procedure. The patients were randomly divided into two groups using a simple randomization (numbers by chance). One group (n = 10; mean age 39.2 ± 13.2 years; range 20–65 years) received BA in six sessions and the other group (n = 10; mean age 46.6 ± 7.8 years; range 38–60 years) additionally received TA (see Figure 2) in all six sessions. HR-HRV recordings were performed during the first and the last acupuncture session.

Figure 2: Tongue acupuncture at the Military Acupuncture Training Centre at the People's Liberation Army General Hospital, Beijing.

The following body acupoints were used in this study: Zusanli (ST36,bilateral), Sanyinjiao (SP6, bilateral), Neiguan (PC6, bilateral), Shenting (GV24), Yintang (Ex-HN3), and Baihui (GV20). The sterile, single-use needles (0.30 × 25 mm, Huan Qiu, Suzhou, China) were inserted perpendicularly, and the needle was stimulated clockwise and counterclockwise for 15 seconds each, with six rotations per second, resulting in 90 rotations per stimulation.

The patients in the TA group received TA in every acupuncture session, immediately before BA. For TA, the points Liver, Heart, and Brain (Figure 3) were always used in this order [1]. The needle was inserted obliquely into the tongue acupuncture point, to a depth of 0.5–1 cun, and immediately removed again; then the next tongue point was treated likewise.

The measurement profile and measurement phases (a–d) of the BA treatment are shown in Figure 4. Four registration periods (5 min each) were compared: one before

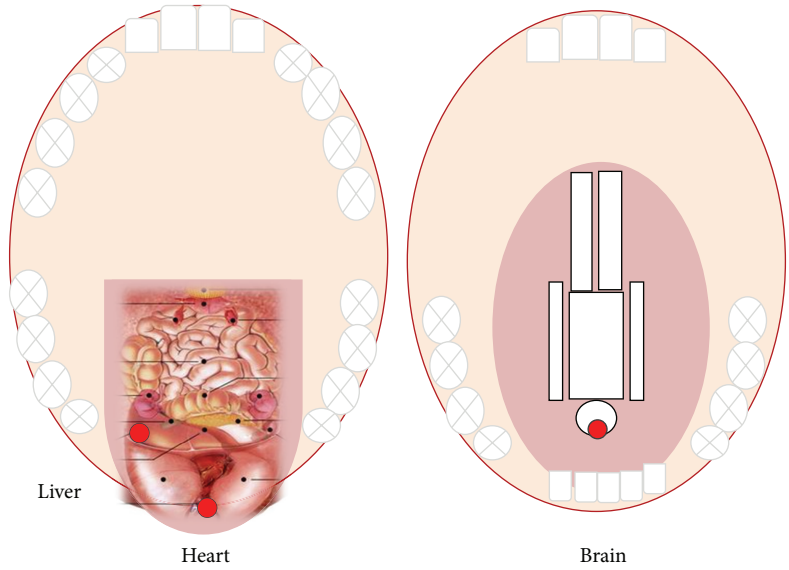

Figure 3: Tongue acupuncture points used in this study.

Table 1: Changes in clinical scores and blood pressure values between the first (M1) and last (M2) treatment session. Values are given as mean ± SD (standard deviation).

	Body acupuncture			Body + tongue acupuncture		
	M1	M2	P	M1	M2	P
HAM-A	18.9 ± 3.9	16.6 ± 3.5	0.008	24.4 ± 7.9	19.0 ± 7.1	<0.001
AIS	15.0 ± 6.7	11.3 ± 5.1	<0.001	13.9 ± 4.0	8.3 ± 3.2	0.002
HRSD	22.2 ± 5.4	19.5 ± 4.8	0.001	22.3 ± 5.9	17.4 ± 4.8	0.002
BPsys [mmHg]	105.3 ± 9.8	103.6 ± 9.8	n.s.	113.3 ± 10.4	113.1 ± 7.4	n.s.
BPdia [mmHg]	66.4 ± 4.3	66.3 ± 4.7	n.s.	69.2 ± 6.4	69.5 ± 6.0	n.s.

HAM-A: Hamilton Anxiety Rating Scale [7]; AIS: Athens Insomnia Scale [8]; HRSD: Hamilton Rating Scale for Depression [9]; BPsys: systolic blood pressure; BPdia: diastolic blood pressure; and n.s.: not significant.

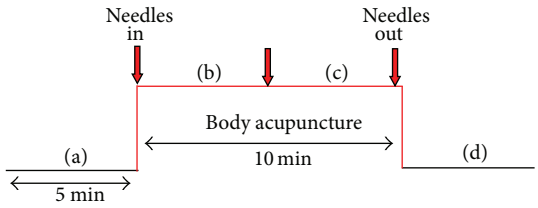

Figure 4: Measurement procedure for body acupuncture.

acupuncture (a), two during acupuncture (b, c), and one as a control after removing the needles (d). In addition, blood pressure was measured at the beginning and at the end of the acupuncture sessions.

2.4. Statistical Analysis. Data were analyzed using SigmaPlot 12.0 software (Systat Software Inc., Chicago, USA). Graphical presentation of results uses box plot illustrations. Testing was performed with Friedman repeated measures ANOVA on ranks and Tukey or Holm-Sidak test. The criterion for significance was $P < 0.05$.

3. Results

Figures 5 and 6 show the mean HR and total HRV from the ECG recordings of both patient groups during the first and last treatment session, respectively. HR had decreased significantly in both groups in the course of the treatment.

In contrast to HR, HRV had increased significantly in the BA group during the course of the treatment (see Figure 6).

Furthermore, continuous HRV monitoring showed significant alterations in the LF/HF ratio within the single treatment sessions (see Figure 7). The comparison between the first and the last treatment, however, did not reach the level of significance.

The direct statistical comparison between the TA and BA group did not yield significant changes; however, there was a marked decrease of HR in the TA group and the decrease of the HAM-A score (see Table 1) showed a higher significance ($P = 0.008$ in the BA group and $P < 0.001$ in the TA group).

The analysis of the three clinical scores revealed interesting results. In all scores there was a significant reduction (see Table 1).

The data of the blood pressure values showed insignificant results (see Table 1). The de qi sensation during TA was

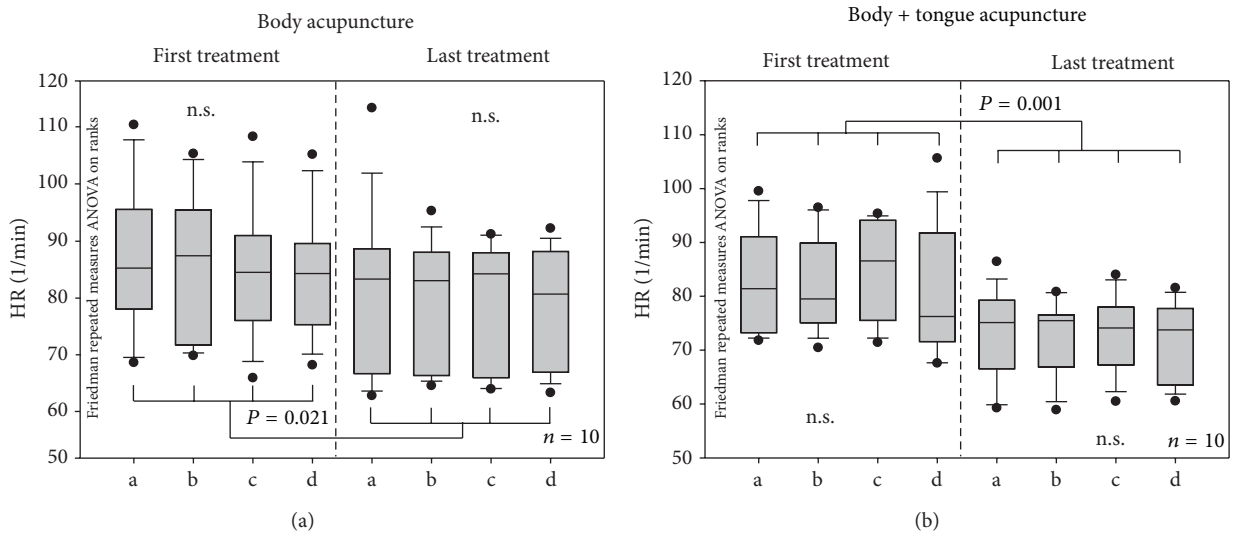

Figure 5: Box plots displaying the changes in mean heart rate (HR). Within the single treatment sessions, no significant effects could be found. When comparing the values of the first session to those of the last session, however, HR had decreased significantly. The ends of the boxes define the 25th and 75th percentiles with a line at the median and error bars defining the 10th and 90th percentiles.

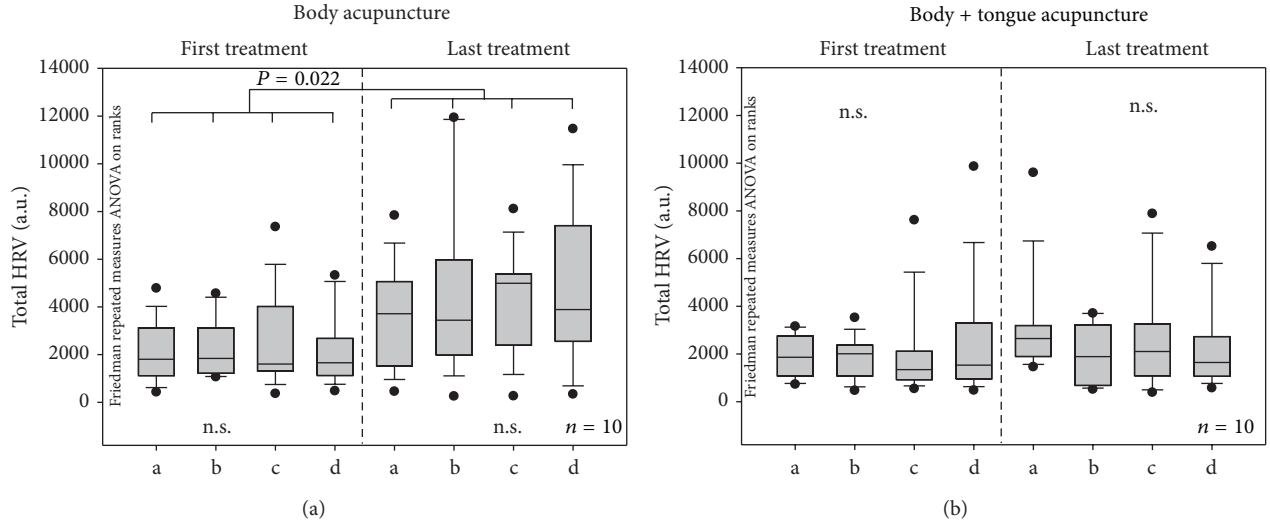

Figure 6: Changes in total heart rate variability (HRV). For further explanations, see Figure 5.

similar to that during BA. After the arrival of qi, the TA patients reported sensations of distension, heaviness, and numbness; in addition, these sensations spread to the throat.

4. Discussion

Tongue acupuncture is an innovative but not commonly used technique in the traditional Chinese medicine [12]. It originated from the theory of TCM through scientific research. Forty points on the tongue were discovered that correspond to organs and certain parts of the body [1]. Studies showed that TA and BA can improve the visual status of children with visual disorders, both peripheral and central in origin [3]. The authors of a rat model study monitored the evoked activity of the digastric electromyography elicited by electrical stimulation of the tongue [13]. In a study dealing with aphasia after stoke, authors mentioned that tongue bleeding, deep insertion, and strong stimulation were adopted by many practitioners [14]. Li et al. found that tongue acupuncture has a better therapeutic effect on stroke [2]. There are also a few other studies available in the database PubMed which also deal with the topic tongue acupuncture; however, there are no publications available in connection with depression or de qi sensation (Section 1).

In Asia and also in Europe, depression is one of the most disabling diseases, causing a significant burden both to the individual and to society [15–17]. Detailed information on this important topic can be found in the discussion section

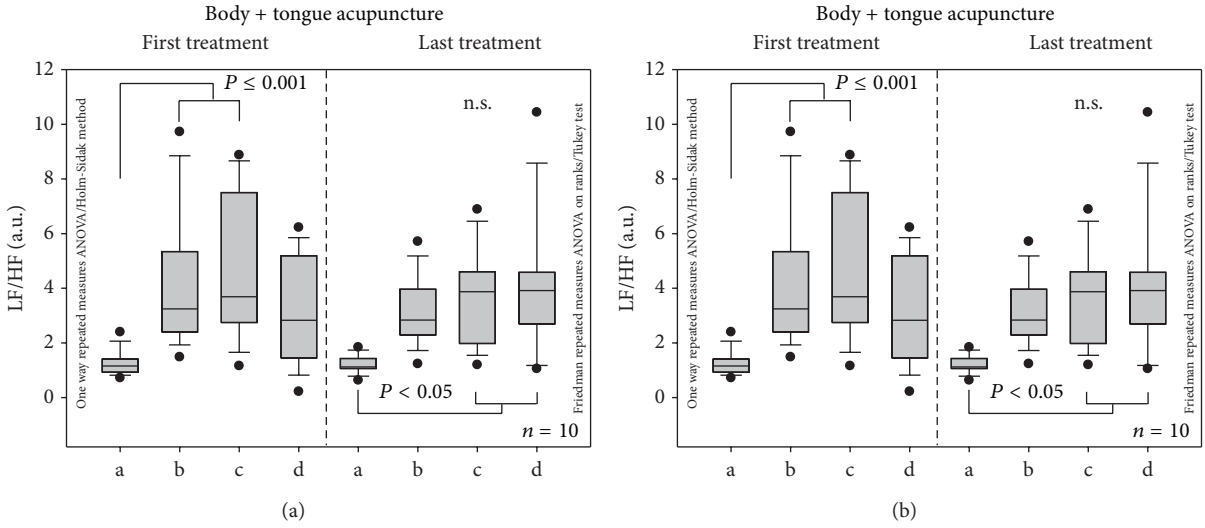

Figure 7: The low frequency (LF)/high frequency (HF) ratio did not change significantly when comparing the first and last treatment. For further explanations, see Figure 5.

of one of our previous publications published recently [15]. As stated in that article, one important way to stop this cost explosion in China and Europe is through increased research efforts in this field. Better detection, prevention, treatment, and patient management are imperative to reduce the burden of depression and its cost [15–17].

As previously described, continuous electrical auricular acupuncture is one special kind and new method to treat patients with neurological diseases like depression [15]. The results of our present study are in accordance with previous investigations [15]. All clinical scores (HAM-A, AIS, and HRSD) showed a significant improvement already after 6 TA/BA and BA sessions. However, it has to be mentioned that the baseline values of the HAM-A score differed between the two treatment groups because randomization was performed by chance and not by score assessment. In addition, HR and HRV, which are reliable indicators of the state of health [5, 6, 15], also improved, partly significantly.

When performing TA, most acupuncturists do not leave the needle in place; they puncture the surface of the tongue and describe the fact that they receive good therapeutic effects in some clinical applications like in apoplectic aphasia rehabilitation [14]. Horizontal and deep puncturing approaches were also sometimes used. This method refers to piercing the tongue from one side to the other [18, 19]. Deep puncturing needs long needles for treatment towards the root of the tongue [20].

In conclusion, our study shows clinical (scores) and neurovegetative (HRV) improvements in parameters after BA and TA acupoint stimulation in patients with depression. It can be stated that invasive tongue stimulation with needles does not have inhibitory effects on BA; on the contrary, it seems that it can enhance acute and treatment effects of BA. The investigation of de qi sensation [21] needs further attention. Up to now, it has not been described in detail in English or even in Chinese scientific literature.

Conflict of Interests

The authors declare that they have no conflict of interests regarding the publication of this paper.

Authors' Contribution

Xian Shi and Huan Wang contributed equally to this study.

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