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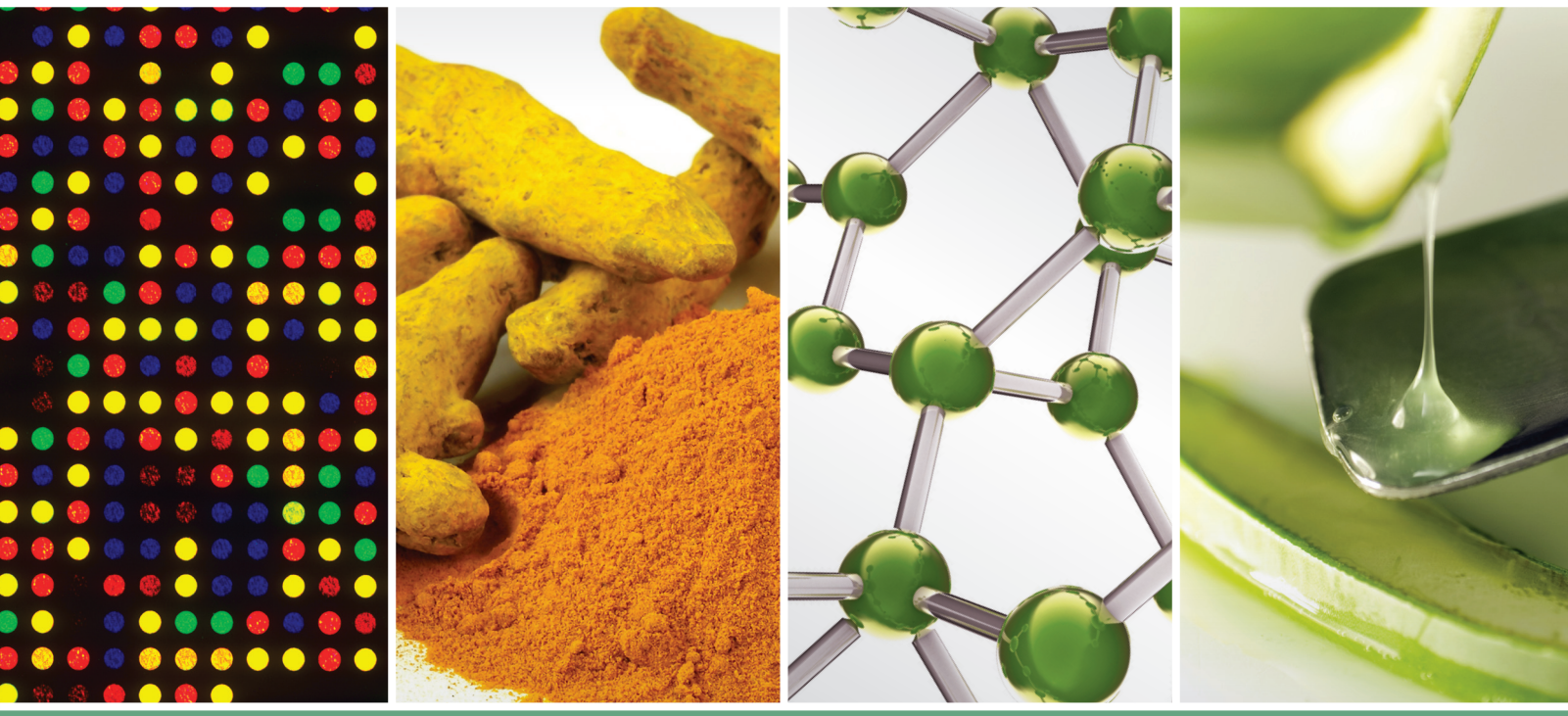
Deqi Sensation in Different Kinds of Acupuncture

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

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The current issue is the 2013 issue which includes 21 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.

As mentioned above, this special issue contains 21 papers, of which two papers are related to the characterization of the Deqi during acupuncture treatment. Deqi sensation often occurs during acupuncture treatment and is believed to be important for a successful acupuncture therapy. So far there exist no questionnaires for children. E. Anders et al. created a sentence based questionnaire for children on the basis of the Southampton Needle Sensation questionnaire (SNSQ). Three papers study the interaction between Deqi and acupuncture by neuroimaging technology. They provide evidence to understand neural mechanism underlying acupuncture. Four papers are related to the physiological mechanism of Deqi. These papers describe current knowledge in understanding of Deqi from a physiological aspect. Three reviews are related to the recent advances in Deqi and acupuncture effects. The current evidence base is not solid enough to draw any conclusion regarding the predicative value of natural Deqi for clinical efficacy or the therapeutic value of manipulation-facilitated Deqi. Six papers focus on Deqi in manual acupuncture compared with other types of acupuncture, of which 4 papers introduce the influence of the Deqi sensation by suspended moxibustion stimulation. Two papers adopt randomized controlled clinical trial and multicenter prospective cohort design to compare the clinical effectiveness of Deqi sensation.

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

Local Anesthesia at ST36 to Reveal Responding Brain Areas to *deqi*

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Background. Development of non-*deqi* control is still a challenge. This study aims to set up a potential approach to non-*deqi* control by using lidocaine anesthesia at ST36. *Methods.* Forty healthy volunteers were recruited and they received two fMRI scans. One was accompanied with manual acupuncture at ST36 (DQ group), and another was associated with both local anesthesia and manual acupuncture at the same acupoint (LA group). *Results.* Comparing to DQ group, more than 90 percent *deqi* sensations were reduced by local anesthesia in LA group. The mainly activated regions in DQ group were bilateral IFG, S1, primary motor cortex, IPL, thalamus, insula, claustrum, cingulate gyrus, putamen, superior temporal gyrus, and cerebellum. Surprisingly only cerebellum showed significant activation in LA group. Compared to the two groups, bilateral S1, insula, ipsilateral IFG, IPL, claustrum, and contralateral ACC were remarkably activated. *Conclusions.* Local anesthesia at ST36 is able to block most of the *deqi* feelings and inhibit brain responses to *deqi*, which would be developed into a potential approach for non-*deqi* control. Bilateral S1, insula, ipsilateral IFG, IPL, claustrum, and contralateral ACC might be the key brain regions responding to *deqi*.

1. Introduction

deqi, also called needle sensation, refers to the sensations of soreness, numbness, fullness, heaviness, and so forth around the acupoints of patients when the needle is inserted to a certain depth. At the same time, the operator may feel heaviness or tension around the needle. As one of the most classic and important concepts originated from Neijing (The Yellow Emperor's Classic of Internal Medicine), *deqi* has drawn increasing attention of researchers recently [1–5]. The studies on *deqi* mainly focused on four directions: (1) identifying the relationship between *deqi* and acupuncture efficacy [6–10]; (2) quantifying the *deqi* sensations and making *deqi* visualization and objectification [11–13]; (3) investigating the influence factors on *deqi* such as insertion site, insertion depth, puncture manipulation and needle retaining time, and body position [14–19]; (4) exploring the mechanisms of *deqi* [20–31].

Whatever direction of investigations on *deqi*, it is essential to establish an appropriate non-*deqi* control. To date, several kinds of sham acupuncture strategies have been employed as non-*deqi* control, which include on-invasive placebo stimulation (Von Frey, Streitberger Needle, etc.) at the same acupuncture point or nonacupuncture point [7, 29, 31], superficial needling at the same acupuncture point or nonacupuncture point [9, 32], or needling at the nonacupuncture point or acupoint unrelated to the research purpose [20, 22, 23, 33].

However, clinical and neuroimaging studies demonstrated that acupuncture feelings were unable to be comprehensively inhibited by sham acupuncture [33, 34]. Therefore, development of non-*deqi* control is still a challenge. Giving the fact that both local anesthetic at the acupoint and general anesthesia had been applied to explore the mechanism of acupuncture in previous studies [35–38], we proposed that local anesthesia would be a potential strategy to be used as an approach of non-*deqi* control. Based on this idea, we set up a non-*deqi* control of acupuncture using local lidocaine anesthesia at acupoint and evaluating with the scoring of subjects' feelings and performed fMRI scanning to obtain the changed brain areas.

2. Methods

2.1. Subjects. Forty healthy, right-handed, adult volunteers (20 females and 20 males, ages ranged from 22 to 25 years) were recruited in this study. Prior to participation, all subjects provided written informed consent. They were also screened to assure their safety and compatibility with MRI recording and eliminate those with history of head trauma, chronic pain, psychiatric and neurological disorders, or other serious illness within 1 month.

2.2. Experimental Design. Each subject was trained to express his feelings about *deqi* correctly and clearly through acupuncturing at right Zusanli (ST36). If the subject rated at least one of single sensation (except sharp pain) at 4 (moderate intensity) or greater using a 10-points visual analogue scale (VAS), he would be included. Then at least 24 hours later, every included participant received two separate fMRI scans which were required in DQ or LA group, respectively. In DQ group, the subjects received fMRI scan and acupuncture stimulation simultaneously. In LA group, they underwent local anesthesia at ST36 firstly, then received scan and acupuncture intervention 5 min later. The two scans were randomly given at least 6 hours intervals. During the scanning, all subjects were instructed to keep supine position, head motionless, and eyes closed; soundproof earplugs were used to block noise. After each scan run, they were asked to finish a sensory questionnaire regarding the type and intensity of feelings they experienced during the scan. All acupuncture manipulations were performed by the same licensed acupuncturist.

2.2.1. Acupuncture Procedures. In both DQ and LA group, the acupuncture intervention was employed at right Zusanli (ST36) by perpendicularly inserting 20 mm deep with sterilized disposable stainless steel acupuncture needles (0.25 × 40 mm, Suzhou Medical Supplies Factory Co. Ltd. China). The entire stimulating process lasted for 8 minutes. During 8 minutes, ON and OFF two states were designed and each total duration was 3 and 5 minutes, respectively (Figure 1). In the ON state, the inserted needle was rotated with moderate reinforcing and reducing method (twisting 60 times/min) for 1 min to generate *deqi*, while in the OFF state, the inserted needle was retained into the ST36 without rotation.

2.2.2. Local Anesthesia Intervention. The local anesthesia at ST 36 was carried out to the subcutaneous depth of 20 mm by infiltrating with 2 mL (5 mL : 0.1 g) lidocaine.

2.2.3. deqi Measurement. After removing the needle, subjects were asked to quantify their stimulating sensations including soreness, numbness, heaviness, fullness, dull or sharp pain, warmth, and coolness by VAS. The VAS was scaled as follows: 0: no sensation; 1–3: mild; 4–6: moderate; 7-8: strong; 9: severe; 10: unbearable. In DQ group, only subjects that rated at least one of the single sensations (except sharp pain) at 4 or greater were enrolled. Only subjects that rated each single sensation less than 1 were included in LA group.

2.2.4. fMRI Scanning and Analysis. Imaging data were collected from a 3T Siemens scanner (Allegra, Siemens Medical System) at the Huaxi MR Research Center, West China Hospital of Sichuan University, Chengdu, China. A standard birdcage head coil was used, along with restraining foam pads to minimize head motion and diminish scanner noise. Thirty axial slices (FOV = 240 mm × 240 mm, matrix = 64 × 64, thickness = 5 mm) parallel to the AC-PC plane covering the whole brain were obtained using a T2∗-weighted single-shot, gradient-recalled echo planar imaging (EPI) sequence (TR = 2,000 ms, TE = 30 ms, flip angle = 90°). The scan covered the entire brain including the cerebellum and brainstem. After the functional run, high-resolution structural information on each subject was acquired using 3D MRI sequences with a voxel size of 1 mm^3 for anatomical localization (TR = 2.7 s, TE = 3.39 ms, matrix = 256 × 256, FOV = 256 mm × 256 mm, flip angle = 7°, in-plane resolution = 1 mm × 1 mm, slice thickness = 1 mm).

Preprocessing and statistical analysis were performed using the Statistical Parametric Mapping software (SPM5, http://www.fil.ion.ucl.ac.uk/spm). Preprocessing of the functional images was composed of the following steps: dropping the first 5 time points; slice time correction; and three-dimensional motion correction. Then spatially smoothed was performed using a 6 mm full-width-at-half maximum (FWHM). After that, the time-series from each voxel was high-pass filtered (1/235-Hz cutoff). Subsequently, the preprocessed fMRI data for each subject was submitted for fixed-effects model analyses using the general linear model (GLM) performed at each voxel across the whole brain. After acquiring the contrast images, individual level analyses were accomplished and statistical parametric maps for the t statistics (spmT) were generated for each contrast image. At the group level, the random-effects model analysis was performed based on inference images (i.e., t-test for contrast images) from the individual level analysis. The group results of one sample t-test for each group were listed at $P < 0.05$, FWE (the DQ group $|t| > 6.14$, the LA group $|t| > 5.86$), and a minimum cluster size of 5 voxels. The different BOLD responses between the DQ group and the LA group were explored in 20 subjects (self-control) based on a paired t-test at $P < 0.0001$, uncorrected ($|t| > 4.16$), and a minimum cluster size of 5 voxels. Then, the significant regions of the paired t-test were defined as the regions of interests (ROIs). In each ROI, the BOLD response changes were extracted and correlated with the *deqi* score changes of the subjects who were included in paired t-test.

3. Results

Of 40 recruited volunteers, 5 subjects were eliminated because of slight *deqi* sensations (all the *deqi* scores less than 4) in training experiment. Consequently, 35 volunteers participated in the following scans. During scanning process, 4 subjects were also eliminated because of slight needling sensations in DQ group and 5 subjects were eliminated due to some degree of sensation retaining (one of the single *deqi* score more than 1) in LA group. When performing the

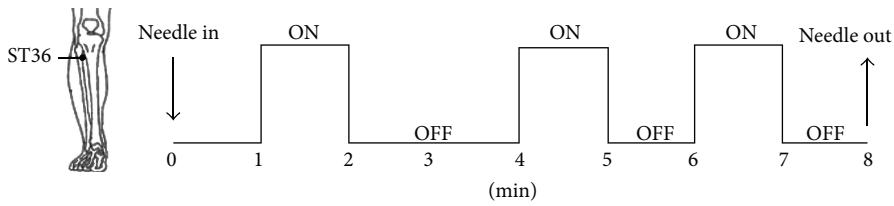

Figure 1: Experimental paradigm of acupuncture run.

Table 1: Differences of *deqi* sensation VAS scores between DQ group and LA group.

deqi sensation	DQ group		LA group		Decreased ratio (%)
	Mean ± SD	95% CI	Mean ± SD	95% CI	
Sourness	2.96 ± 2.64	1.92–4.01	0.17 ± 0.43	0.01–0.34	94
Numbness	2.29 ± 2.55	1.28–3.30	0.08 ± 0.30	−0.03–0.20	96
Fullness	6.23 ± 1.89	5.48–6.98	0.46 ± 0.57	0.24–0.68	92
Spread	3.26 ± 2.78	2.16–4.36	0.12 ± 0.34	−0.01–0.25	96
Dull pain	1.46 ± 2.55	0.45–2.47	0.02 ± 0.08	−0.01–0.05	98
Sharp pain	1.16 ± 1.37	0.62–1.70	0.03 ± 0.12	−0.01–0.08	97
Coolness	—	—	0.07 ± 0.26	−0.03–0.17	—
Warmth	0.096 ± 0.50	−0.10–0.29	—	—	—

VAS: visual analogue scale; SD: standard deviation; CI: confidence interval.

data analysis, 4 subjects in DQ group and 2 subjects in LA group were excluded because larger amount of head motion had happened during scanning. Finally, 27 subjects and 28 subjects were, respectively, included in DQ group and LA group; 20 subjects in both DQ group and LA group were involved as self-control.

3.1. The deqi Scores Were Reduced by Local Anesthesia at ST36. The average scores of *deqi* sensations in each group are as follows (Table 1). The score of coolness in DQ group and warmth in LA group did not conform to normal distribution. Except coolness and warmth, other sensations were significantly reduced more than 90 percent by local anesthesia.

3.2. The Brain Responses Were Deleted by Local Anesthesia at ST36. Figure 2(a) showed group activations and deactivations of the DQ group evoked by acupuncture stimulation at ST36. The remarkable activated areas included bilateral inferior frontal gyrus (IFG), precentral gyrus (primary motor area, M1, supplementary motor area, SMA), postcentral gyrus (S1), inferior parietal lobule (IPL), thalamus, insula, anterior cingulate gyrus (ACC), claustrum, putamen, superior temporal gyrus (STG), midbrain and cerebellum, ipsilateral (right) transverse temporal gyrus (TTG), and contralateral (left) middle frontal gyrus (MFG) (FWE, $P < 0.05$) (Table 2). Based on this threshold, no deactivated areas were found.

Figure 2(b) showed the brain responses which were deleted by local anesthesia. Under this condition, only contralateral cerebellum was activated (FWE, $P < 0.05$). It was interesting to note that at group level few regions responding to acupuncture stimulation were found, but at individual level lots of BOLD signal intensity changes displayed. Considering the possibility that different *deqi* intensity elicited different cortical activation, we divided the LA group into three subgroups based on the sum score of *deqi* (non-*deqi* group: 10 subjects, averaged sum score of *deqi* was 0; *deqi* group A: 9 subjects, averaged sum score of *deqi* was 0.81 ± 0.29; *deqi* group B: 9 subjects, averaged sum score of *deqi* was 2.17 ± 0.47). We found no different activation between the intersubgroup results using t-test ($P > 0.01$, uncorrected for all voxels, figure not shown).

Figure 2(c) presented results between these two groups. Controlling for BOLD response to LA group, we found that increased *deqi* sensations were associated with activation in bilateral S1, insula, ipsilateral IFG, IPL, claustrum, and contralateral ACC ($P < 0.0001$, uncorrected) (Table 2). No obvious difference was demonstrated between the deactivated regions of the two groups. All of these activated areas were defined as ROIs, and each ROI BOLD response changes had no significant correlations with each single sensation score changes or sum score changes of *deqi* between the two groups ($P > 0.01$, figure not shown).

4. Discussion

To our knowledge, this study was the first to establish the non-*deqi* control using lidocaine anesthesia at the acupuncture point ST36. Although the data (Table 1) showed us more than 90 percent other than 100% of *deqi* sensations were inhibited, it still should be able to provide a strong evidence

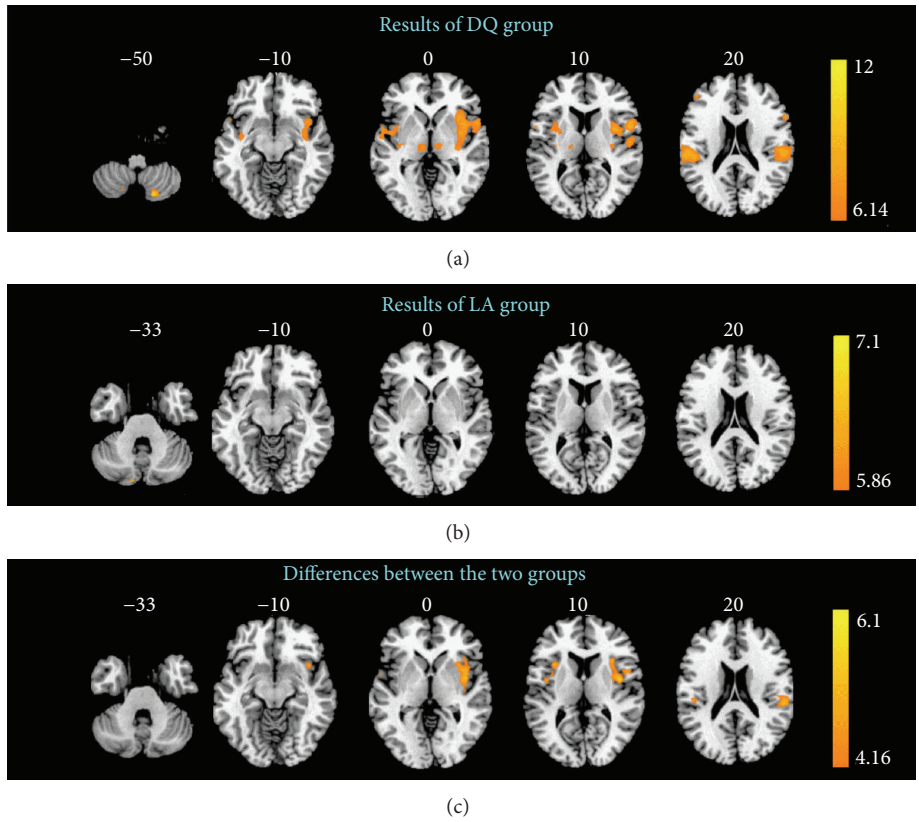

Figure 2: Group-level BOLD responses for both (a) DQ and (b) LA groups ($P < 0.05$, FWE) and (c) the differences between them ($P < 0.0001$, uncorrected).

for supporting that lidocaine anesthesia at the acupuncture point would be a promising approach for non-*deqi* control because all responding brain regions seen in DQ group (Figure 2(a)) disappeared in LA group (Figure 2(b)). In other words, retaining intensity of *deqi* is not efficient to give rise to brain response. In view of brain response to *deqi*, lidocaine anesthesia at acupoint would be an alternative to be used as a new non-*deqi* control.

By means of this control, we found that the activated brain regions were bilateral S1, insula, ipsilateral IFG, IPL, claustrum, and contralateral ACC (Figure 2(c)). These results were quite different from those in previous studies. In this study, the number of activated brain regions was remarkably reduced. However, more activated brain areas including the secondary somatosensory cortex (S2), the cerebellum, the thalamus, the primary motor cortex (M1), the superior temporal gyrus (STG), the visual cortices, the premotor and supplementary motor cortex ((pre)SMA), the basal ganglia, and the medial temporal gyrus (MTG) could be found to be activated in previous studies [29, 30, 39, 40] apart from those activated brain areas in our study. To some degree, current activated brain areas (bilateral S1, insula, ipsilateral IFG, IPL, claustrum and contralateral ACC) might be regarded as the net activated brain regions response to *deqi*, which dominantly associated with sensory and emotion. It also implied that the components of *deqi* mainly include perception and emotion.

However, it needs to perform more to confirm the results with more considerations. Firstly, except applying VAS as a tool to evaluate *deqi*, we should choose more different scales to evaluate *deqi*. Additionally, the sensations of *deqi* would be felt by operator and subjects at the same time based on traditional concepts of acupuncture. So,what would happen at operator's side after local anesthesia administering at acupoint is also waiting for more researches to be carried out.

5. Conclusions

The application of local anesthesia at ST36 is able to block most of the *deqi* feelings and inhibit brain responses to *deqi*, which would be a potential and promising approach for non-*deqi* control. Bilateral S1, insula, ipsilateral IFG, IPL, claustrum, and contralateral ACC might be the key brain regions responding to *deqi*.

Conflict of Interests

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

Table 2: Significant BOLD response changes of DQ group and intergroup.

Regions	BA		DQ group ($P < 0.05$, FWE)					DQ versus LA ($P < 0.0001$, uncorr.)				
			Talairach			t	Voxels	Talairach			t	Voxels
			x	y	z			x	y	z		
Inferior frontal gyrus	9/47	L	−56	13	30	7.89	7					
		R	59	15	16	7.77	30	45	14	−3	5.08	13
Middle frontal gyrus	46	L	−42	45	23	7.92	16					
Precentral gyrus	4/6	L	−56	6	11	6.56	6					
		R	53	12	8	8.19	21					
Postcentral gyrus	2/40	L	−59	−25	18	9.47	50	−56	−21	43	4.68	5
		R	53	−25	21	8.28	48	56	−28	21	5.38	21
Inferior parietal lobule	40	L	−65	−31	29	10.05	56					
		R	62	−28	29	9.86	49	53	−28	24	4.88	7
Thalamus		L	−6	−17	4	7.80	47					
		R	6	−17	6	7.34	37					
Insula	13/40	L	−48	−28	18	8.94	43	−33	15	10	4.75	10
		R	42	8	−5	8.60	79	42	−2	8	5.77	53
Claustrum		L	−33	6	5	7.05	9					
		R	36	0	3	8.74	26	33	12	2	5.16	17
Anterior cingulate gyrus	24/32	L	−3	2	41	6.45	5	−6	2	39	4.65	6
		R	3	2	44	6.82	7					
Putamen		L	−27	0	8	6.52	7					
		R	30	−17	6	7.71	19					
Superior temporal gyrus	22/38	L	−59	−28	15	7.92	35					
		R	53	−11	9	8.20	34					
Transverse temporal gyrus	41/42	R	53	−17	12	6.93	5					
Midbrain		L	−9	−18	−2	6.77	10					
Cerebellum	Posterior	L	−18	−66	−40	6.50	6					
		R	18	−75	−39	11.50	40					

Note: the coordination of voxel with the maximal t within each region is listed.

Authors' Contribution

Ling-min Jin and Cai-Juan Qin contributed equally to this work.

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Research Article

An Exploratory Survey of *Deqi* Sensation from the Views and Experiences of Chinese Patients and Acupuncturists

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Deqi sensation is believed to be important in clinical efficacy according to TCM theory. The measuring method of *Deqi* sensation has significant implications for the result of research trials. This study makes an investigation on acupuncture-experienced patients and expert acupuncturists in China and aims to find out the patient's needling sensations and acupuncturist's sensations which can be acceptable as descriptors of *Deqi* sensation, so as to provide foundation for more systematic and sensitive quantitative evaluation method of *Deqi* sensation. Results of this survey indicated that the *Deqi* sensation noted by both patient and acupuncturist is equally important to the treatment efficacy. It is found that there are some differences between the patients' real-life experience and the acupuncturists' expectations on patients' *Deqi* sensation. The "dull pain," "aching," "sore," "numb," "distended," "heavy," "electric," "throbbing," "warmness," "coolness," "spreading," and "radiating" can be considered as the main manifestations of *Deqi* sensations. The acupuncturists believed that *Deqi* sensations were mainly "pulling," "tight," and "throbbing." We suggest developing a questionnaire measuring the *Deqi* sensations which includes both the sensations of the patient and acupuncturist, and this would be very important and necessary for a better understanding of the relationship between *Deqi* sensation and acupuncture effects in future studies.

1. Introduction

Deqi, which first appeared in the "*Huang Di Nei Jing*," refers to the reaction of movement of qi (vital energy) of the human body when acupuncture needles are inserted into acupoints. It is believed that *Deqi* was closely related to the treatment efficacy. In clinic, *Deqi* is mainly testified by needle sensation, which includes the patients' sensations and the acupuncturists' sensations. The patient's needle sensations mainly include sour, numb, swelling, heavy, pain, hot, cold, and the complex feeling and spreading based on these feelings; when the patients have those needling sensations, the acupuncturist can also feel heavy, tense, or needle stuck, or needle tremor [1–3]. The central mechanism of *Deqi* has been partly explored in some studies [4–9], but it does not have a well understanding. Preliminary findings suggest that *Deqi* may be an important factor of acupuncture analgesia [10–12]. Measuring the patients' *Deqi* sensation by using the international scale was originated from the end of the 1980s [13]. In recent years, in order to effectively improve the quality of acupuncture research on *Deqi*, quantitative measurement of *Deqi* attracts increasing attention. The representative scales include the MASS scale compiled by Kong et al. (the MGH Acupuncture Sensation Scale) [14] and the Southampton

Needle Sensation Questionnaire written by White et al. [15]. In addition, some investigators developed scales in Korean [16]. Yu et al. have found that the Chinese version of MASS has good repeatability and internal consistency [17]. However, a standardized, valid, and reliable scale for quantitatively measuring the "*Deqi*" is still lacking.

In traditional acupuncture, the acupuncturists must pay attention to eliciting and controlling of *Deqi*. However, modern evaluation tools for *Deqi* and its related studies all ignore the acupuncturists' sensations. By taking a systematic investigation of the ancient and modern literature, we found that the current evaluation tools can be further improved based on well understanding of *Deqi*'s connotation. In order to develop a validated method to measure the *Deqi*, we performed a descriptive survey with the following three specific aims: (1) understanding Chinese patients' and acupuncturists' attitudes and beliefs on acupuncture sensations and *Deqi*, (2) exploring the influence factors of *Deqi* and the effect of *Deqi* on acupuncture treatment efficacy, (3) summarizing the patients' *Deqi* sensations reported by patients and senior acupuncturists, and (4) investigating the acupuncturist's perceptions on *Deqi*.

In China, the health care system includes both modern medicine and TCM. As acupuncture is very popular in China, *Deqi* sensations in an acupuncture treatment session are widely accepted by the majority of Chinese patients. Some patients even require obtaining the needling sensations or some other special acupuncture feelings on their own initiative [18]. The patients' attitude towards *Deqi* sensation was significant different between Chinese patients and those from the US [19]. So in this study, we investigated individual patients' experiences in an actual clinical setting and then consulted expert acupuncturists who have rich clinical experience. The survey is made by observing a homogeneous population undergoing the same style of TCM.

2. Methods

2.1. Survey Development. Prior to the formal investigation, a structured interview was setup through a literature review involving both ancient and modern, Chinese and English, and then the terms frequently used for describing the patients' and acupuncturists' perception on *Deqi* were collected. The Chinese literature includes the ancient books, modern acupuncture text books, and the published articles related to *Deqi*. The English literature includes the questionnaires of *Deqi*, or needle sensation, and scales used for measuring *Deqi* [13–16, 20, 21] and its related investigations [19, 22, 23]. The terms in the lists from the English literature were translated by two translators, respectively. We unified the terms that own the same meaning in Chinese but with different expressions in English, such as the terms "stretch," "expansion," "distention," and "fullness," usually appearing in the English literature, are all translated into "*Zhang*" (fullness/distention) in Chinese, and then we used the item "distention" in English in this paper.

The draft questionnaires were developed based on the interview with four doctoral candidates and four experts with senior professional titles from the School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine. These experts and doctoral candidates have rich experience in administrating acupuncture and being treated with acupuncture. Then, two expert acupuncturists and five patients completed the draft questionnaires. We also interviewed them regarding their opinions on using the questionnaires and modified the draft according to their comments. The major modifications for patient's questionnaire include making a detailed and more clear explanation to distinguish the similar items such as "pulling" and "tight," "spreading" and "radiating." In the options of the question "which terms can describe the *Deqi* sensations of the patients?" some additional interpretations have been added for the terms that may be puzzled to common patients. For example, "dull pain" is interpreted as "mild, moderate or minor pain without a strong inimical feeling," "sharp pain" is interpreted as "a severe pain with a sense of injury," "twinge" as "an unbearable pain with the highest intensity," "pain" as "a pain unable to clarify its nature." In the questionnaire for the acupuncturists, the questions of "spreading distance" and "the direction of spreading" of needling sensation were added.

Finally, the second presurvey was conducted through the interview on another six acupuncture-experienced undergraduates who were not majored in medicine. No modification was made in the first interview. After one week, we altered the order of the questions and conducted the interview for the same subjects again. The results were consistent with those obtained in the first interview.

2.2. Survey Content. There are two types of questionnaires, one is for the patients and the other is for the expert acupuncturists, which are completed by the patients and the experts, respectively.

The patient's questionnaire contained two parts and one open-ended question. Part 1 includes four single choice questions on the patients' perception of *Deqi*. Part 2 includes questions about the patient's sensations experienced during acupuncture administration. There are two phases in part 2. Phase 1 involves questions mainly asking about the patients' needling sensations. Twenty-six terms are separated into four categories: pain, temperature, sensation spreading, and others. One supplementary blank was at the end for subjects to describe sensations in their own words. Phase 2 includes three questions asking about the patients' emotions during acupuncture. An open-ended question is added at the end, "What is your impression on *Deqi*?"

There are also two parts and one open-ended question in the questionnaire for the experts. It includes some questions in the questionnaire for the patients in order to get experts' perceptions on *Deqi* sensation of patients based on their clinical experience. Part 1 includes five multiple choice questions and three single choice questions regarding the understanding of *Deqi* by the experts. The questions in part 2 aimed to inquire expert's perceptions on needling sensations of the patient (the same questions in patient's questionnaire) and sensations felt by expert's needling hand. An open-ended question is added at the end, "What are your opinions on this questionnaire of *Deqi*?"

2.3. Administration. As the *Deqi* occurrence rate in Chinese clinical trials is 100% [24], it is hard to calculate the sample of the subjects. According to the suggestions of the experts, we performed a survey to 40 acupuncturists with senior professional titles and 40 patients, respectively. The survey was conducted in the Beijing TCM Hospital affiliated to Capital Medical University, Huguosi TCM Hospital, and Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine in April 2012. All patients could complete the questionnaire by themselves. All questionnaires were completed by those patients and acupuncturists independently. All investigators have been trained before the investigation. The acupuncturists and patients were reminded that this questionnaire is related to the *Deqi* sensation only deriving from manual acupuncture with filiform needles (as there are varieties of needles in Chinese clinical treatments). The investigators tried to not disturb the subjects during completing the questionnaires and answered any questions of the subjects in a unified way. Only when the investigators found some missed questions or apparently contradictory options, they would take some necessary reminding.

2.4. Statistical Analysis. The questionnaire data was independently collected by two persons. We made a statistics after verification and amending. Descriptive statistics were performed by using the computer and presented by percent (%).

When inputting the data, we combined some terms which describe similar sensations, such as "warm" and "burnt," considered to be a different degree of "warm," are merged into "warm," "cool" and "cold" are merged in to "cool."

Types of patients' needling sensations perceived by patients and understood by acupuncturists were compared using chi-square analysis. Chi-square analysis and Fisher's exact test (when appropriate) were then performed to explore the effect of expressing by patients and acupuncturists on types of patients' acupuncture sensations. A level of $P < 0.05$ was determined to be of statistical significance, and all analyses were two-sided. Statistical analysis was performed using SPSS Statistics 17.0.

3. Results

3.1. Participants. A total of 40 patients participated in this survey; 70% of them were men, with an average age of 60.2 years old. Each of them had prior acupuncture experience, and 83% of the respondents had more than 10 times acupuncture treatment experiences. When needles are insert, 58% of the patients stated that they achieved needle sensations in each treatment, while the others always (22%) or occasionally (20%) have such feelings, and nobody stated that they had never had such feeling. Forty acupuncturists participated in this survey; 65% were women, with the average age of 48.5 and working time of 20.7 years.

3.2. The Patients' Attitudes and Beliefs towards Deqi. In this study, nearly 70% of the patients never heard of "*Deqi*." Among the patients who know about *Deqi*, four thought that *Deqi* is a sensation during acupuncture, one thought that *Deqi* meant the channels were unblocked, and three of them cannot explain the specific meaning. 85% of the patients expected to have the needle sensations upon the treatment, and only one did not expect to have needling sensation. About 90% of the patients thought needling sensation is closely related to the treatment efficacy, and others did not know their relationship. About 58% of the respondents said that the acupuncturist will ask them about their needle sensations during every acupuncture treatment session. Nearly 40% of the patients said that they were always asked by their acupuncturists. The patients in this study all have been asked about their needling sensation by their acupuncturists during the treatment, as shown in Table 1.

Table 1: Patients' attitudes and beliefs about acupuncture sensation (*Deqi*).

Questions	Attitudes and beliefs	Number/%
Have you heard of *Deqi*?	Have heard	12/30%
	Never	28/70%
Do you expect to have needling sensation during acupuncture administration?	Expected	34/85%
	Dispensable	5/12.5%
	Try to avoid	1/2.5%
	Hate	0/0%
Have your acupuncturists asked you about your needling sensations?	Every time	23/57.5%
	Often	16/40%
	Seldom	1/2.5%
	Never	0/0%
Do you think needling sensation is close to the acupuncture treatment efficacy?	Yes	36/90%
	No	0/0%
	Not sure	4/10%

3.3. The Acupuncturists' Understanding about Deqi. In this study, 95% of the acupuncturists in China thought that "*Deqi*" should be elicited in the treatment, while others thought the treatment without needling sensation can also achieve the efficacy. Some experts said that needling sensation could not be elicited in every point due to limitation of treatment time. They said that the patients expected to get a stronger needling sensation, which is inconsistent with the results concluded from the questionnaires for the patients.

Most acupuncturists (90%) held that acupuncturists sensations felt by their needling hand and the needling sensations of the patients are the typical characteristics of *Deqi*. Compared to the acupuncturists, the patients are more easily to get needling sensation. In this study, all of the acupuncturists believed that the sensations of the acupuncturists can be a sign of *Deqi*.

About 73% of acupuncturists thought that *Deqi* sensation is related to the treatment efficacy, but only 38% of them thought that the symptoms can be relieved immediately. Most acupuncturists believed that the patients' sense of *Deqi* and the acupuncturists sensations are equally important to the treatment efficacy, as shown in Table 2.

Table 2: Acupuncturists' understanding about *Deqi*.

Questions	Understanding	Number/%
Do you expect to get *Deqi* sensation in the acupuncture treatment?	Yes	38/95%
	No	1/2.5%
	Do not care	1/2.5%
Do your patients expect to get *Deqi* sensation in the acupuncture treatment?	Expected	29/72.5%
	Dispensable	9/22.5%
	Try to avoid	0/0%
	Very fear	0/0%
	Not sure	1/2.5%
What do you think are the signs of *Deqi*?	Patients needle sensation	36/90%
	Acupuncturists experiencing sensations	39/97.5%
	Muscle throbbing	20/50%
	Immediate relief	15/37.5%
Which are more likely to occur, the patients needle sensations or the acupuncturists sensations?	Acupuncturists experiencing sensations	11/27.5%
	Patients needle sensations	20/50%
	At the same time	9/22.5%
Do you think the *Deqi* sensation is related to the clinical efficacy?	Has	29/72.5%
	No	1/2.5%
	Not sure	10/25%
Between the acupuncturists sensations and the patients needle sensation, which do you think is more relevant to its efficacy?	Acupuncturists experiencing sensations	8/20%
	Patients needle sensations	13/35%
	With same significance	18/45%
	Not related	1/2.5%

Table 3: Types of patients' *Deqi* sensation.

Sensation	Experienced by patients %	Considered by acupuncturists %	*P* value
Related to pain	92.5%	97.5%	0.608
Dull pain	47.5%	60%	0.262
Shape pain	10%	2.5%	0.356
Twinge	5%	2.5%	1.000
Deep pain	17.5%	30%	1.000
Superficial pain	27.5%	20%	0.284
Pricking	32.5%	7.5%	0.005
Throbbing pain	12.5%	10%	1.000
Aching	65%	85%	0.039
Pain	10%	0	0.124
Related to temperature	25%	92.5%	0.000
Warmness	45%	92.5%	0.000
Burning	2.5%	12.5%	0.203
Coolness	2.5%	47.5%	0.000
Other feelings			
Penetrating	17.5%	10%	0.330
Sore	60%	87.5%	0.005
Numb	47.5%	75%	0.012
Distended	72.5%	85%	0.172
Heavy	12.5%	77.5%	0.000
Pressure	2.5%	30%	0.001
Pinch	2.5%	7.5%	0.608
Pulling	17.5%	37.5%	0.045
Tight	7.5%	30%	0.010
Electric	42.5%	50%	0.501
Formicating	10%	22.5%	0.130
Throbbing	42.5%	45%	0.491
Related to spreading	72.5%	100%	0.000
Spreading	60%	82.5%	0.026
Radiating	17.5%	57.5%	0.000

Regarding the relationship between *Deqi* sensation and treatment efficacy, most acupuncturists thought that the efficacy is closely related to the existence of *Deqi* sensation (87%), the realization of qi spreading to the affected parts (47%), and the intensity of *Deqi* sensation (37%). In addition, one-third of the acupuncturists thought that the time for inducing *Deqi* sensation and the direction of sensation spreading may affect the efficacy. Only a few patients thought that the lasting time of *Deqi* sensation (11%) and what kind of sensation (8%) may affect the efficacy.

In addition, the acupuncturists held that the acupoint location (87.5%), point selection (82.5%), and the acupuncture manipulation (90%) are the three key elements in acupuncture. The physiques of the patients (80%), acupuncturist's needling skill (67.5%), needle depth (60%), the thickness of needle (57.5%), the type of disease (45%), the patient's emotional and psychological states (40%), acupoints selection (35%), needle inserting site (35%), needle retention time (22.5%), season while needling (25%), and time of acupuncture administration (15%) may all affect the efficacy.

3.4. The Patients' Perceptions of Deqi Sensation. The most common acupuncture sensations reported as experienced by patients were "distended" (72.5%), "aching" (65%), "sore" (60%), those "spreading" (60%), and, reported as considered by acupuncturists were "warmness" (92.5%), "sore" (87.5%), "aching" (85%), "distended" (85%), and "spreading" (82.5%), as shown in Table 3.

In this survey, 82.5% of the patients believed that *Deqi* sensation is not harmful in the treatment. However, nearly half of the patients considered that *Deqi* sensation is tolerable; none of them felt *Deqi* cannot be tolerated. Half of the respondents stated that *Deqi* sensation is comfortable. Some patients indicated that *Deqi* is just a series of sensations; they do not care whether it is comfortable or not, as shown in Table 4.

Table 4: Patients' affections about *Deqi* sensation.

Questions	Affections	Number/%
What do you think of needle sensation/*Deqi* in the treatment?	Harmful	1/2.5%
	No harm	33/82.5%
	Unknown	6/15%
What do you think of *Deqi* sensation?	Negligible	4/10%
	Gentle	21/52.5%
	Strong	7/17.5%
	Unbearable	0/0%
	Sometimes strong, sometimes weak	7/17.5%
What is your usual perception of *Deqi* sensation?	Comfortable	20/50%
	Uncomfortable	0/0%
	Does not matter	20/50%

3.5. The Relationship between Patients' Experience and Acupuncturists' Consideration of Deqi Sensation. In this study, we not only asked patients to select the terms on behalf of the needle sensation, but also invited some expert acupuncturists to filter them. It showed that there are no statistical differences among the 14 descriptors of the all 26 descriptors ($P > 0.05$). However, there are some differences between the patients' real-life experience and the acupuncturists' expectations among the others, as shown in Table 3.

As long as the patients or acupuncturists select one option among the feelings in the same category, it will be considered to select this kind of feeling in statistics. After comparison, it is found that there is no significant difference between the patients and acupuncturists in selecting the pain related feeling ($P > 0.05$), which indicated that the majority of patients and acupuncturists believed that *Deqi* sensation is associated with pain.

There are significant differences between patients and acupuncturists in selecting the temperature feel and feeling spreading ($P = 0.000$), which suggested that patients actually feel the temperature changes and needling sensation spreading occurred less than the acupuncturists' expectation.

There are no differences between the "dull pain," "distended," "electric," and "throbbing" between two groups of subjects ($P > 0.05$). All of these sensations are selected by more than half of the patients and acupuncturists, indicating that the feelings are thought to present signs of *Deqi* sensations.

Referring to the terms "sharp pain," "twinge," "throbbing pain," "burning," "penetrating," "formicating," their supporting rate has no statistical difference between the two groups ($P > 0.05$). Moreover, all are below 20%, indicating that these feelings mentioned above are not the typical *Deqi* sensations. One-third of the patients selected "pricking" significantly higher than the selection rate of acupuncturists ($P = 0.005$).

3.6. The Acupuncturists' Experience of Needle Grasping Sensation. The most common sensations reported by acupuncturists were "pulling" (95%), which was described as "as a fish biting the hook" in ancient books, and "tight" (70%) as shown in Table 5.

Table 5: Types of acupuncturists experiencing sensation.

Sensation	Experienced by acupuncturists %
Pulling/heavy/like a fish biting the hook	38/95%
Tight	28/70%
Throbbing	6/15%
Opposable	1/2.5%

4. Discussion

4.1. The Choice of the Respondents. One purpose of this survey is to filter the descriptors of the patients' *Deqi* sensation and the acupuncturists' sensations, so as to develop proper clinical evaluation questionnaires on *Deqi*. So it is expected to select acupuncture-experienced subjects, especially those patients who already recognized the *Deqi* sensation. This study is different from some previous studies which selected naive volunteers without any acupuncture experience as their subjects [13, 14, 22]. It has been reported that acupuncture not only benefits the chronic pain [25, 26], but also can be an effective adjunctive treatment for facilitating stroke rehabilitation [27, 28]; therefore, acupuncture is widely used for facilitating stroke rehabilitation in China [29, 30].

The long treatment course and large amount of stimulation in this treatment are particularly in consistent with the requirements of this survey. So in this study, we selected the patients from three outpatient acupuncture clinics of Beijing TCM hospitals for the survey. 70% of the respondents suffered from apoplexy and the others from facial paralysis, trauma, headache, low back pain, and gastrohelcoma. More than 80% of these patients have received more than 10 sessions of acupuncture treatment. They had more experiences in perceiving *Deqi* sensation and could rule out the needle sensations by accident. Compared with the respondents in experimental models, a survey based on these respondents may reflect the real phenomena of *Deqi* sensation in the real world clinical setting.

4.2. The Chinese Patients' and Acupuncturists' Attitudes of Deqi. The majority of the patients thought that needling sensations are related to the treatment efficacy and excepted to experience these sensations in the treatment. Nearly half of the patients thought *Deqi* is comfortable. Although some patients may have felt uncomfortable sometimes, they also thought it is not harmful. Our result is consistent with Mao's et al. result [31]. Regarding the open-ended questions, two patients said that eliciting the *Deqi* sensations indicated that the acupuncturist had good needling skills.

In this survey, three quarters of the 40 experts thought *Deqi* sensation is closely related to the treatment efficacy. Although 25% of the acupuncturists were not sure about the relationship between *Deqi* sensation and treatment efficacy, they still excepted to elicit the *Deqi* sensation in clinical.

It may be influenced by the acupuncture education and the demands of the patients. Only one acupuncturist thought *Deqi* sensation is not related to treatment efficacy. So it is obviously shown that the acupuncturists and patients, especially the patients who suffered more severe diseases, are eager to achieve *Deqi* sensation and highly expected its influence on efficacy.

4.3. The Patients' Deqi Sensation. This survey was a retrospective study, which filtered the terms to describe patient's *Deqi* sensations based on their memories. 92.5% of patients reported at least one pain related term. There are three terms used to describe the intensity of pain, "dull pain," "sharp pain," and "twinge." Half of the patients chose dull pain, four of them chose sharp pain and dull pain, and one patient chose dull pain and twinge at the same time as the twinge occasionally occurred and it is difficult to distinguish them. Although most patients cannot distinguish pain and *Deqi* sensation, "dull pain" is widely accepted to be one of the *Deqi* sensations. In two terms of "deep pain" and "skin pain" associated with location of pain, more patients chose skin pain, indicating that the patients may have an incorrect understanding of *Deqi* sensation. *Deqi* sensation is the needle sensation when the needle was inserted into the acupoints with a certain depth, which pointed out that the pain caused by skin penetrating during needle inserting should be distinguished so as to avoid confusion of the skin pain and *Deqi* sensation. Among the twenty-six terms for needle sensations in this questionnaire, "fullness" was the most common sensation (72.5%), followed by the "aching" (65%) and "sore" (60%); approximately half of the patients selected "dull pain," "numb," "spreading," which can be considered as the characteristics of *Deqi* sensations.

In previous studies of filtering *Deqi* sensation terms, the investigated objects include both patients and acupuncturists [13, 14, 20, 22, 23]. This survey is quite different from previous studies. We filtered the terms of *Deqi* sensations by the patients and expert acupuncturists in the same hospital at the same time. After comparing, it is found that there exist some differences between the real-life experiences of patients and acupuncturists' expectation.

It was found that there are no significant differences between the patients (92.5%) and acupuncturists (97.5%) in selecting the pain related terms ($P > 0.05$), suggesting that both of them believe that *Deqi* sensation is associated with pain. There are experimental studies that confirmed that the basic material for generating acupuncture needles sensation is mainly the pain receptors located in the acupoints with a depth [32, 33]. The dull pain, aching, sore, and distended sensation is consistent with its reflection in brain [34], so it showed that *Deqi* and pain cannot be completely separated in physiology.

There are much more acupuncturists (92.5%) selecting the temperature related sensation than the patients (25%) ($P = 0.000$). It suggests that patients actually rarely feel the temperature changes during acupuncture than the acupuncturist expected. A lot of heat- or cold-inducing needling manipulations recorded in acupuncture classics may be the reason that most acupuncturists tend to choose the warm feeling as the sign of *Deqi* (92.5%). Although the sense of cool is usually mentioned in the literature, but only 47.5% acupuncturists had successfully elicited a sense of cool and achieved a better efficacy at the same time. (This might be caused by the types of diseases, and the cool sensation is more difficult to be elicited.) As there is only 1 patient who had experienced such feeling, significant differences existed between the two groups ($P = 0.000$). However, we believed that the difference was just due to the small sample in this survey.

Although it has a significant statistical difference ($P = 0.000$) between the patients (72.5%) and acupuncturists (100%) in selecting the sensation spreading ($P = 0.000$), the choosing rates of the two groups of people are relatively high, which means that propagated sensation along channel is also one of the typical manifestations of *Deqi* sensations.

Among the twenty-six terms, "dull pain," "sore," "aching," "numb," "distended," "electric," "warmness," and "spreading," their supporting rate reached 50% or above, and these feelings are the common feelings appearing in *Deqi* sensation. However, the supporting rate of "sharp pain," "twinge," "throbbing pain," "burning," "penetrating," and "formicating" were below 20%, indicating that these are not the typical signs of *Deqi* sensations.

About 1/3 of the patients chose the "sting" significantly higher than the choice rate of the acupuncturists ($P = 0.005$). The terms "pricking" and "stinging" occurring rate is above 60% among the young females, which is nearly one time higher than the 32.5% in this study [22]. It obviously showed that pricking always appeared accompanied with *Deqi* sensations, but most acupuncturists thought that pricking is only a feeling during needle inserting and does not belong to *Deqi* sensation [13, 34–37]. Recently, it has been found that pricking pain is not commonly regarded as *Deqi* sensation, so the acupuncturists should avoid pricking pain to the patients.

The choose rates of "coolness," "heavy," and "radiating" among the acupuncturists are all above 50%, while they are below 20% among the patients. The "coolness" discussed above is one type of *Deqi* sensations as mentioned in ancient books. However, "coolness" is hard to be elicited in the clinical due to the type of disease, which may be the main reason that there was a significant difference between the patients and acupuncturists. In two hundred cases of retrospective investigation, 57.5% of patients achieved a heavy sense [31], and another two hundred and twenty seven cases in a survey conducted in UK stated that the heavy sense choosing rate is 20% [15], which confirmed that heavy is a possible sense of *Deqi* sensation. There are "radiating" related terms in the literature of Vincent et al. [13] and Park et al. [22]. A survey of Korean women with a similar sample size reported that "radiating" appearance rate is 76.3% [23], while it disappeared in the MASS and SNSQ list. In this study, in order to facilitate patients' selections, we added explanations for the terms radiating and spreading. Radiating: needles sensation spread without fixed directions; spreading: needles sensation spread with a fixed direction.

4.4. The Acupuncturist's Needle Grasping Sensation of Deqi. In recent *Deqi* studies, more attention is paid to the patients' needle sensations than the acupuncturists sensations [13–16].

However, according to traditional theory the acupuncturists' sensations are more important in eliciting and controlling *Deqi*. Therefore, this survey adds more terms of the description of the acupuncturists' sensations. In this study, most expert acupuncturists believed that *Deqi* sensation is mainly manifested by "pulling" and "tight", which is the same as described in ancient Chinese medicine. A few of them thought "throbbing" is beneficial to the treatment of cerebrovascular disease caused by motor dysfunction and other diseases, which is regarded as one kind of *Deqi* sensation. However, most acupuncturists do not agree with "opposable" mentioned in some Chinese pieces of literature (5%).

4.5. Limits. Some acupuncture sensations had to be translated from English into Chinese, and we have to add certain additional interpretations for better understanding by Chinese patients. Then, all the terms had to be retranslated to English again, whereby the delicate meaning of some of the items may not have been fully conveyed in its Chinese equivalent. The sample size of this study was not big enough, and the scope of this survey is narrow.

All of the objects in this study were acupuncture-experienced patients, and more are men. However, this investigation can still reflect the general recognitions of *Deqi* sensations among the Chinese patients and acupuncturists. In the future, we would make an investigation with a larger sample and analyze the relation of the frequency of occurrence of different *Deqi* sensation with curative effect.

5. Conclusion

Results of this survey indicated that acupuncturists and patients, especially the patients in serious condition, are eager to get *Deqi* sensations and highly expected to get better efficacy due to stronger *Deqi* sensation.

Different from previous studies, this survey filtered the terms of *Deqi* sensations by the patients and experts in the same hospital at the same time. After comparing, it is found that there exist some differences between the real-life experiences of patients and acupuncturists' expectation. It is found that pain related feeling and sensation spreading feeling are the major manifestations of *Deqi* sensations. However, the patients actually feel the temperature changes, and acupuncture conduction occurred less than the acupuncturists' expectation.

The "dull pain," "sore," "aching," "numb," "distended," "electric," "throbbing," "warmness," "spreading," "coolness," "heavy," and "radiating" can be considered as the main manifestations of *Deqi* sensations, while "sharp pain," "twinge," "pricking," "throbbing pain," "burning," "penetrating," "pinch," and "formicating" may not be the typical signs of *Deqi* sensations. The acupuncturists' *Deqi* sensations are mainly described as "pulling," "tight," and "throbbing".

Conflict of Interests

The authors declare that they do not have a direct financial relationship with the commercial identities mentioned in this paper.

Authors' Contribution

Hong-Wen Yuan and Liang-Xiao Ma contributed equally to this work.

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Review Article

Appraisal of the *Deqi* Concept among Contemporary Chinese Acupuncturists

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Deqi, an important component of the traditional theory of acupuncture and moxibustion, is the key factor in determining clinical therapeutic effect of acupuncture. In this paper, based on the digging up, arrangement, and in-depth analysis of the famous contemporary Chinese acupuncturists' perspectives of *deqi*, the authors summarize the concept and manifestation, as well as the properties of *deqi*, and correlativity of *deqi* with acupuncture manipulation through reviewing modern clinical research. Proposals for more scientific and standardized acupuncture research are introduced to reexamine and restore the implication of *deqi* in combination with the clinical practice.

1. Introduction

Western medicine influence has played an important and challenging role in the development of modern acupuncture leading to the establishment of the integrative medicine school of thought. Modern acupuncturists in China have enhanced acupuncture theory, basing their work on scientific knowledge. Modern China has been the starting point of studies on the relationship between meridians and nerves. In spite of the tendency to integrate scientific rationale in the acupuncture theory, most doctors still acknowledge the importance of preserving the classical theory with its cultural background and extended classical bibliography. Therefore, modern acupuncturists in china, with their experience and viewpoint, embody the actual acupuncture and the link between past and present.

Chinese medicine has evolved over thousands of years, building up through the accumulation of clinical experiences. Experience and oral transmission are ineluctable pillars of Chinese medicine and acupuncture heritage. Since time immemorial to the present day, *deqi* has always been a key point in practice and research of the acupuncturist. The importance given to *deqi* derives from its clinical significance, as well as the practitioner's traditional and conservative views in feudal society that associate the difficulty of *deqi* technique with mystical beliefs that go beyond rational explanation. This paper is as a complete summary as possible of the experience of renowned Chinese acupuncturists since 1949 and their viewpoint about *deqi*. Our intention is to provide new elements for modern research and guidance for clinical application.

2. Materials and Methods

2.1. Object of the Study. The famous contemporary acupuncturists involved in our research are selected from the following:

(1) those with honor given by the Ministry of Personnel of China, the Ministry of Health, and the Drug

Administration of China, specializing in acupuncture;

(2) acupuncturist expert experience-albums which are in great influence include albums such as the *Clinical Essentials of the contemporary Chinese Acupuncture* [1], *Clinical Guideline of Acupuncture and Moxibustion* [2], *Integration of contemporary Zhe Jiang Acupuncture Study* [3], *Collection of the Beijing Famous Acupuncturists* [4], and the *Essence of the Famous Acupuncturists* [5];

(3) chief editors and subeditors of acupuncture and moxibustion textbooks.

A total of 140 acupuncturists were selected.

2.2. Source of the Literature and Search Strategy. The theory and the experience of the modern famous specialists were kept in 2 ways: one in a form of a network information database and one kept in a form of the literature of cultural relics. Our research combined these 2 sources in the method shown as follows:

(1) the following electronic databases were searched, regardless of publication status: the Chinese National Knowledge Infrastructure Database (CNKI) (1949–2013), the Chinese Science and Technology Periodical Database (VIP) (1989–2013), the Chinese Biomedical Database (CBM) (1978–2013), the Wanfang Database (1985–2013), and PubMed Database (1966–2013). All searches ended in April 2013. The search terms included "the names of acupuncturists above," "*de_qi*" (getting *qi*), "*qi_zhi*" (arrival of *qi or qi arrival*), and "*zhen_gan*" (acupuncture sensation or needling sensation);

(2) collecting the literature of acupuncture and moxibustion with the names of acupuncturists above in the title.

2.3. Inclusion Criteria. Studies meeting the following three criteria were included: (1) taking "*de_qi*" (getting *qi*), "*qi_zhi*" (arrival of *qi or qi arrival*), or "*zhen_gan*" (acupuncture sensation or needling sensation) as subject; (2) concerning direct expression of personal experience or viewpoint; (3) quoting acupuncturists' consensus or professional opinion.

2.4. Exclusion Criteria. The following studies were excluded: (1) duplication: the same content with the same authors published in different journals; (2) mentioning "*de_qi*" (getting *qi*), "*qi_zhi*" (arrival of *qi or qi arrival*), or "*zhen_gan*" (acupuncture sensation or needling sensation), but without a critical point of view or without a comment.

3. Results and Discussion

3.1. The Literature Research and Study Selection. Our initial searches identified 352 references (344 from Chinese databases and 8 from English database) and 30 works of literature. After study selection, a total of 81 references (19 works of literature and 62 studies) were included (Figure 1).

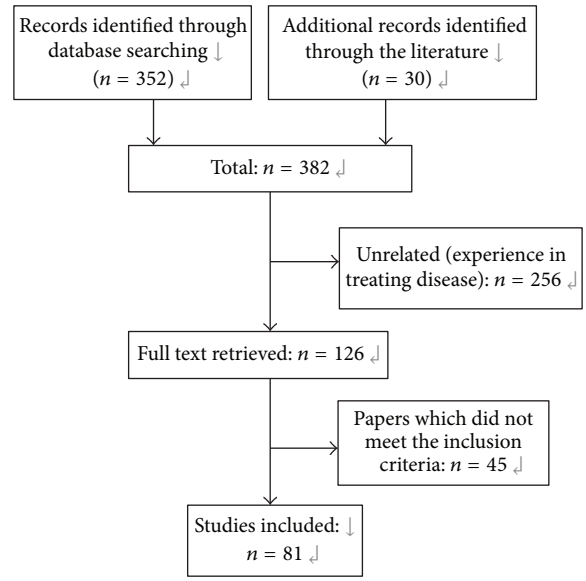

Figure 1: Flowchart of the literature search and study selection.

3.2. Concept and Manifestation of Deqi

3.2.1. Historical Origin of Deqi. The theory of *deqi* (getting *qi*) and arrival of *qi* originated from *The Yellow Emperor's Inner Canon*, which occurred many times in different chapters. It was elucidated more deeply in the following books such as *The Classic of Difficult Issues, The Great Compendium of Acupuncture and Moxibustion, The Ode of the Golden Needle, and Song to Elucidate Mysteries*. For two thousand years and through the various dynasties, the *deqi* concept has been central to academic thinking.

The purpose of acupuncture, moxibustion, or other forms of stimulation is the dredging of meridians and regulating of blood and *qi*. Even though *qi* does not have a material form, thus cannot be palpated, special importance is given to the regulating of its flow. Because scientific development and theories are being based on physical material, it is thus challenging for people not acquainted with eastern culture to understand such a concept [6]. The arrival of *qi* and *deqi* mentioned in *The Yellow Emperor's Inner Canon* stresses on the feeling of doctors but did not consider patient's sensation as *deqi* and *qi* arrival. Mention of patient soreness, numbness, pain, or similar sensations secondary to needle stimulation only appears in the literature at the end of the *Qing* Dynasty, in *The Inner Chapters of Acupuncture and Moxibustion* [7] which is to become the rudiment of *deqi* theory in actual clinical acupuncture today.

3.2.2. Knowledge of Deqi from the Ancient Time to the Present Day. Dr. Cheng [8] considers the arrival of *qi* and *deqi* the same. The concept of *qi* contains the description of

both doctors and patients feelings. This view is accepted by most acupuncturists nowadays, such as the description in Chinese acupuncture textbooks: *deqi,* which is called the "arrival of *qi*" in ancient time and is called the "needling sensation" nowadays. *Deqi* means when the needle has been inserted to the desired depth, and manipulation techniques such as lifting and thrusting or twirling and rotating are applied to obtain meridians sensation in the puncturing location" [9]. Needling sensation refers to patient's feeling of soreness, numbness, distension, heaviness, pain, formication, and electrical sensation around the acupoint when the needle is inserted. At the same time, the operator may feel tenseness around the needle" [10]. Dr. Li [11] believes that *deqi* is a feeling and a reaction between the relevant feelings of patient and doctor, which cannot be considered as *deqi* when it lacks in either one.

The view of *deqi* in the ancient medical literature differs from the current acupuncture and moxibustion circle. The ancients described it as the tenseness feeling beneath the operator fingers, while the current acupuncture and moxibustion circle pays more attention to the feeling of patients, which often includes soreness, numbness, distension, and heaviness. Modern researchers [12] divided the patients' feeling into thirteen types such as pain, soreness, deep oppression, heaviness, distension, chirobrachialgia, numbness, stabbing pain, dull pain, and the feelings of warmth, cold, spasm, and others. Simultaneously, they observe the occurrence of the frequency and intensity of needling sensation shown as follows: sore sensation, oppression sensation, tingling, numbness, and dull pain are more common, while warm sensation and cold sensation are less. Other scholars [13] made a clinical investigation and found that distension, soreness, electrical sensation, and numbness sensation have separately accounted for 94%, 81%, 81%, and 78% of the most common needling sensations, respectively. It is necessary to point out that needling sensation is a new term mentioned by the modern scholars who combined Western medicine knowledge with acupuncture research. It is beneficial for us to intuitively recognize all kinds of acupuncture stimuli. However, in the actual clinical, all kinds of needling sensation had difficulty in guiding the reinforcing and reducing methods. Thus, many physicians put forward their own views on the relationship between the needling sensation and *deqi*.

3.2.3. Indications of Deqi in Different Perspectives

(1) *Besides the Sensation of Soreness, Numbness, Distension, and Heaviness, Other Feelings Can Be Combined.* Doctors like Qiu [14], Wang [15], Cheng [16], Shi [17], Zhang [18], Ge [19], Wei [20], and so forth all consider that the needling sensation does not only include soreness, numbness, distension, and heaviness in a local area, but also sensation transmission along the meridians or the arrival of *qi* at pathological sites. Dr. Liu [21] has pointed out that the slow transmission of sensation such as soreness, numbness, distension, and heaviness differs from the rapid radiating feeling of numbness by stimulating the nerve. Dr. Sun and Dr. Gao [22] believe that if the doctor feels a sunken or tense sensation beneath the needle, it is an indication of *deqi*. Patient in this case must have a feeling of soreness and distention beneath the needling point, or even an outward spreading feeling. "It can also be observed visually," says Wei [23], if the skin around the needle appears tense, with a raised or sunken phenomenon, which is also regarded as a form of *deqi*.

(2) *Emphasizing Deqi Lies in the Doctor's Feeling.* Dr. Peng [24] believes that some of the patients who do not respond sensitively to the needle insertion or the feeling of sunken or tension beneath the needle are the indication of *deqi*. Dr. Wang [25] considers that the indications of *qi* arrival do not only consist of the patient's and the doctor's feeling beneath the needle, but also include the feeling of the doctor's other hand when pressing the skin near the acupoint during acupuncture procedure. Dr. Feng [26] thinks that the present *deqi* beneath the needle is known by asking the patient, and there is a certain subjective conjecture for the patient's description of the needling sensation. If the *qi* beneath the needle is mainly recognized by the doctor's feeling, it is more concrete and easier to control the needling. Dr. Chen [27] considers that in some special cases such as coma, emptiness beneath the needle, or noncooperation of the patient that causes the patient to be unable to reflect subjective feelings, the doctor must carefully observe the objective indications such as the sinking and tension beneath the needle and moving up and down of the muscle or limbs. But the most important at this point, which should be taken as the primary evidence, is the efficacy of the treatment. Dr. Zhang [28] thinks that the *deqi* sensation beneath the needle, as well as the changes and recovery of the pulse after needling, is more important than the patient's sensation. The sensation of *deqi* beneath the needle of the doctor's hand and the patient's needling sometimes is synchronous but sometimes not.

(3) *Other Views.* Dr. Jin [29] considers that the sensations of soreness, numbness, heaviness, and distension are just some superficial feelings in the local area which cannot be equally indicated as *deqi*. Dr. Lai [30] thinks that, nowadays, habitually equalizing *deqi* to needling sensation, or seeing the strength of needling sensation as *deqi* and determining the efficacy, is a cognitive mistake. The general feelings of the patient such as soreness, numbness, distension, and heaviness are original, primary, and initiative. Only doctors who identify the pathogenesis can do the manipulation of the reinforcing or reducing methods to achieve the real sense of therapeutic effect of *deqi*. In addition, the clinical practice has shown that some patients can also get a good efficacy with weak needling sensation or even with no needling sensation at all. In the modern acupuncture, such as wrist-ankle acupuncture, intradermal acupuncture, and abdominal acupuncture, needling sensation is not required for the patients, but many diseases can be cured. Therefore, the concept of latent needling sensation is raised [31], in which, during the acupuncture treatment procedure, the patient does not feel any of the needling sensations such as soreness, numbness, distension, and heaviness, but instead the doctor has a feeling beneath his hand. There is an obvious change of the electric conduction amount that can be detected by

the meridian detector, which is proved by responding to the tissue at the acupoint. And the clinical efficacy is considered to be the criterion of the judging of *deqi*.

Thus, it is obvious that the needling sensation is not the only manifestation of *deqi*. As we all know, many physiological functions related to meridian phenomenon cannot be directly perceived, such as blood circulation, nerve conduction, muscle discharge, electrical impedance of skin, and hormone secretion. Therefore, it is very normal that the functional activity of the meridian is not directly perceived by people [32]. Another study [33] has shown that the sensitivity of the needling sensation may be related to the individual differences of the secretion levels of endogenous opioid peptides and antiopioid. Dr. Liu and others [34] use a self-developed apparatus to conduct a quantitative analysis of the frequency, speed, time, intensity, and subtle changes of the acupuncture operator to indicate the *deqi* of acupuncture, which has been all the time reacted to the subjective concept, which can be objectively detected through the mechanical monitoring.

3.3. The Properties of Deqi

3.3.1. The Identification of Upright and Pathogenic Properties of Deqi. As early as 2,500 years ago, it was recorded in *The Yellow Emperor's Inner Canon* that the arrival of grain's *qi* is referred to as a sensation of "comes slowly and softly" after *deqi* which has the feeling of relaxation and alleviation; conversely, the arrival of *xie qi* is referred to as a sensation of fierce after *deqi*, with an unsmooth and dull feeling beneath the needle or even unable to manipulate the needle, which is hard for the patient to tolerate. Dr. Cheng [8] explains the upright *qi* and *xie qi* as follows: "If some neuron gets sick due to the overexcitement, the reflectivity will be stronger with a second stimulation. Hence, the sunken and tense feelings beneath the needle are produced and cause *xie qi* which is a morbid state. If the disease-free nerve is punctured, the reflectivity is brisk and ease, which is the state of mildness, called the upright *qi*." In combination with the clinical practice, Dr. Qiu [14] also explains that *xie qi* refers to acute pain such as stomachache, colicky pain due to gallstone or nephrolith, high fever, or spastic limbs, which the body condition is in an extreme tense and lead to a fierce response after needling and cause the sensation of tense and dull pain due to spasm and contraction beneath the needle. "The upright *qi* refers to when symptoms were relieved with acupuncture needle insertion and the needling sensation turns soft and keeps constant, neither of tension nor emptiness." Dr. Tian [35] summarizes briefly that the upright *qi* is mild, while the *xie qi* is quick and tense.

3.3.2. The Relationship between Deficiency, Excess, Cold, and Heat Syndrome and the Indications of Deqi. Dr. Wang [15] thinks that the patient with cold syndrome has mostly a dull sensation beneath the needle and feels sore, while the patient with heat syndrome has a sensation of tense and knotting beneath the needle and feels distensile; the patient with deficiency syndrome has a loose and slippery sensation and feels numb; the patient with excess syndrome has a resisting and knotting sensation beneath the needle with a feeling of spicy pain. Dr. Peng [24] raises that, in the elderly with deficiency syndrome, the best needling sensation is the change of emptiness to sinking and tension sensation with a heat sensation beneath the needle as the best result, while, for the strong patient with excess syndrome, the best needling sensation is the change of sinking and tension to emptiness sensation with a cold sensation beneath the needle. The needling sensation of soreness and numbness is normally obtained with the neutral manipulation.

3.3.3. Feelings of Deqi in Different Parts. Dr. Yang [36] summarizes the feelings of *deqi* in different levels of the tissue during acupuncture as follows: when the needle is punctured into the dermal part, the pain is sensitive; when punctured into the vessels, a little pain is felt; when punctured into the fascia, slight distension is felt; when punctured into the muscles, soreness and distension are felt; when punctured into the nerve, numbness and radiating sensations are felt; when punctured into the periosteum, pain is felt. The summary of Dr. Li [11] is similar to the above opinion. Dr. Yu [37] points out that pain is the sensation which is easily aroused when the hand, foot, head, or face is punctured, and it is also one of the needling sensations. Dr. Zhang [18] thinks that there are different needling sensations when acupoints from different parts are punctured. For the acupoints on the limbs, chest, and abdomen, or back transport points, the needling sensations are mostly soreness, distension, heaviness, numbness, and so forth. After the 500 times observations by puncturing EX-HN 3 (*yìntáng*) and GV 20 (*bǎihuì*), Dr. Liu and Ji [21] summarize that when the superficial fascia layer is punctured, there are only a slight distension sensation and sunken and tense feelings beneath the hand. According to clinical experiences, Dr. Wei [23] mentions that when blood vessels are punctured, there will be a heat or a burning sensation. Dr. Huang [38] stresses on *deqi* in the superficial layer. When a special needling manipulation is done in the dermal layer, the patient will generally have a slight sensation of numbness, distension, or radiation. He thinks that the appearing of the sensation is also good for getting the sensation of *deqi* in the deep layer, so that the effect of dredging and unblocking meridians could be achieved in real sense.

These views are derived from clinical experiences by acupuncturists from several decades, and nowadays, they are gradually explained by modern researches [39–43]. Related studies show that acupuncture effect signals are mainly initiated by somatosensory receptors and afferent fiber in the dermal layer, hypodermis, muscle, aponeuroses, tendon, interosseous membranes, and the periosteum. Different types of nerve fiber relatively conduct different types of sensation; for example, soreness, dull pain, and hotness are transmitted by slow-conductive fibers, Aδ and C fibers, numbness, and tingling by faster-conducting Aβ/γ fibers, and pressure is transmitted through multiple different types of nerve fibers. Morphophysiology has shown that nerve innervations and tissue structures are actually closely interrelated to each other.

For example, Aδ and C fibers are mostly distributed in tendons [44]. Therefore, pain sensation in the deep region may include soreness, heaviness, diffusion, and duration. Another research [45] has indicated that the acupoints are densely distributed in regions such as the top region of the head, temporal region, and the central part of the trunk and extremities. These densely distributed regions have outstanding fundamental substances required to stimulate the transmission. Therefore, mastering the characteristics of the needling sensation in different parts of our body tissues may help doctors to accurately locate the depth and angle of the needle and to stimulate diverse receptors in different tissue layers to impulse different types of conducting fibers for certain effect. It has a certain guiding significance in manipulation of acupuncture.

3.4. Deqi and Acupuncture Manipulation

3.4.1. Relationship between Deqi and Traditional Reinforcing and Reducing Methods. Modern Chinese acupuncturists think that reinforcing and reducing methods can only be proceeded after *deqi*. Dr. Jin [29] has pointed out that, by classifying the characteristics of *deqi*, we can either decide to use the reinforcing or reducing method. In times of *qi* arrives slowly, the sensation beneath the needle should gradually be filled, which also means that grain's *qi* has arrived, so the reinforcing method should be carried out. If there is a compact and fast sensation during the arrival of *qi*, which means that *xie qi* has arrived, so the reducing method should be used. Dr. Zhang [46] also believes that the reinforcing or reducing method should be based on examining and evaluating the condition of patients somatic function. Dr. Lu [47] has pointed out that *deqi* is even reflected after the reinforcing and reducing methods. If the reinforcing and reducing methods have reached their own standard, reinforcing method requires the sensation beneath the needle to be tense and full, which was loose and puff before the procedure. The reducing method requires the unsmooth and tight sensation beneath the needle to be changed.

3.4.2. Relationship between Deqi and the Quantity of Stimulus. Currently in China, many Chinese acupuncture specialists gradually show evidence of westernizing in the knowledge of the acupuncture theory [48]. Take Dr. Zhu [49] for example; she has proposed that the main theory of acupuncture and moxibustion treatment of a disease is by stimulating and adjusting the internal organ nervous system, especially by adjusting and controlling the function of the senior central nervous system. Dr. Zhang [28] has also mentioned that, from the modern medicine point of view, the function of acupuncture and moxibustion can be classified as "function of physics" (change in the morphological area) and "function of chemistry" (changes in the physiology, pathology, and biology areas). The therapeutic effect of acupuncture and moxibustion is likely to be carried out by regulating the neurohumor.

Dr. Yang [50] considers that the therapeutic effect of acupuncture is mainly carried out by moderate stimulation of physical effect. Dr. Huang [38] considers that, in most situations, the stimulation intensity is at direct ration relationship with the *deqi* sensation.

Dr. Cheng [51] considers that there is no difference in the reinforcing and reducing methods, but only in the stimulation intensity which can be adjusted by changing the strength of *deqi* sensation. Dr. Lu [47] considers that the theory mentioned prior does not entirely correspond in reality. This is because light stimulation can excite and strong stimulation can restrain nerves in terms of the nerve response to the stimulation, but we consider reinforcing and reducing methods in terms of meridians, *qi* and blood. Since the two theories exist in different bases, the two cannot be compared in the same platform. At the moment, there is not enough evidence to prove that nerves are equal to the meridians, so there still needs to be a further discussion on replacing reinforcing and reducing methods with the stimulation intensity. Dr. Jin [29] agrees with the above mentioned point of view and thinks that even though there is no common standard of acupuncture technique between ancient and modern times, we can cross-reference and apply it in clinical practices. Even though Dr. Yang [50] thinks that the quantity of needling stimulus decides the therapeutic effect, he repeatedly emphasizes that the relationship between reinforcing, reducing, and the intensity of the stimulation is not simple. These two concepts exist in intersecting and embracing relationships.

3.4.3. Relationship between Deqi and Retaining Needle Time. In the times of *The Yellow Emperor's Inner Canon*, the concept was to take the needle out immediately once patients feel *qi* arrival, which brings about the end of the acupuncture treatment procedure. Doctors, who have inherited the original decree of *The Yellow Emperor's Inner Canon* including Dr. He [52], Dr. Cheng [53], and Dr. Peng [24], consider that there is a need to wait for *qi* arrival if you do not get the sensation after needling. Once after *deqi*, the doctor takes the needle out immediately, and there is no limit in the treatment time. Nowadays, there are only a small amount of doctors who retain the needle just the way as it is recorded in *The Yellow Emperor's Inner Canon* and today, the occupation standard for retaining the needle has become 20 to 30 minutes. Dr. Je [54] thinks that, in order to get the most ideal therapeutic effect, there is a need to retain the needle after *deqi* in order to keep *qi*, and maintain the needling sensation, and the quantity of the stimulus. Dr. Luo [55] considers that, in the treatment of some chronic pain illnesses, the needle should be retained for about 1 hour or even longer, to keep patients with a certain needling sensation and enough quantity of stimulus, so as to obtain a better effect. Dr. Guo [56] mentions that retaining needle time should be determined by the state and duration of illness.

3.4.4. Relationship between Deqi, Acupuncture Therapeutic Effect, and Prognostic Prediction. Dr. Peng [24] considers that there is a most ideal needling sensation suitable for patients with different body constitutions and ages. Dr. Qiu [57] has also mentioned that different therapeutic effects can

be gained just by changing the direction of the needling sensation in one acupoint. For example, RN12 *(Zhōng Wǎn)* acupoint which is selected in the treatment of stomachache requires the needling sensation to scatter around the surrounding region to relieve pain; needling sensation for treatment of vomit is required to transfer downward.

Dr. Yu [37] thinks that different classifications of needling sensation establish different therapeutic effect. Needling sensation such as numbness and electrical sensation is suitable in the treatment of excess syndromes and acute diseases; tic sensation is suitable for visceral ptosis and paralysis; Dr. Guan [58] has proposed "highly efficient needling sensation" which is a sensation with special therapeutic effect in treating certain diseases, such as in treatment of sciatica and needling sensation of GB30 *(Huán Tiào)* spread down to the foot which belongs to one of the highly efficient needling sensation.

Dr. Cheng [59] considers that the length of time required to *deqi* does not only influence the therapeutic effect but can also be used as a determination of patient's condition, treatment, and prognosis. "Faster the *deqi*, higher the rate of *deqi*, brings better the therapeutic effect".

4. Questions and Expectations

Deqi is a specialized term used in acupuncture, and it has a significant role in selecting the needle manipulating methods, determining the therapeutic effect of acupuncture and body response. In the present, objectively and quantitatively standardizing the measurement for *deqi* state of the patient presents a significant challenge in this field [60].

The preliminary summary of famous contemporary acupuncturists' viewpoint about *deqi* can help the acupuncture practitioner, in combination with clinical practice, to revert to the original intention of *deqi* in future research. It is of vital importance to reexamine and restore the implication of *deqi* under more scientific and standardized acupuncture research for further guidance in exploring the therapeutic mechanism of acupuncture.

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Research Article

Peripheral and Spinal Mechanisms of Acupoint Sensitization Phenomenon

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This study was carried out on adult female Sprague-Dawley rats to observe the position, size, and sensitivity change of inflammatory reactions on body surfaces induced by colorectal import of inflammatory irritant mustard oil. Colorectal distension (CRD) was adopted as a visceral noxious stimulus to record the activities of spinal dorsal horn wide-dynamic range (WDR) neurons activities at spinal segments L1–L3. The study also observed the activations of WDR neurons by electro-acupuncture (EA) on acupoints of Zusanli-Shangjuxu before and after different intensities of CRD stimulation and the dose-response relationship between stimulus and response. The results show that in the case of visceral inflammation, the number of exudation points of neurogenic reaction on body surfaces increased along with the severity of visceral inflammation (Li et al. 2006). The area of peripheral receptive fields of WDR neurons also enlarged along with the intensity of visceral inflammatory response. The activation effect of EA on WDR neurons was positively correlated with the severity of visceral inflammation. Therefore, we concluded that the function of acupoints can be sensitized by visceral noxious stimuli. When the function of internal organs was damaged, the number of reaction points on body surfaces, the size of acupoints' receptive fields, and the sensitivity of acupoints changed accordingly.

1. Introduction

Acupoints are special locations on body surfaces where the Qi of viscera is transfused. It is the key step underlying the interaction between meridians and viscera. Visceral diseases can induce mechanical hyperalgesia on the corresponding acupoints on body surfaces which is manifested as pain when pressed. The size and function of acupoints change accordingly with the change of the visceral functions. The diagnostic and therapeutic effects of acupoints on splanchnic diseases enhance in pathological conditions. This phenomenon is called "acupoint sensitization".

A previous study [1] demonstrated that when splanchnic disease occurred, acupoints on body surface turned from the silent mode in physiological condition to the activated or sensitized mode in pathological condition. When acupoints are activated or sensitized, the regulatory or therapeutic effects of acupuncture on corresponding viscera change in both quality and quantity. At the present, the mechanism behind acupoints sensitization phenomenon is largely unknown. Adopting colorectal import of inflammatory irritant mustard oil and the colorectal distension (CRD) as the method of visceral noxious stimulation, this study observed the body surface inflammatory reactions and activities of wide-dynamic range (WDR) neurons, explored the dose-response relationship of acupoint sensitization, and investigated the regulatory effect of acupuncture in acupoint sensitization and related spinal cord mechanism.

2. Method

2.1. Experiment of Inflammatory Exudation Points

2.1.1. Experimental Animals. 20 clean level healthy male Sprague-Dawley rats, weighing 250–300 g, were obtained from the Laboratory Animal Center of the Military Academy of Medical Sciences.

2.1.2. Induction of Inflammatory Condition. This study used the method of colorectal import-inflammatory irritant mustard oil. A tube was inserted into the rat's colon and rectum through anus at the depth of 2 cm to 3 cm, and different doses of 2.5% mustard oil (mustard oil; Sigma-Aldrich, St. Louis, MO) were inserted when needed.

2.1.3. Exudation Points of Neurogenic Inflammation on Body Surfaces. Evens blue (EB) was injected (5 mg per 100 g body weight of rat) into the rats' tail vein to mark the exudation points of neurogenic reaction on body surfaces. The concentration was 50 mg/mL.

2.2. Experiment on Spinal Cord

2.2.1. Animals and Surgical Procedures. 43 clean level healthy male Sprague-Dawley rats, weighing 250–300 g, were obtained from the Laboratory Animal Center of Military Academy of Medical Sciences. Rats were fast for 12 hours before experiment but water was not deprived.

Rats were anesthetized with an intraperitoneal injection of 10% urethane (1.0~1.2 g/kg) and then were placed in supine position on the operating table for tracheal intubation. One hundred μg atropine was administered through intraperitoneal injection to reduce secretions from the trachea. Rats were placed in the stereotaxic apparatus after operation, injected intraperitoneally of 2% gallamine triethiodide (2 mL/rat), and connected to the breathing machine (Parameters: tidal volume: 4 mL/100 g; respiratory rate: 60 breaths per minute; respiratory quotient: 1 : 1). The body temperature of experimental rats was maintained at 37°C by electric blanket during the operation and experiment. Rats were also anesthetized during colorectal infusion of mustard oil.

The skin around the waist of the rats was cut along the midline of the back to expose and fix the spinal segments L1–L3. The coordinate of WDR neuron is 0.5–1.5 mm beside the midline of the back of spinal cord and 500–1500 μm beneath the surface of spinal cord. A microelectrode was used to record the neuron discharge activity, and the electrical signals were collected and processed by microelectrode amplifier and PowerLab electrophysiological recording system.

2.2.2. Identification of WDR Neurons. Neurons located in the spinal dorsal horn that respond to given noxious stimulations (e.g., clamping skin, CRD and so on) and nonnoxious stimulations (e.g., brushing, touching skin, and so on) with electric discharge are called WDR neurons. Only WDR neurons were conducted as objects of this study.

Seventy-seven WDR neurons were recorded at the spinal segments $L_{1\sim3}$ of the 43 experimental SD rats in this study.

2.2.3. Visceral Noxious Stimulation. Colorectal distension (CRD) was adopted in the experiment. A 4 to 6 cm long balloon made from a disposable condom tip was tied to on a 4 mm diameter hose. The other end of the hose was connected to the sphygmomanometer and pressure transducer through the T-type channel. In the experiment, the balloon was inserted into the rat's straight colon through anus to the depth of about 4 cm to avoid direct stimulation to anus and bowel wall. Before the balloon was placed into the colon, 3–5 drops of tepid paraffin oil were smeared on the balloon' surface. The distance from balloon end to anal was about 0.5 cm. A pressure of 20–80 mmHg was applied through the sphygmomanometer with the duration of about 20 s. Pressures of more than 40 mmHg were regarded as visceral nociceptive stimulus [2, 3]. The interval between two CRD stimulations was kept more than 10 min to avoid possible sensitization of colon caused by overstimulation.

2.2.4. Electroacupuncture. Electroacupuncture was applied at the acupoints of "ZUSANLI-SHANGJUXU" at the recorded homolateral discharging neurons with the frequency of 20 Hz for 30 seconds. The intensity was 1.5 times of the intensity of the Aδ fiber threshold stimulus (about 1.82 ± 0.64 mA [4]).

2.3. Experiment Process

2.3.1. Observation of Exudation Points of Neurogenic Reaction on Body Surfaces. Twenty rats were used in the experiment. Different doses of mustard oil (20, 50, 100, 150, 200 μL) were imported into the rat's colon. Two-three hours after importing, evens blue (EB) was injected into the rats' tail vein as the marking pigment [5]. The distribution and size of exudation points (blue points) of neurogenic reaction on body surfaces were observed and recorded after different doses of mustard oil were imported.

2.3.2. Observation of Colorectal Inflammatory Reaction and the Size of Receptive Fields. 11 rats were used in the experiment. At least 4 points which could increase the discharge of WDR neurons were measured and identified by the acupuncture needle along the horizontal and vertical axes at the acupoints of ZUSANLI-SHANGJUXU, and the size of peripheral receptive field was marked. Fifty μL and 200 μL of mustard oil were imported into the colon of rats successively to induce colorectal inflammatory reaction. Then, acupuncture was used again as the probe to detect and record the discharging reactions of WDR neurons and the size of peripheral receptive fields. The purpose was to observe the changes of WDR neurons at peripheral receptive fields before and after the colorectal inflammatory reaction.

2.3.3. Effect of Different CRD Stimulations on the Discharging Reactions of WDR Neurons. Thirty-two rats were used in the experiment. The discharging reactions of WDR neurons at ipsilateral peripheral receptive fields of "ZUSANLI SHANGJU XU" acupoints were recorded. Different levels of CRD stimulations (nonnoxious stimulations: 20 mmHg; light noxious stimulations: 40 mmHg; moderate noxious stimulations: 60 mmHg and strong noxious stimulations: 80–100 mmHg) were applied to rats to observe the discharging reactions of WDR neurons after stimulations as well as the dose-effect relationship between CRD stimulation and WDR neuron reaction.

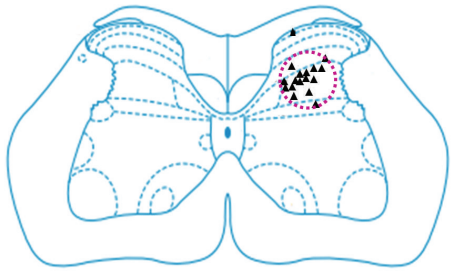

Figure 1: The locations of identified WDR neurons in the spinal cord. ▲ indicates the location of a neuron.

2.3.4. Observation of the Effect of Acupuncture on Discharging Reactions of WDR Neurons. Electroacupuncture was administered for 30 seconds before and after the application of different intensities of CRD stimulation. We recorded the discharging reactions of WDR neurons and observed the effect of acupuncture on WDR neuronal discharging reactions before and after CRD stimulations.

2.4. Histological Location. After the single cell recording, pontamine sky blue was imported from a glass microelectrode into the DCN neuron group to mark the position of electrode's recording by passing 20 μA of negative direct current through the microelectrode for 20–30 min by the microelectrode amplifier. Then, the rats were executed and perfused through the heart with 4% of paraformaldehyde. The rats' lumbar spinal cord was removed and fixed in the paraformaldehyde. Two days later, the lumbar spinal was made into frozen sections for H and E staining. Locations that were not recorded in the DCN neuron group were weeded out. As shown in Figure 1, most WDR neurons marked in this experiment were located in Rexed layers IV and V, and a few were in Rexed layers I and VI.

2.5. Data Collection and Analysis. Software such as Powerlab data acquisition system, Chart 5.0, and SPSS13.0 were used for data collection and analysis. The volume of neuronal discharge per second and the activation/inhibition rate were calculated. The mean and standard deviation before and after the electroacupuncture intervention were calculated as the descriptive statistics and represented by $\overline{X} \pm$ SE. The activation/inhibition rate was represented by $\overline{X} \pm$ SE%. The independent t test was used for the comparison between groups. $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Dose-Effect Relationship between Different Doses of Mustard Oil Imported into the Colon and the Exudation of Neurogenic Reaction on Body Surfaces. Two hours after the injection of mustard oil, colonic mucosa hyperemia and edema were viewed clearly under low power lens (×40). Sporadic and abundant polymorphonuclear leukocytes, tissue damage, and bruises were viewed on the mucous membrane under high power lens (×400), but the same expression was not viewed in the saline injection group.

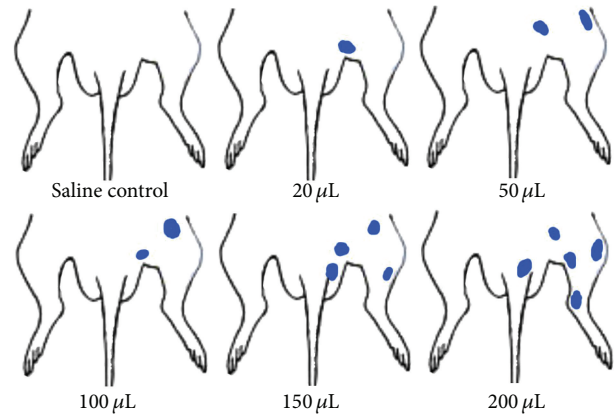

Figure 2: The distribution of EB exudation points on body surfaces after injection of mustard oil into the colon.

After the injection of different doses of mustard oil into the colon, the number of EB exudation points increased along with the dose of mustard oil. Generally, 0–2 EB exudation points were observed with the dose of 20 μL, 1–3 points with the dose of 50 μL, 2-3 points with the dose of 100 μL, and 2–5 points with the dose of 150 μL. When the dose was increased to 200 μL, EB exudation points increased to 3 ~ 7. It indicated that the number of exudation points is in proportion to the inflammatory reaction level of organs (Figure 2). Exudation points were largely located in the lower extremities of the body, crotch, and pars basilar is of tail. Whereas, in the rats group injected with equal doses of saline, no regular EB exudation points was observed.

3.2. Changes of Peripheral Receptive Field of WDR Neuron in Spinal Dorsal Horn in the Colorectal Inflammatory Reaction. We recorded 11 WDR neuronal discharge activities at L_{1-3}. Normally, the peripheral receptive field of this type of neurons is relatively small, with an average size of 0.61 ± 0.17 cm^2. After the injection of 50 μL mustard oil, the average size of peripheral receptive field increased to 0.85 ± 0.43 cm^2. When the dose of mustard oil increased to 200 μL, the average size of peripheral receptive field increased to 1.13 ± 0.87 cm^2. It showed that the receptive field transformed from the relatively small size under the physiological condition to the relatively big size under the pathological condition (Figure 3).

3.3. The Activating Effect of CRD Stimulation on WDR Neurons. We recorded 8 WDR neurons and observed their discharge reactions induced by CRD stimulation at 20, 40, 60, 80, and 100 mmHg. The result is that the background discharge of WDR neurons increased gradually from 4.32 ± 1.13 spikes/s to 21.42 ± 2.68 spikes/s after CRD stimulation at 100 mmHg. The increasing rate was 495.83 ± 43.53% of background discharge ($P < 0.05 \sim 0.001$). It demonstrated that visceral noxious stimulation notably activated WDR

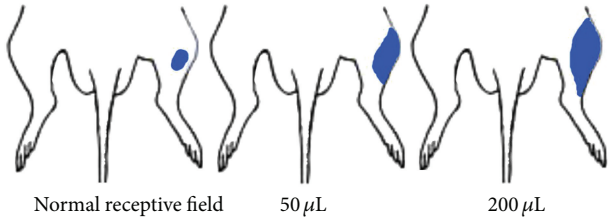

Figure 3: The peripheral receptive field of WDR neurons in the spinal cord after the injection of mustard oil into the colon.

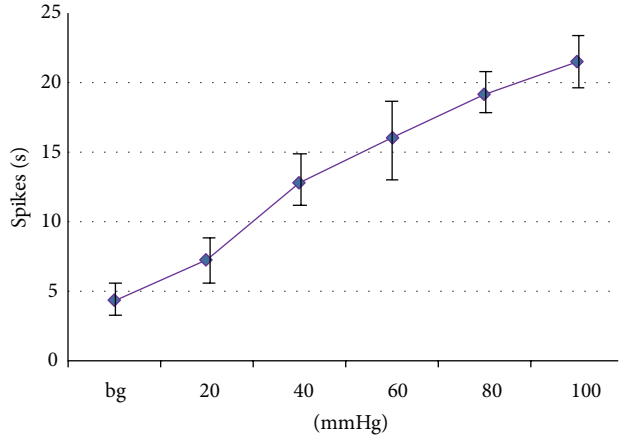

Figure 4: Activating effect of different intensities of CRD stimulation on WDR neurons.

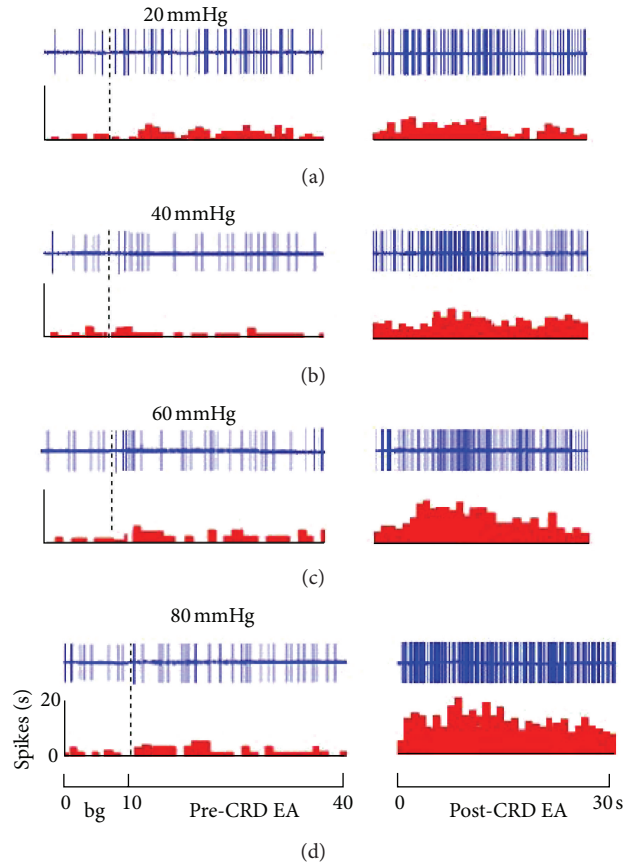

Figure 5: The responses of WDR neurons to EA before and after CRD. Note: upper rows showing original unit discharges and lower rows showing histograms.

neurons and increased the number of neuronal discharge per unit time (Figure 4).

3.4. Effect of Acupuncture on the Discharge Activities of WDR Neurons before and after CRD Stimulation. EA was applied to rats before and after different intensities of CRD stimulations. Results showed that as the intensity of CRD stimulation increased, its activating effect on WDR neurons in spinal dorsal horn also increased remarkably. No obvious change was observed in the discharge activities of WDR neurons if EA was given before the CRD stimulation. If EA was given after the CRD stimulation, its activating effect on WDR neurons was notably enhanced (Figure 5).

The activating reaction induced by EA was observed in 15 WDR neurons at 20 mmHg CRD (Figure 5). Before CRD, WDR neurons had no activating reaction to EA stimulation compared with background activity ($P > 0.05$). After CRD, EA had significant activating effect on WDR neurons. There was a significant difference before and after CRD ($P < 0.05$).

The activating reactions induced by the same intensity of electroacupuncture were observed in 14 WDR neurons at 40 mmHg CRD. The result showed that the neuronal discharge increased $43.38 \pm 3.67\%$ after CRD compare to that before CRD. There was a very significant difference ($P < 0.001$).

Sixty mmHg and 80 mmHg CRD were applied to WDR neuron No. 13 and No. 14, respectively, to observe the activating effect of EA. The result showed that after high intensity noxious stimulation, discharging activities induced by EA increased $71.61 \pm 8.82\%$, and $94.32 \pm 10.41\%$ respectively, and the difference was significant ($P < 0.001$).

It is clear that at the range of 20 to 80 mmHg, the activating effect of EA of the same intensity on WDR neurons increased as the CRD intensity increased. CRD intensity and the EA activating effect presented a linear quantity-effect relationship (Figure 6).

4. Discussion

The connection between acupoints and viscera is bidirectional and reciprocal. The gut-associated acupoints on body surfaces can treat corresponding visceral diseases. It is also a mirror that specifically reflects the visceral function and the QI-XUE change of the human body [6]. In pathologic state, the connection between internal organs and acupoints is closer than in normal condition [7]. When diseases occur in internal organs or deep tissue, visceral nociceptive afferent can facilitate the somatic afferent. hyperalgesia and skin sensitization occur at corresponding acupoints or positions on body surfaces, which reflects in the increase and relative concentration of the tender points or sensitive points on the skin [8].

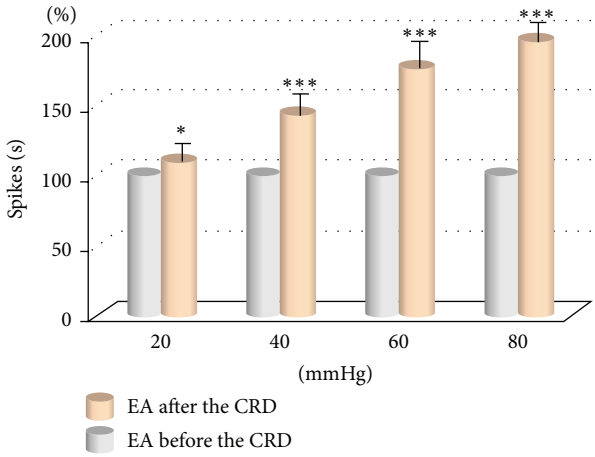

Figure 6: The response of WDR neurons to EA at different CRD. $^{*}(P < 0.01)$; $^{***}(P < 0.001)$.

Recently, some researchers proposed the idea that acupoints are dynamic, that is, the size and function of acupoints are not in the static state; the functioning of acupoints is an active and dynamic process. The function and size of acupoints change with the state of the body, especially the function of their corresponding internal organs [6, 9]. In other words, as the visceral function changes, the functional activity of acupoints switches from the silent mode in physiological condition to the activated or sensitized mode in pathological condition [10, 11].

Our experiment showed that with visceral inflammatory reaction caused by colorectal injection of inflammatory irritant mustard oil, the number of EB exudation points and the average size of receptive field of WDR neurons on body surfaces increased as the visceral inflammatory reaction intensified. The number of exudation points and the size of receptive field were in proportion to the degree of visceral inflammatory reaction. Some researchers presented that C fibers might mediate this neurogenic exudation reaction [12]. Others thought exogenous noxious small organic molecules, such as mustard oil, could activate ion channel of pain TRPA1 [13, 14]. When tissue was damaged, some endogenous compounds might also activate TRPA1 [15] and lead to the increase of permeability and hyperalgesia.

Experiments confirmed that 20–100 mmHg CRD stimulations obviously increased (activated or sensitized) reactions of WDR neurons in the spinal cord $L_{1\sim3}$ induced by noxious and non-noxious stimulations to the receptive field. When EA was applied at the receptive field after CRD stimulation, the discharging activity of WDR neurons notably increased compared to that before the CRD stimulation and the receptive field also expanded. Meanwhile, the discharging activity of WDR neurons increased as the CRD intensified. The two factors presented an obvious linear quantity-effect relationship. It indicated that visceral noxious stimulation caused the sensitization of corresponding acupoints (or positions) on body surfaces and further enhanced the effect of acupuncture.

It is generally believed that when visceral lesions occur, the abnormal phenomenon of hyperpathia on acupoints is the result of the facilitation or sensitization of the function of spinal cord and/or the center up spinal cord. Afferent impulse in internal organs or deep tissue can sensitize wide dynamic range (WDR) neurons and facilitate stronger reactions of the neurons to the afferent nerve on body surfaces [16, 17]. Repeated stimulation to the peripheric receptive fields of neurons in the spinal cord dorsal horn can also lead to the expansion of the receptive field [18]. It suggests that the mechanism behind the change of perigheric receptive field of sensory neurons may relate to the change of acupoint size.

5. Conclusion

Visceral noxious stimulation can increase the number of EB exudation points, reduce the reaction threshold of WDR neurons in the spinal cord dorsal horn, increase background discharge levels, enlarge the receptive fields of neurons, and sensitize the function of acupoints. It demonstrated that the pathological change of internal organs' functional activity lead to the sensitization of spinal center and further to the changes of the size and function of acupoints on body surfaces. The spinal cord takes part in the dynamic process of acupoint sensitization. A linear quantity-effect relationship can be found between the noxious stimulation and the body response.

Conflict of Interests

There is no conflict of interests associated with the coauthors of this manuscript.

Acknowledgments

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Research Article

Efficacy of Acupuncture for Primary Insomnia: A Randomized Controlled Clinical Trial

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Objectives. To investigate the six-week influence of acupuncture on sleep quality and daytime functioning in primary insomnia. *Methods*. The study was a double-dummy, single-blinded, randomized, placebo-controlled clinical trial. A total of 180 patients with primary insomnia were randomly assigned to 3 groups: verum group underwent verum acupuncture plus placebo; estazolam group underwent estazolam plus sham acupuncture; sham group underwent sham acupuncture plus placebo. The outcome was measured by Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and the 36-item short-form health survey (SF-36). *Results*. The three groups showed significant improvement compared with the pretreatment baseline. Compared with the other two groups, the verum group reported improved sleep quality (SQ) and vitality (VT), decreased daytime dysfunction (DD) and sleepiness (ESS score). The differences were kept from the treatment period to the end of the trial. *Discussion*. Verum acupuncture appeared to be more effective in increasing sleep quality and daytime functioning than sham acupuncture and estazolam. *Trial Registration*. The trial is registeded with ClinicalTrials.gov ISRCTN12585433.

1. Introduction

Insomnia is a common clinical complaint. The predominant features are difficulty initiating or maintaining sleep or nonrestorative sleep. Sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning [1].

About 23.2% of adult population in the United States experiences insomnia [2]. The prevalence of insomnia ranges from 11.7% to 37% in some European countries [3–5], 9.2% to 11.9% in Asia [6–8]. The prevalence varies considerably depending on the definition used. When daytime consequences of insomnia are taken into account, the prevalence is between 9% and 15% [9].

Disorders of the sleep-wake cycle have negative impact on daytime functioning. It is considered to be associated with fatigue, sleepiness, decreased alertness, concentration and mood disturbances, and so forth [10–15], although there still remains discrepancy about how to assess daytime impairments objectively [16–19]. In the long run, daytime deficits heighten the risk of absenteeism, impaired work performance [2, 20–22], and higher odds for automobile accidents [23, 24]. The disturbances have resulted in high economic burden [25, 26].

For chronic insomnia, hypnotic medications (benzodiazepine receptor agonists, in particular) and cognitive-behavioral therapy (CBT) are first-line treatments. Benzodiazepine receptor agonists (BZRAs) are efficacious in the short-term management of insomnia. But there is very limited evidence of the long-term treatment efficacy of these agents [27]. They are also related with the adverse effects of residual daytime sedation, cognitive impairment, dependence, and so forth. CBTs have demonstrated efficacy in randomized clinical trials (RCTs). However, these techniques are not widely used due to lack of trained therapists [28]. The guidance for clinicians in choosing the best treatment is limited so far.

As an alternative therapeutic method, acupuncture offers another option for insomnia. It is based on the theory of meridians of Traditional Chinese Medicine (TCM). Meridian

is considered to be a network of passages of the energy power, Qi. According to ancient TCM classic of Nei Jing (Inner Classic), insomnia is a consequence of the vicious cycle of "daytime low-spirit" and "nighttime hyperarousal state." Acupuncture is considered to be beneficial to restore the normal sleep-wake cycle by regulating and restoring the natural flow of Qi. That may explain why acupuncture is usually conducted in daytime but not at night.

Acupuncture is one of the most common therapies for insomnia in China. Nevertheless, its evidence is plagued by methodology design limitation. Ten systematic reviews between 2003 and 2010 on acupuncture treatment of insomnia drew different conclusions. Their results were far from uniform. Only two reviews suggested that acupuncture was beneficial for insomnia [29]. More high methodological quality clinical trials are needed to further study the efficacy of acupuncture for insomnia.

Most of the clinical trials of acupuncture for insomnia focused on the effects of sleep quality; however, daytime functioning was not highly considered. The National Institutes of Health has emphasized the analyses including measures of sleep, daytime functioning, and quality of life [28]. We have conducted a small sample pretest on the influence of acupuncture on daytime functioning and sleep quality of insomnia [30]. The study suggested that insomnia sufferers were usually more energetic at daytime when they undertook acupuncture.

Based on the results from our previous pilot study, we designed a randomized controlled trial to investigate the efficacy of verum acupuncture, estazolam, and sham acupuncture on sleep quality and daytime functioning for insomnia.

2. Methods

2.1. Design. This trial was randomized, double-dummy, single-blinded, and placebo-controlled. It compared the efficacy of verum acupuncture, estazolam, and sham acupuncture for insomnia. Outcome measurements were assessed at baseline, posttreatment period, and 2-month follow-up. The trial was performed according to the principles of the Declaration of Helsinki (Version Edinburgh 2000). The protocol was approved by the Medical Ethical Committee of Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University (Beijing TCM hospital) in August 2009.

2.2. Participants. The patients were recruited mainly by hospital-based advertisements from out-patient clinic of Beijing TCM hospital between August 2009 and May 2011. The inclusion criteria were (1) aged 25–75 years; (2) diagnosed from Diagnostic and Statistical Manual of Mental Disorders-Text Revision, 4th ed (DSM-IV-TR); (3) experienced insomnia for 4 weeks or longer before the start of observation period; (4) not yet received any psychoactive medications.

The exclusion criteria were (1) having depression, anxiety or schizophrenia; (2) diagnosis of serious disease of heart, brain, kidney, or liver; (3) history of sleep apnoea; (4) treatment with investigational drugs in the past six months; (5) ever having acupuncture for insomnia or receiving acupuncture for any indication during the last year; (6) pregnancy, breast-feeding.

After the specified assessor's evaluation, subjects who met the inclusion criteria were instructed that they would be randomly assigned to the verum acupuncture group, the sham group, or the estazolam group. Patients intending to the trial obtained informed consent. Subjects in the sham group were given the choice of extending 4 weeks of treatment with verum acupuncture free of charge after the completion of the trial.

2.3. Sample Size. Based on our previous pilot study of acupuncture for primary insomnia [30], Epworth Sleepiness Scale (ESS) score decrease was 5.19 ± 3.81 in the acupuncture group and 1.90 ± 3.93 in the control group. The difference was statistically significant. Based on 0.9 power to detect a significant difference ($\alpha = 0.05$, two-sided), 50 patients were required for each group. To compensate for a dropout rate of 20%, 60 patients per group were recruited.

2.4. Randomization and Allocation. The computerized randomization scheme was designed by Research Center of Clinical Epidemiology Affiliated to Peking University. The random allocation sequence was generated with a block of 6. Patients' screening sequence numbers were printed outside the envelope, and the group names were printed inside. All envelopes were numbered in sequential order. Then the subjects were randomly assigned to the three groups in a 1 : 1 : 1 ratio.

2.5. Blinding. Patients were blinded to the type of acupuncture and the medicine they received. A double-dummy method was adopted to raise the degree of blindness. The efficacy of verum acupuncture plus placebo drug, estazolam plus sham acupuncture, and placebo drug plus sham acupuncture was compared in the trial. In addition, outcome assessors and statistician were blinded to the group assignments. Due to the procedure of the acupuncture technique, it was not possible to blind the acupuncturists.

2.6. Intervention

2.6.1. Verum Acupuncture Group. Subjects assigned to the verum group were needled at the points of Shenting (DU-24), Sishencong (EX-HN1), Baihui (DU-20), Sanyinjiao (SP-6), and Shenmen (HT-7) using stainless steel needles (0.32 × 40 mm, HuaTuo, China). The acupoints selection was based on our previous study on primary insomnia [30], literature review [31], and the experts' experience in treating insomnia [32]. Baihui (Du-20), Shenting (DU-24), and Sishencong (EX-HN1) were punctured at a depth of 10 mm obliquely. Sanyinjiao (SP-6) was punctured 10 mm straightly and Shenmen (HT-7) was inserted 5 mm perpendicularly. Needle manipulation, that is, lifting and thrusting, rotating or twirling, was applied to achieve "De Qi," a needle sensation of feelings of soreness, numbness, fullness, burning, heaviness, aching, and so forth, based on subjective reporting of the patients [33]. Needles retention was 30 minutes. The acupuncture was performed every other day for six weeks.

One estazolam placebo tablet was taken 30 min prior to bedtime in the day without acupuncture intervention. The placebo medicines were produced by Beijing Yimin Pharmaceutical Co, Ltd. It had exactly the same appearance as true estazolam.

2.6.2. Estazolam Group. In the estazolam group, subjects were treated with estazolam and sham acupuncture for six weeks. Estazolam (1 mg) was given 30 min prior to bedtime every other day. In the day without estazolam intervention, sham acupuncture was conducted by needling the acupoints of Binao (LI-14), Shousanli (LI-10), Yuji (LU-10), and Fengshi (GB-31). According to lecture review and clinical experiences, the acupoints were mainly used for local disease and having no therapeutic effect for insomnia.

Stainless steel needles of the same specifications were inserted superficially at the acupoints and kept for 30 minutes. Manual stimulation and De qi were avoided.

2.6.3. Sham Group. Subjects assigned to sham group were treated with sham acupuncture and estazolam placebo tablet for six weeks. Sham acupuncture treatment was the same as in the estazolam group. In the day without acupuncture intervention one estazolam placebo tablet was given 30 min prior to bedtime.

2.7. Quality Control. All acupuncturists and assessors had at least 15 years of professional experience. They were required to undergo special training prior to the trial to guarantee consistent practices. The training program included diagnoses, inclusion and exclusion criteria, location of the acupoints, acupuncture manipulation techniques, and completion of case report forms (CRFs). Periodic monitoring guaranteed accuracy and quality throughout the study.

2.8. Outcome Measures

2.8.1. Sleep Measures. PSQI is a self-rated questionnaire which assesses sleep quality and disturbances. Nineteen individual items generate seven "component" scores: subjective sleep quality (SQ), sleep-onset latency (SOL), total sleep time (TST), habitual sleep efficiency (SE), sleep disturbances (Dyssomnia), use of sleeping medication, and daytime dysfunction (DD) [34]. Since the medicine was limited in the trial, the component score was omitted.

2.8.2. Daytime Functioning. Epworth Sleepiness Scale (ESS) is a simple, self-administered questionnaire designed to measure the subject's genera1 level of daytime sleepiness [35]. It can be used to evaluate the chance of dozing in the daytime [36].

2.8.3. Quality of Life. SF-36 is constructed to survey health status in the medical outcomes study [37]. It includes 36 self-report items regarding daytime functioning [38]. The items are grouped into 8 dimensions: physical functioning (PF), social functioning (SF), role physical (RP), bodily pain (BP), mental health (MH), role emotional (RE), vitality (VT), and general health (GH) [37].

The questionnaires of ESS, PSQI, and SF-36 used in the trial were Chinese versions proved to be reliable and valid in China [35, 39, 40].

2.9. Statistical Analysis. All analyses were performed on the intention-to-treat (ITT) population of participants who had at least one treatment. Missing data were replaced according to the principle of the last observation carried forward. The significance level used for statistical analysis with 2-tailed testing was 5%. Data values were presented by mean ± SD, 95% confidence intervals (CI), or percentage.

We conducted chi-square test for the case of proportions and analyses of variance (ANOVA) for testing the baseline differences between treatment groups. For PSQI, ESS, and SF-36 scores, Mauchly's test of sphericity was applied to judge whether there were relations among the repeatedly measured data. If any $P \leq 0.05$, multivariate analysis of variance (MANOVA) was performed and data in different groups of each measurement time were compared pairwise. The method of Bonferroni was used to do pairwise comparisons of the repeatedly measured data in different measurement times of each treated group. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.5 statistics software.

3. Results

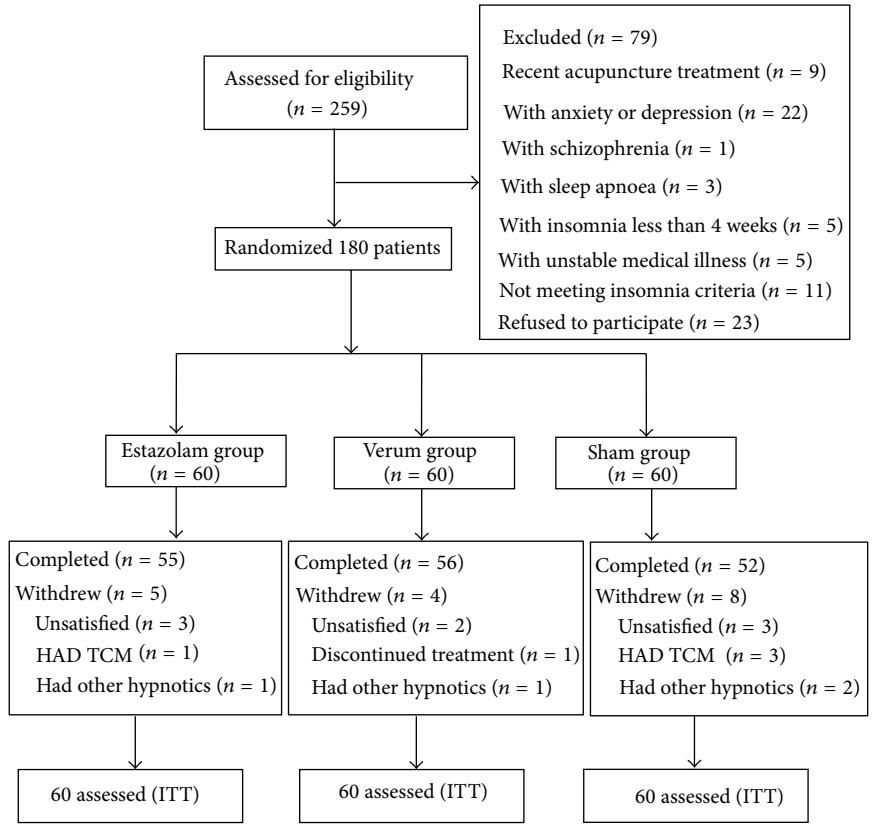
3.1. Study Population (Figure 1). A total of 259 participants were assessed for eligibility; 79 were excluded (23 refused to participate when informed the possibility of being assigned to the sham group, 56 were excluded for having depression, anxiety, schizophrenia, sleep apnoea, and other diseases). 180 patients were randomized to the verum group, estazolam group, or sham group (Figure 1).

Seventeen subjects (9.4%) withdrew during the study period, 5 (8.3%) from the verum acupuncture group, 4 (6.7%) from the estazolam group, and 8 (13.3%) from the sham group. None of the subjects withdrew due to adverse events.

Demographic and Clinical Features (Table 1). Table 1 presents the baseline characteristics. There were no significant differences identified in demographic and clinical features of the three groups. (The baseline data of SF-36 were listed in Table 2.)

3.2. Outcome Measurements

3.2.1. Sleep Measure: PSQI (Figure 2). Figure 2 presents changes of PSQI and subscales among the three groups. Compared with baseline, the verum, estazolam, and sham groups had better global score of PSQI and sleep quality, decreased sleep-onset latency and dyssomnia, longer sleep duration (only in the estazolam group), and higher sleep efficiency (not obvious in the sham group) ($P < 0.05$). Daytime dysfunction score increased in the estazolam group while decreased in the verum group ($P < 0.05$). However, most of the variables returned to baseline level at follow-up



ITT; intention to treat.
Verum group: verum acupuncture + placebo;
Estazolam group: estazolam + sham acupuncture;
Sham group: sham acupuncture + placebo.

Figure 1: Trial profile.

Table 1: Demographic and clinical characteristics of the ITT population (Mean ± SD).

Variables	Verum group ($n = 60$)	Estazolam Group ($n = 60$)	Sham Group ($n = 60$)	x^2 F value	P value
Age, years	47.5 ± 13.3	50.1 ± 15.6	49.2 ± 12.0	0.54	0.59
Sex, male/female	19/41	21/39	18/42	0.36	0.84
Education attainment, y	10.2 ± 3.5	9.7 ± 4.2	11.4 ± 3.7	0.42	0.25
Insomnia duration, y	6.3 ± 2.1	5.7 ± 3.9	6.2 ± 4.8	0.33	0.57
Married	40	39	42		
Widowed	9	10	9	0.45	0.98
Single/separated/divorced	11	11	9		
Chronic medical illness	7	4	9	2.14	0.34
ESS	8.4 ± 2.7	8.2 ± 2.1	8.9 ± 2.2	1.26	0.29
PSQI total score	11.5 ± 2.0	12.1 ± 1.8	11.9 ± 2.2	1.42	0.24
SQ	2.8 ± 0.7	2.6 ± 0.6	2.5 ± 0.8	2.30	0.10
SOL (min)	55.5 ± 10.9	59.0 ± 13.1	56.0 ± 13.1	1.39	0.25
TST (min)	285.0 ± 54.5	273.0 ± 62.7	263.0 ± 59.1	2.10	0.12
SE (%)	70.2 ± 10.8	73.5 ± 8.9	71.6 ± 10.6	1.57	0.21
Dyssomnia	1.4 ± 0.7	1.5 ± 0.9	1.5 ± 0.8	0.33	0.72
DD	2.2 ± 0.7	2.1 ± 0.7	2.1 ± 0.6	0.53	0.59

ITT: intention to treat. verum group: verum acupuncture + placebo; estazolam group: estazolam + sham acupuncture; sham group: sham acupuncture + placebo. ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; SQ: sleep quality; SOL: sleep-onset latency; TST: total sleep time; SE: sleep efficiency; DD: daytime dysfunction; results from x^2 or ANOVA test for categorical and quantitative variables, respectively.

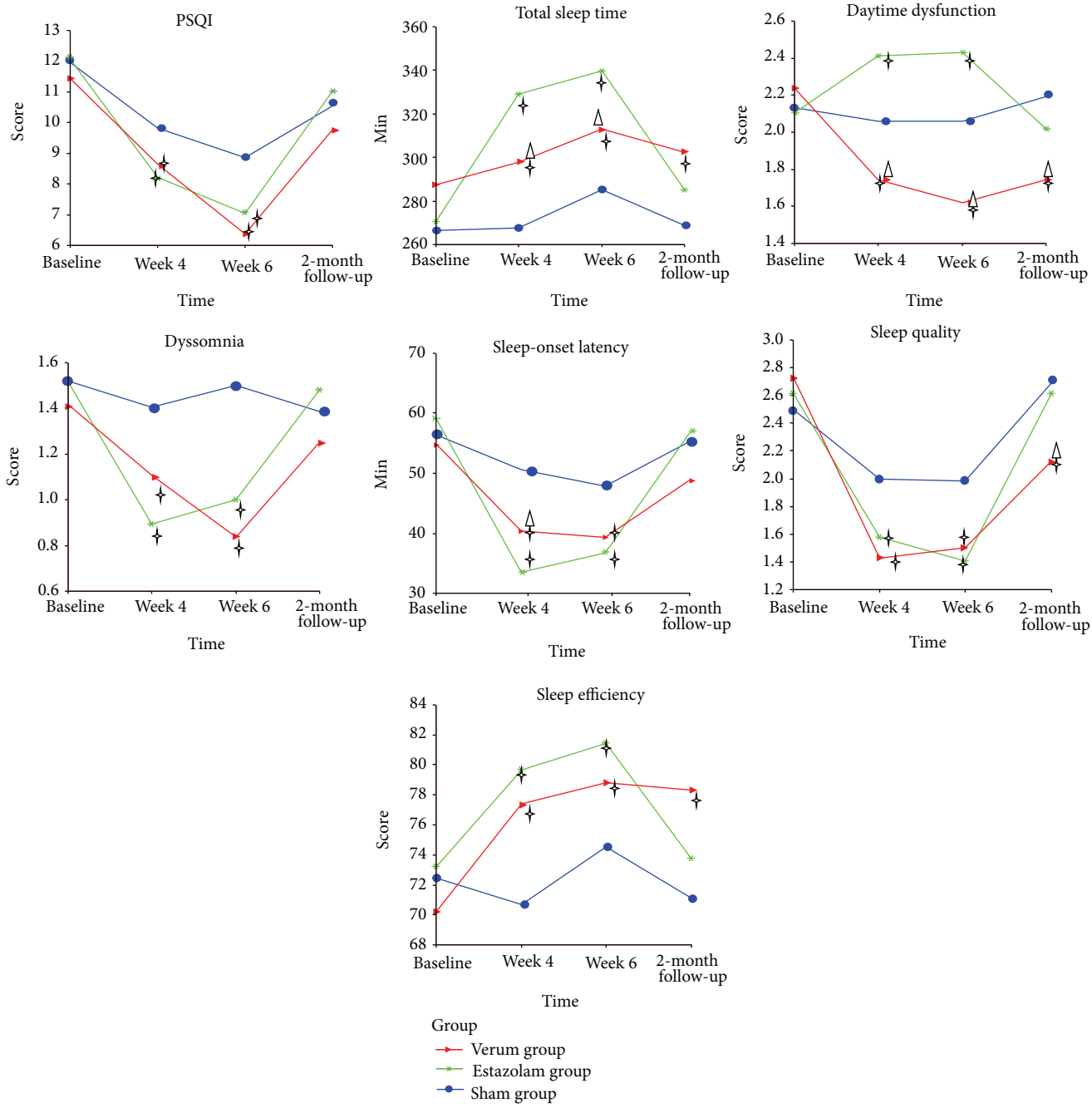


Figure 2: Change in Pittsburgh Sleep Quality Index and subscale scores at different times. Using repeated measures and multivariate analysis of variance (MANOVA) process of the general linear model and giving comparison among different groups and different measure time pairwise. $^{\dagger}P < 0.05$, versus sham acupuncture group at the same time point. $^{\triangle}P < 0.05$, versus estazolam group at the same time point.

in the sham and estazolam groups. The significant differences in SQ, TST, SE and DD were well maintained to follow-up period in the verum group ($P < 0.05$). Subjects in verum group had lower DD and higher SQ scores than those receiving estazolam and sham acupuncture ($P < 0.05$). Both the verum and estazolam groups had significantly reduction in most of PSQI subscale scores at posttreatment compared with the sham group ($P < 0.05$). Whereas the difference in PSQI total score, SOL was not significant among the three groups at the 2-month follow-up.

3.2.2. Daytime Functioning

Epworth Sleepiness Scale (ESS) (Figure 3). Figure 3 shows ESS data. There was significant decrease compared with baseline in the verum and sham groups. In the estazolam group, ESS score increased at the treatment phase and returned to baseline at follow-up. Compared with estazolam and sham groups, verum acupuncture group showed significant reduction in ESS score at the treatment and follow-up period ($P < 0.05$).

Table 2: Change in SF-36 (Mean ± SD) from baseline to 2-month follow-up.

Item timepoint	Verum group	Estazolam group	Sham group	*P*		
				Verum versus sham	Verum versus estazolam	Estazolam versus sham
PF						
Baseline	85.6 ± 10.8	88.1 ± 8.3	86.4 ± 10.4			
Week 6	88.4 ± 9.6	89.8 ± 6.4	87.7 ± 8.5	0.68	0.35	0.18
2-month follow-up	89.8 ± 7.7	87.9 ± 8.3	86.6 ± 9.1	0.05	0.24	0.42
RP						
Baseline	53.5 ± 10.0	55.1 ± 13.5	56.3 ± 10.9			
Week 6	63.1 ± 12.5*	64.2 ± 13.4*	59.7 ± 13.3	0.18	0.63	0.07
2-month follow-up	61.4 ± 14.3*	58.5 ± 16.7	57.2 ± 13.4	0.15	0.31	0.66
BP						
Baseline	84.7 ± 12.9	87.1 ± 8.0	85.3 ± 10.0			
Week 6	87.0 ± 13.6	89.7 ± 10.1	86.6 ± 11.3	0.85	0.24	0.18
2-month follow-up	86.3 ± 15.8	87.7 ± 13.8	83.5 ± 13.2	0.30	0.63	0.13
GH						
Baseline	35.7 ± 10.1	36.1 ± 8.6	33.2 ± 6.9			
Week 6	38.0 ± 10.2	36.0 ± 10.9	34.7 ± 10.6	0.11	0.31	0.53
2-month follow-up	36.6 ± 8.6	34.5 ± 10.7	33.8 ± 8.1	0.11	0.21	0.69
VT						
Baseline	36.8 ± 9.4	33.6 ± 9.9	34.4 ± 7.1			
Week 6	44.6 ± 13.1*	32.1 ± 10.1	37.7 ± 10.5	0.002	<0.001	0.01
2-month follow-up	42.3 ± 12.0*	32.1 ± 8.5	35.4 ± 10.0	0.001	<0.001	0.10
SF						
Baseline	73.6 ± 12.0	75.6 ± 9.7	72.1 ± 10.4			
Week 6	81.6 ± 11.5*	80.7 ± 17.0*	74.4 ± 15.7	0.02	0.75	0.03
2-month follow-up	76.3 ± 13.9	77.9 ± 15.6	73.0 ± 13.0	0.24	0.56	0.08
RE						
Baseline	31.3 ± 7.7	33.4 ± 6.3	32.3 ± 9.0			
Week 6	37.4 ± 19.5*	42.1 ± 16.5*	33.8 ± 17.0*	0.29	0.16	0.02
2-month follow-up	38.0 ± 16.4*	34.3 ± 14.3	31.8 ± 16.2	0.04	0.21	0.42
MH						
Baseline	48.1 ± 19.0	41.1 ± 18.4	47.5 ± 13.2			
Week 6	52.2 ± 17.9	54.3 ± 20.8*	48.6 ± 17.2	0.32	0.56	0.12
2-month follow-up	50.0 ± 19.3	48.6 ± 19.9	44.7 ± 14.6	0.14	0.70	0.27

SF-36: 36-item short-form health survey; MH: mental health; PF: physical functioning; RP: role-physical; BP: bodily pain; VT: vitality; GH: general health; SF: social functioning; RE: role-emotional.
Data from multivariate analysis of variance (MANOVA) and repeated measures. (Mauchly's test of sphericity: $P < 0.05$.) * Comparison within each group with baseline $P < 0.05$.

3.2.3. Quality of Life

SF-36 (Table 2). Table 2 presents the data of SF-36. Compared with baseline, role physical and social functioning were improved in the verum and estazolam groups; role emotional was improved in the three groups ($P < 0.05$). The verum group reported greater feeling of vitality compared with baseline.

Verum acupuncture showed significant improvement in VT compared with the other two groups. Both the verum acupuncture and estazolam groups resulted in obvious improvement in SF, RE scores compared with the sham group ($P < 0.05$).

3.2.4. Other Clinical Outcomes

(1) Needle Sensations Measuring (Figure 4). Figure 4 presents the ratio of De qi points to total points. The subjects were required to describe the needle sensation of every acupoint when needle manipulation was performed (tingling, burning, heaviness, fullness, numbness, soreness, and aching, etc.). De qi sensation was recorded "Y" and "N" for no obvious

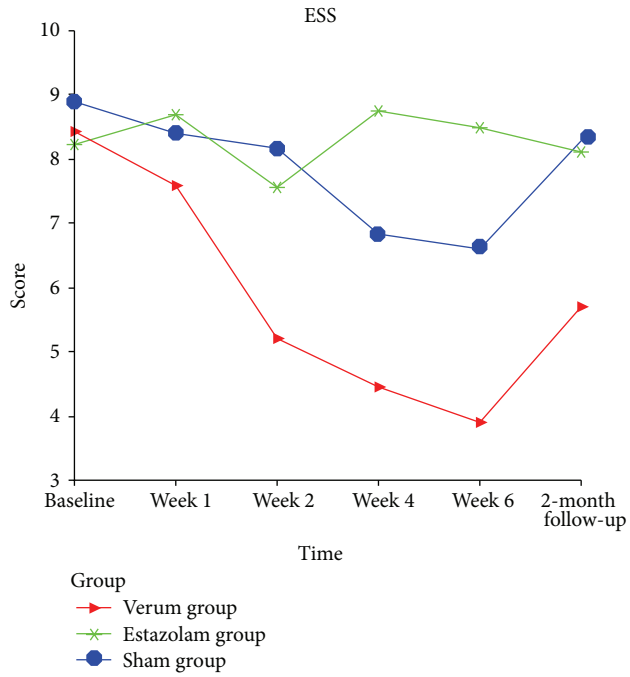


Figure 3: Change in Epworth Sleepiness Scale score from baseline to 2-month follow-up. Data from repeated measures and multivariate analysis of variance (MANOVA) process of the general linear model.

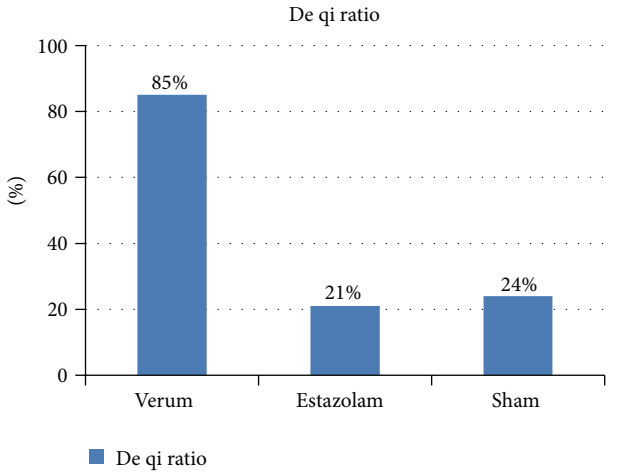


Figure 4: De qi ratio. De qi ratio means the ratio of De qi points to total points in three groups.

sensation. In the verum group, De qi sensation was obvious in 85% acupoints, while in the sham and estazolam groups De qi sensation was reported in only 24% and 21% acupoints. The results showed that De qi manipulation was well controlled in the trial.

(2) Adverse Events (Table 3). In the verum acupuncture group 15 subjects developed local hematoma, 5 subjects complained of headache, and 5 subjects reported dizziness. In the estazolam group 18 subjects had local hematoma, 10 subjects reported headache, and 7 subjects developed dizziness. In the sham group 11 subjects developed local hematoma, 12 subjects reported headache, and 6 subjects developed dizziness. A total of 10 subjects had local muscle convulsion. All adverse events were mild.

Table 3: Adverse events.

Symptom Group	Number	Severity	Disposal	Result
Local hematoma				
Verum	15			
Estazolam	18	Mild	Cold compress	Reablement
Sham	11			
Headache				
Verum	5			
Estazolam	10	Mild	Resting	Reablement
Sham	12			
Dizziness				
Verum	5			
Estazolam	7	Mild	Resting	Reablement
Sham	6			
Muscle convulsion				
Verum	2			
Estazolam	6	Mild	Massage	Reablement
Sham	2			

4. Discussion

This study was a double-dummy, single-blinded, randomized, placebo-controlled clinical trial. The aim was to investigate the efficacy of acupuncture in patients with primary insomnia.

The results of the present trial showed that all treatments were effective compared with pretreatment baseline. Improvements of sleep quality, total sleep time, sleep efficiency, daytime functioning achieved in the verum group were well maintained to follow-up, whereas the effect of sham acupuncture and estazolam was not significant when the intervention ended.

Verum acupuncture was better than sham acupuncture and estazolam in improving sleep quality (at 2-month follow up). One of the most notable results of the trial was that verum acupuncture could significantly improve daytime functioning. Subjects in verum group achieved lower DD and ESS scores compared with the other two groups. They reached higher VT (the feeling full of energy [37]) scores at the same time. No significant within-group and between-group differences in PF, BP, and GH were detected. The possible reason might be that most of the subjects in our clinic were young and middle-aged and their health-related quality of life was not affected by insomnia critically. Thus, the SF-36 was not sensitive enough to detect the health status for insomnia on the cohort of patients recruited in our study.

Few studies used placebo acupuncture as comparison for investigating the efficacy of acupuncture in insomnia. The results of our trial can be compared with those obtained in

an RCT by Yeung et al. [41], which compared electroacupuncture with placebo acupuncture. Compared with noninvasive placebo acupuncture, electroacupuncture showed statistically significant improvements in SE in their study. By contrast with the trial by Yeung et al., our data suggested that verum acupuncture could produce significant improvements in sleep quality, total sleep time, sleep efficiency, and daytime functioning than sham acupuncture. The differences might be due to different treatment durations (3 weeks versus 6 weeks), differences of the acupuncturists, acupoints, and needle manipulation procedures.

Double-dummy technique in our trial might also attributed to the difference. The technique was common in clinical drug trials [42, 43], and it has been tried in some clinical trials with acupuncture, for example, the trial which demonstrated the efficacy of acupuncture for migraine prophylaxis [44]. The design helped to increase compliance. In Chinese acupuncture clinic, it is difficult to only prescribe west medicine to a subject in a trial, which will result in high dropout rate. Double-dummy control of placebo medicine and sham acupuncture was applied in our trial to make blinding practicable.

In our trial the function of De qi was considered. "De qi" was based on subjective reporting of the patient (soreness, numbness, fullness, radiating sensation, etc.) and was regarded as a sign of efficacy according to TCM. Most contemporary acupuncturists still seek De qi and believe it fundamental for efficacy [33]. Manual stimulation was applied to the verum group, and the results showed that De qi sensation was obvious in 85% acupoints, which ensured the efficacy of verum acupuncture. With nonspecific points and no manual stimulation, De qi sensation was reported only in 21–24% acupoints in the sham and estazolam groups. The placebo effect produced by sham acupuncture was considered to have less influence upon the disease, although needle pricking might induce nonspecific physiological reactions. The significantly improvements of verum acupuncture than sham acupuncture demonstrated the importance of De qi.

According to TCM theory, the states of "energetic daytime function" and "powerful nocturnal sleep" form a circulation. If the circle is broken, the vicious spiral of "daytime low-spirit" and "nighttime hyperarousal state" will occur. Acupuncture is considered to play an important role in reestablishing the normal sleep-wake cycle. The result of the present study was in accordance with the theory.

Points selection is crucial for efficiency. Based on literature review and TCM clinical experiences, Shenting (DU-24), Sishencong (EX-HN1), Baihui (DU-20), and Shenmen (HT-7) are most common in the treatment of insomnia, depression, anxiety, and so forth. Sanyinjiao (SP-6) is important to induce sedation and tranquilization. The points of sham group are mainly for local disease, having no relationship with treatment for insomnia. The results showed the overall effect of verum acupuncture on both nocturnal sleep and daytime functioning.

As a benzodiazepine derivative, estazolam is efficacious in increasing sleeping time as well as reducing awakenings during the night [45]. It was chosen as the control drug for its wide applications in the treatment of insomnia in China. As hypnotic drugs are recommended to be used preferably intermittently rather than regularly [46], estazolam was given every other day in our trial.

The present study was limited by the lack of objective sleep assessments. It should be complement with multiple sleep latency test (MSLT), polysomnography or actigraph. One potential limitation was the lack of assessment of cognitive abilities problems (e.g., attention, concentration, and memory), for the related questionnaires (e.g., Dysfunctional Beliefs and Attitudes About Sleep Scale, the Pre-Sleep Arousal Scale, and the Sleep Hygiene Awareness and Practices Scale) were not widely used in China. Subgroups classification should also be considered, such as difficulty initiating and maintaining sleep or nonrestorative sleep. The previous study has suggested that some subgroups of patients with insomnia might be more inclined to increase sleepiness [38].

The present trial showed that ESS scores of estazolam group were not stable at the treatment time. It was considered that daytime somnolence was the most common adverse event of estazolam and would result in increased ESS scores. The somnolence effect usually ended by noon [47]. So different time points of assessment would lead to ESS score difference. The assessment time point should be taken into account in future research.

In summary, our study presented some important data on the treatment of primary insomnia with acupuncture. The trial implied that verum acupuncture was superior in improving sleep quality and daytime functioning of primary insomnia compared with estazolam and sham acupuncture. Further research could be conducted with objective measure (PSG, MLST), subgroup design, and assessment of cognitive abilities problems.

Disclosure

This was not an industry supported study. It was not for any off-label or investigational use. The authors have indicated no financial conflict of interests.

Conflict of Interests

The authors declared that they had no conflict of interests.

Authors' Contribution

Lin-Peng Wang, Jing Guo, Cun-Zhi Liu, and Jie Zhang contributed to the design of the study and drafting the paper. Jing Guo wrote the final paper. Gui-Ling Wang, Jing-Hong Yi, and Jin-Lian Cheng participated in the design of the trial. All authors read and approved the final paper.

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Research Article

Investigating the Effects of Three Needling Parameters (Manipulation, Retention Time, and Insertion Site) on Needling Sensation and Pain Profiles: A Study of Eight Deep Needling Interventions

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Introduction. In traditional Chinese acupuncture, needle sensation (*deqi*) is purported to contribute to a therapeutic outcome. While researchers have attempted to define *deqi* qualitatively, few have examined the effects of needling parameters on its intensity. *Methods*. 24 healthy subjects completed eight interventions scheduled at least one week apart, which involved manual acupuncture to LI4 or a designated nonacupoint (NAP) on the hand, with real or simulated manipulation each three minutes and needle retentions of one or 21 minutes. Intensities of needling sensation and pain were reported every three minutes and sensation qualities were reported post-intervention. *Results*. Immediately after needle insertion, similar levels of mean needle sensation and of pain were reported independent of intervention. At subsequent measurement times, only two interventions (one at LI4 and one at NAP) maintained statistically significantly elevated needle sensation and pain scores and reported higher numbers of needle sensation descriptors. For both, the needle was retained for 21 minutes and manipulated every three minutes. Neither intervention differed significantly in terms of levels of pain, and needle sensation or numbers and qualities of needle sensation described. *Conclusion*. In this group of healthy subjects, the initial needling for all eight interventions elicited similar levels of needle sensation and pain. These levels were only maintained if there was ongoing of needle manipulation and retention of the needle. By contrast, the strength of needle sensation or pain experienced was independent of insertion site.

1. Introduction

Many traditional Chinese acupuncturists consider the elicitation of *deqi* (needling sensation) during needling as essential for a therapeutic outcome [1]. *Deqi* is often described by acupuncture recipients as a constellation of sensations including soreness, numbness, distension, aching, or heaviness [2]. However, it is only in recent decades that research has been undertaken to determine the nature of the *deqi* phenomena and develop reliable instruments to measure and quantify the sensations that arise during acupuncture [3].

Interestingly, on one hand, authors strive to differentiate those needle sensations that they regard as aspects of *deqi* from ones that reflect the acute pain associated with needle insertion and retention. Yet, on the other hand, various psychometric instruments developed to measure the qualities and often the intensities of the *deqi* sensations tend to have much in common with both the content and approaches that characterise the reliable and valid McGill Melzack Pain Questionnaire (MMPQ). This is not unexpected, since Melzack [4, 5] and colleagues cast widely for descriptors (sensory, affective, and evaluative) that people used to describe pain and then grouped them into categories of similar sensation, and within each grouping, ordered the terms from minimally discomforting or painful, through to the most intense.

In an early example, Vincent and colleagues [6] in 1989 adapted the MMPQ to create a new scale of 20 sensory descriptors to measure the sensations of acupuncture. Interestingly, in this study, with a sample of 65 volunteers, needling both at acupoints and nonacupoints provoked similar levels

of needle sensation on the scale, suggesting that *deqi* was not exclusive to acupoints. This instrument, as with others that grew out of the MMPQ, has been criticised for these origins from a pain questionnaire and consequently of potentially measuring pain in addition to the supposedly nonpainful sensations arising from acupuncture [7].

A range of psychometric instruments to measure *deqi* has subsequently been developed. Common modifications have been to select only a subset of the 20 categories included in the MMPQ and to expand single descriptors from the MMPQ into a Visual Analogue Scale (VAS) or similar scale, where the intensity of that one quality can be further refined: for example, ache, tingling, numbness, with each ranging from none to unbearable [8]. In some instruments, the descriptors have been sourced from subjects after receiving acupuncture. Others have included descriptors selected by acupuncturists. For example, MacPherson and Asghar [9] developed a classification of needle sensations associated with *deqi* based on ratings by 20 TCM acupuncture experts. Two clusters of sensations were identified. One was linked with *deqi* (aching, dull, heavy, numb, radiating, spreading, and tingling) while the other related to acute needling pain (burning, hot, hurting, pinching, pricking, sharp, shocking, stinging, and tender). White and colleagues [10], based on their qualitative interviews with patients, developed the 17-item Southampton Needle Sensation Questionnaire (SNSQ). Kong et al. [8] developed the Massachusetts General Hospital Acupuncture Sensation Scale (MASS) which uses 13 Likert scales for 12 sensory descriptors as well as a scale for other sensations, a mood scale and an acupuncture sensation spreading scale. It has been translated into the Chinese language for use in Asia [11]. Benham et al. [1] used a modified single VAS for recording and monitoring *deqi* sensations while Kou et al. used several scales for recording five *deqi* sensation variables [12].

While many authors have attempted to define the qualities that make up the *deqi* experience, few studies have evaluated the influence of needling parameters such as depth of needling, presence or absence of needle manipulation, and duration of needle retention on the presence and maintenance of the *deqi* sensation [1, 13]. The present study examined three such needling parameters in relation to the reporting of *deqi* by healthy subjects as measured by a single VAS. In addition, it reported the qualities of the needle sensation experienced and the intensity of pain at the needling site. The three parameters studied were site of needle insertion, needle manipulation, and duration of needle retention.

This research comprised one component of a comprehensive examination of the effects of different needling parameters on regional pressure pain threshold. All subjects received the same baseline threshold measurements prior to each needling session: this involved them relaxing supine on a treatment table for ten minutes while pressure pain threshold (identified by the subjects as when the pressure sensation first becomes discomforting) was measured with an algometer at sites on the limbs and head. Ethics approval was obtained from the University of Technology, Sydney (UTS) Human Research Ethics Committee prior to commencing the study (UTS HREC 2009-067A). This study closely follows the design and protocols developed in 1999 at UTS and applied to related research into acupuncture and pressure pain threshold in six previous postgraduate research programs [14, 15].

2. Aim

The aim is to investigate the effect of three needling parameters on the strength and quality of *deqi* (henceforth referred to as "needle sensation") reported and the strength of pain at the needling site. The three parameters comprised site of needle insertion, needle manipulation, and duration of needle retention. Outcome measures were quantitative VAS reporting of intensity of pain and of needle sensation. Qualitative descriptors of the needle sensation were also recorded.

3. Methods

3.1. Study Design. The study formed one arm of a comprehensive examination of the effects of different acupuncture needling parameters on regional pressure pain threshold in healthy subjects. This needling component of the overall research employed a randomised single blind (subject) within subjects with repeated measures design using a standardised protocol.

3.2. Subjects. The 24 study subjects (12 men and 12 women) were volunteers from the broader university staff and student community, recruited via the UTS Faculty noticeboards and/or word of mouth. Study inclusion criteria were healthy adults with no medical history of chronic musculoskeletal disorder, aged between 18 and 45. Exclusion criteria included regular users of analgesic or other drugs that may dampen pain perception, haemophilia, and use of anticoagulant medication that may interfere with blood clotting. Participants were required to abstain from analgesic medication on experimental intervention days.

3.3. Interventions. For each intervention session, a single 0.22 mm × 30 mm sterile stainless steel disposable needle (Viva USA) was inserted at either the acupoint, LI4 or the nonacupoint, NAP and for either one or 21 minutes. Insertion on all occasions was perpendicular (90°) to the skin and to a depth of 15–20 mm, thereby not only puncturing the skin but also underlying structures such as muscle, fat, and fascia. The intervention was applied unilaterally on the right arm. The needling parameters examined, site of insertion, needle manipulation, and needle retention time, are defined below.

3.3.1. Site of Needle Insertion. LI4: acupoint, located as the highest point of the *adductor pollicis* muscle when the thumb is adducted [16].

NAP: nonacupoint located within the same dermatome as LI4, on the dorsal aspect of the hand, midway along the medial shaft of the second metacarpal bone (see Figure 1). This point is equidistant between the two extra acupoints *luozhen* (stiff neck) and *yao tong xue* (low back pain acupoint). No reference to a classical acupoint at this site has been documented [17, 18].

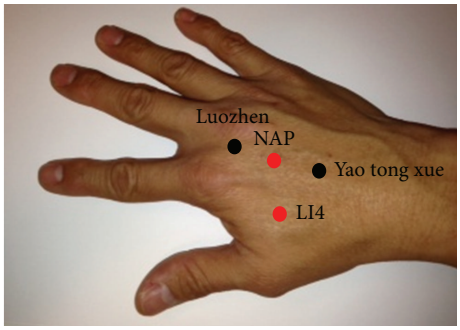


Figure 1: Location of LI4 and NAP in relation to the two extra acupoints *luozhen* and *yao tong xue*.

Table 1

Intervention	Site	Retention time	Manipulation
LI4m^{+1}	LI4	1 minute	Present
LI4m^{-1}	LI4	1 minute	Absent (simulated manipulation)
LI4m^{+21}	LI4	21 minutes	Present
LI4m^{-21}	LI4	21 minutes	Absent (simulated manipulation)
NAPm^{+1}	NAP	1 minute	Present
NAPm^{-1}	NAP	1 minute	Absent (simulated manipulation)
NAPm^{+21}	NAP	21 minutes	Present
NAPm^{-21}	NAP	21 minutes	Absent (simulated manipulation)

3.3.2. Needle Manipulation. Manipulation present—needle manipulation involved rotating the needle for five seconds between the thumb and index finger through a large 540–720° angle in a bidirectional manner. This was applied every three minutes.

Manipulation absent—every three minutes, the acupuncturist rested his hand in the same position as above and lightly moved his fingers on the back of the subject's hand to mimic movements that would accompany needle manipulation. This is referred to as "simulated manipulation."

3.3.3. Needle Retention Duration. Duration of needle insertion was either one minute or 21 minutes. Note that for the one minute duration needling interventions, the needle was only present during this initial period (t = 0-1). However the acupuncturist applied simulated manipulation of the "virtual" needle every three minutes throughout the 21-minute "intervention" period, as described above. At 21 minutes, the acupuncturist ensured that the "removal" of the "needle" was evident to the subject.

3.3.4. Intervention Parameter Combinations. Each intervention involved deep needle insertion and one of the following eight sets of parameters (Table 1).

Outcome Measures: *Subjects' Perceptions of Intervention Needle Sensation and Pain.* Needling sensation was defined for the subjects as *any sensation other than needling pain*. Subjects quantified the intensity of the needle sensation using a 100 mm VAS designated to range from no sensation/pain to intense sensation/pain. For all interventions, every three minutes, subjects reported in turn: needling sensation (*Do you feel any needling sensation at this point in time*) and pain intensity (*Are you experiencing pain at present*) on a 100 mm VAS with a sliding scale (held up for them by the acupuncturist). These measurements occurred immediately after true or simulated manipulation and the VAS scores were recorded by the acupuncturist. At each measurement occasion, subjects were encouraged to describe the needle sensations they were reporting, as a check on their understanding of reporting needle sensation rather than pain. At the completion of each session, subjects recorded global needle sensation and pain ratings, again using a 100 mm VAS. Where they recorded a needle sensation they included a written description of the sensations experienced.

3.4. Intervention Sequence Allocation. Since all subjects received four interventions to each of two needling sites, it was assumed that they would realise that two locations were being used. In previous studies that have used the same protocol and insertion sites, postintervention feedback from subjects (many of whom were final year acupuncture interns at UTS) showed that while most subjects were aware of different locations being needled, both sites were thought to be acupoints and the NAP location was even reported by some subjects to be an extra point [19].

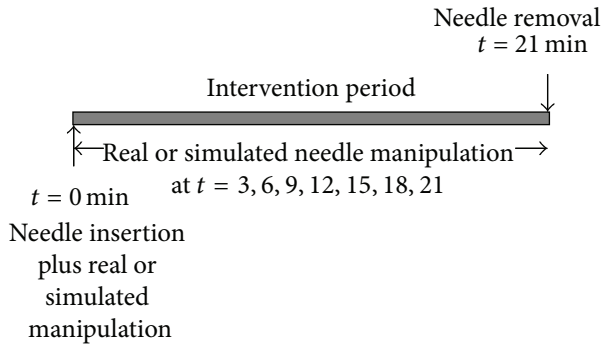
To control for possible changes in expectations that might gradually develop during the eight experimental sessions, careful stratified randomisation of presentation order of interventions was implemented. This included using an 8×8 matrix to allocate the order of intervention presentations across the 24 subjects so that there would be equal numbers of subjects completing each intervention at sessions one through to eight. Thus, all interventions were similarly exposed to potential changes in expectations based on the varying extent of exposure by different subjects to the set of interventions.

A random sequencing of the eight interventions for each subject was achieved using an envelope method that was also stratified by gender to match as closely as possible the sequencing by gender. Each sequence was printed on a slip of paper and sealed into an individual envelope marked F or M. At the beginning of their first session, the subjects chose one of the available envelopes and this determined their unique sequence of interventions. Each subject completed eight intervention sessions spaced at least one week apart.

Throughout the 21 minute intervention period, a curtain was positioned to prevent subjects from observing their right arm and the acupuncturist's activities. This both standardised and restricted interactions with the acupuncturist and facilitated his realistic application of simulated manipulation to an actual or virtual needle. The same acupuncturist applied all interventions; the 21 minute intervention period was standardised; manipulation was applied or simulated every three minutes; all subjects completed all study interventions and data were not analysed until the end of the study to avoid possible biases related to researcher expectations.

3.5. Intervention Procedure. Throughout each session, the subject lay supine on the treatment table. Prior to receiving each intervention, as part of the broader research program, a standardised series of baseline pressure pain threshold measurements were recorded from ten regional sites. The study's acupuncturist (with >35 years of clinical experience) then initiated the 21-minute intervention protocol for this arm of the research, summarised in the following timelines.

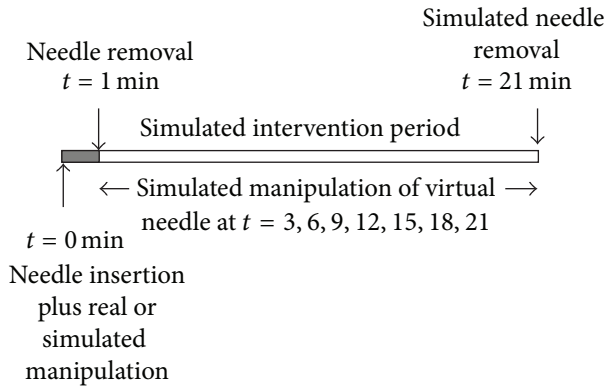
Timeline for the four interventions with needle retention for 21 minutes



(i) Real or simulated needle "manipulation" at $t = 0, 3, 6, 9, 12, 15, 18, 21$.

(ii) VAS pain and needle sensation scores recorded at $t = 1, 4, 7, 10, 13, 16, 19, 22$.

Timeline for the four interventions with needle retention for one minute



(i) Real or simulated needle "manipulation" at $t = 0$.

(ii) Simulated "needle" manipulation at $t = 3, 6, 9, 12, 15, 18, 21$.

(iii) VAS pain and needle sensation scores recorded at $t = 1, 4, 7, 10, 13, 16, 19, 22$.

3.6. Statistical Analyses. Statistical analyses comprised one way ANOVA for correlated samples with Tukey post hoc testing, Chi square I (goodness of fit), and basic descriptive statistics for each time interval and intervention.

4. Results

4.1. Needle Sensation and Pain Intensity Profiles during the Intervention Period. In Figure 2, the left hand graph displays the mean needling pain intensity scores (% of 100 mm VAS) for the eight interventions at three-minute intervals during the 21-minute intervention period. The right hand graph presents the mean needle sensation intensity scores similarly.

At time $t = 1$, there was no statistically significant difference between the interventions for either the mean VAS scores for pain (ANOVA $F_{7,161} = 1.74$, $P = 0.103$) or for needle sensation (ANOVA $F_{7,161} = 0.48$, $P = 0.85$). Mean values ranged from 6.7% to 16.9% for pain and 15.9% to 21.8% for needle sensation. However at the subsequent time intervals, these elevated levels were either maintained (for two interventions) or fell away rapidly for the remaining six. As a result, at time intervals $t = 4$ through to $t = 22$, there were multiple statistically significant differences among the means for pairs of interventions for both needle pain (ANOVA F statistic values between 5.33 and 12.54, $P = 0.000$ in all cases) and needle sensation means (ANOVA F statistic lay between 4.07 and 9.19, $P = 0.000$ in all cases). For both sets of profiles, post hoc Tukey testing revealed similar statistically significant patterns that included the following main features. Both interventions that involved 21-minute needle retention and ongoing manipulation maintained similarly elevated mean VAS scores that did not differ statistically significantly from each other, at each measurement period (in all cases for both pain and needle sensation, the values of the ANOVA F statistics lay between 1.48 and 0.0, with associated P values of between 0.24 and 0.95). For pain the mean elevations were between 16% and 18% and for needle sensation were between 12% and 19%.

With respect to both needling pain and needle sensation, the sets of profiles for the remaining six interventions showed similar, rapid decreases in mean scores. In all intervention comparisons, for pain and needle sensation, the values of the ANOVA F statistics for the individual measurement times lay between 1.94 and 0.27, with associated P values of between 0.09 and 0.93. By $t = 4$, the mean pain scores were <4% for all six intervention profiles and for needle sensation the mean scores were <7% by $t = 7$.

These two patterns within the sets of profiles reflected statistically significant differences. With the pain profiles, post hoc analyses (Tukey post hocs, in all cases statistical significance at least $P < 0.05$) showed that the LI4m^{+21} intervention mean VAS levels were statistically significantly higher than those for the six interventions that did not involve 21-minute duration and manipulation, for all time intervals from $t = 4$ to $t = 22$, with the single exception of NAPm^{+1} at $t = 10$. For the similar NAPm^{+21} intervention, the mean VAS scores were also statistically significantly higher than all other interventions from $t = 7$ to $t = 22$ and also for LI4m^{-21} and NAPm^{-1} at $t = 4$.

The needle sensation profiles for both LI4m^{+21} and NAPm^{+21} showed similar patterns to those for needling pain. However, there were more comparisons where their mean increases did not differ statistically significantly from the means for the remaining six interventions. This was the case

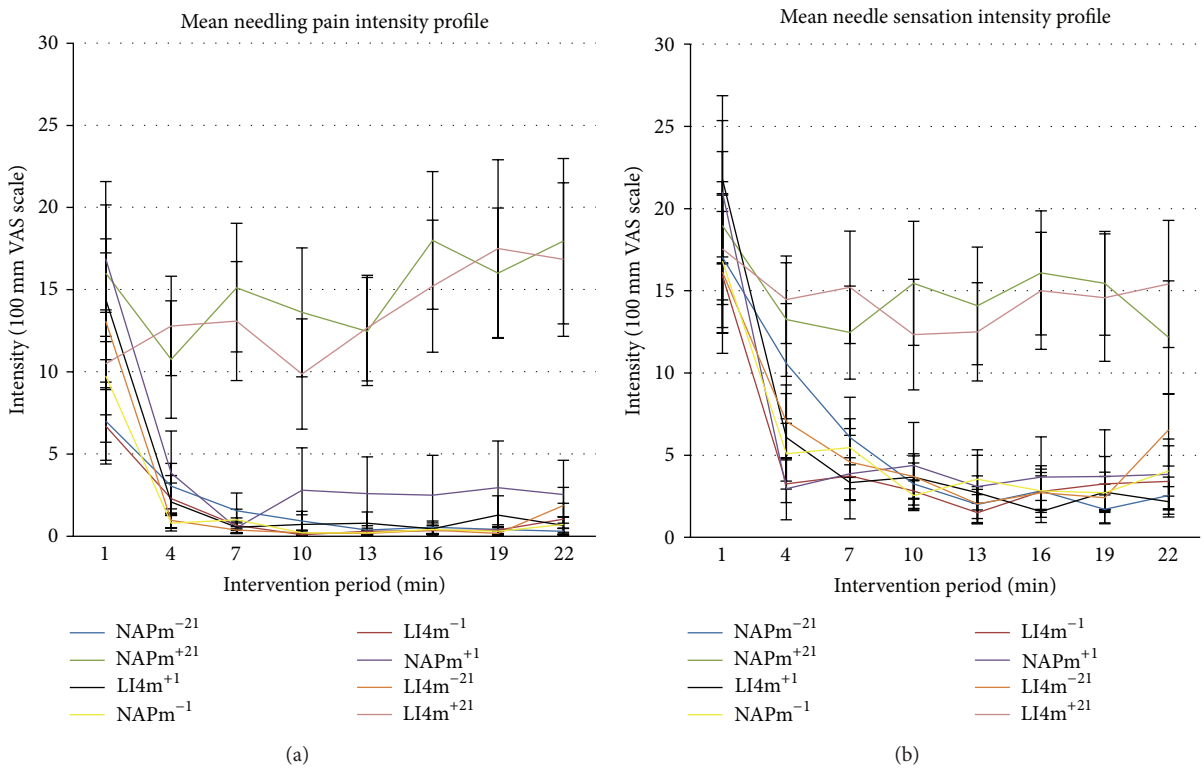


FIGURE 2: The mean pain intensity scores (left hand graph) and the mean sensation intensity scores (right hand graph) for the eight interventions at three-minute intervals during the 21-minute intervention period. The error bars depict ±1 standard error of the mean. The same colour key applies to both graphs.

for both interventions for four comparisons at $t = 4$ ($LI4m^{+1}$, $NAPm^{-1}$, $LI4m^{-21}$, $NAPm^{-21}$) and for one at $t = 7$ (with $NAPm^{+1}$) and at $t = 22$ (with $LI4m^{-21}$). There was one additional nonsignificant comparison involving $LI4m^{+21}$ at $t = 10$ (with $NAPm^{+1}$) and seven involving $NAPm^{+21}$, comprising three at $t = 7$ ($NAPm^{-21}$, $LI4m^{-21}$, $NAPm^{-1}$) and four at $t = 22$ ($LI4m^{-1}$, $NAPm^{+1}$, $LI4m^{+1}$, $NAPm^{-1}$).

In summary, the continued application of needle manipulation and retention of the needle were important for maintaining elevated needle sensation as well as pain associated with needling. By contrast, both the needle pain and sensation experienced was independent of insertion site.

4.2. Relation between Pain and Needle Sensation Perceptions. The following four graphs show for each intervention, the number of subjects at each three-minute recording interval who reported experiencing each of the following: neither pain nor needle sensation; both pain and needle sensation; only pain; or only needle sensation.

From the frequencies of subjects among interventions reporting neither pain nor needle sensation (Figure 3(a)) or both pain and needle sensation (Figure 3(b)), the profiles for the pair of interventions that included needle retention and ongoing manipulation during the 21-minute period are clearly different from the remaining six interventions, for the time intervals other than $t = 1$ following the initial needle insertion. For this pair, most subjects experienced both pain and needle sensation at each interval; while for the remaining six, the reverse was the case, with most subjects not experiencing either pain or needle sensation. These frequencies were similar across the 21-minute intervention period. The profiles for simultaneous presence of pain and needle sensation (Figure 3(b)) are strikingly similar to the profiles shown in Figure 2 for both the mean needle sensation intensity and the mean pain intensity.

By contrast, virtually no subjects reported pain alone (Figure 3(c)) for any intervention or time interval. Similarly, needle sensation in the absence of pain (Figure 3(d)) was only experienced by a small proportion of subjects at any time interval. It is interesting that although four of the interventions involved only one minute of needling there were still several reports of pain and/or needle sensation throughout the entire 21 minute reporting period.

In summary, the experiences of needle sensation and pain were closely linked with respect to duration and presence of manipulation but not to location of needling.

From the pain and needle sensation profiles for individual interventions shown in Figure 4, all interventions had two common features. At $t = 1$ (when all had the common experience of a needle being inserted and retained for one minute) significantly more subjects reported the presence of both pain and needle sensation than other possibilities ($P < 0.05$ for all eight interventions, Chi square I). The reporting of pain alone was either absent at most of ($LI4m^{-21}$, $NAPm^{+1}$, $NAPm^{-1}$) or even all of the three-minute measurement periods ($NAPm^{-21}$).

The eight profiles clustered into two distinct two response patterns: one shared by the pair with 21-minute needle

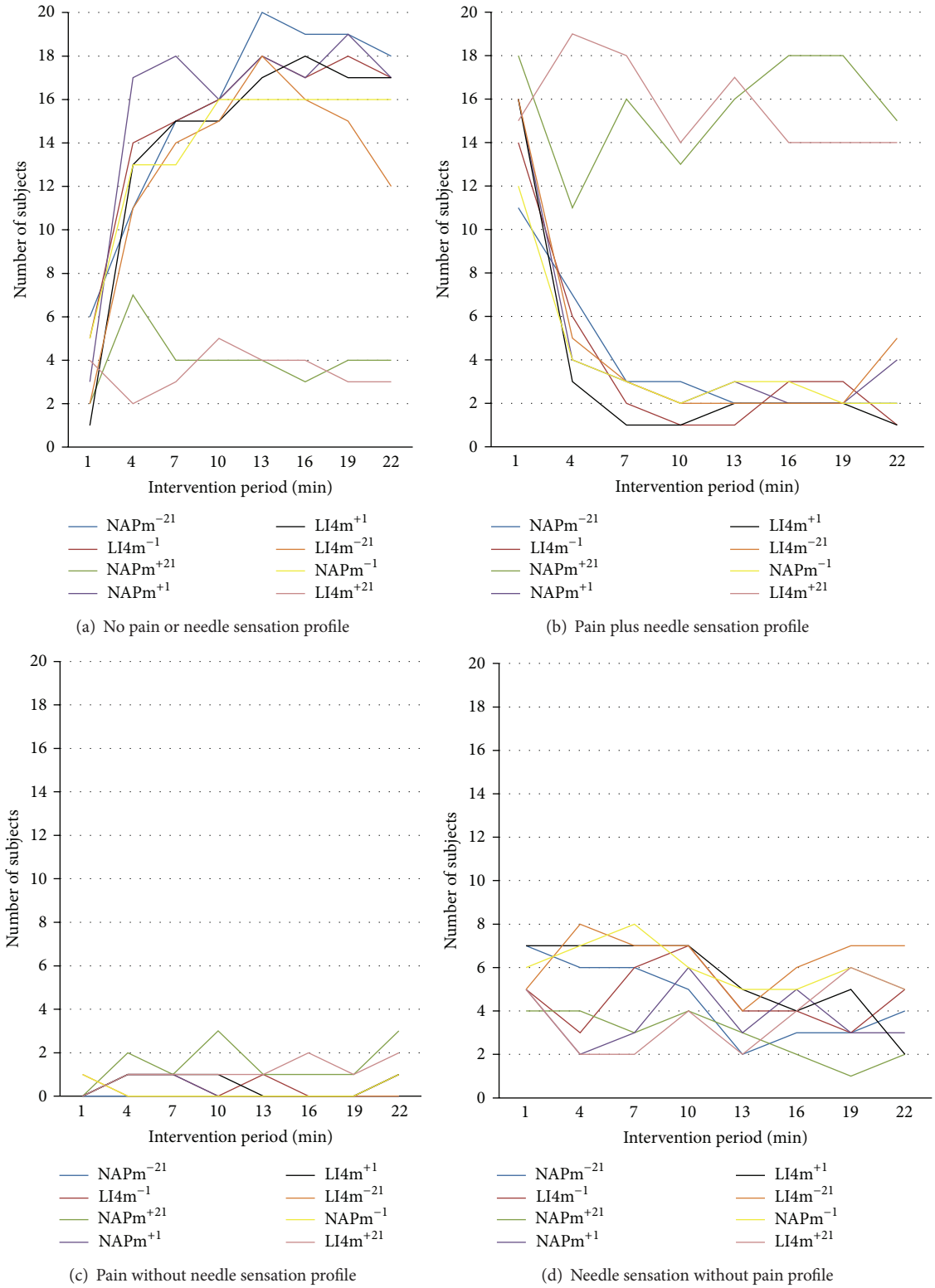


FIGURE 3: Comparison of the eight interventions with respect to the number of subjects at each three-minute recording interval who had: neither pain nor needle sensation (a); both pain and needle sensation (b); only pain (c); or only needle sensation (d). In all cases, total number of subjects = 24.

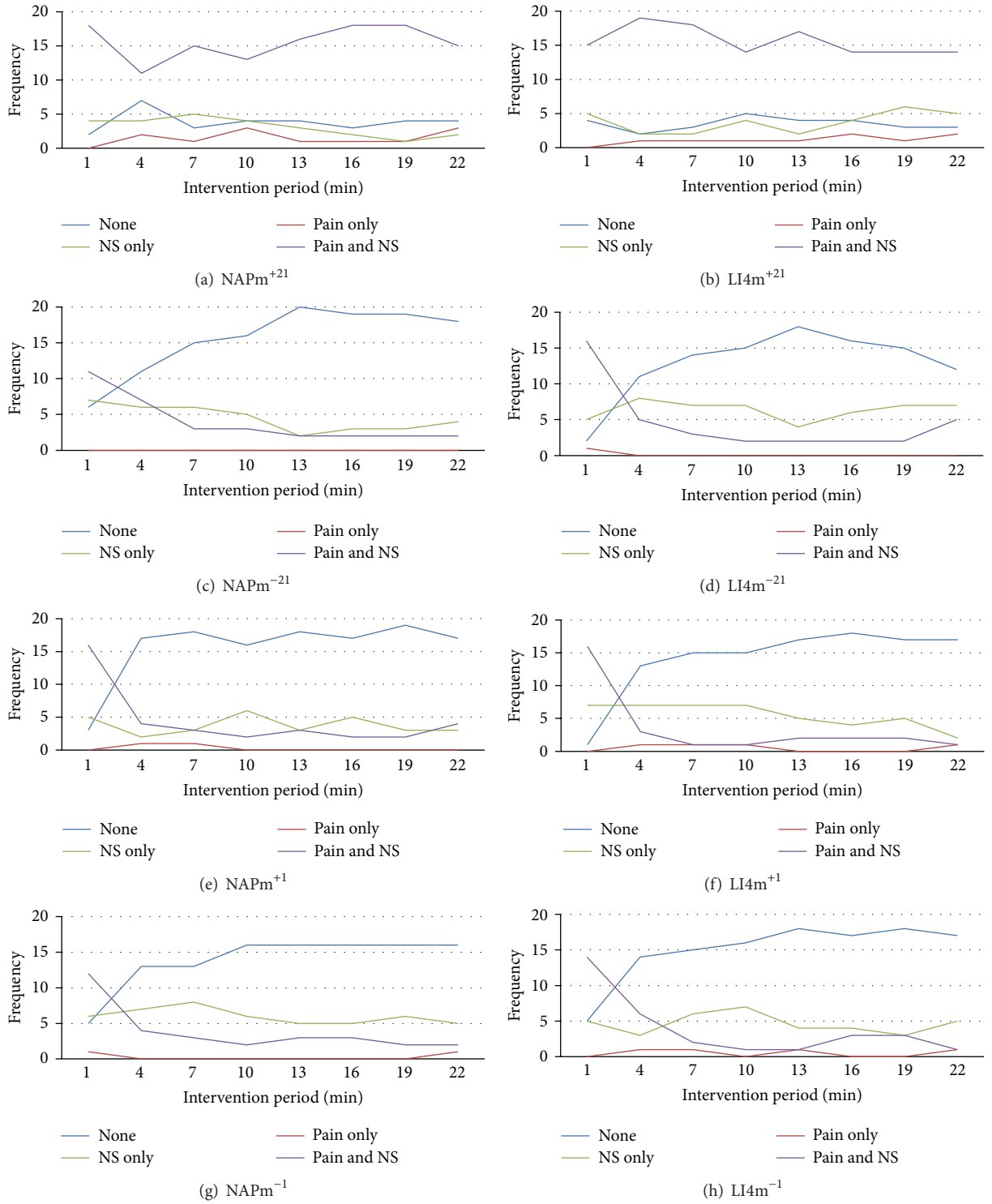


FIGURE 4: Comparison within each of the eight interventions of the number of subjects at each three-minute recording interval who had neither pain nor needle sensation; both pain and needle sensation; only pain; or only needle sensation. Total number of subjects = 24.

retention and repeated manipulation, and the other by the remaining six interventions.

Pattern 1: for all measurement intervals including $t = 1$, significantly more subjects reported the presence of both pain and needle sensation ($P < 0.05$, Chi square I).

Pattern 2: for all measurement intervals except $t = 1$, significantly more subjects reported absence of both pain and needle sensation ($P < 0.05$, Chi square I). This applied whether the needles were retained for one minute or 21 minutes; and with the one-minute retentions, whether or not

Table 2

Category	Descriptors (in order of intensity rank)
1	Flickering, pulsing, quivering, throbbing, beating, pounding
3	Pricking, boring, drilling, stabbing
4	Sharp, cutting, lacerating
5	Pinching, pressing, gnawing, cramping, crushing
6	Tugging, pulling, wrenching
7	Hot, burning, scalding, searing
8	Tingling, itchy, smarting, stinging
9	Dull, sore, hurting, aching, heavy
17	Spreading, radiating, penetrating, piercing
18	Tight, numb, squeezing, drawing, tearing
19	Cool, cold, freezing
21	Electricity
22	Warm
23	Indescribable

manipulation was applied. Therefore, again the distinguishing parameter values were needle retention and application of manipulation but not site of insertion.

4.3. Qualities of Needle Sensation: Needling Sensation Descriptors. At the end of each session, subjects reported the needling sensations they had experienced during the intervention. Note that subjects were not limited to a single descriptor. Since these unsolicited descriptors reported by subjects were found to be in good agreement with ones from the MMPQ, they have been grouped according to MMPQ categories [4, 5]. This system addresses both quality and intensity of a descriptor, so that interventions could be compared in terms of both the number and the intensity of descriptors used, both within individual MMPQ descriptor categories and overall. Three additional categories were created for unrepresented terms: "warm" (since the MMPQ category commences with "hot"), "electricity", "and can't describe."

The categories that contain descriptors provided by subjects are shown in Table 2.

Study subjects' results are summarised in Table 3 and Figure 5. Among the eight interventions, more descriptors (41 and 43) were reported for the pair of 21-minute interventions with manipulation compared with the other six interventions (22 to 29). The different numbers of descriptors reported are not explained by differing numbers of reports of no sensation among the eight interventions. For the pair of one-minute interventions without manipulation, the number and intensity scores are identical and are also similar to those for the one-minute NAP intervention with manipulation ($NAPm^{+1}$). The intensity and number of descriptors for the one-minute LI4 with manipulation ($LI4m^{+1}$) closely resembles the findings for the 21-minute LI4 without manipulation intervention ($LI4m^{-21}$).

The MMPQ based descriptor intensity profiles are shown for the eight interventions in Figures 5(a)–5(h). The MMPQ

Table 3: Total Number (N) and intensity (I) of sensory descriptors reported for the eight interventions (no sensation responses are shown in parentheses).

Intervention	$NAPm^{+}$		$NAPm^{-}$		$LI4m^{+}$		$LI4m^{-}$	
	I	N	I	N	I	N	I	N
21 min	81	41(2)	33	22(7)	87	43(2)	53	27(6)
1 min	43	27(3)	41	24(7)	55	29(6)	41	24(7)

categories relevant to these results are listed in the caption together with the three ungrouped additions of electricity, warm, and indescribable.

For all eight interventions, descriptors were reported from the same five descriptor categories that included 8, 9, 18, and the additional 21 (electricity) and 22 (warm). The most frequently reported descriptors were from category 8 and included some form or intensity of tingle, sting or itch. The second most frequently used terms were from category 18 (typically numbness). Less frequent but reported for all interventions were category 9 terms (dull ache). Far less frequent were the ungrouped terms "warm" and "electricity."

Figure 5 indicates that, in general, the descriptor profiles were very similar for each pair of equivalent LI4 and NAP interventions. The only minor exception was that category 9 terms were reported more frequently among the LI4 interventions. The two LI4 interventions involving manipulation had the highest intensity scores among all interventions for category 9 terms and for the four LI4 interventions, category 9 terms were reported 21 times compared with 12 times for the four NAP interventions. However these reports only involved a minority of subjects for the four interventions at either site (20 reports compared with 12).

5. Discussion

The findings for both needle sensation and pain among the eight interventions are strikingly consistent in terms of providing both positive and negative instances, all of which support the conclusion that needle manipulation and needle retention are important for maintaining an elevation in needle sensation and pain. By contrast, no additional or differential effect was shown for the site of needling insertion although one was an acupoint (LI4) and the other was not (NAP). These findings related to both quantitative VAS scores as well as to the qualitative descriptors spontaneously reported by subjects and discussed later in this section.

Another clear relationship among the findings was that needling pain and needle sensation overwhelmingly were present or absent together. This may relate to the role of acute pain in helping to protect the body. Its role is one of warning and alerting the conscious organism about the presence of a noxious or potentially harmful sensory stimulus. This is demonstrated by the similar role of pain across such diverse perceptual experiences as, for example, touch, sound, light, or taste. Therefore, piercing the intact skin and underlying tissues with a needle represents an invasive threat and should activate appropriate sensory mechanisms. Deep piercing

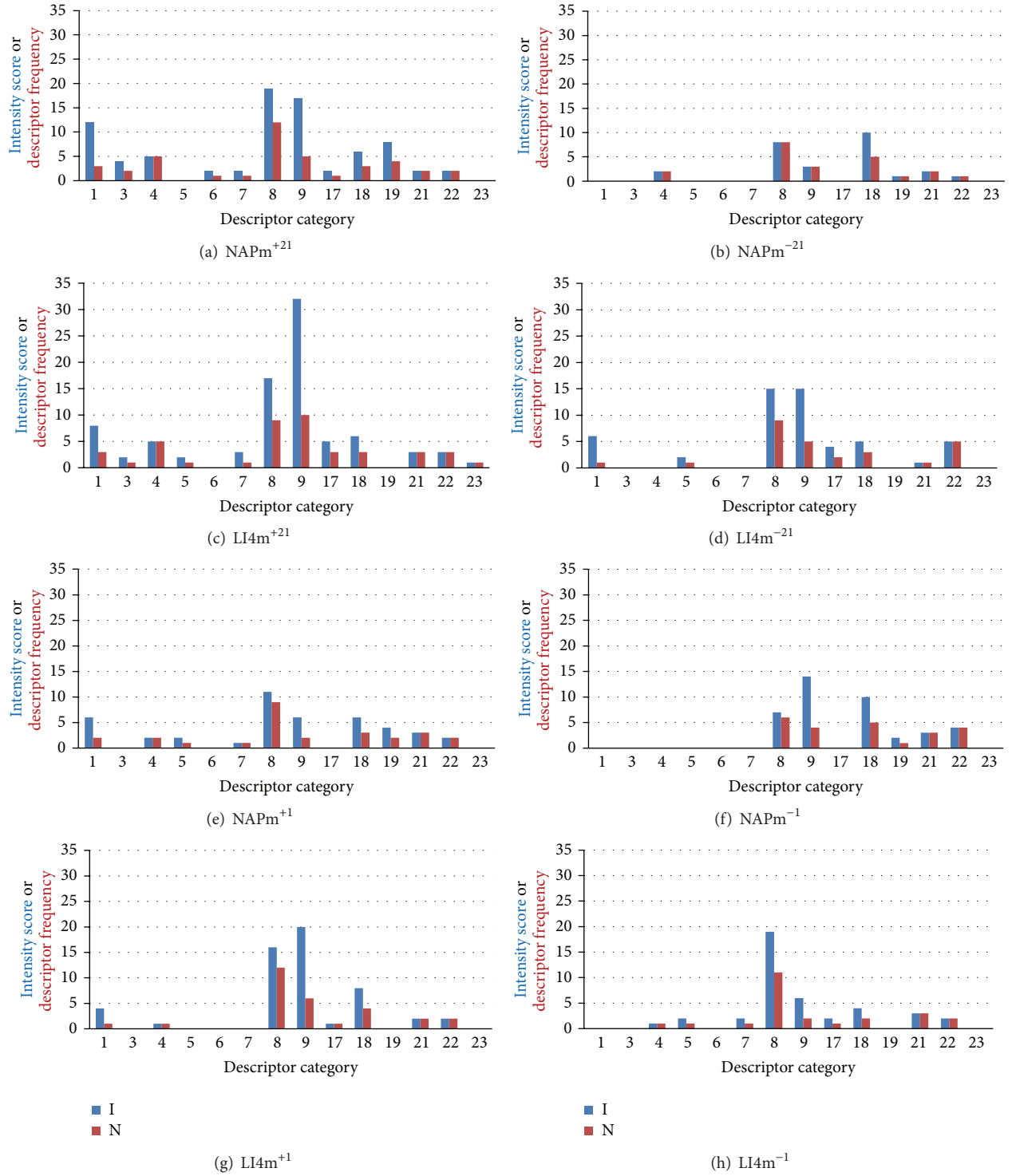


FIGURE 5: Profiles for each intervention for the frequency (N) and intensity (I) of sensory descriptors reported from each descriptor category list. (1) flickering, pulsing, quivering, throbbing, beating, pounding; (3) pricking, boring, drilling, stabbing; (4) sharp, cutting, lacerating; (5) pinching, pressing, gnawing, cramping, crushing; (6) tugging, pulling, wrenching; (7) hot, burning, scalding, searing; (8) tingling, itchy, smarting, stinging; (9) dull, sore, hurting, aching, heavy; (17) spreading, radiating, penetrating, piercing; (18) tight, numb, squeezing, drawing, tearing; (19) cool, cold, freezing; (21) electricity; (22) warm; (23) indescribable.

together with needle manipulation, by involving more stimulation would augment the sensory input and be expected to produce a more intense sensory perception of discomfort and pain. Since "*deqi*" or needle sensation is encouraged by mechanical manipulation and deep needle insertion (as opposed to shallow insertion without manipulation), it would be expected that pain would also be elicited. Therefore, pain or discomfort would be a likely accompaniment to "*deqi.*" Is it possible, for example, that the original concept of *deqi* embraced the whole range of sensations elicited by needling, including acute pain? What is not known from the early literature is whether originally *deqi* was ever demonstrated—*as opposed to being assumed*—to be restricted solely to acupoints, rather than an experience associated with needling living tissues more generally.

The qualitative descriptors used by the subjects in this study were the subjects' own individually and spontaneously provided words. Therefore it is noteworthy first, that the profiles for qualities of needle sensation were similar for NAP and LI4 and second, that the terms fitted almost perfectly into the category groupings developed for the well validated MMPQ [4, 5]. Moreover, both the number of descriptors as well as the intensities of the descriptors used for the two interventions that produced the significantly higher needle sensation and pain scores during the interventions ($LI4m^{+21}$ and $NAPm^{+21}$) were higher than for the remaining six interventions. Again, while these two findings did not differentiate between acupoint and nonacupoint locations, they did provide another linking of pain with needle sensation.

MacPherson and Asghar [9] developed a qualitative and quantitative classification of needle sensations associated with *deqi* based on ratings by 20 TCM acupuncture experts. Two clusters of sensations were identified. One cluster was linked with *deqi* and comprised seven sensations: aching, dull, heavy, numb, radiating, spreading, and tingling. The second cluster related to acute needling pain and included nine sensations: burning, hot, hurting, pinching, pricking, sharp, shocking, stinging, and tender. In the present study, it is noteworthy that the needle sensation descriptors primarily fell into these authors' *deqi* descriptor cluster. All eight interventions reported descriptors from five descriptor categories, comprising 8, 9, 18 and the ungrouped additional "warm" and "electric." The most frequently reported descriptors among interventions were from category 8 and included some form or intensity of tingle, sting, or itch. The second most frequent terms were from category 18 (typically numbness). Less frequent but reported for all interventions were category 9 terms (dull ache). Far less frequent were the ungrouped terms "warm" and "electricity." These findings do support the notion that subjects were, at least primarily, discriminating and reporting on needle sensation, rather than pain.

The study also showed that needle sensation was maintained only when the needle was both retained and received ongoing manipulation (Figure 2). A plausible explanation is that mechanical manipulation causes injury to the tissues around the needle and one of the body's reactions to this injury is pain (needle sensation or *deqi*). This may contribute to activation of the body's defensive system by increasing blood flow to the site of insertion [20], which in turn modifies delivery of oxygen, neurohumoral and anti-inflammatory mediators to the site [21].

Subjects spontaneously provided needle sensation descriptors that also describe pain: qualitatively and quantitatively and relevant here is the concept of "pain threshold," that is, the intensity of a nonpainful sensory stimulus when it begins to take on *the beginnings of discomfort, the beginnings of pain.* Obviously the stimulus quality prior to this level was not perceived as painful. An individual's pain threshold is not constant and experimental studies have confirmed the enhancing effect of anxiety on ratings of pain intensity [22], unpleasantness [23] and pain threshold [24]. In response to experimental cold pressor pain stimulation, McCaul and Haugtvedt [25] found that distraction is a better coping strategy than attention to sensations when subjects are asked to report pain threshold and tolerance. Wagner and colleagues [26] reported that induced sad effect leads to reduced heat pain thresholds in healthy subjects. This was regarded as probably due to altered lateral thalamic activity, which is potentially associated with changed attentional processes.

The descriptors in the MMPQ are not the sole preserve of pain. They are merely descriptors of sensory experiences, in terms of quality and intensity, and may not necessarily be describing something that is unpleasant or potentially noxious. Even some of the more intense descriptors may, in some sensory experiences and in certain settings, reflect positive and very pleasurable sensations in healthy individuals, as for example with the pressure of deep, strong massage or the spreading and radiating heat from a heat lamp.

Pain may contribute to "*deqi*" with respect to clinical effects associated with needling, given the linking of pain with endogenous endorphin system activation. Certainly it has been extensively demonstrated that pain induces the synthesis of beta endorphins by the pituitary gland and when released, these affect the central and peripheral nervous system and relieve pain by binding to specific opioid receptors in these areas [27].

Vincent and colleagues' early study [6], using a modified MMPQ, found that similar levels of needle sensation were produced at both acupoints and nonacupoints, suggesting that *deqi* was not exclusive to acupoints. The present study strongly supports these findings. For both acupoint and nonacupoint with manipulation and a needle retention time of 21 minutes ($LI4m^{+21}$ and $NAPm^{+21}$), the level of needle sensation remained constant at around 15% compared to the other interventions which dropped below 5% (Figure 2). These findings were evident both quantitatively, from VAS sensation intensity scores during the needling period, and qualitatively, from the sensation descriptors provided by subjects (Figures 5(a) and 5(c) and Table 3).

Typically and necessarily, studies of needle sensation have involved healthy study subjects. This is perhaps incongruous, given that the intent of clinical acupuncture interventions is to restore balance or health when there is some imbalance or illness. That is, is it appropriate to assume that needle sensation may be linked in either a causative or a correlative manner with a specific, measurable physiological response; and if so, what clinical response(s) could be regarded as being appropriate to examine in relation to presence or levels of

needle sensation in a healthy subject? Pain threshold has been a common choice here. Not only can it be quantified with VAS and MMPQ style instruments, but measurement is neither invasive nor injurious to tissues. However, it may be regarded as counter intuitive that acupuncture, a process hypothesised to restore bodily functional balance, should modify the resting pain threshold in a healthy individual. On the other hand, if needle sensation is regarded as simply part of the sensory system's alerting of the presence of an invasive, potentially noxious insult to the tissues, then the recruitment of defences would be typical and expected.

It is important to stress that the subjects in this study were selected on the basis of being in good health, since the aim of the study was to obtain baseline information about the influence of the three parameters being researched. Whether the responses to the same set of interventions would be different for patients with specific clinical conditions is unknown. However, the profiles and other data collected in the present research could serve as a baseline for related clinically oriented research.

In the present study, there was little evidence of a significant placebo effect in that in general, subjects did not report further pain or needle sensation after needle removal in the one minute retention interventions. The limited number and range of sensations reported after needling for these interventions typically included numbness and tickling/tingling and Figure 4 shows that needling sensation and pain were reported by a small minority of these subjects throughout the 21 minute intervention period. It is possible that numbness or tingling experienced after needling may be due to the arm and hand being left immobile for 21 minutes and rather than being a placebo effect, it is an actual physiological response to this unnatural inactivity. Our group had previously encountered a similar phenomenon in a study where subjects received, as the control intervention, inactive laser, with some subjects reporting feelings of heaviness, numbness, and tickling/itching [19]. These findings suggest that studies may need to take such factors into account, not only when considering "placebo" responses, but also with respect to subjects' perceived responses to potentially "real" interventions.

6. Conclusion

This study examined three needling parameters (site of insertion, manipulation, and retention time) in relation to the outcome measures of intensity of pain or needle sensation and qualitative descriptors of the needle sensation. Results showed that while the levels of needle sensation and pain were similarly intense following needle insertion for all interventions, initial intensity levels faded away rapidly unless the needle was both retained and manipulation repeated. Neither the eliciting nor maintaining of needle sensation or pain was restricted to a designated acupoint, with similar outcomes obtained at both LI4 and NAP. Typically, both pain and needle sensation were present (or absent) together and very few subjects reported pain or needle sensation in isolation.

The needle sensation descriptors spontaneously reported by subjects were in good agreement with the MMPQ pain descriptors. Based on the MMPQ categories, the descriptors reported by subjects did not differentiate between the two needling sites in terms of either quality or the intensity of the terms used. However, they did discriminate between the two 21-minute interventions with manipulation present, compared with the other six interventions. More descriptors and greater intensity scores were reported for the former pair of intervention compared with other interventions, all of which reported very similar lower intensity scores and numbers of descriptors.

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Research Article

The Characterization of Deqi during Moxibustion in Stroke Rats

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The efficacy of acupuncture and moxibustion is closely related to Deqi phenomenons, which are some subjective feelings. However, no one has reported the objective characterization of Deqi. Our preliminary research has found a phenomenon of tail temperature increasing (TTI) obviously in some stroke rats by suspended moxibustion at the acupoint dà zhuī (DU 14), which is similar to one characterization of Deqi during moxibustion that moxibustion heat is transferred from the original moxibustion acupoint to the other areas of the body. We wonder whether TTI is the objective indicator of Deqi characterization in animals. The present study showed that the stroke rat's recovery was also associated with TTI phenomenon. This suggests that TTI phenomenon is one objective characterization of the Deqi in stroke rats. Application of the TTI phenomenon contributes to explore the physiological mechanism of Deqi.

1. Introduction

It is considered that the clinical efficacy of acupuncture and moxibustion is closely related to Deqi phenomenon in traditional Chinese medicine. The characterizations of the Deqi during acupuncture treatment have been elaborated in acupuncture textbooks, which are some subjective feelings, such as soreness and heaviness [1]. Meanwhile, the characterizations of the Deqi during moxibustion treatment have also been clarified in clinical heat-sensitive moxibustion practice over the past decade [2], including the following: (a) moxibustion heat penetrates deep into the tissues or internal organs of the body; (b) moxibustion heat is transferred from the original moxibustion acupoint to the other areas of the body; (c) moxibustion heat could elicit other sensations, including pressure, soreness, heaviness, and dull pain, at the surface of the skin or deep tissues. However, the above characterizations are also some subjective feelings. The objective characterization of Deqi during moxibustion has not been reported yet. Our preliminary research has found a phenomenon of tail temperature increasing (TTI) obviously in some stroke rats by suspended moxibustion (SM) at the acupoint dà zhuī (DU 14), which is similar to the characterization (b) of Deqi during moxibustion in humans [3]. We hereby propose the hypothesis that TTI is the objective indicator of Deqi characterization in stroke rats during moxibustion. The present study was designed to verify this hypothesis.

2. Methods

2.1. Animal Preparation. A total of 75 adult male Sprague-Dawley rats (220 to 250 g) were used in the experiment. The rats were maintained in a cage at room temperature 23 ± 2°C, with controlled humidity 60 ± 5% and 12-hour day/night cycle, with a maximum of five rats per cage. Firstly, 30 rats were divided randomly into 2 groups: (1) Sham operation with SM for 60 min group (sham, $n = 10$) and (2) ischemia with SM for 60 min group (M, $n = 20$). They were all treated for 3 days. According to the tail temperature change, the M group was further divided into two subgroups, including a nonincreasing subgroup (≤1°C an average of 3 days, non-TTI group) and an increasing subgroup (>1°C an average of 3 days, TTI group). Then, four points around the rat's torso were heated in five TTI rats. Secondly, another 45 rats with transient middle cerebral artery occlusion (tMCAO) operation were divided randomly into 2 groups: (1) ischemic control group (C, $n = 15$) (2) ischemia with SM for 60 min

group (M60, $n = 30$). Rats in M60 group were treated with SM for 7 days. Like the first part of the experiment, the M60 group was also further divided into two subgroups, respectively, including the M60-non-TTI subgroup and the M60-TTI subgroup. All experimental procedures involving the use of animals were conducted in accordance with NIH Guidelines and approved by the Animal Use and Care Committee for Jiangxi University of TCM.

2.2. Preparation of Experimental Stroke Model in Rats. The rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (3%) at a dose of 30 mg/kg. Core body temperature was monitored using a rectal probe and maintained at 37 ± 0.5°C by a heating lamp and a heating pad. The middle cerebral artery occlusion was achieved by the Intraluminal Filament method as previously described [4]. After 2 h of occlusion, the fishing line advanced to the origin of the middle cerebral artery was withdrawn to allow for reperfusion. Sham-operated rats were manipulated in the same way, but the MCA was not occluded. Adequacy of vascular occlusion and reperfusion was assessed by Laser Doppler Monitoring (PeriFlux 5000, Perimed AB, Stockholm, Sweden) of cerebral cortical perfusion. Regional cerebral blood flow in the middle cerebral artery territory was reduced to <20% of baseline, after advancing the fishing line to the origin of the MCA, and reconstituted to >60% of baseline after removal of the fishing line. Rats dying within 24 hours after surgery or displaying a neurological score of 0 were excluded from the final analysis.

2.3. Suspended Moxibustion. A special cage in which the rat can maintain a comfortable position and the rat's motion is restricted was used while testing. The cage was convenient to the operation of SM. Room temperature was maintained at 25 ± 2°C for the entire experimental process. In the first part of the experiment, DU 14, which is considered very important for brain functions [5], was heated by SM using a moxa (exclusively used on animals, length 12 cm, diameter 0.6 cm, made by the Affiliated Hospital of Jiangxi University of TCM, China). Then, five rats, selected randomly from the TTI group, received SM operation at four points. The first point was DU 14. The second point was located at the one that was 2 centimeters right beside the acupoint of DU 14. Both of them were heated at approximately 3 cm high over the hairless skin. The third point was located at the extension line of the longitudinal axis of the rat. The fourth point was located at perpendicular of the tail's midpoint. The third and fourth points both had the same distance far from rat's tail midpoint, which was identical to the distance between the acupoint of DU 14 and rat's tail midpoint. In the second part of the experiment, the heating point was also the acupoint of DU 14.

2.4. Tail Temperature Measurement. The rats' midpoint tail temperature was recorded once every 2 minutes precisely by an electrodigital thermometer (Shanghai Medical Instrument Factory, Shanghai, China) in process of SM treatment. The testing environment was kept quiet, and the room temperature was maintained at 25 ± 2°C. The rats were placed in a cage for 30 min before the experiment started.

2.5. Neurological Assessment. Neurological assessment was performed at 0, 1, 3, and 7 days after transient middle cerebral artery occlusion by a researcher who was unaware of the experimental groups, using a modified neurological severity score, which were graded on a scale of 0 to 18 (normal score, 0; maximal deficit score, 18), as previously described [6].

2.6. Statistical Analysis. Data was analyzed using one-way analysis of variance (ANOVA) with post hoc Newman-Keuls multiple-range test for multiple groups. The pearson correlation coefficient was also calculated between the neurological deficits score and change of tail temperature. SPSS 10.0 was used for analysis. $P < 0.05$ was considered statistically significant. All values were expressed as the mean ± SD.

3. Results

3.1. Quantitative Analysis of Experimental Animals. In the first part of the experiment, 2 of the 20 ischemic rats (1 death and 1 displaying 0 score) met at least one of the exclusion criteria. 9 ischemic rats exhibited TTI, and 9 subjects showed non-TTI. In the second part, 2 of the 15 rats in C group (2 death) and 3 of the 30 rats in M60 group (2 death and 1 displaying 0 score) met at least one of the exclusion criteria. There were 13 subjects in M60-non-TTI subgroup and 14 subjects in M60-TTI subgroup. Thus, 28 rats of the first part and 40 rats of the second part were included in the final analysis.

3.2. Tail Temperature Change following Suspended Moxibustion. In the first part of the experiment, tail temperature began to quickly increase immediately after suspended moxibustion. At about 5–10 min, the temperature reached a relatively stable level but less than 1°C on average. 9 tMCAO rats, as well as the sham rats, maintained this level (non-TTI) throughout the treatment session. However, the other 9 tMCAO rats exhibited TTI (more than 2°C on average). Furthermore, the tail temperature in the rats with TTI increased to a peak value at around 15 min, and the peak temperature was maintained until 40 min, at which a decline began to appear. At about 50 min, the tail temperature decreased to a level similar to that of the non-TTI or sham rats. The results were similar during the 3 consecutive days (Figure 1). Five stroke rats were randomly selected from TTI group and received SM operation for 60 min at four points, respectively. The tail temperature exhibited TTI by heating the first point. However, heating the other three points did not elicit TTI (Figure 2).

3.3. Neurological Deficits Score. To investigate the efficacy of SM for 60 min with TTI, we examined the neurological deficit score of tMCAO rats in the second part of the experiment. The results revealed that the M60-TTI group significantly reduced neurological deficit score at 3 days after reperfusion, compared with the C group ($P < 0.05$). This group further ameliorated the neurological deficit score at 7 days after reperfusion, compared with the C and M60-non-TTI ($P < 0.05$) groups. The M60-non-TTI group reduced neurological

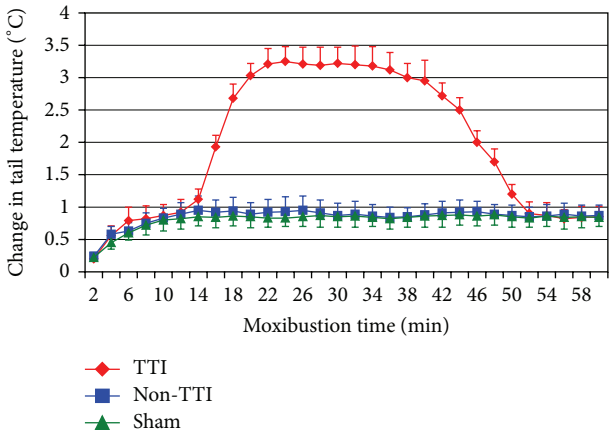

Figure 1: Change in tail temperature induced by SM in the first part of the experiment. Because the change of tail temperature was similar among the three consecutive testing days, data of the first day were presented as a representative. Data were expressed as mean ± SD.

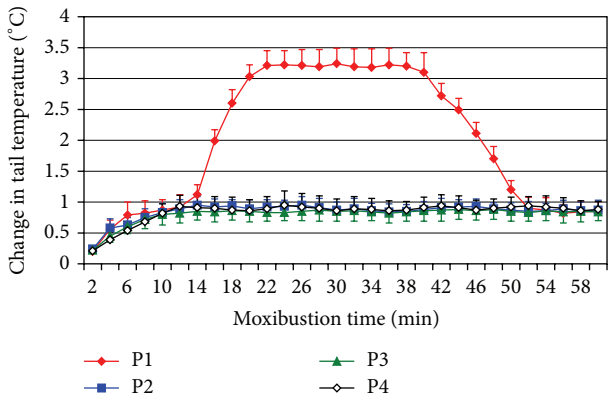

Figure 2: Change in tail temperature induced by SM at four points, respectively, around TTI rat's torso. Data were expressed as mean ± SD. P1: first point; P2: second point; P3: third point; P4: fourth point.

deficits score markedly at 7 days compared to the C group ($P < 0.05$) (Figure 3).

3.4. Behavior Correlation with Tail Temperature Increase. In order to explore the relationship between the reduction of neurological deficits score and the change of tail temperature increase induced by SM, we calculated the intersubject Pearson correlation coefficient between both mentioned above. We found that the reduction of neurological deficits score was positively correlated with the change of tail temperature increase induced by SM ($R = 0.807$, $P < 0.01$) (Figure 4).

4. Discussion

Deqi is a composite of unique sensations that is produced during acupuncture or moxibustion stimulation. We have paid attention to the clinical characterizations of Deqi during moxibustion for 20 years and summarized its characterizations as previously described. Furthermore, we have confirmed the efficacy of SM with Deqi is superior to that without

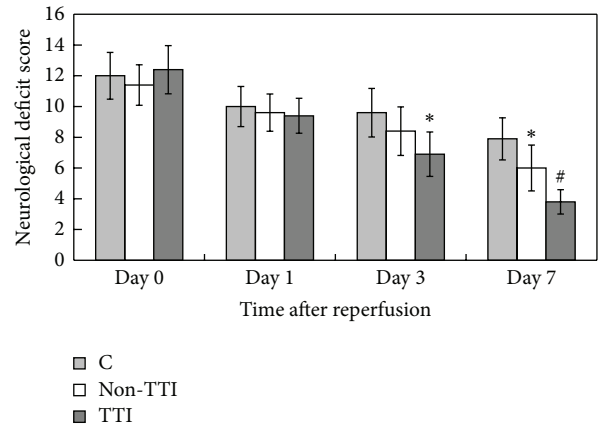

Figure 3: SM on neurological deficit score in the tMCAO rats. Data were presented as mean ± SD. $^{*}P < 0.05$ versus C group; $^{\#}P < 0.05$ versus C and M60-non-TTI groups using one-way analyses of variance.

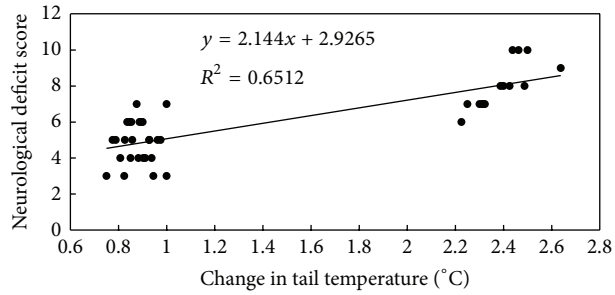

Figure 4: The change of tail temperature increase correlated with the neurological deficits score. $r = 0.807$, $P < 0.01$.

Deqi in clinic [2, 7–9]. Further investigation of the biological mechanism of Deqi during moxibustion depends on establishing the objective assessment of Deqi characterization, especially in animal study. However, few investigators have reported the objective characterization of Deqi in animals. In our previous study, we have accidentally found a TTI phenomenon in some stroke rats by SM at the DU 14 [10]. Based on the TTI phenomenon similar to one of Deqi characterizations during SM in clinic, we wonder whether TTI is the objective indicator of Deqi characterization in animals.

In this study, we have observed the change rule of TTI induced by SM at the DU 14 of tMCAO rats. The tail temperature in the rats with TTI increased beyond other subjects at about 15 min, and the peak temperature was maintained until 40 min, at which the decline began to appear. At about 50 min, the tail temperature decreased to a level similar to that of the non-TTI or sham rats. The results also suggested that TTI did not appear in sham-operated rats. This indicates that TTI is relevant to the model of stroke. It is consistent with the fact in clinic that Deqi phenomenon during SM is highly relevant to the morbid condition of human body [2, 11].

The tail is far from the heating acupoint. How is the TTI induced? In order to exclude the impacts of the conductive (the second point) and radiant (the third and fourth points)

heat on TTI generation, we set three other heating points except DU 14 as comparisons. The results showed that heating on three other heating points, respectively, exhibited no TTI. This proclaimed that conductive heat and radiant heat were not the reasons of inducing TTI phenomenon. However, in traditional Chinese channel theory, DU 14 and the tail are both on the DU channel (Governor Vessel) [5]. Stimulating the DU14 with SM could provide heat for the tail through the channel. The results of neurological deficit score further revealed that the tMCAO rats with TTI during SM recovered better than those without. This confirmed that the efficacy of SM was closely related to TTI phenomenon. It is also consistent with the fact in clinic that clinical efficacy of moxibustion is closely related to Deqi phenomenon. From this perspective, TTI could be considered as a characterization of Deqi in tMCAO rats during SM.

Why did not the other 13 tMCAO rats exhibit TTI? It is similar to the observation in clinic that acupoints that can be stimulated to cause Deqi phenomenon may have different locations in subjects who are afflicted with the same disease [2]. In the present study, the point (DU 14) for SM treatment was fixed. Therefore, some of them exhibited TTI, while others did not. Acupoints other than DU 14 were stimulated in the 13 tMCAO rats in order to produce TTI. As the occurrence rate of TTI is 40–60% in our previous study [3], the number of moxibustion-treated groups we designed is twice of the other groups (such as sham or C group) so that the number of non-TTI or TTI rats selected from the total tMCAO rats is almost the same as the sham or C group.

In conclusion, this study reported a TTI phenomenon in tMCAO rats with SM and proved this phenomenon was associated with the tMCAO rat's recovery. There was enough reason to believe that TTI phenomenon was one of the Deqi characterizations in tMCAO rat. Application of the TTI phenomenon contributes to explore the physiological mechanism of Deqi.

Abbreviations

SM: Suspended moxibustion
TTI: Tail temperature increase
tMCAO: Transient middle cerebral artery occlusion.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

R. X. Chen designed and carried out the study and supervised the project. Z. M. Lv and Z. Y. Liu established the models. Z. M. Lv, D. D. Huang, and Z. Y. Liu performed the moxibustion and temperature measurement. D. Y. Xie performed the neurological assessment. R. X. Chen and Z. M. Lv collected and analyzed the data, discussed the interpretation of the results, and wrote the paper. All authors read and approved the final paper. Zhimai Lv and Zhongyong Liu contributed equally to this work.

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Review Article

Acupuncture De-qi: From Characterization to Underlying Mechanism

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De-qi refers to the participant's subjective sensations and objective body responses as well as the acupuncturist's perceptions while the acupuncturist needles certain acupoints in the participant's body. In recent years, De-qi is getting increasing attention of the researchers and many efforts have been made to understand its mechanism. By the broad literature survey, this paper explores the subjective De-qi sensation of the patients, its influencing factors, and the resulting physiological responses. The purpose of this paper is expected to find out a possible mechanism of De-qi and to provide certain scientific evidence for acupuncture fundamental research and clinical practice.

1. Introduction

De-qi, originated from *Neijing* (*Internal Classic*), is regarded as one of the most important principles and the key to the successful acupuncture treatment since it is related to clinical efficacy [1–3]. In recent years, researches in this field mainly focus on qualitative and quantitative evaluations of De-qi by scales, influencing factors of De-qi and physiological responses aroused by De-qi. The mechanism of acupuncture De-qi is still not well explained although a little progress has been made.

2. Study on the Subjective De-qi Sensations

Subjective De-qi sensations refer to participants' subjective feelings triggered by De-qi during needling and needle sensation of the acupuncturist. Nowadays, it is mainly evaluated by the scale survey, including questionnaires based on the feeling of patients and opinions of experienced acupuncturists. Many scales include both qualitative description and quantitative evaluation (e.g., VAS score) of De-qi.

In Vincent and his colleagues' study, the McGill Pain Questionnaire (MPQ) was modified by 10 experienced acupuncturists into a final scale that consists of 20 items concerning pain and needle sensations and was applied to 125 participants who received acupuncture. A principal component analysis identified 7 factors, and the first was a composite of dull-heavy sensations which included pulling, numbness, heaviness, dullness and aching. These feelings were very similar to the description of De-qi sensations in TCM [4]. However, all the sensations in the scale were primarily drawn from a pain questionnaire which was not focused specifically on De-qi. This could mislead patients to use painful sensations to describe De-qi. In a qualitative study of De-qi, 29 experienced acupuncturists separated 25 sensations into two clusters: one associated with De-qi and another with acute pain. De-qi cluster included aching, dull, heavy, numb, radiating, spreading, and tingling sensations, while the cluster associated with acute pain contained hot burning, hurting, pinching, pricking, sharp, shocking, stinging, and tender sensations [5]. However, this study did not involve patients' perceptions during acupuncture. Kim et al. studied the real-life patient's experience of insertion, manipulation, and retention stages of acupuncture through in-depth interview, group discussion, and expert panel assessment for content validity. The result indicated that "refreshing or relieving,"

"dull," "tingling," "painful," and "electrical shock" sensations were how patients feel throughout the whole phases [6].

In order to develop a sensation questionnaire that was able to discriminate between pain and De-qi, White et al. [7] developed the Southampton Needle Sensation Questionnaire which was designed following qualitative interviews with patients, literature review, and consultation with experts. The questionnaire was then piloted and validated in 227 patients. Two clusters of needling sensations were demonstrated in the final questionnaire, namely, "Aching De-qi" (De-qi with pain) and "Tingling De-qi" (De-qi only). The former included deep ache, dull ache, discomfort, heaviness, pressure, and bruised and stinging pain, while the latter contained tingling, warm, spreading, fading, numb, twinge, and throbbing sensations. In addition, they found that among 17 items in the final questionnaire only "sharp pain" had a significant partial correlation with the pain VAS score, so it should not be considered as an indicator of De-qi sensation. Kong et al. [8] developed a subjective acupuncture sensation scale (SASS) which contains stabbing, throbbing, tingling, burning, heaviness, fullness, numbness, soreness, and aching when they launched a pilot study on acupuncture analgesia. In their clinical practice with the scale, they found that numbness and soreness induced by acupuncture had a significant correlation with analgesia, which indicated that De-qi had a certain relationship with curative effect. After years' of application of the scale, "stabbing" and "burning" sensations were replaced by "sharp pain," "deep pressure," "dull pain," "warmth," and "cold." The modified scale was called "MGH Acupuncture Sensation Scale" (MASS). When translating MASS into Chinese version, researchers removed "sharp pain" from the scale because it is not commonly regarded as a kind of De-qi sensation. However, overall validity and reliability of the modified scale were not much affected [9].

In a study with the purpose of describing Chinese patients' acupuncture experience, the most common types of needling sensations reported by 200 subjects were "distension" (94%), "soreness" (81%), "electric shock" (81%), and "numbness" (78%). 82% of the subjects believed that needling sensation was very important for acupuncture treatment and 68% further indicated that the stronger the needling sensation was, the more effective the therapy would be. Meanwhile, 81% of subjects regarded needling sensation as a very comfortable and relaxing sensation. The result also showed that the needling sensation had a migratory nature. 89% of subjects reported that the needling sensation travelled away from the puncturing points or travelled among the needling points. However, the duration and intensity of migratory sensation differed among patients [10]. Hui et al. [11] investigated the perception of De-qi of Chinese and American acupuncturists. The result indicated that 47 out of 86 acupuncturists agreed that dull pain was considered De-qi and over half believed that it was beneficial, while sharp pain was not De-qi and harmful. They also found that Chinese patients enjoy De-qi experience, whereas those in the US did not.

Different subjective De-qi sensations actually indicating different nerve fibers have been activated. Wang et al. found that numbness was conveyed mainly by Aβ/γ fibers, distention and heaviness by A delta fibers, and soreness by C fibers [12]. Beissner et al. showed that pricking sensation was closely linked to A delta fibers, while dull and pressing sensations were related to C fibers [13]. Furthermore, these fibers attach to different areas of the brain. Thus, different De-qi sensations may trigger different brain reactions based on the types of afferent nerve fibers involved and finally lead to various therapeutic effects. For example, Kong et al. [14] demonstrated that there was a significant correlation of analgesia with SASS ratings of numbness and soreness, but not with stabbing, throbbing, tingling, burning, heaviness, fullness, or aching when they needled on LI4, ST36, and SP6.

According to the researches mentioned above, it could be concluded that perception of De-qi by patients are consistent with that described in Traditional Chinese Medicine, such as "sore", "numb", "distended", "heavy", "electric", and "warm" "cold" sensation. It is a special sensation between pleasant and outright pain, or tolerable dull pain for patients, therefore, sharp pain should not be included. De-qi sensation is also a sign to acupuncturists that indicates the curative effect has been initiated. Most of the experienced acupuncturists and patients believe that De-qi has a significant impact on curative effect.

3. Influencing Factors of De-qi

3.1. Specificity of Acupoints. Specificity of acupoints is one of the influencing factors of De-qi. In a study that applied EA on paired acupoints of ST36-ST28 and CV4-CV12, significant differences of De-qi intensity were found in soreness, fullness, and heaviness between ST36-ST28 and in fullness between CV4-CV12 [15]. Acupoints in these two groups share the same meridian category and tissue structure, but vary in nerve innervations: ST36 is innervated by L3/4 while ST28 by T12. Therefore, nerve innervations of acupoints have a significant influence on De-qi.

Although De-qi is affected by nerve innervations, researchers found that there was no correlation between direct stimulation to nerves around the acupoints and obtaining De-qi sensation. In an ultrasound imaging study, Streitberger et al. [16] found no association between the number of nerve contacts and De-qi when applying acupuncture on PC6. In some cases, De-qi sensation had not been elicited even when the needle was inserted into the nerve. Similar studies found that De-qi sensation was well achieved before the needle touched the median nerve under PC6, suggesting that irritation of the nerve was not directly involved in generating it [17]. Therefore, De-qi should be a physiological phenomenon triggered by both the central and peripheral nerve systems rather than a simple reaction to direct neural stimulation.

Although De-qi sensation could be elicited at both acupoints and nonacupoints, the subsequent physiological responses are different. Feng et al. [18] found that after needling ST36 with De-qi, the limbic/paralimbic regions such as amygdale, hippocampus, and anterior cingulated gyrus emerged as network hubs. However, this trend did not occur when needling nonacupoint nearby, although De-qi sensation was also elicited. This result indicated that the effect

of De-qi on central nerve system might be based on the function of acupoints. Wei et al. [19] investigated the effect of EA at LI4 and non-acupoint on blood flow in the middle cerebral artery. It demonstrated that there were no significant differences in De-qi intensity between LI4 and non-acupoint, but the application of EA at LI4 caused a significant decrease in ipsilateral blood flow velocity (BFV) and further decrease in the poststimulation period, EA at non-acupoint did not alter the value of both BFVs during the stimulation period. It only caused significant decrease in both BFVs during the poststimulation period.

The above studies showed that acupoints and non-acupoints might induce different central responses; even the same De-qi sensation was elicited by the same needling techniques. Therefore, the specificity of acupoints plays an important role in De-qi's effects on physiological function.

3.2. Acupuncture Manipulation. Many researches proved that acupuncture manipulation had a significant impact on De-qi. Rotation is the most commonly used manipulation for eliciting De-qi. Benham et al. [20] found that De-qi VAS scores were higher during deep needling (15–25 mm) on ST36 with bidirectional rotation when compared to superficial (5 mm) needling with mock bi-directional rotation in the sensations of stabbing, tingling, heaviness, soreness, and aching. Park et al. [21] demonstrated that the introduction of needle rotation significantly increased deep, dull, and heavy sensations, but not pricking and sharp sensations. Another study indicated that rotating the needle in real acupoints (LR3 and GB40) with De-qi activated secondary somatosensory cortex bilaterally, the left frontal lobe, the right side of the thalamus, and the left side of cerebellum more significantly than those without rotation, but this trend did not occur in non-acupoints [22]. This result showed that acupuncture with needle rotation could activate certain parts of the brain, but this effect could be achieved by stimulating on acupoints.

"Needle grasp" sensation felt by acupuncturist during needling is an important indicator of De-qi. It has been described in *Biao you fu (Song to Elucidate Mysteries) as follows*: "the arrival of qi like a fish biting on a fishing line." Langevin et al. [23] believed that connective tissue is the foundation of grasp sensation from the aspect of mechanical signaling. Their study observed that needle rotation was accompanied by marked thickening of the SC connective tissue layer in the area surrounding the needle. Winding of tissue around the needle leads to the generation of a mechanical signal by the pulling of collagen fibers and matrix deformation during rotation. Then, the signal was transmitted into cells and caused the subsequent downstream effects. This may be the mechanism of the Meridian qi migratory. A similar study pointed out that the pull-out force was significantly greater with needle rotation than that without rotation because of the winding of tissues around the needle [24]. This result suggested that the pull-out force could be used as an indicator that evaluates De-qi quantitatively.

The depth of needling may also affect De-qi sensation. In an ultrasound guided study, Park et al. [21] demonstrated that pricking and sharp sensations were more frequently received when pressed but not inserted into the skin surface and needled at the lower bolder of dermis. Deep, dull, heavy, spreading, and electric shock sensations occurred when the needle was inserted 2–15 mm beyond the first perimuscular fascia. In a study that measures participants' De-qi sensation and pain threshold by comparing superficial needling and deep needling with and without rotation on SP6, SP9, ST36, and GB39, Choi et al. [25] found that deep needling with bi-directional rotation had a marked effect in increasing both De-qi sensation and pain threshold, which is better than that of deep needling without rotation or superficial needling. Therefore, the depth of needling and the rotation manipulation have a cooperative effect in generating De-qi sensation and curative effects.

3.3. Methods of Stimulation. Stimulation method is another factor that affects De-qi. Some studies compared the different subjective De-qi sensations and physiological responses caused by manual acupuncture and EA. Kong et al. [26] demonstrated that the sensations of manual acupuncture on LI4 were mainly soreness and distension, while those of EA were mainly tingling and numbness. Their research also found that fMRI signal increased in precentral gyrus, postcentralgyrus/inferior parietal lobule, and insula during EA while decreased in posterior cingulated, superior temporal gyrus and insula during manual needling manipulation. Therefore, different brain mechanisms may be involved during different methods of stimulation. Leung et al. [27] proved that De-qi sensations were qualitatively and quantitatively different between manual and electrical acupunctures. De-qi VAS score significantly increased after EA on LI4 in comparison to manual acupuncture. The most predominant De-qi sensation with EA was tingling, whereas in the manual acupuncture aching was the most predominant one. When studying the impact of manual acupuncture and tactile stimulation on De-qi, Hui et al. [28] found that manual acupuncture on LR3, LI4, and ST36 could elicit higher frequency and intensity of De-qi sensation than tactile stimulation. The most significant difference between two methods lies in aching, soreness, pressure, and dull pain.

3.4. Psychological Factors. Some believe that De-qi might be a central phenomenon of awareness and consciousness because they found that sham laser acupuncture, which was inactivated and had no cutaneous sensory input, could elicit the same De-qi sensation as verum laser acupuncture at LI4, LU7, and LR3 with regard to frequency, intensity, and quality [29]. However, a great many researches pointed out that De-qi is a kind of physiological response triggered by acupuncture and has less relativity with psychological factors. Xiong et al. [30] explored the relationship among De-qi, psychological factors, and clinical efficacy when treating primary dysmenorrhea by needling on ST36, SP6, and CV3. Psychological factors of patients including belief in acupuncture, the level of nervousness, anxiety, and depression were quantitatively assessed. The result showed that psychological factors contributed little to De-qi and the correlation between De-qi and therapeutic efficacy was greater than that between psychological factors and clinical efficacy.

Many studies also showed patients' expectancy of De-qi sensation or their acupuncture experience did not influence what they acutely experienced during needling significantly. In Park and colleagues' study [31], the expected sensations of 38 acupuncture naive female volunteers were penetrating, tingling, pricking, and burning. However, they experienced aching, pulling, heavy, dull, electric, and throbbing sensations when the needling was done on LI4. Their study between acupuncture experienced and naive also supported that previous experience did not affect people's expectation and would not hinder people from experiencing De-qi [32]. Studies mentioned above showed that psychological factors might have certain influence on De-qi, but it is not the decisive factor.

In conclusion, the specificity of acupoints, needling manipulation, and methods of stimulation are key factors that affect De-qi, whereas psychological factors have comparatively less influence on it. Specificity of acupoints may be the intrinsic factor of De-qi, which could be elicited by external factors like needling manipulation and methods of stimulation. De-qi is most likely to be elicited when needling acupoints in appropriate depth with certain manipulations.

4. Objective Response to De-qi

4.1. Autonomic Response to De-qi. Autonomic response refers to a series of physiological changes of the body triggered by external stimuli, mainly including changes of skin conductance, heart rate, blood pressure, and blood flow. These changes, with an immediate presence, are controlled by autonomic nervous system. Abnormality of autonomic function, such as sympathetic nerves overactivation, has a relation with chronic pain in certain diseases [33, 34]. Researches show that acupuncture De-qi could regulate autonomic responses by balancing sympathetic nerve and parasympathetic nerve activities.

Sakai et al. [35] found that acupuncture on right trapezius muscle with De-qi suppressed sympathetic nervous activity and stimulated parasympathetic nervous activity, manifested as reduced heart rate and the ratio of low frequency components to high frequency components of heart rate variability (index of sympathetic activity) and increased systolic pressure. Thus, acupuncture De-qi may play its analgesia role by inhibiting sympathetic and exciting parasympathetic nerve activity. Acupuncture De-qi also has influence on blood flow and skin temperature around acupoints. Kuo et al. [36] found that acupuncture on LI-4 could cause stress reaction of parasympathetic nerve, which raised skin temperature of the palm through cutaneous vessels vasodilatation and increased blood flow of LI-11 when De-qi (soreness and numbness sensations) occurred. Therefore, changes of blood flow and skin temperature may be the mechanism through which certain De-qi sensations (e.g., soreness and numbness) occurred. Sandberg et al. [37] studied the influence of different stimulations (ST36 superficial puncture, muscle puncture without De-qi, and muscle puncture with De-qi) on participants' blood flow of the skin and muscle. They found that muscle blood flow increased following both muscle puncture without De-qi and muscle puncture with De-qi, with the latter being more obvious in the initial 5 min. Besides, skin blood flow also increased for 5 min following De-qi. On the contrary, no increase was found following superficial puncture.

4.2. Effects of De-qi on Electroencephalogram. Electroencephalogram (EEG) is another objective indicator of De-qi and its change is significantly associated with autonomic nervous functions. Yin et al. [38] demonstrated that participants with higher De-qi sensation during needle retention showed significant changes in alpha band powers over the periods before, during, and after needle retention while those with lower De-qi sensations did not. The result indicated a good correlation between EEG changes and De-qi sensation. Sakai et al. [35] showed that De-qi induced by acupuncture manipulation not only caused autonomic changes (HR and SBP), but also nonspecifically increased the power of all spectral bands except the gamma band of EEG and the correlation between De-qi and EEG changes was good. Besides, their preliminary result reported that acupuncture without De-qi sensation induced much less effects on EEGs and autonomic functions. Tanaka et al. [39] reported that acupuncture increases all bands of EEG power, and this phenomenon occurred only with autonomic changes triggered by acupuncture. Previous studies also showed that autonomic nerve functions were closely related to EEG changes [40]. Therefore, autonomic changes induced by acupuncture with De-qi are probably mediated through the central nervous system. Changes in EEG are related to specific De-qi sensation induced by acupuncture manipulation, but not to a general arousal state.

4.3. Effect of De-qi on Limbic-Paralimbic System and Subcortical Structure of the Brain. Several studies observed the impact of De-qi on brain fMRI blood oxygen level-dependent (BOLD) signals and found out that acupuncture needle sensations of De-qi without sharp pain and De-qi with sharp pain are associated with different patterns of fMRI BOLD signal activation and deactivation in limbic-paralimbic system and subcortical structure of the brain.

Fang et al. [41] found that acupuncture produced extensive deactivation of the limbic-paralimbic-neocortical system. In their study, amygdale (acupoints LV2 and ST40) and hippocampus (acupoints LR2, LR3, and ST44) showed a fMRI BOLD signal deactivation in participants who experienced De-qi without sharp pain. Asghar et al. [42] reported different fMRI BOLD signals of brain between De-qi and acute pain when needling at LI4. Predominately, De-qi sensation deactivated the BOLD signals in the limbic/subcortical structure and the cerebellum, whereas acute pain sensation (De-qi > pain contrast) increased the signals in these areas. Hui et al. [43] showed a fMRI BOLD signal decrease in limbic and paralimbic structures of cortical and subcortical regions in the telencephalon, diencephalon, brainstem, and cerebellum when participants experienced De-qi sensation only (including dull pain but not sharp pain) at ST36. However, when De-qi sensation was mixed with sharp pain, the hemodynamic response was mixed, showing a predominate signal increase.

In general, predominant De-qi sensation deactivated the fMRI BOLD signals in the limbic-paralimbic system

and the subcortical structure of the brain, while the sharp sensation activated the BOLD signals in these regions. The decreases in fMRI BOLD signals are not clearly explained yet, but increasing clues point to that it is a manifestation of neuronal deactivation [44]. Limbic-paralimbic system and neocortical structure play an important role in processing the cognitive and affective dimensions of pain signals and act as the regulatory center of emotion, cognition, consciousness, autonomic, endocrine, and immunological functions. Therefore, it is possible that acupuncture De-qi performs its comprehensive function by inhibiting neuronal activity in the limbic-paralimbic system and the subcortical structure of brain.

5. Discussion

Nowadays, the studies on subjective De-qi sensation are mainly based on the scale survey, including both qualitative description and quantitative evaluation. These studies found that De-qi sensation is a special sensation between pleasant and outright pain. The most common perception of De-qi sensation by patients is consistent with that described in TCM, such as "sore," "numb," "distended," "heavy," "electric," and "warm" sensations. Different De-qi sensations may trigger different brain reactions based on the types of afferent nerve fibers involved and finally lead to various therapeutic effects. It should be noted that there are some limitations in the existing scales. In TCM theory, De-qi sensation felt by acupuncture practitioner is even more important than that felt by patients. Park et al. [45] also found that needle sensations of practitioners are more objective than those of patients. However, most of the scales did not take practitioners' needle sensations into consideration.

Many studies proved that specificity of acupoints, needling manipulations, and stimulation methods are key affecting factors of De-qi, while the psychological factor has relatively less influence. It is found that De-qi is most likely to be elicited when needling acupoints in appropriate depth with certain manipulation. The acupuncture practitioners are vital to elicit De-qi sensation because they locate the acupoints and conduct all the manipulations. Therefore, the background of the practitioner such as their experiences in acupuncture practice should be taken into account in future studies on influencing factors of De-qi.

De-qi could trigger a series of objective changes from the center to the periphery, including changes of autonomic functions such as HR, blood flow, skin temperature, and deactivation of fMRI blood oxygen level-dependent (BOLD) signals in the limbic/paralimbic system and the subcortical structures of the brain as well as EEG changes. Increasing clues point to the fact that deactivation of fMRI BOLD signals is a manifestation of neuronal deactivation. Therefore, it is possible that acupuncture with De-qi obtains its curative effects by affecting autonomic functions through the central nervous system and regulating neuronal activity of the limbic-paralimbic system and subcortical structure of the brain. A series of cascade reactions may be activated to ultimately restore the homeostasis inside the patients' body by regulating nerve-endocrine-immune network as a whole after De-qi is well achieved. However, most of the researches on acupuncture De-qi that we mentioned were carried out on healthy subjects but not on patients. Subjects in diseased condition will respond differently in comparison with healthy subjects. For example, Liu et al. [46] reported that during acupuncture both hypothalamus response and De-qi score were different between heroin addicts and healthy subjects. Compared to healthy subjects, the De-qi score of heroin addicts was significantly higher and the activation of hypothalamus was more robust. In *Neijing* (*Internal Classic*), it is described that people with excess constitution can obtain De-qi easily, while people in deficient state may hardly experience it. Therefore, subjects in diseased conditions should be observed in future De-qi researches.

6. Conclusion

As an important component of acupuncture, De-qi is getting increasing attention of the researchers. Current researches partly revealed the underlying mechanism of De-qi from the aspect of subjective De-qi sensations, its influencing factor, and the resulting physiological responses. Further researches, particularly on De-qi in diseased condition, are needed in order to understand De-qi more objectively and comprehensively.

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Research Article

The Observation of the Change of TCE Caused by Different Acupuncture Stimulation

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Purpose. To observe the change of transcutaneous CO_2 emission on meridian points or nonacupoints when the different needle sensations were gotten and study the associativity between Deqi acupuncture and periphery constitution energy metabolism effect. *Method*. 20 healthy volunteers were punctured on Neiguan (P6) in different ways including sham, shallow, Deqi acupuncture, and Deqi plus pressed P5, and measured TCE of different points before, during, and after acupuncture. *Result*. Needle sensations of sham acupuncture and shallow acupuncture were less than those of Deqi acupuncture. TCE of meridian points increased significantly and showed the specificity of meridian/channels. *Conclusion*. Verum acupuncture could cause the stronger needling sensations including distention, aching, numbness, and tingling than sham and shallow acupuncture. The strength of needling sensation caused by Deqi acupuncture is moderate and brought the best curative effects in TCE measurement. Deqi acupuncture could improve the energy metabolism of the points on the corresponding meridian/channel.

1. Introduction

Usually, effective acupuncture is also called Deqi acupuncture (arrival of Qi) [1]. Deqi/Qi arrival (with its uniquely human characteristics like Qigong and Yin-Yang) is accepted by parts of the international academic community [2]. When inserting the needle to a certain depth, both the acupuncturist and the patient will feel something is changing; this means Qi arrival or Deqi sensation. Deqi is an important part of acupuncture or meridian/channel researches, a main way of judgment of acupuncture effects and clinical curative effects [3].

The experiment design of double blind, control, and random is the golden standard in the Western medicine scope. In many acupuncture clinical trials, including the famous reports from Germany study groups, the acupuncture curative effects are queried because of the placebo or sham acupuncture design [4].

So, it is a challenge that we must face: whether the efficiency of acupuncture is better than placebo or, further, the acupuncture is only playing a role of psychology comfort.

To answer this question, therefore, we did a group of experiments for the comparison between placebo acupuncture, sham acupuncture, and verum acupuncture.

We did a serious transcutaneous CO_2 emission measurement on acupoints using Fewil Q.F. microdetector of CO_2 emission (which originally was invented by Professor W. Franyo, remade by Professor Zhang WB, Beijing, China) to study the curative effects of acupuncture. The previous experiments showed that the transcutaneous carbon dioxide (CO_2) emission (TCE) could reflect the skin tissue energy metabolism to a certain degree. And TCE will be a sensitive index to observe the acupuncture curative effects [4].

According to Professor Hu's studies, pressure could block the acupuncture effects [5]. We specially designed that using 1 kg pressure on the channel of Pericardium, and observed the change of needling sensation and TCE of the point.

2. Methods and Material

2.1. Selection of Study Participants. Through advertisements on the campuses, 20 healthy volunteers (8 male, 12 female)

with a mean age of 29.00 ± 9.22 years were enrolled among the staffs and graduate students from the Institute of Acupuncture and Moxibustion of the China Academy of Chinese Medical Sciences. All participants who had received acupuncture before, could distinguish the needle sensation and gave informed consent. The experimental procedure was approved by the Ethics Committee of the Institute of Acupuncture and Moxibustion of China Academy of Chinese Medical Sciences.

2.2. Acupuncture. Each volunteer underwent 4 measurements (two different kinds of sham acupuncture and two different kinds of verum acupuncture, see below) in random order every other day. To avoid discrepancies in manipulation, all acupuncture operations were performed by the same medical practitioner.

The volunteers lay down on the back and exposed the right arm, so the acupoint Neiguan (P6), Quze (P3), and other observational points could be marked in accordance with a textbook on acupuncture and moxibustion [1] (see Figure 1). Needle retaining time was about 20 minutes.

2.3. Acupuncture Point. Neiguan (P6) is located on the pericardium meridian, 2 cun below wrist crease, between 2 tendons. All the locations of acupoint including the following were mentioned in Professor Cheng' *Chinese Acupuncture and Moxibustion* [6].

2.4. Measurement Points. Quze (P3), is located on the pericardium meridian, in the elbow fossa, on the elbow crease, ulnar of biceps brachii tendon.

Point A: located on the pericardium meridian, in the middle between P3 and P5.

Point B: 1 cm besides Point A, radial side.

2.5. Pressed Point. Jianshi (P5): 1 cun below P6.

2.6. Sham Acupuncture

2.6.1. Placebo. Sham acupuncture was performed using a single-use acupuncture needle tube (Tianxie brand, Suzhou, China) which was tapped on P6, but no needle was inserted (see Figure 2).

2.7. Shallow Acupuncture. Shallow acupuncture was performed using a single-use acupuncture needle with tube (Tianxie brand, Suzhou, China) which was tapped on P6; the insertion of needle into the skin was only 1 or 2 mm. (see Figure 3).

2.8. Verum Acupuncture

2.8.1. Deqi Acupuncture. Acupuncture stimulation was done manually, using single-use acupuncture needle (0.25 × 25 mm, Tianxie brand, Suzhou, China). The doctor inserted the needle on P6 through a tube to retain depth and then repeated lifting, thrusting, twisting, and rotating until both the practitioner and the volunteer felt the Qi arrival or needling sensations like soreness, numbness, aching, pressure, or tingling; then the insertion was stopped. The needle was remained in place for 20 mins and then removed (see Figure 4).

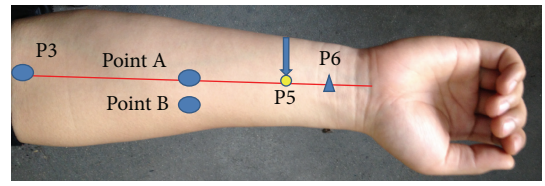

Figure 1: The location of the points.

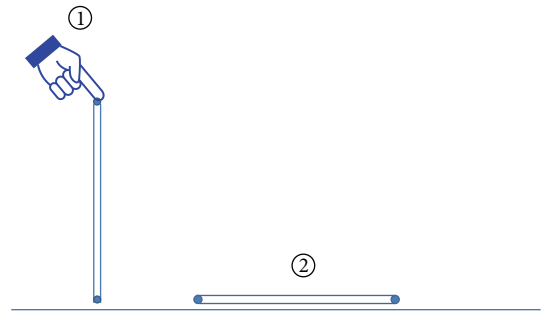

Figure 2: Sham acupuncture.

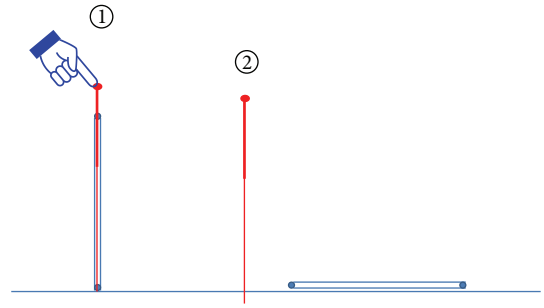

Figure 3: Shallow acupuncture.

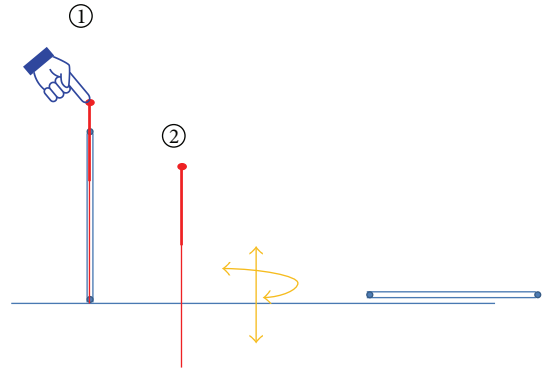

Figure 4: Verum acupuncture.

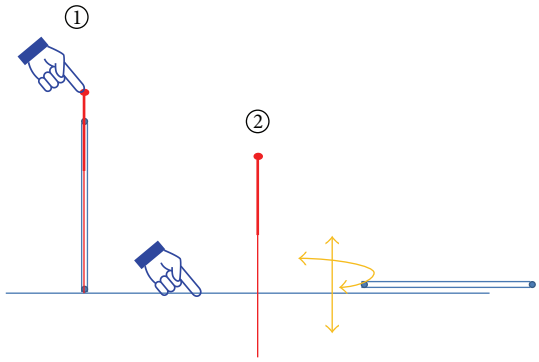

Figure 5: Acupuncture and pressed P5.

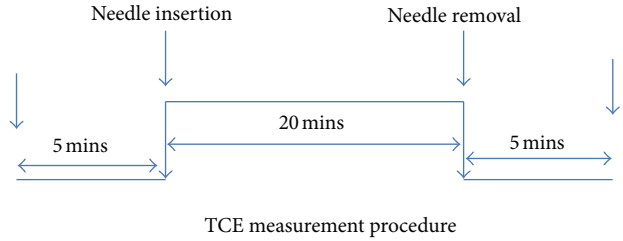

Figure 6: TCE measurement procedure.

2.8.2. Acupuncture and Pressure on P5. A similar operation like pure acupuncture after the needle insertion was performed until the Qi arrival. Then, manipulator used a spring manometer which fixed in a universal bracket pressed on P5 with 9.8 N pressure (Pressure area 1 × 1 cm). The pressure was controlled by adjusting the height of the gauge. The needle was left in P6 for 20 mins before its removal (see Figure 5).

2.9. Measurement

2.9.1. TCE Measurements. The Fewil Q. F. carbon dioxide measuring instrument was designed by Professor W. Franyo (Hungary) in 1976 and improved by Professor Zhang WB (China) in 1996, which could measure the micro-carbon dioxide of the skin (see Figure 6).

Before the experiments, the fan and the air-conditioner were turned on, so the lab was at well ventilated and constant temperature (26 ± 1°C) and humidity (40–60%). The laboratory technician and the doctor wore tasks to avoid influencing the accuracy of the instrument.

The measurement procedure was like below (see Figure 7).

Firstly, the instrument measured the air carbon dioxide of the room 3 times. And then, the technician measured the transcutaneous carbon dioxide (CO_2) emission of P3, Point A and B on the skin 3 times before, during, and after sham or verum acupuncture.

2.9.2. The Inquiry and Record of Needling Sensation. During the experiment, all volunteers wore eyeshade and were asked the feeling using for reference the needling sensations questionnaire which is made by Harvard Medical School [6]

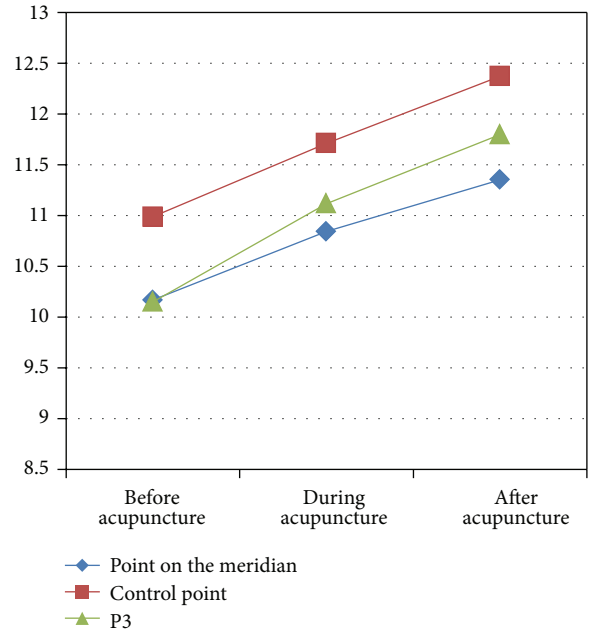

Figure 7: The change of point's TCE caused by sham acupuncture.

and, respectively, assessed by visual analogue scale (VAS). Zero means "no sensation at all," and 10 means "too much to bear."

The questions were unified:

> "I will puncture you. Do you have something special?
>
> Do you feel aching, soreness . . . and so on?
>
> If yes, please describe it and tell us the degree. 0 means nothing and 10 stands for too much to bear."

3. Analysis of Data

The average of 3 times measurement of CO_2 of the points and the room air was calculated. M stood for the TCE of points and N for the air. Considering the influence of air, the modified TCE = $M - (N * 0.1)$. One percent is coefficient based on past experience.

A one-tailed Fisher's exact test was used to analyze a possible connection between stimulation and perception. A P value of <0.05 was considered significant.

4. Results

4.1. The Needling Sensation on Acupuncturing P6. Recording and comparing 20 volunteers' needling sensations, it was found that the most commonly appeared sensations were distention and heaviness (pressure), the other were aching, numbness, tingling, and hotness in the same order of occurance (see Table 1).

The needling sensation degree was different according to the stimulation way. It was interesting that even though the acupuncturist did give verum needling for the volunteers, some of them still felt distention or numbness feeling. But the feeling was very mild and did not exceed 3 in VAS.

Table 1: The needling sensation of 4 types acupuncture (number of needling sensations gainer/figures of VAS).

	Heaviness/VAS	Distention/VAS	Aching/VAS	Numbness/VAS	Tingling/VAS	Hot/VAS
Sham		3/1.5		1/2		
Shallow	1	8	5	6	3	
Deqi acupuncture	20/2.8	18/5.33	10/5.4	11/4.05	7/4.21	2/2
Acupuncture + press		14/5.71	9/5.06	13/7.11	3/6.17	

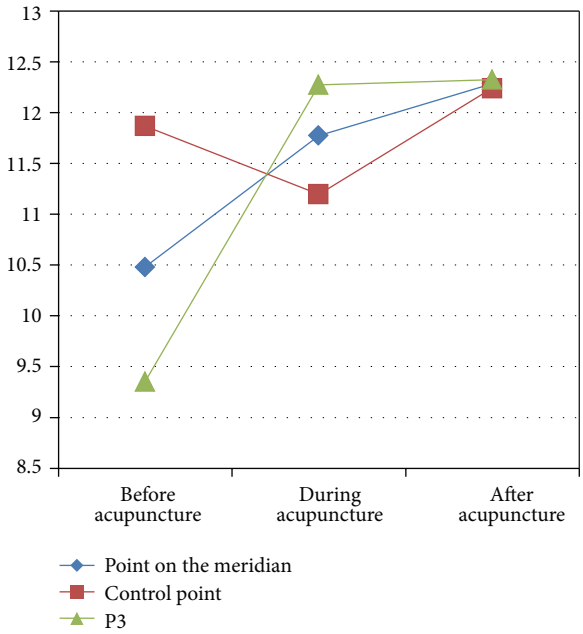

Figure 8: The change of points' TCE caused by shallow acupuncture.

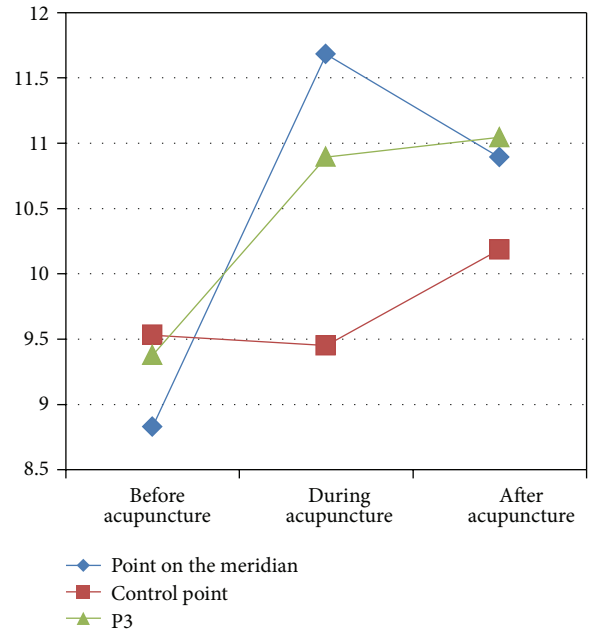

Figure 9: The change of points' TCE caused by Deqi acupuncture.

For the Deqi acupuncture, all the volunteers could feel needling sensations including heaviness, distention, aching, numbness, tingling, and hotness. The strength of sensations was between 2 and 6 and was not very strong, but that of the stimulation caused by Deqi acupuncture plus pressed P5 was much stronger than pure acupuncture. The VAS was between 4 and 9 (see Table 1).

In the group of sham acupuncture, the change tendency of TCE of Points A (on the meridian), B (control point), and P3 (Quze) was almost the same and without significance. The TCE of all the points increased over the time.

But in the other 3 groups, despite the shallow acupuncture, the TCE of P3 and Point A increased during acupuncture with significance, while the TCE of Point B decreased. Among these acupuncture experiments, the change of TCE of the Deqi acupuncture which increased significantly was the biggest.

When we did sham acupuncture, TCE of all the points was increased almost evenly (see Figure 7).

But when the skin got stimulated, even though very mildly like shallow acupuncture, TCE of the point on the meridian and P3 was increased in different way while that of the control point decreased first and then increased (see Figure 8).

Similarly, after Deqi acupuncture stimulation, the change of TCE of the point on the meridian and P3 was different from control point. TCE of both points on the meridian and P3 increased during acupuncture and then decreased after acupuncture. On the contrary, TCE of the control point decreased during acupuncture and then increased after acupuncture (see Figure 9).

When we put pressure on P5, the change of TCE of those points was just like that of Deqi acupuncture (see Figure 10).

In these later 3 conditions, the changes of TCE of control point were similar as if they were not affected by acupuncture stimulation and embodied the specificity of meridian (see Figure 11).

5. Discussion

The neiJing says: "The needle will wander in the channel when you acupuncture in the right Qi point." [Miraculous Pivot, Lingshu, the 4 chapter]. That means after a doctor stimulates an acupoint, some response will be invoked like Qi arrivals. And only Qi arrival and the effects could be gotten; the faster Qi arrival the faster taking effects. When the Qi is coming, both the manipulator and the patient could feel it. The feeling below the doctor's needle is like heaviness, tense, and fullness, while the patient is feeling aching, distention, tingling, and so on. Some scholars thought that acupuncture might be a special pain stimulus, whose autonomic concomitants could

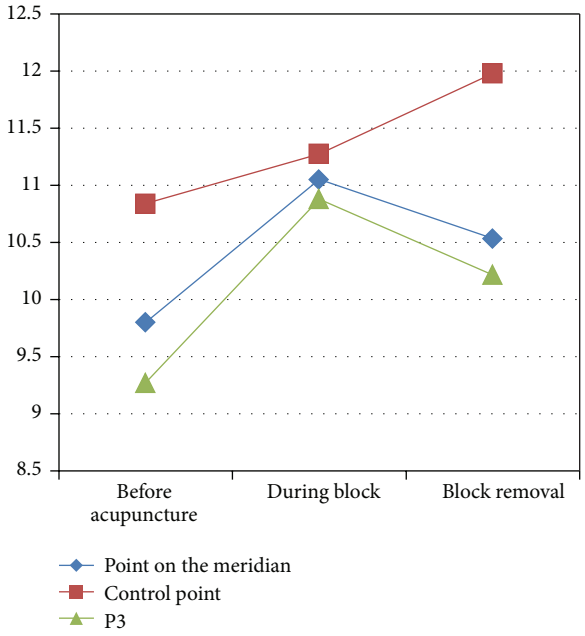

Figure 10: The change of points' TCE caused by acupuncture plus pressure.

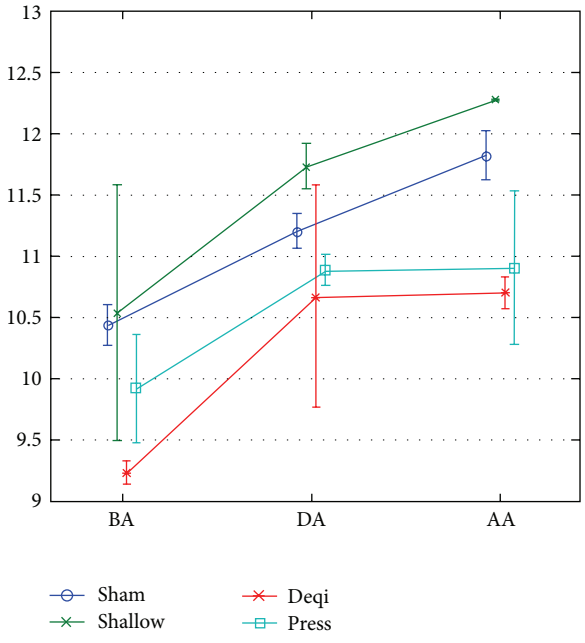

Figure 11: ANOVA for TCE changing before, during, and after acupuncture in 4 types of stimulations.

explain its nonanalgesic effects [7]. Zhou's study indicated that different kinds of needling sensations might be associated with different nerve innervations, but it did not explain the relationship between the extension of the sensations and effects [8]. For the sham acupuncture, a study group from Germany thought that sham laser acupuncture could serve as a valid placebo control in laser acupuncture studies. But laser acupuncture is much different from hand acupuncture [9].

In another experiment of the authors, the result showed that the stronger stimulation caused stronger needling sensation [10]. There are more and more similar studies on Deqi recently. For example, Choi did a single-blinded experiment on fifty-three healthy volunteers which received three different forms of acupuncture including superficial needling (0.3 cm) and deep needling (2 cm) to observe the change of the threshold. The result showed that needle rotation and acupuncture sensation play an important role in verifying the effect of acupuncture [11].

In this experiment, the authors used questionnaire to investigate the needling sensations after 4 kinds of acupuncture stimulation and found that the traditional distention, aching, and tingling were still the main ones.

TCE was used to measure the performance of the skin energy metabolism of the points. Among 4 stimulations, Deqi acupuncture could get the moderate feeling but with the best curative efficacy. Acupuncture plus pressed P5 caused stronger feeling; therefore, the change of TCE between before and after acupuncture was not obvious. That means the appropriate acupuncture stimulation works best in the clinic, and the needling sensation is not equal to Deqi, positively related to the clinical effects [2].

It is meaningful that the shallow acupuncture could cause the increasing of TCE of both the meridian and the control points. In other words, even the microacupuncture stimulation could improve the whole body energy metabolism, which is nonspecific. on the Contrary, the Deqi acupuncture could improve that significantly. That is why sham acupuncture or acupuncture on "nonacupoint" could get the clinical effects but not as good as Deqi treatment—effective acupuncture stimulus.

The Qi arrived in Deqi acupuncture; furthermore, the TCE of P3 and Point A which is on the same meridian increased significantly. It showed the existing of specificity of traditional meridian/channel.

6. Conclusion

(1) Verum acupuncture could cause the stronger needling sensations including distention, aching, numbness, and tingling than sham and shallow acupuncture.

(2) The strength of needling sensation caused by Deqi acupuncture is moderate and brought the best curative effects in TCE measurement.

(3) Deqi acupuncture could improve the energy metabolism of the points on the corresponding meridian/channel.

Acknowledgments

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Research Article

Comparative Effectiveness of the Deqi Sensation and Non-Deqi by Moxibustion Stimulation: A Multicenter Prospective Cohort Study in the Treatment of Knee Osteoarthritis

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Substantial evidence has supported that moxibustion stimulates a unique phenomenon of Deqi, heat-sensitive moxibustion sensation. This study consisted of a multicenter, prospective cohort study with two parallel arms (A: heat-sensitive moxibustion sensation group; B: nonheat-sensitive moxibustion sensation group). All forms of moxibustion were applied unilaterally on the right leg with a triangle shape of three acupuncture points simultaneously (bilateral Xi Yan (EX-LE5) and He Ding (EX-LE2)). After one month the primary outcome parameter GPCRND-KOA showed significant differences between groups: trial group 5.23 ± 2.65 (adjusted mean ± SE) 95% CI [4.44~6.01] versus control group 7.43 ± 2.80 [6.59~8.26], $P = 0.0001$. Significant differences were manifested in total M-JOA score during the follow-up period ($P = 0.0006$). Mean knee circumference indicated significant difference between the groups ($P = 0.03$; $P = 0.007$). Overall, this evidence suggested that the effectiveness of the Deqi sensation group might be more superior than the non-Deqi sensation one in the treatment of KOA. This study was aimed at providing scientific evidence on the Deqi sensation of moxibustion and at showing that heat-sensitive moxibustion sensation is essential to achieve the preferable treatment effects of KOA.

1. Background

Acupuncture stimulates the Deqi, a sensory response which literally means "the arrival of meridian Qi" according to traditional Chinese medicine (TCM) [1, 2]. The classical TCM textbook of *Huangdi Neijing* states that the Deqi must be felt by the therapist, and it is also necessary for therapist to concentrate in order to ensure the Deqi [3]. The essence of acupuncture therapy was expressed in *Nine Needle* and *Twelve Sources* (from *Huangdi Neijing*), "the arrival of meridian Qi ensures the therapeutic effects." This chapter describes the importance of activating meridian Qi and prompting it to transmit to the affected body part. Therefore, a lot of researchers confirmed that the Deqi is the key experience related to clinical efficacy of acupuncture [4, 5].

For acupuncture needle, multiple unique sensations experienced by the patient around the applied part of needle manipulation are often described as suan (aching or soreness), ma (numbness or tingling), zhang (fullness/distention or pressure), and zhong (heaviness) [6]. The Deqi stimulated by needle is believed to be closely related to clinical effects [7]. And there is also evidence to support that the increasing clinical effects were associated with the Deqi by needle stimulation [8–10].

Unlike acupuncture needle, which involves thrusting or twisting of needles and induces various Deqi phenomena, moxibustion implements heat stimulation of various temperature levels from mild skin warming to acupuncture points. Suspended moxibustion is the most common therapy in China. It involves burning of moxa on the acupuncture

points at a distance. The Deqi by moxibustion stimulation is different from the one simulated by acupuncture needle as well. Substantial evidence has supported that moxibustion stimulates a unique of Deqi, that is, heat-sensitive moxibustion sensation [11]. A lot of observations and researches were adopted to confirm this phenomenon in the 1990s [12].

For humans, acupuncture points include two states: stimulated state and resting state. For healthy people, acupuncture points are in a resting state, and moxibustion only stimulates local superficial heat sensation. When people get sick, the acupuncture points on the surface of body are activated and sensitized. Several Deqi sensations are induced and called heat-sensitive moxibustion sensation. The first of all, penetrating heat, is the feeling from the applied part of the skin sinking into the underlying tissues or organs. In the second, expanding heat is the feeling of heat spreading out from the spot receiving moxibustion. The third, transmitting heat, refers to the sensation of heat moving from spot receiving moxibustion along a certain route. These sensations indicate that meridian Qi has been stimulated, and transmission has occurred [13]. However, there is lack of experimental data to indicate how heat-sensitive moxibustion sensation (the Deqi by moxibustion stimulation) compares with conventional local superficial heat sensation (non-Deqi by moxibustion stimulation).

Moreover, several articles and research reports have reported the effectiveness and safety of moxibustion for the treatment of knee osteoarthritis (KOA) [14–17]. Moxibustion has anti-inflammatory or immunomodulatory effects to fight against chronic inflammatory conditions in humans. For KOA, especially, is it necessary for moxibustion to produce the phenomenon of obtaining Qi in order to improve the curative effect? Therefore, it would be valuable to know whether there is difference between the moxibustion sensations in the treatment of KOA. The rigorous multicenter prospective cohort study trial was planned in order to determine the relationship of the Deqi by moxibustion stimulation and therapeutic effect.

2. Methods

2.1. Objective. The aim of this study is to compare the effectiveness of heat-sensitive moxibustion sensation and nonheat-sensitive moxibustion sensation in the treatment of patients with moderate-to-severe swelling KOA in China.

2.2. Sample Size. The sample size for testing the difference between the effective rates was calculated by the SPSS 13.0 programme. The outcome was the guiding principle of clinical research on new drugs in the treatment of KOA (GPCRND-KOA) [18]. According to previous pilot study, the effective rate in heat-sensitive moxibustion sensation group is 80% and 50% in the other group. If we apply a two-sided 5% significance level, 90% power the calculated required sample size is approximately 36 participants in each group. Allowing for a 20% loss to followup, a total of 45 participants were required in two groups:

$$n = \left\{ \frac{Z_{1-a}\sqrt{2pq} + Z_{1-\beta}\sqrt{p_1(1-p_1) + p_2(1-p_2)}}{p_1 - p_2} \right\}^2, \quad (1)$$

$$p = \frac{(p_1 + p_2)}{2}, \qquad q = 1 - p.$$

2.3. Design. A multicenter (four centers in China), prospective cohort study was conducted by the Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine (TCM) in Nanchang, the first Affiliated Hospital of Anhui University of TCM in Hefei, Jiangsu TCM Hospital in Nanjing, and Shanxi TCM Hospital in Xian. The patients were recruited at either outpatient service or inpatient department and had already made their own choice of moxibustion therapy. Thus, the groups were divided by the appearance of acupuncture point's Deqi sensation stimulated by suspended moxibustion. In trial group, patients felt the Deqi sensation when the acupuncture point was stimulated by moxibustion heat. In the control group, patients felt local superficial heat sensation (non-Deqi sensation) when the acupuncture point was stimulated by moxibustion heat.

2.4. Participants

2.4.1. Recruitment. Patients were recruited in China for this nonrandomized prospective multicenter open comparative cohort study from July 30, 2010 to July 30, 2011. The ethics committees of the Affiliated Hospital with Jiangxi University of TCM approved the study and the consent procedure. Oral and written informed consent was obtained after verbal information about the study was provided by the physician. The signed consent form was sent to the central study center, and a copy was kept at the physician's office.

2.4.2. Inclusion Criteria. Participants meeting the following criteria were included: patients met the diagnostic criteria for GPCRND-KOA; the GPCRND-KOA scale for KOA count should be more than 5 points, moderate-to-severe swelling KOA; the age of patients was from at least 38 years to no more than 70 years, and regardless of genders. According to the following KOA diagnosis standard, the following criteria were included simultaneously: knee joints appeared swelling; floating patella test was negative; patients accepted the treatment protocol in this trial; patients had stopped receiving previous treatment before recruitment for two weeks.

2.4.3. Exclusion Criteria. Participants with one or more than one of the following criteria should be excluded: participants suffered from serious life-threatening disease, such as the heart disease or disease of brain and blood vessels, liver, kidney, and hematopoietic system, as well as psychotic patients; patients with diabetes, diabetic polyneuropathy, and polyneuropathic disturbances; the pregnant patients or

patients in lactation period. The following conditions were also excluded items: acute knee joint trauma or ulceration in its local skin, complicated with serious genu varus/valgus and flexion contraction.

2.5. Study Interventions. The moxibustion therapies were implemented by qualified specialists of acupuncture in TCM with at least five years of clinical experience in this study. All treatment regimens were standardized between four centers practitioners by means of video, hands-on training, and internet. Both groups of patients were requested to receive no other treatments such as physical therapies, pain-killing medicines, or acupuncture treatment from other places.

In the two groups, 22-millimeter (diameter) × 120-millimetre (length) moxa sticks (produced by Jiangxi provincial TCM Hospital, China) were applied. The patients usually laid in the comfortable supine position for treatment, with 24°C ~30°C temperature in the room. Loose trousers are suggested to wear, in order to make knee joints to be exposed.

2.5.1. The Heat-Sensitive Moxibustion Sensation Group. The moxa sticks were ignited by the therapist, and three acupuncture points (bilateral Xi Yan (EX-LE5) and He Ding (EX-LE2)) with triangle shape should be implemented simultaneously by suspended moxibustion. The warm suspended moxibustion was applied 3 centimetres away from the surface of the skin to search for the heat-sensitive moxibustion sensation. In this group, these acupuncture points were brought mild warmth without burning by moxa sticks and manipulated until the patient reported the characteristic of heat sensitization sensation; it is commonly called Deqi. Patients felt comfortable in the moxibustion manipulation.

The following patients' sensation suggested the Deqi: penetrating heat sensation due to moxa heat, defining as the heat sensation conducting from the moxa local skin surface into deep tissue or even into the joint cavity; expanding heat sensation due to moxa heat, defining as the heat sensation spreading the surrounding little by little around the moxa point; transmitting heat sensation due to moxa heat, defining as the heat sensation transferring along some pathway or direction, even to the ankle or hip conduction. In the course of manipulation, the therapist continued for 15 minutes in per treatment session. Patients received the treatment two times/day in 1st week (one time/day from 2nd week) for a total of 35 sessions over 30 days.

2.5.2. The Nonheat-Sensitive Moxibustion Sensation Group. Common practices were similar to the first group. Only one difference was that patients in this group felt local superficial heat sensation. No Deqi sensations were stimulated in this group.

2.6. Outcome Measures. Ministry of Health of the People's Republic of China (MHPRC) has proposed the GPCRND-KOA [18]. The GPCRND-KOA scale was used widely and authoritatively recommended by China Clinic Trial. In the scale, a patient with KOA was assessed, including pain, the relation between activity and pain, function impairment, and special exams (Table 1). This scoring system was previously validated [19]. The degree of KOA is divided into three levels: mild <5 scores; moderate 5~9 scores; severe >9 scores. In the terms of swelling knee, knee circumference was assessed at each time point. The parameter was measured in centimeters across the middle of a patella, with ordinary tape measure [20].

Therapeutic effect was evaluated by comparing baseline and final conditions reported by the patient. This trial also recorded adverse effects reported by patients during treatment. The outcome measures above were assessed before the treatment (month 0), at the end of the treatment period (month 1), and 6 months after the end of the treatment period (month 7).

2.7. Statistical Methods. Statistical analyses were based on the intention-to-treat (ITT) principle, including all patients with baseline values to receive treatment. All tests were exploratory and two sided with a level of significance of 5%. The statistician who conducted the analyses remained blind to treatment group, and data were only unblended once all data were summarized, and analyses were completed. Statistical analyses were performed according to a predefined statistical analysis plan using SAS for Windows, version 9.2 (SAS Institute, Cary, NC, USA). We adopted multilevel models analysis of covariance (ANCOVA) or generalized estimating equations (GEE). In these models, physicians considered random effects, and fixed effects were GPCRND-KOA (continuous), patient's age and gender, Body Mass Index (BMI), knee circumference (continuous), and previous treatment. Results are presented as adjusted mean or proportioned with a standard error (SE) and/or 95% confidence interval (CI).

2.8. Adverse Events. We defined adverse events as unfavorable or unintended signs, symptoms, or disease presenting after treatment; however, they were not necessarily related to the moxibustion intervention. Adverse events were analyzed descriptively by frequencies, percentages, and by chi-squared or Fisher's exact test (if feasible).

3. Results

3.1. Population and Baseline. Among 266 screened patients, 106 could not be included in the study, mainly because they did not meet all eligibility criteria (Figure 1). Patients were recruited by 28 physicians experienced in the treatment of KOA (15 acupuncture doctors and 13 conventional doctors). After the search of the Deqi, 160 patients experienced heat-sensitive moxibustion sensation; 51 patients had no Deqi sensation. Since a sample of 90 people was calculated in our trial, we selected 45 patients from each queue separately by random drawing.

After seven months, 2 patients missed. Reasons for missing follow-up data were not contactable.

Patients' preferences resulted in the following baseline differences: patients in the trial group showed lower severe BMI scores, while the GPCRND-KOA score was higher in

Table 1: List of GPCRND-KOA.

Item	Grade/classification	Score
Pain or discomfort in night when lying in bed	No	0
	Pain in activity or some position	1
	Pain in nonactivity	2
Morning stiffness or pain worse when getting out of bed	No	0
	<30 minutes	1
	≥30 minutes	2
Pain or discomfort in walk	No	0
	After walking in some distance	1
	Pain at beginning of walk or worse	2
Arise from seat	Independent	0
	Need assistance	1
The maximum walk distance (accompanied with pain)	Unrestricted	0
	Restricted, >1 km	1
	300 m~1 km	2
	<300 m	3
Daily activities	Board standard airstairs	
	Independent	0
	Difficulty	1
	Unable	2
	Step down standard airstairs	
	Independent	0
	Difficulty	1
	Unable	2
	Squat or bend knees	
	Independent	0
	Difficulty	1
	Unable	2
	Walk over rough terrain	
	Independent	0
	Difficulty	1
	Unable	2

the control group. The males of the trial group were more than those of control group. In the previous treatment, there were obviously differences among the two treatment groups, as well as gender (Table 2).

3.2. Outcome Parameters

3.2.1. Total GPCRND-KOA Score. After 1 month the primary outcome parameter GPCRND-KOA showed significant differences between groups: trial group 5.23 ± 2.65 (adjusted mean ± SE) 95% CI [4.44~6.01] versus control group 7.43 ± 2.80 [6.59~8.26], $P = 0.0001$ (Table 3). Significant differences in total M-JOA score were also evident during the follow-up period ($P = 0.0006$).

3.2.2. Knee Circumference. Reductions in mean knee circumference at months 1 and 7 compared with control group were observed, and they were significant. Significant differences presented between the groups ($P < 0.05$) were shown in Table 4.

3.3. Safety. No adverse events were reported in the 90 participants.

4. Discussions

In this observational comparative effectiveness study, patients with KOA who presented heat-sensitive moxibustion sensation significantly reduced pain and possessed better function after one month than the ones who received conventional local superficial heat sensation, according to the total GPCRND-KOA score. Both of the groups substantially improved during the observation period. After 7 months, exploratory analysis indicated that the differences between the two groups were still significant. Significant differences were also evident for knee circumference.

The design of the study (observational and multicenter setting) allows evaluation of a therapy's comparative effectiveness considering the acupuncture point's own reactions and the Deqi sensation. Both the evaluation of the results and the statistical analysis were carried out in a blind fashion to improve the objectivity and validity of the study outcomes.

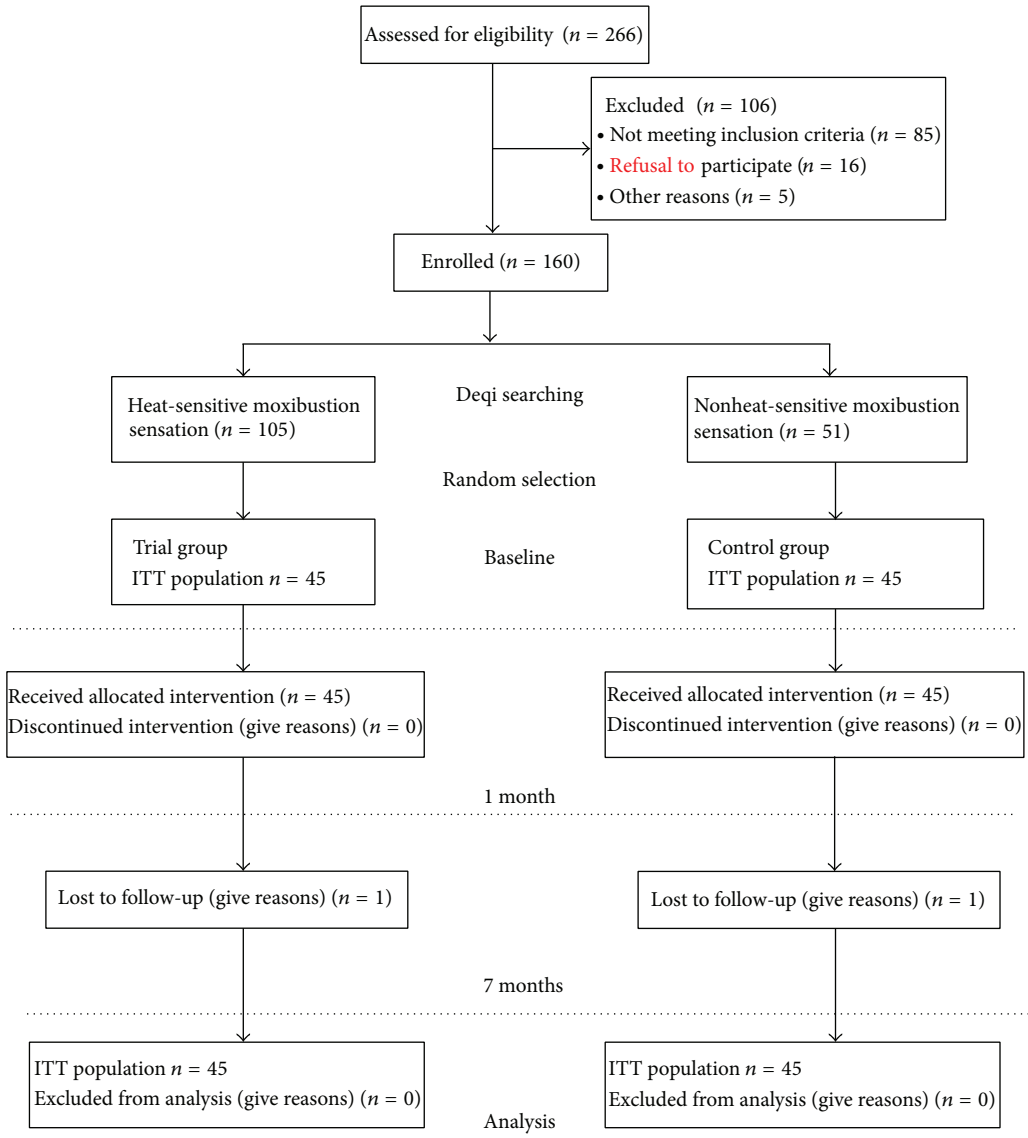

Figure 1: Flow diagram.

The aim of this study was to compare the Deqi effect and non-Deqi effect stimulated by suspended moxibustion and to confirm that heat-sensitive moxibustion sensation simulated by moxibustion is a sign of the Deqi. Thus, Deqi sensation occurrence preferences were chosen to take it into account, and it made randomization not possible. The observational design resulted in relevant baseline differences of the two groups. In the trial group GPCRND-KOA appeared higher compared with the conventional group. In the previous treatment, there were obvious differences between the two groups. To take baseline differences into account, we adjusted our analyses of these factors. However, it is possible that other unknown and unmeasured factors might have influenced the results. Therefore, the nonrandomized design is a clear limitation of our study considering the internal validity of our results.

In this study, we investigated the relationship between the Deqi sensation and therapeutic effect according to moxibustion stimulation. Previous studies manifested that the Deqi (heat-sensitive moxibustion sensation) was elicited in 70% of the moxibustion procedures of patients [21]. The frequency and intensity of individual sensations were significantly higher in KOA. Among the sensations typically associated with the Deqi, penetrating heat, expanding heat, and transmitting heat were most common [22]. Being consistent with their prominent roles in TCM, bilateral Xi Yan (EX-LE5) and He Ding (EX-LE2) showed the most prominent sensations [13, 21].

In terms of the Deqi sensation of acupuncture needle, it has been demonstrated that most of the Deqi sensations are conveyed by different nerve fiber systems. Aching, soreness, distension, heaviness, warmth, and dull pain are conveyed by the slower conducting Aδ and C fibers, whereas numbness is conveyed by the faster conducting Aβ fibers [23, 24]. However, there is lack of experimental data to indicate the basic substances that contribute to the Deqi sensation of moxibustion. Further research is required to discover the underlying mechanisms of the Deqi in moxibustion.

Table 2: Baseline characteristics of study patients.

Items	Trial group	Control group	*P* value
Age, mean (SD), years	56.13 (7.55)	59.34 (7.21)	0.04
Sex *n* (%)			0.0002
Female	12 (26.67)	32 (71.11)	
Male	33 (73.33)	13 (28.89)	
Duration of knee pain *n* (%)			0.67
<5 years	33 (73.33)	30 (66.67)	
5–10 years	9 (20.00)	11 (24.44)	
>10 years	3 (6.67)	4 (8.89)	
BMI, mean (SD), kg/m′	22.12 (3.12)	24.22 (3.30)	0.002
GPCRND-KOA grade *n* (%)			0.51
Severe	31 (68.89)	28 (62.22)	
Moderate	14 (31.11)	17 (37.78)	
Knee circumference, mean (SD), cm	40.26 (3.31)	42.21 (3.25)	0.005
GPCRND-KOA score, mean (SD)	13.45 (3.28)	11.12 (3.13)	0.0006
Previous treatment (past half year, %)			0.041
Pharmaceutical intervention	31 (68.89)	18 (40.00)	
Physiotherapy	11 (24.44)	20 (44.44)	
Previous acupuncture treatment	3 (6.67)	5 (11.11)	

BMI: Body Mass Index; GPCRND-KOA: guiding principle of clinical research on new drugs in the treatment of KOA score; SD: standard deviation; KOA: knee osteoarthritis.

Table 3: Comparison of GPCRND-KOA scores.

Variable	Month 1		Month 7	
	Mean	95% CI	Mean	95% CI
Trial group	5.23	4.44~6.01	4.78	4.37~5.18
Control group	7.43	6.59~8.26	6.11	5.45~6.76
P value	0.0001		0.0006	

* Adjusted means or proportions and confidence intervals (CI) from multilevel models (ANCOVA or GEE) with fixed effects. All data are intended to treat. Both groups $n = 45$. SD: standard deviation; GPCRND-KOA: guiding principle of clinical research on new drugs in the treatment of KOA score; KOA: knee osteoarthritis.

Table 4: Comparison of knee circumference.

Variable	Month 1		Month 7	
	Mean	95% CI	Mean	95% CI
Trial group	38.32	37.07~39.56	37.22	36.24~38.19
Control group	40.30	39.95~41.64	39.10	38.39~40.19
P value	0.03		0.007	

* Adjusted means or proportions and confidence intervals (CI) from multilevel models (ANCOVA or GEE) with fixed effects. All data are intended to treat. Both groups $n = 45$. SD: standard deviation; GPCRND-KOA: guiding principle of clinical research on new drugs in the treatment of KOA score; KOA: knee osteoarthritis.

Both the total GPCRND-KOA score and reduction in knee circumference were evident in the Deqi sensation of heat-sensitive phenomenon and conventional local superficial heat sensation by applying suspended moxibustion. What is more important is that our trial result conforms to the theory of TCM, "the arrival of meridian Qi ensures the therapeutic effects." The effectiveness of the Deqi sensation group might be more superior than the non-Deqi sensation one in the treatment of KOA. In a word, this study is aimed at providing scientific evidence for the Deqi sensation of moxibustion and at showing that heat-sensitive moxibustion sensation is essential to achieve the preferable treatment effects for KOA.

Authors' Contribution

Rixi Chen and Mingren Chen obtained fund of the research project. Jun Xiong wrote the final paper. Tongsheng Su, Jianhua Sun, Meiqi Zhou Zhenhai Chi, Dingyi Xie, and Bo Zhang contributed to the trial implement. All authors read and approved the final paper.

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Review Article

Is Deqi an Indicator of Clinical Efficacy of Acupuncture? A Systematic Review

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Objective. Despite the systematic literature review of the current evidence, we aim to answer the question " is Deqi an indicator of clinical effects in acupuncture treatment?" *Methods*. We systematically searched CNKI, VIP, Wanfang Data, PubMed, Embase, and the CENTRAL for three types of study: (1) empirical research probing into the role of Deqi in acupuncture; (2) mechanism studies examining the effect of Deqi on physiological parameters in animal models and human subjects; (3) clinical studies that compared the outcome of acupuncture with Deqi with that of acupuncture without Deqi. Two reviewers independently extracted data, undertook qualitative or quantitative analysis, and summarized findings. *Results*. The ancient Chinese acupuncturists valued the role of Deqi as a diagnostic tool, a prognosis predictor, and a necessary part of the therapeutic procedure. Findings from modern experimental research provided preliminary evidence for the physiological mechanism that produced Deqi. Few clinical studies generated conflicting evidence of the comparative effectiveness of acupuncture with Deqi versus acupuncture without Deqi for a variety of conditions. *Conclusion*. The current evidence base is not solid enough to draw any conclusion regarding the predicative value of natural Deqi for clinical efficacy or the therapeutic value of manipulation-facilitated Deqi.

1. Introduction

Deqi (in Chinese pinyin, literally translated as "arrival of qi") refers to a composite of sensations felt at the needling site after adequate needle insertion with or without proper manipulation. The production of such a special response of the human body is believed to be based on the flow of qi (energy) along channels referred to as meridians in the body. The term is also known as "needling sensation" in more contemporary textbooks and literatures [1]. Typically, the needling sensation is characterized by specific sensory perceptions such as soreness, numbness, distension, and heaviness. However, perceptions of Deqi vary with recipients, manipulation techniques, and the modes of acupuncture stimulation applied. Less frequently, acupuncture recipients may have feelings of coldness, warmth, itching, aching, or twitching, and such a sensation can sometimes be conducted from the needling site towards a more distant area along the meridian. In the meanwhile, the practitioner feels tenseness, drugging, sinking, and vibrations around the needle tail [2].

According to a study [3] that quantitatively defined the uniqueness of the patient's Deqi sensations, aching, soreness, and pressure were found to be most closely related to acupuncture Deqi, as different from tactile stimulation. However, it was also found that the Deqi sensations were mixed with moderate sharp pain feelings in almost one third of all needling procedures, although the less welcomed sharp pain feelings in the form of stabbing, burning or pricking are generally considered to be the result of inadvertent noxious stimulations, rather than that of adequate needling practice. This difference could be evidenced by the variations identified in hemodynamic response between characteristic

Deqi sensations and acute pain in fMRI studies described at the last two lines of Table 1.

Moreover, some of the Chinese acupuncture researchers distinguish between two types of the Deqi phenomenon by the perception of the needling sensation by part of either the recipient or the therapist or that by them both. The former is defined as an "implicit" Deqi experience, and the latter is defined as an "explicit" Deqi experience, primarily for convenience of investigation.

While a few acupuncture practitioners and theorists [33–35] declare the value of evocation of qi for diagnostic, therapeutic, and prognostic purposes, as well as in accurately orientating points and providing guidance for manipulation, others [36] argue that the manifestation of the needling sensation is merely a message sent by the human body saying that it has received external stimulations and that implicit Deqi practices can also be effective. Aiming at the current academic controversy surrounding the relationship between Deqi and therapeutic effects of acupuncture, we conducted a systematic review of three types of study centering on the topic. Adopting an evidence-based approach, we aimed to summarize the current evidence profile for the Deqi phenomenon and explore the possibility of converging to a solid conclusion.

2. Material and Methods

2.1. The Literature Search. We searched three Chinese and three English electronic databases from their respective inception dates to June, 2013, for relevant studies. These included China National Knowledge Infrastructure (CNKI), VIP Data, Wanfang Data, Embase, PubMed, and the Cochrane Central Register of Controlled Trials (CENTRAL). No restriction on the language or the type of publication was made. The Chinese characters used to perform the search included "deqi" (reaching of qi), "qizhi" (arrival of qi), "zhengan" (needling sensation), "zhenci" (acupuncture) and "zhenjiu" (acupuncture and moxibustion), stated here in the Chinese pinyin. English search terms included "deqi", "de qi", "acupuncture sensation", "qi arrival", "needle sensation", "needling sensation", and "needling response". The references of relevant reviews and the included literatures were checked for possible identification of additional studies.

2.2. Study Selection

2.2.1. Inclusion Criteria. In this review, we included the following three types of study:

(1) empirical research describing the role of Deqi in acupuncture therapy;

(2) research on the physiological mechanisms that produce the Deqi sensation;

(3) clinical studies comparing an acupuncture-with-Deqi (hereinafter referred to as AWD) experimental intervention with an acupuncture-without-Deqi (hereinafter referred to as AOD) control.

For the third type of study, we distinguished between two types of the Deqi experience, one being the natural result of needle insertion (defined as natural Deqi) and the other being the product of repeated facilitating manipulations (defined as facilitated Deqi). Based on the result of a pilot search, "natural Deqi" is most frequently viewed by researchers as an exposure in cohort studies, and "facilitated Deqi" is generally considered a part of the interventional procedure in controlled trials. We included both types of the Deqi experience with the aim to have a glimpse of the full picture of the Deqi phenomenon.

For clinical trials, we stipulated that an AWD interventional procedure shall involve intramuscular needle insertion (typically 1-2 cm) followed by manual stimulation until the patient (or the acupuncturist) felt needling sensations and needle retention from 20 to 30 minutes, whereas an AOD control shall be described as either intramuscular or minimal and superficial or subcutaneous needle insertion (typically 0.3 cm) followed by 20 to 30 minutes needle retention without any manipulation. The guidelines for acupoint prescription, treatment session duration, and frequency shall be exactly the same for both groups of intervention in all respects.

2.2.2. Exclusion Criteria. We excluded the studies that focused on acupuncture techniques other than the manual therapy; in view of that, laser or electrical acupuncture may involve quite distinct patterns of stimulation in terms of intensity and frequency. Consequently, the needling sensations elicited and mechanisms of actions could be of sufficient divergence that deserves specialized attention beyond the scope of our study [37, 38]. Clinical studies in which nonpenetrating placebo acupuncture is adopted as the control, such as the Streitberger needle (producing tactile stimuli), or nonacupoints were chosen as the testing sites were excluded for better control of the confounding factors and to minimize the difference between the two manipulation methods in comparison, thus allowing us to concentrate on the effects of Deqi.

Two researchers (S. Zhang and W. Mu) independently managed citations identified from the aforementioned literature search using NoteExpress software (version 2.7, Aegean-Soft, Beijing, China) [39]. Firstly, duplications were found and eliminated from the initial combination of search results. Secondly, the apparently irrelevant literatures were excluded after reading the titles and abstracts. Thirdly, the full texts of the potentially relevant studies were read, and ineligible studies were ruled out. Help from a third researcher (H.-C. Shang) was sought whenever there was disagreement.

2.3. Data Collection and Quality Assessment Tool. Two reviewers (S. Zhang and W. Mu) designed the data extraction sheet and independently extracted data from original studies. General information on the publication year, the disease type, the treatment course, the outcome measurements, and the methodological characteristics of the included clinical studies is collected and crosschecked. We used the Grade Profiler software version 3.2.2 [40] for evaluation of the quality of included clinical studies following instructions described in

Table 1: A summary of studies on Deqi mechanism in acupuncture.

Study ID	Acupoints	Instrument	Results
Lin 1991 [4]	Acupoints on the human thorax	Voll's electroacupuncture devise and electric resistance tester	The electric resistance at acupoints on the human thorax was not correlated with the existence of Deqi sensations at the same point.
Ma 1998 [5]	NA	NA	It is hypothesized that activation of the stretch-activated ion channels is a mediator of the Deqi sensation and the transduction of stimulation signals.
Huang et al. 2012 [6]	LI3, LI4, LI5, LI11	Speckle laser blood flow scanner	AWD at LI11 increased microvascular perfusion at 3 meridian acupoints.
Watanabe et al. 1994 [7]	LI10	DP1100 system	The latency of the event-related potential triggered triggered by AWD was greater than that by electric stimulation. This showed that AWD may influence CNS functions.
Huang 1999 [8]	ST36	EGEG-2DZ	EGG amplitude and the waveform reaction area in two types of Deqi groups differed greatly from those in AOD control.
Sandberg et al. 2003 [9]	ST36	PPG	AWD markedly increased muscle and skin blood flow compared with AOD.
Zhang et al. 2009 [10]	ST36	CDU	AWD greatly changed hemodynamic parameters of the anterior tibial artery.
Yu et al. 2008 [11]	ST36, LI11	CDU	AWD at both points markedly increased the average displacement of the surrounding connective tissues.
Karst et al. 2003 [12]	LI11	Flow cytometry	AWD significantly increased the respiratory burst of neutrophils and slightly dropped beta-endorphin levels.
Streitberger et al. 2008 [13]	LI4	NA	AWD induced more frequent occurrence of vegetative effects and increased occipital EEG power compared with placebo.
Huang et al. 2009 [14]	PC6	PCS	AWD at PC6 markedly increased TCE values measured at a nonacupoint on the meridian.
Huang et al. 2010 [15]	PC6	PCS	AWD at PC6 markedly increased TCE values measured at two nonacupoints on the meridian and at PC3.
Takamoto et al. 2010[16]	#	Functional near-infrared spectroscopy	AWD decreased oxy-Hb concentration in SMA, pre-SMA, and the anterior dorsomedial prefrontal cortex for all stimulated points.
Zhang et al. 2011 [17]	SJ5	PET	AWD activated BA7, -13, -20, -22, -39, -42, and -45.
Lai et al. 2009 [18]	TE5	PET	AWD markedly activated BA13 and 42 and the left cerebellum compared with sham needling.
Chen et al. 2012 [19]	TE5	SPECT	AWD significantly activated BA6, -8, -19, -21, -28, -33, -35, -37, and -47, parahippocampal gyrus, lentiform nucleus, claustrum, and red nucleus, and it deactivated BA9 and -25 compared with sham needling.
Pan et al. 2008 [20]	SP6	fMRI	AWD activated the cortex, the subcortical limbic system, the cingulated gyrus, the lentiform nucleus, the corpus albicans, and the inferior semilunar lobule, and it deactivated the anterior central gyrus and the anterior cingulate.
Zeng 2009 [21]	SJ5	fMRI	AWD markedly activated BA13, -22, -37, -40, -44, -45, and -47, hippocampus, amygdale, and substantia nigra.
Chen et al. 2011 [22]	LI4	fMRI	AWD activated BA4, -6, -9, -13, -17, -18, -19, -21, -22, -23, -29, -30, -35, -36, -37, -39, -40, -41, -42, -43, -44, and -46, and it deactivated medial frontal gyrus, BA24, and the right superior frontal gyrus.
Fang et al. 2012 [23]	LI4	fMRI	AWD deactivated the right amygdale, the cingulated gyrus, the midbrain, the medial frontal gyrus, and the cuneus gyrus.
Fang et al. 2012 [24]	LR3	fMRI	AWD deactivated the limbic-paralimbic-neocortical network and strengthened the connection of these deactivated brain regions.

Table 1: Continued.

Study ID	Acupoints	Instrument	Results
Tan et al. 2009 [25]	ST36	fMRI	AWD activated functional areas of the cerebral limbic system and dropped serum gastrin levels.
Zhang 2011 [26]	ST36	fMRI	AWD activated cerebral areas SI and SII, the left temporal cortex, the insular cortex, the motor, and supplementary motor cortices, the cingulated gyrus, the hypothalamus, and the amygdaloid body.
Hu et al. 2012 [27]	ST36	fMRI	AWD deactivated the cerebral limbic system and the functional regions associated with language, cognition, and motor control.
Wu et al. 1999 [28]	LI4, ST36	fMRI	AWD at both points activated the hypothalamus and the nucleus accumbens, and it deactivated the rostral part of the anterior cingulate cortex, the amygdala formation, and the hippocampal complex compared with no such effects from AOD.
Gong et al. 2003 [29]	ST36, ST37	fMRI	AWD at both points activated bilateral cingulated gyrus, insular lobe, superior wall of lateral sulcus, and precentral gyrus. AOD at both points activated the left posterior central gyrus. Different cerebral areas were activated during Deqi and non-Deqi at the same point.
Claunch et al. 2012 [30]	LI4, ST36, LR3	fMRI	AWD at all three points deactivated the right subgenual, the right subgenual cingulate, the right isthmus of the cingulum bundle, and the right BA31.
Asghar et al. 2010 [31]	LI4	fMRI	Marked deactivation of the brain area was observed during Deqi in contrast to the occurrence of a mixture of activations and deactivations in the acute pain group.
Hui et al. 2005 [32]	ST36	fMRI	Attenuation of signal intensity in the limbic and paralimbic structures of cortical and subcortical regions in telencephalon, the diencephalon, the brainstem, and the cerebellum was observed during AWD compared with signal increase with the acute pain and the AOD group.

#: acupoints and nonacupoints within the right extensor muscle in the forearm; AOD: acupuncture without Deqi; AWD: acupuncture with Deqi; BA: brodmann area; CDU: color Doppler ultrasound; CNS: central nervous system; EGG: electrogastroenterogram; fMRI: functional magnetic resonance imaging; NA: not available; PCS: percutaneous carbon dioxide sensor; PET: positron emission tomography; PPG: photoplethysmography; SI: secondary somatosensory cortex; SII: primal somatosensory cortex; SMA: supplementary motor area; SPECT: single-photon emission computed tomography; TCE: transcutaneous CO_2 emission.

the Grade Handbook [41]. The quality of evidence generated from these studies was classified into one of the following four grades.

High Quality. Further research is very unlikely to change our confidence in the estimate of effect.

Moderate Quality. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low Quality. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very Low Quality. We are very uncertain about the estimate.

Any disagreement was resolved by discussion. Information on the testing sites, the instrument used, and the reported results of mechanism research was also collected and summarized. We did not assess the quality of studies providing empirical insights into the relationship between Deqi and acupuncture effects as well as those exploring the physiological mechanisms underlying acupuncture Deqi.

2.4. Data Analysis. Where possible, we used Review Manager version 5.2 [42] provided by the Cochrane Collaborations, for data analysis. Pooled analysis was preferred if sufficient data was provided and homogeneity across studies can be met. When meta-analysis was impossible, comparison between groups was performed for individual studies. If original data was reported, both continuous and dichotomous data were extracted and processed to yield a relative effect. For dichotomous data, a summary risk ratio was presented, and for continuous data a mean difference was calculated, both with 95% confidence intervals. In case of original data being ordinal data, we transformed it into dichotomous data and processed accordingly. The summary statistic was also incorporated into the Grade Profiler and was demonstrated in the summary of the findings tables.

3. Results

3.1. Results of the Literature Search. A total of 10,492 studies (8,188 from CNKI, 219 from VIP, 1,349 from Wanfang, 209 from PubMed, 465 from Embase, and 62 from CENTRAL) were identified through initial electronic searches; 7,504 studies were left after duplicates were eliminated; and 482

studies were identified after a preliminary screening that ruled out apparently irrelevant studies, comments, or review. A second round of screening excluded ineligible studies after reading the full text. Finally, we included 169 studies in this review: 145 in Chinese and 24 in English.

3.2. Discussions on Deqi and Acupuncture Effects in Ancient Medical Books. We identified 120 articles discussing the role of Deqi in acupuncture therapy from a variety of perspectives. The majority of them cited original texts from ancient Chinese acupuncture classics or textbooks and provided a personal interpretation of the old texts. Some of the studies gave detailed accounts of the practitioner's experiences of eliciting the arrival of qi using different manipulation techniques and offered their insights into the interaction between Deqi and clinical effects. These studies formed the empirical evidence base primarily in favor of the decisive or supporting role of Deqi in relation to acupuncture therapeutic effects. In this section, we cited some of the most exhaustively discussed pieces of quotation from ancient Chinese medical books and gave each of them a plain-English explanation.

In ancient China, the ability to evocate the arrival of qi in the meridian was deemed the criterion for assessing the acupuncturists' level of mastery of professional skills. As was recorded in the Spiritual Pivot (pinyin: Ling Shu), the second text of the Yellow Emperor's Classic of Internal Medicine (Huangdi Neijing) states: "Ordinary acupuncturist treats patients by needling acupoints on the limbs and joints, while an experienced practitioner is able to feel and elicit the arrival of qi in the channel;" see [43].

Further elaboration on the significance of Deqi for an acupuncture treatment was found in a later part of the same treatise, in which the author remarked: "No matter how many times you have manipulated, operate until the needling response arrives. Only when it arrives, will acupuncture be effective. This effect, it is said, is as swift as if the winds blow away the clouds and clear the azure sky. These are the Dao of acupuncture" [43]. A similar statement can be found in the first text of the Yellow Emperor's Classic of Internal Medicine, the Basic Questions (Su Wen), which claimed that "Whether you practice deep or superficial needling in local or distant acupoints, what matters to efficacy is the arrival of qi," [44] indicating the pivotal role of reaching qi in therapeutic effects regardless of needling depth or selection of points. Furthermore, in the Systematic Classic of Acupuncture and Moxibustion (Zhenjiu Jiayi Jing), the Jin Dynasty scholar Huang Fumi described his manipulation method for eliciting Deqi sensation as "Applying superficial needling and keeping the needle within for minutes to weaken and dispel the evil qi. To navigate the flow of spirit and qi till they accumulate around the needle" [45]. From the previous descriptions, it is not hard to tell that evocation of the arrival of qi was recognized as an indispensable part of the whole treatment procedure.

Also, it was asserted that analysis of the unique features of Deqi sensations in different contexts provided valuable information in relation to the nature of the disease and aided in the differentiation of the TCM syndrome patterns. Citing the famous verse Make It Plain (Biaoyou Fu) written by Dou Hanqing, the Yuan Dynasty philosopher and acupuncturist, he was found saying: "When the needle penetrated the skin, it went further into the heaven level (tian bu), human level (ren bu) and earth level (di bu, these levels refer to the three depths of needle insertion) of the fleshy exterior of human body. At this time, one can determine whether the meridian qi was in deficit or in excess by feeling the power of qi flowing beneath the needle tip. Similarly, one can distinguish between the heat or cold patterns of the zang-fu viscera by sensing the tempo of qi traveling" [46].

Moreover, some of these medical works gave insights into the interaction between the speed of qi arrival and the onset of therapeutic effect, as well as the prognostic values of the Deqi sensations. For instance, Yang Jizhou, the Ming Dynasty acupuncture theorist, remarked in the Compendium of Acupuncture and Moxibustion (Zhenjiu Dacheng) that "Therapeutic effects closely follow the arrival of qi. If the qi comes sooner after the operation, the ailment is easier to cure and the onset of the therapeutic action is rapid. Otherwise, the disease could be hard to cure or even incurable" [46].

A piece of writing collected in the Classic of Difficult Issues (Nan Jing), a medical classic purportedly written by the legendary Chinese physician Bian Que (407–310 B.C.), stated that "If the needle was retained peacefully at the site to await the arrival of qi yet it never came along, it meant the patient has run out of his/her qi in the meridian and faced the imminent danger of death" [47]. Descriptions of the prognostic values of the Deqi sensations perceived by the practitioner were found in a later passage of the Compendium of Acupuncture and Moxibustion, which claimed, "The easier qi arrived, the sooner effects showed off. The needling sensation you perceived can help you predict prognosis. A tightened and dragging needling sensation was indicative of good prognosis, whereas feeling nothing at all indicated poor outcomes" [46].

3.3. Studies Exploring the Mechanism Underlying Deqi Sensation. A total of 40 studies were included and reviewed in this section:20 in Chinese and 20 in English. Generally speaking, we observed a shift of focus on mechanism studies from measuring changes in biochemical parameters at the acupoints before and after the arrival of qi to examining the neural correlates of Deqi sensations using advanced neuroimaging techniques (most frequently fMRI). Two subthemes were identified. One group of studies tried to explain why the Deqi sensations could be so varied at different points, and the other group examined the Deqi phenomenon at different depths, following varied stimulations, and measured the corresponding sensations produced. All studies were first categorized by themes and then ordered by the experimental model used. The main findings were summarized separately.

Three included studies used animal models to examine the changes in tissue shape or physiological parameters before and after applying AWD. Shi and Zhang [48] found transformation of the subcutaneous connective tissues around the puncturing pore to a whirl as well as dislocated endomysium, vessels, and nerves in the adjacent area, while muscle cells remained intact. Similarly, in an experiment [49] by Langevin and colleagues, significantly thickened layers of subcutaneous

Table 2: A summary of studies on mechanisms underlying varied Deqi sensations.

Study ID	Acupoints	Instrument	Results
Bossy et al. 1984 [51]	Jing points at the hand	NA	Deqi resulted from correct stimulation of the various structures in relation to an acupoint, such as group II afferent fibers.
Wang et al. 1985 [52]	PC6, LU11	NA	Numbness and soreness were conveyed by Group II and Group IV fibers, and heaviness and distention by Group III fibers.
Wang and Liu 1989 [53]	PC6, PC9, LI1, LU10, LU11	NA	Needling stimulation primarily activated slowly adapting receptors. The type of receptors varied with the location of acupoints.
Kuo et al. 2010 [54]	LU5, LU7	LDF	Strong Deqi sensations, heat and numbness, felt at LU5 were correlated with increased blood flow at LU5.
Kuo et al. 2004 [55]	SI6, SI8	LDF	AWD increased blood flow at acupoints. The speedy flowing of tissue fluid along the body stalk may explain the occurrence of propagated sensation along the meridian.
Kuo et al. 2004 [56]	LI4, LI11	LDF	Deqi sensations such as soreness, numbness, and heat coexisted with increased blood flow at acupoints.
Lee et al. 2010 [57]	SP3, KI2	Ultrasound dopplerography	Deqi-related warm, radiating, and energetic feelings were correlated with decreased blood flow velocity.
Zhang et al. 2011 [58]	SJ5	fMRI	Deqi sensations perceived at SJ5 were mainly soreness, numbness, distending, and heaviness, corresponding to activated left temporal lobe and superior temporal gyrus. By contrast, tingling was felt at a neighboring nonacupoint, and the left limbic lobe and hippocampal gyrus were excited.

Abbreviations: fMRI: functional magnetic resonance imaging; LDF: laser doppler flowmeter; NA: not available.

Table 3: A summary of mechanism studies on needling intensity and Deqi.

Study ID	Acupoints	Instrument	Results
Deng and Zhou 2010 [59]	ST36	PowerLab 4/25	A marked difference was observed in muscular contractility at Deqi depth compared with that at two non-Deqi depths.
Choi et al. 2012 [60]	SP6, SP9, ST36, GB39	SASS	Pressure pain threshold and Deqi sensation increased as acupuncture simulation intensified (needling with rotation > deep needling > superficial needling).
Park et al. 2011 [61]	NA	Ultrasound imaging	Pricking and sharp sensations appeared more frequently when shallower tissues were needled, whereas deep, dull, heavy, spreading, and electric feelings predominated in deeper tissue levels. The introduction of needle rotation in addition to oscillation intensified deep, dull, and heavy rather than pricking and sharp sensations.

Abbreviations: NA: not available; SASS: subjective acupuncture sensation scale.

connective tissue around the needle and collagen winding along the needle track were found in rats administered AWD, and it was thus hypothesized that mechanical coupling is a mechanism of needle grasp perceived by the acupuncturist. Using self-developed Ca^{2+} selective electrode and push-pull microperfusion technique, Guo et al. [50] compared the impact of AWD on Ca^{2+} distribution at acupoints in a rabbit with that of AWD at adjacent nonacupoints. For the first time, it was found that AWD at an acupoint promoted the redistribution of Ca^{2+} in the body towards aggregation along the same meridian.

Findings of the researches in [4–32, 51–61] exploring the mechanism of acupuncture Deqi sensation in healthy human subjects were summarized in Tables 1, 2, and 3.

3.4. Clinical Studies Examining the Correlation between Deqi and Therapeutic Effects. Identified were eight eligible clinical studies evaluating the interaction between Deqi and the therapeutic effects of manual acupuncture for a variety of diseases and conditions. These studies were further divided into two categories: (1) cohort studies observing the predictive value of Deqi experiences for acupuncture effects and (2) clinical trials testing the comparative effectiveness of AWD versus AOD through proactively making "qi arrival" happen (by applying manipulations). In two studies [62, 63], medicinal therapy was used in combination with acupuncture, and in one study [64] subcutaneous needle placement was coadministered. Sample sizes ranged from 19 to 338. Details on the general characteristics of the relevant clinical studies were presented in Table 4.

The findings of each clinical study were presented individually as it was impossible to conduct a meaningful meta-analysis with consideration of obvious clinical heterogeneity across the studies. As a result, the credibility of each outcome

Table 4: Characteristics of the included clinical studies.

Study ID	Type of disease	Sample (T/C)	Comparison (exposure)	Treatment course	Outcome measures
Ma 2012 [65]	Primary hypertension	293 totally	Patient-reported natural Deqi after intramuscular needle insertion versus noncharacteristic Deqi sensations	One 30 m session	Blood pressure
Mei et al. 2010 [62]	Bell's palsy	28/22	Intramuscular insertion and manipulation + medication versus nonmanipulation + medication	Five 30 m sessions per week for 4 weeks	Effective rate based on HBS, 16PF, HAMA, and DSS (VAS)
Xu et al. 2013 [63]	Bell's palsy	167/171 159/157	Intramuscular insertion and manipulation until Deqi + medication versus nonmanipulation + medication	Five 30 m sessions per week for 4 weeks	Facial-nerve function (HBS), FDI, WHO HR-QoL, DSS (VAS), and adverse events
Lund et al. 2006 [66]	Pelvic pain in late pregnancy	35/35 22/25	Intramuscular insertion and manipulation until the patient-reported Deqi versus subcutaneous insertion and nonmanipulation	Two 30 m sessions per week for 5 weeks	Pain intensity (VAS) at rest/during daily activities and NHPQ
Haker and Lundeberg 1990 [67]	Epicondylalgia	86 in total 44/38	Intramuscular insertion and manipulation until Deqi versus subcutaneous insertion and nonmanipulation	Ten 20 m sessions (2 or 3 times weekly), and followup after 3 and 12 months	Patient-reported pain improvement, lifting test, and vigorimeter test
Xiong et al. 2011 [68]	Primary dysmenorrhea	45/45 (67/64, 60/60 for Xiong et al. 2012 [69])	Intramuscular insertion (1-2 cm) and manipulation until Deqi versus nonmanipulation	Five consecutive 30 m sessions per menstrual cycle and for 3 courses	Effective rate, pain intensity (VAS), pain duration, and DSS (nervousness using VAS, acupuncture confidence questionnaire, EPQ, and 16PF were added in Xiong et al. 2012 [69])
Chen 2011 [64]	Cervical spondylosis	36/34	Intramuscular insertion and manipulation until Deqi + intradermal needle placement versus subcutaneous insertion and nonmanipulation + intradermal needle placement	Ten 20 m sessions, and followup at 1 and 3 months	NPQ, MPQ, and SF-36
Zheng 2012 [70]	Migraine	9/10 (completed) Ongoing study	Intramuscular insertion and manipulation until Deqi versus subcutaneous insertion and nonmanipulation	Twelve 30 m sessions, lasting for 8 weeks. Followup at 1 and 2 months	Migraine assessment tool (self-devised), pain intensity (VAS), pain duration, response rate, and safety

The latter set of numbers in the "Sample" column refers to the number of participants included in data analysis. Abbreviations. DSS: Deqi sensation scale. It is a tool providing typical descriptors of the needling sensations for patients to choose from those the best that represent their experience. Combining with VAS, it allows rating of the intensity of response to each sensation ranging from "none" to "unbearable pain," or on a numeric scale. EPQ: eysenck personality questionnaire; FDI: facial disability index; FDIP: FDI physical function scores; HAMA: the Hamilton anxiety scale; HBS: House-Brackmann scale; m: minute; MPQ: the McGill pain questionnaire; NHPQ: the Nottingham health profile questionnaire; NPQ: the Northwick Park questionnaire; 16PF: 16 personality factor questionnaire; VAS: visual analog scale.

that involves one single study was assessed using the Grade Profiler. The items "inconsistency" and "publication" were not applicable and thus omitted. The quality of evidence provided by these individual studies was graded from "very low" to "high."

3.4.1. Cohort Studies Shed Lights on the Predictive Value of Deqi for Therapeutic Effects. Despite the continuous efforts, we identified only one study [65] in which patients were grouped in terms of whether they naturally experienced Deqi sensations after being acupunctured at Quchi point (LI11). Only

Table 5: Summary of findings table for the evidence of the predicative value of natural Deqi for clinical efficacy.

Outcomes	Natural AWD compared with natural AOD for primary hypertension Illustrative comparative risks (95% CI)		No. of participants (studies)	Quality of the evidence (grade)
	Natural AOD	Natural AWD		
Blood pressure (SP) Scale from 0 to 200	The mean systolic blood pressure in the control groups was 152.225 mmHg	The mean systolic blood pressure in the intervention group was 15.88 mmHg lower (16.34 to 15.42 mmHg lower)	183 (1 study)	⊕⊖⊖⊖ very low[1,2,3,4]
Blood pressure (DP) Scale from 0 to 200	The mean diastolic blood pressure in the control groups was 93.093 mmHg	The mean diastolic blood pressure in the intervention group was 6.42 mmHg lower (6.74 to 6.10 mmHg lower)	183 (1 study)	⊕⊖⊖⊖ very low[1,2,3]

[1]This single cohort study has appropriate eligibility criteria, but it suffers from subjective measurement of exposure (patient-reported Deqi sensation) and very short treatment course (one session and no followup).
[2]Very narrow CI. Confidence interval < 1/10 effect size.
[3]A single study is very likely to be biased.
[4]It was observed that the mean difference of blood pressure was 15.88 lower in AWD group compared with AOD group. The effect size is large.

one treatment session involving ventricular needle insertion at a depth of 3 cm, remaining of the needle for 30 minutes, and needle removal was administered on 293 patients with primary hypertension. Of the 164 patients having Deqi, 110 were given further stimulations such as needle twirling or rotating in the following 30 minutes, and only 54 were left unintervened until the end of the treatment. Therefore, we gathered the original data of the 129 patients perceiving no natural Deqi and of the 54 patients having Deqi sensations but left unmanipulated to study "whether natural Deqi is predictive of acupuncture efficacy" or "whether natural Deqi is an indicator of better efficacy in comparison with non-Deqi."

It was found for both groups of patients that blood pressure levels, either systolic pressure (SP) or diastolic pressure (DP), were reduced after treatment (measured before needle insertion and upon needle removal). However, the effect on the AOD group was not clinically significant (mean = −3.232 and SD = 0.963 for SP; mean = −1.132 and SD = 0.747 for DP). The natural AWD group experienced remarkably decreased blood pressure compared with the AOD group (MD = −15.88, 95% CI (−16.34, −15.42) for SP; MD = −6.42, 95% CI (−6.74, −6.10) for DP). In summary, evidence of very low quality showed that, although AOD can change the readings of blood pressure, only Deqi serves to predict clinically relevant effects and is an indicator of greater efficacy (Table 5).

3.4.2. Clinical Trials Intended to Verify Whether AWD Is Superior to AOD in Attaining Efficacy. A total of seven controlled clinical trials were identified. Involving an AWD and an AOD group, they addressed the question "could evocating Deqi sensations facilitated by needling manipulation be a key procedure contributing to the acupuncture effects?" We classified them into two groups according to the type of target disease. Two trials investigated acupuncture for Bell's palsy, and five studies were concerned with various pain conditions. A summary of findings from the two groups of studies was presented separately in Tables 6 and 7.

Mei et al. [62] compared the effects of AWD and AOD, both combined with conventional western medication (prednisone, vitamins B1 and B12, and mecobalamin), on inpatients with Bell's palsy. Outcome measurement was effective rate based on subjective assessment of patient improvement on the House-Brackmann scale (HBS). For ease of comparison, the risk ratio for effective rate was calculated, and no statistical difference was observed between the two groups (RR = 1.40, 95% CI (1.00, 1.97)). This showed that, with western drug being the basic therapy, AWD had no better effects than AOD in terms of improving facial nerve function; however, evidence for generating this conclusion was graded very low in quality; hence, the finding is questionable.

Xu et al. [63] also investigated the comparative effects of AWD versus AOD for Bell's palsy, with prednisone as the basic treatment for both groups. We calculated the risk ratio for complete recovery rate (number of full recoveries/total patient number) using the MH fixed-effect model. Incorporating it (RR = 1.27, 95% CI (1.14, 1.42)) into the Grade system, high-quality evidence showed that AWD helped a moderately greater number of patients make full recovery than AOD. Furthermore, the AWD group attained even greater complete recovery rate (OR = 4.16, 95% CI (2.23, 7.78)), became less facially disabled on facial disability index (FDI) (DLSM (differences of least squares means) = 9.80, 95% CI (6.29, 13.30)), and enjoyed better quality of life measured with WHO Qol-bref (DLSM = 29.86, 95% CI (22.33, 37.38)) at six months following treatment, adjusted for age, sex, treatment center, interval between onset of disease and session commencement, and baseline scores. Logistic regression analysis of a subset of patients (262/338) who completed the Deqi sensation scores (DSS) on a visual analog scale (VAS) showed that higher DSS was slightly predictive of improved facial nerve function (grade-one scores on the HBS) (adjusted OR = 1.07, 95% CI (1.04, 1.09)).

Lund et al. [66] compared the effects of AWD versus AOD on pelvic pain in 70 women in late pregnancy. After 10 treatment sessions, participants in both groups exhibited marked systematic group changes towards lower levels of pain intensity at rest and during routine activities, and in emotional responses and energy losses. However, the same pattern of change in pain intensity and resembling proportions of

Table 6: Summary of findings table for the evidence of comparative effects of AWD versus AOD for Bell's palsy.

AWD compared with AOD for Bell's palsy						
Study ID	Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (grade)
		AOD (assumed risk)	AWD (corresponding risk)			
Mei et al. 2010 [62]	Effective rate (followup: 3 months) Assessment of changes in facial nerve functions based on House-Brackmann scale[1]	Study population 636 per 1000	890 per 1000 (636 to 1000)	RR 1.40 (1.00 to 1.97)	50 (1 study)	⊕⊖⊖⊖ very low[2,3,4,5]
Xu et al 2013 [63]	Complete recovery rate (followup: 6 months) House-Brackmann score graded by 3 assessors	Study population 708 per 1000	899 per 1000 (807 to 1000)	RR 1.27 (1.14 to 1.42)	338 (1 study)	⊕⊕⊕⊕ high[3,5,6,7]

[1]Patient-important outcome.
[2]Randomization methods and allocation concealment not mentioned. Stratified and randomized assignment and binding of the patient were mentioned. For acupuncture trials, blinding of the practitioner is impossible. None lost to followup. No selective outcome reporting.
[3]This item was omitted here because we assessed one single study.
[4]Subjective assessment based on any observed improvement on HB scale for facial nerve function. RR has a wide CI; it almost equals effect size and covers 1.0.
[5]A single study is very likely to be biased. However, it was omitted here to avoid all evidence being "very low" in quality and therefore indistinguishable.
[6]Computer-generated random number sequence, randomized assignment, allocation concealment (sealed opaque envelope, and a designated personnel kept it) and blinding of the patient, recruiter, and assessor were described. For acupuncture trials, blinding of the practitioner is impossible; 22/338 dropouts, ITT analysis done. No selective outcome reporting.
[7]Subjective outcome, but rigorously controlled. Specifically, three skilled experts rated scores according to the House-Brackmann scale. For RR, narrow CI equals 1/10 effect size.

participants reporting decreased pain were observed, and it was concluded that no difference in effect exists between groups. We performed a secondary data analysis for the primary outcome (pain intensity at rest) and described the intervention effects with the more easily interpretable risk ratios. Originally, pain intensity at rest in the morning and evening was rated on an ordinal scale (VAS), and the change in score was classified into "lower" "unchanged", and "higher" groups. We defined the "lower" category as the event and calculated the ratio of events for each group (effective rate). Similarly, low-quality evidence indicated that AWD had no better effects than AOD for both outcomes (RR = 0.99, 95% CI (0.69, 1.41) for pain intensity at rest; RR = 1.06, 95% CI (0.73, 1.54) for pain intensity during activities).

Haker and Lundeberg [67] performed a comparative study of AWD and AOD for lateral epicondylalgia. In this study, significant differences were observed between the two techniques immediately following 10 treatment courses in relation to patient-reported recovery (subjective outcome) and pain threshold on gripping and lifting (objective outcome), but such differences disappeared at the 3-month or the 1-year followups. For the subjective outcome, we transformed ordinal data into dichotomous data and calculated the risk ratio using the previously mentioned method. It was found patients receiving AWD reported markedly less elbow pain (RR = 1.35, 95% CI (1.05, 1.73)), but the evidence was low in quality. The AWD group also exhibited enhanced pain-free grip strength and lifting strength in the vigorimeter test and the 3 kg lifting test ($P < 0.05$), respectively. It was then concluded that AWD is superior to AOD in the short-term symptomatic alleviation of elbow pain.

Xiong et al. [68] investigated the effects of acupuncture on primary dysmenorrhea and the correlation of Deqi with such effects. We used the MH fixed-effect model to calculate the risk ratio for effective rate of AWD to AOD in terms of clinical symptom improvement; the criteria for judging "full", "partial," "slight," or "no" recovery were based on the assessment tool described in the Guidance on Practices in Clinical Research of TCM for Dysmenorrhea [71]. Moderate evidence demonstrated that women in the AWD group experienced significantly greater overall recovery compared with the AOD group (RR = 2.24, 95% CI (1.51, 3.32)). Moreover, they also had an average of 2.78 points greater reduction in pain intensity on the 0–10 VAS (MD = −2.78, 95% CI (−3.61, −1.95)) and had further shortened pain duration ($P < 0.001$). Logistic regression analysis indicated certain correlation between the Deqi sensation scores and the analgesic effects of acupuncture ($R = 0.654$, $P < 0.001$). In a later paper [69] by the same author, data of 30 additional participants was added in the analysis. We chose to report the findings of this study because original data was lacking in the latter paper, but it is worth mentioning that Xiong and colleagues further identified stronger correlation between the acupuncture therapeutic effects and Deqi sensation scores than between efficacy and psychological factors (belief, nervousness, depression, etc.).

Chen [64] reported a trial comparing the analgesia effects of AWD with those of AOD combined with intradermal needle placement for neck pain. The patient-reported Northwick Park questionnaire (NPQ) and the McGill pain questionnaire (MPQ) were collected after the fifth session, upon treatment (ten sessions) completion, at 1- and 3-month followup. For the former outcome, patients in the AWD group experienced greater alleviation of neck pain-associated conditions at treatment conclusion (MD = −17.86, 95% CI (−23.65, −12.07)), and they remained in such a good state after three months (MD = −20.30, 95% CI (−25.32, −15.28)). With regards to the more general feelings of pain, the AWD group perceived less intense pain sensations compared with the AOD group

Table 7: Summary of findings table for the evidence of comparative effects of AWD versus AOD for pain.

Study ID and descriptions	Outcomes	Acupuncture with Deqi versus acupuncture without Deqi for pain Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (grade)
		AOD (assumed risk)	AWD (corresponding risk)			
Lund et al. 2006 [66] Subject: acupuncture for pelvic pain in late pregnancy Setting: two maternity healthcare departments in Sweden	Effective rate for change in morning pain intensity after treatment assessed with change in VAS scores, grouped into "lower," "unchanged," and "higher"	Study population 727 per 1000	720 per 1000 (502 to 1000)	RR 0.99 (0.69 to 1.41)	47 (1 study)	⊕⊕⊖⊖ low[1,2,3,4,5]
	Effective rate for change in evening pain intensity after treatment assessed with change in VAS scores, grouped into "lower," "unchanged," and "higher"	Study population 682 per 1000	723 per 1000 (498 to 1000)	RR 1.06 (0.73 to 1.54)	47 (1 study)	⊕⊕⊖⊖ low[1,2,3,4]
Haker and Lundeberg 1990 [67] Subject: acupuncture for epicondylalgia Setting: outpatients in Sweden	Effective rate for patient reported recovery after treatment assessed with a scale from "unchanged"/"worse" to "excellent" recovery	Study population 658 per 1000	888 per 1000 (691 to 1000)	RR 1.35 (1.05 to 1.73)	82 (1 study)	⊕⊕⊖⊖ low[2,4,6,7]
Xiong et al. 2011 [68] Subject: acupuncture for primary dysmenorrhea Setting: outpatients from Tongji Hospital, Wuhan, China	Effective rate for pain relief after treatment assessed with the efficacy assessment guideline for TCM for primary dysmenorrhea	Study population 378 per 1000	847 per 1000 (571 to 1000)	RR 2.24 (1.51 to 3.32)	90 (1 study)	⊕⊕⊕⊖ moderate[2,4,7,8]
	Pain intensity after treatment assessed with VAS, scale from 0 to 10	The mean pain intensity score in the control group was 4.48	The mean pain intensity score in the intervention group was 2.78 lower (3.61 to 1.95 lower)		90 (1 study)	⊕⊕⊕⊖ moderate[2,4,7,8]
Chen et al. 2011 [22] Subject: acupuncture plus intradermal needle placement for cervical spondylosis Setting: volunteers recruited in two Guangdong hospitals in China	Neck pain after treatment assessed with the Northwick Park questionnaire, scale from 0 to 100	The mean neck pain score in the control group was 23.56	The mean neck pain score in the intervention group was 17.86 lower (23.65 to 12.07 lower)		70 (1 study)	⊕⊕⊖⊖ low[2,4,7,9]
	Pain after treatment assessed with the McGill pain questionnaire, scale from 0 to 60	The mean pain score in the control group was 20.35	The mean pain score in the intervention group was 7.80 lower (10.3 to 5.3 lower)		70 (1 study)	⊕⊕⊖⊖ low[2,4,7,9]

Table 7: Continued.

Study ID and descriptions	Outcomes	Acupuncture with Deqi versus acupuncture without Deqi for pain Illustrative comparative risks (95% CI) AOD (assumed risk)	 AWD (corresponding risk)	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (grade)
Zheng 2012 [70] Subject: acupuncture for migraine Setting: outpatients from two acupuncture clinics in Beijing, China Note: this study is ongoing by the time of publication, so incomplete data was reported.	Total migraine hours per 4 weeks after treatment	The mean total migraine hours per 4 weeks in the control group were 21.95 hours	The mean total migraine hours per 4 weeks in the intervention group were 19.33 hours longer (9.19 to 29.47 hours longer)		19 (1 study)	⊕⊖⊖⊖ very low[2,7,10,11]
	Migraine pain intensity (total VAS score per 4 weeks) after treatment assessed with VAS, scale from 0 to 10	The mean migraine pain intensity score in the control group was 11.70	The mean migraine pain intensity score in the intervention group was 7.01 higher (2.8 to 11.22 higher)		19 (1 study)	⊕⊖⊖⊖ very low[2,7,10,11]

[1]Randomization method and blinding of the patient not mentioned. Randomized assignment, binding of outcome assessor, and allocation concealment mentioned. For acupuncture trials, blinding of the practitioner is impossible; 3/70 patients were lost to followup; reasons explained; no ITT analysis. No selective outcome reporting.
[2]This item was omitted here because we assessed one single study.
[3]For this single study, findings presented evident individual variations in both groups. The calculated CI equals 1/3–1/2 effect size.
[4]A single study is very likely to be biased. However, it was omitted here to avoid all evidence being "very low" in quality and therefore indistinguishable.
[5]Patient-important outcome.
[6]Randomization methods, allocation concealment, and blinding of the patient not mentioned. Randomized assignment and binding of outcome assessor mentioned. For acupuncture trials, blinding of the practitioner is impossible; 4/86 patients were lost to followup; reasons explained; no ITT analysis. No selective outcome reporting.
[7]Subjective assessments. The calculated CI equals 1/9–2/3 effect size.
[8]Random number table, randomized assignment, allocation concealment, and blinding of the patient and assessor described. For acupuncture trials, blinding of the practitioner is impossible. No dropouts. No selective outcome reporting.
[9]Central randomization, randomized assignment, and the use of sealed envelope described. Placebo acupuncture was used, and the patient was blinded. However, blinding of the outcome assessor was not mentioned. For acupuncture trials, blinding of the practitioner is impossible. It is highly suspected that the physicians act as assessors; hence, the risk for measurement bias is high. No dropouts. No selective outcome reporting. Imbalanced baseline was reported.
[10]Central and block randomization and allocation concealment described. The outcome assessor was blinded, but both the patient and the acupuncturist were aware of the allocation. For acupuncture trials, blinding of the practitioner is impossible. High dropout rate (22/59); reasons explained. No selective outcome reporting.
[11]The trial is ongoing by the time of publication. Preliminary results were published (19/48 cases planned), with high risk of biases.

both after ten sessions and at 3 months (MD = −7.80, 95% CI (−10.30, −5.30); MD = −9.06, 95% CI (−11.19, −6.93)). Despite promising results, the strength of this conclusion as an evidence was weakened by imbalanced baseline. It was reported that the AWD group had higher mean NPQ and MPQ scores at baseline, indicating worse pain conditions, and the difference was statistically significant. Thus, it may introduce the thoughts that the AWD group had greater analgesic effects because the more pain-enduring patients were more likely to exhibit improvement.

The last included and most recent study is about AWD versus AOD for migraine by Zheng [70]. A selection of outcomes was discussed here as the trialists used a self-devised migraine assessment tool which lacked validation and calculated response rate in an uncommon way. Patient-important outcomes such as total migraine length and total pain intensity scores (measured with VAS) were measured every four weeks during the eight-week treatment and at 1- and 2-month followups. It was observed that the AOD group generally had a 19.33-hour reduction greater than the AWD group in migraine length per four weeks after treatment (MD = 19.33, 95% CI (9.19, 29.47)); however, no difference between the two groups was detected at 1 and 2 months of followup (MD = 5.41, 95% CI (−4.45, 15.27); MD = 5.90, 95% CI (−4.24, 16.04)). Patients in the AOD group also experienced better pain relief in that total pain score after treatment was 7.01 points lower on average than the AWD group (MD = 7.01, 95% CI (2.80, 11.22)); again such differences disappeared 1 and 2 months later (MD = 0.52, 95% CI (−3.92, 4.96); MD = −5.05, 95% CI (−9.97, −0.13)). In this study, preliminary findings based on data analysis of 19 patients showed that AOD had better short-term analgesic effects than AWD on migraine. However, this evidence was rated very weak in strength as further data analysis including more patient statistics is very likely to change the results.

4. Discussions

Acupuncture is an integral component of the traditional Chinese medicine. Since ancient times, the unique phenomenon of Deqi had been observed and widely illustrated in medical books on acupuncture and moxibustion. Recent years have witnessed growing academic interests in the mechanism and utility of Deqi sensations. However, in the past, the exquisite delicacy of Deqi experiences could only be imaged in poetic languages such as in the Make It Plain verse, which stated: "If your feelings are gentle, smooth and slow, the qi has yet to come. When it came, you perceived heaviness, tenseness and unsmoothness underneath the needle. The arrival of qi feels like a fish just swallowed the bait. It sinks and surfaces. When it did not come, you may sense the emptiness as calm and lonely as you were standing in a secluded hall" [46]. Now with the development of acupuncture theories and advanced techniques such as fMRI, a preliminary attempt has been made to reveal the biochemical and physiological basis for the production of the Deqi sensation. Constant efforts have also been made to quantify insertion depths, stimulation intensity, and manipulation procedures, and other factors are believed to have contributed to the effect of Deqi [72]. However, the current evidence profile is insufficient to draw any well-argued conclusion, and a clear mechanism underlying the Deqi sensation remains to be clarified.

In this review, we found that few cohort studies were designed to examine whether Deqi could be a predicator of greater acupuncture efficacy, and evidence generated from controlled clinical trials that can answer the question of "whether manipulation-facilitated AWD is superior to AOD for therapeutic purposes" is also insufficient to come to any solid conclusion. Specifically, one cohort study provided low-quality evidence for the natural emergence of Deqi sensations following needle insertion as an indicator of greater reduction on blood pressure in patients with primary hypertension. Considering AWD versus AOD for Bell's palsy, very low- or high-quality evidence drawn from the two studies came to contradictory findings. And for the analgesic effects of acupuncture, moderate-quality evidence supported the more positive role of AWD for primary dysmenorrhea in terms of enhancing overall recovery and reducing pain. However, very low-to-low quality evidence from the other six studies again provided us with only a complex of contradictions concerning the comparative effects of AWD and AOD. Despite that, the results of the correlation analysis reported in a few studies showed that patients with higher Deqi scores experienced better analgesic effects.

5. Conclusion

In summary, ancient Chinese acupuncture theorists and practitioners recognized the dominant role of evocation of the arrival of qi in achieving the best clinical effect. Results of mechanism studies provided preliminary scientific evidence for the production and effects of the Deqi sensation. The current evidence from clinical studies was insufficient to prove the interaction between Deqi and clinical efficacy. Continuing efforts are needed to provide both experimental and clinical evidence for the explanation of such a correlation.

Conflict of Interests

The authors declared that they had no financial conflict of interests.

Authors' Contribution

Shuo Zhang and Wei Mu contributed equally to this work.

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Research Article

Deqi Sensation in Placebo Acupuncture: A Crossover Study on Chinese Medicine Students

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Objective. To evaluate the similarity of deqi sensation of real and noninvasive placebo acupuncture in healthy people with knowledge of Chinese medicine. *Methods*. In a crossover design, volunteers recruited from Chinese medicine college students were randomized to two groups to receive two phases of intervention with a one-week washout interval. In Group A, the participants were firstly treated by real acupuncture and then by sham needle, and the treatment sequence was reversed in Group B. VAS for pain intensity and deqi sensation was evaluated as outcomes. *Results*. Sixty-three volunteers were recruited and 60 were included and finished the study. In Group A, VAS was higher in Phase I than in Phase II ($P = 0.017$). Only treatment methods were selected as factor to VAS difference ($P = 0.046$) in ANOVA test. More positive deqi was reported in Group A in Phase I when treated by real acupuncture ($P = 0.039$), but the difference was not significant in Phase II ($P = 0.301$). *Conclusion*. The noninvasive placebo acupuncture device can effetely simulate the deqi sensation as real acupuncture, but it is less likely to evoke the active effect of deqi in real practice. This trial is registered with Chinese Clinical Trial Registry: ChiCTR-ORC-09000505.

1. Background

Deqi or acupuncture sensation is a unique phenomenon in the practice of acupuncture. In a previous report, deqi was described as the combination of various sensations, for example, aching, dullness, heaviness, numbness, radiating, tingling and spreading, and so forth [1]. The mechanism of deqi has been studied and is characterized as the stimulus conducted by a wide spectrum of nerve fibers from the perspective of neurophysiology [2]. It is believed that the effect of acupuncture depends on the due acquisition of deqi, and this idea was supported by acupuncture analgesia in which the analgesic effect can be acquired only when deqi is felt by patients [3]. However, deqi is not always stressed in clinical studies. The main clinical study method of acupuncture is randomized control trail (RCT); thus, it must follow the common methodology principles, that is, randomization, appropriate control, blinding, and repeatability. Though deqi is an important factor for effectiveness, it is difficult to duplicate from one patient to another because of the difference in manipulation by practitioners and the variety of patients' response even to the same dosage of deqi. A study reported that Chinese patients had more intensive sensation of deqi than US patients, hence, leading to better therapeutic effects [4]. Therefore, a reliable control treatment capable of shielding deqi is crucial to the success of acupuncture RCTs.

In a brief review of six clinical studies during the nearest decade in which deqi was clearly reported, three of them with a total of 851 cases had negative results [5–7], compared to the rest three studies with positive outcomes with 308 cases in total [8–10]. Besides the sample size, the use of sham acupuncture is another key factor for effectiveness. Two of the studies reported the use of noninvasive sham needle (Park's sham device [7] and Streitberger's device [6]) with observed patients cumulated to 258. Since placebo control was introduced by Vincent et al. in 1995 as a rigorous and consensus approach to enhance the methodological quality

of acupuncture trials, a series of placebo control methods have been applied in acupuncture trials. For instance, sham needling invasive to subcutaneous or dermal tissues at non-acupoints [10, 11], noninvasive sham needle with a blunt tip, sham laser acupuncture [12], and sham electrode on acupoints without electricity [13]. The authors found that there is a trend that the newer the report is, the more confirmed that deqi will attribute to the active interventional effect. Therefore, in our opinion, an ideal placebo device should refrain the confounding of deqi during its intervention. The previous reports indicated that deqi is generated by the stimulus to the nerve system; hence, the invasive sham acupuncture methods will more or less produce active effects. Based on this assumption, we assume that the less the intensity of deqi is, the less confounding effect will contaminate the study outcome. And the noninvasive sham needles are believed to produce the least quantity of deqi because they do not penetrate skin hence cause the least activation of neural receptors. And this assumption founds the rationale basis of the study.

In this work, we presented a crossover study to evaluate the deqi sensation and placebo effect of a noninvasive sham needle device. The participants are college student volunteers specializing in Chinese medicine or acupuncture from Guangzhou University of Chinese medicine. They have comprehensive knowledge on acupuncture and deqi; thus, it is hopeful to reveal whether noninvasive sham devices are able to imitate deqi as placebo control in acupuncture RCTs. The study is reported in accordance with CONSORT 2010 statement [14] and STRICTA 2010 extension for acupuncture [15].

2. Design and Methods

2.1. Trial Design. The study was designed as a randomized, two-arm, single-blind, and crossover clinical trial. The study subjects were randomly allocated to two groups (Group A and Group B) and then sequentially received two phases of intervention of real acupuncture and noninvasive sham needle or vice versa. The two phases were separated by a one-week washout interval to eliminate the residual effect by the former phase. The outcomes included the quality of deqi sensation and pain intensity. The study objective is to evaluate the similarity of deqi sensation of real and placebo acupuncture in healthy people with comprehensive Chinese medicine and acupuncture knowledge.

2.2. Ethics Review and Informed Consent. The study protocol was reviewed and approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (no. 2008GL-27), and registered in the Chinese Clinical Trial Registry (no. ChiCTR-ORC-09000505), which is a primary registry in the WHO registry network (http://www.chictr/org/en/). All patients were required to provide informed consent.

2.3. Inclusion Criteria. Participants were included only when they met the following inclusion criteria:

(i) age 20 to 23 years (both males and female are included),

(ii) physically and mentally healthy confirmed by a physician,

(iii) having studied Chinese medicine and acupuncture for at least two years,

(iv) having finished the courses of basic Chinese medicine and acupuncture,

(v) having acupuncture experience beforehand,

(vi) no acupuncture therapy within the 3 months prior to study entry,

(vii) good protocol compliance and agreeing to sign an informed consent document.

2.4. Exclusion Criteria. Participants would be excluded if they had one of the following conditions:

(i) skin lesions on the surface of selected acupoints,

(ii) skin diseases affecting the skin surface of selected acupoints,

(iii) complaint of acute or chronic pain,

(iv) use of analgesics or psychotropic drugs,

(v) pregnancy or lactation,

(vi) rejection or fear of acupuncture,

(vii) considered not suitable to participate the trial by the researchers.

2.5. Sample Size and Randomization. As no data can serve as referred parameters, we assume that the sample size is 60 in total. The participants were randomized to two groups to, respectively, receive noninvasive sham needle and real acupuncture in the reverse order. The random allocation sequence was generated by an independent statistician with the use of SAS software (SAS Institute, Cary, NC, USA, version 9.2 (TS2 M3), licensed to THE SECOND CLINICAL COLLEGE OF GUANG ZHOU U, Site 11201875). The allocation codes were sealed into 60 opaque envelopes and all participants would be allocated in accordance with the randomized code of the corresponding envelopes.

2.6. Device and Intervention. There were two kinds of interventions in the study, that is, the noninvasive sham needle and real acupuncture. The instruments were also known as Park Sham Device set produced by DongBang Acuprime (http://www.acuprime.com/). The Sham device is composed of a blunt sham needle in two plastic tubes one slides into the other connected with a sticky opaque base on the skin. When the sham needle is inserted, it only hits the skin surface without penetration; thus, it is supposed to only produce the pinprick feeling but without active acupuncture effects. On the other hand, when the real needles pass through the tube, they will penetrate the skin and thus produce active effects. The sham needles and real needles in this study were 0.3 mm × 40 mm in size. The practitioners can manipulate

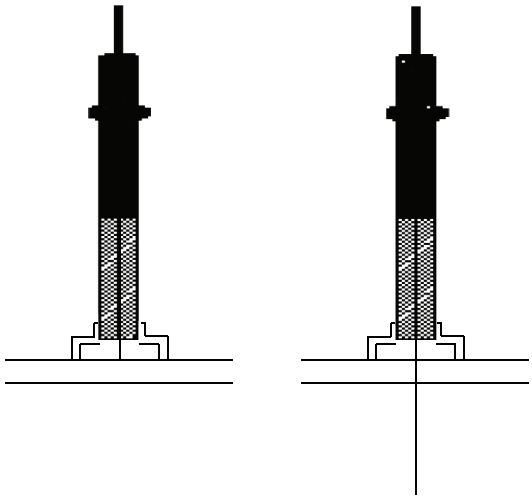

Figure 1: The mechanism of noninvasive sham needle.

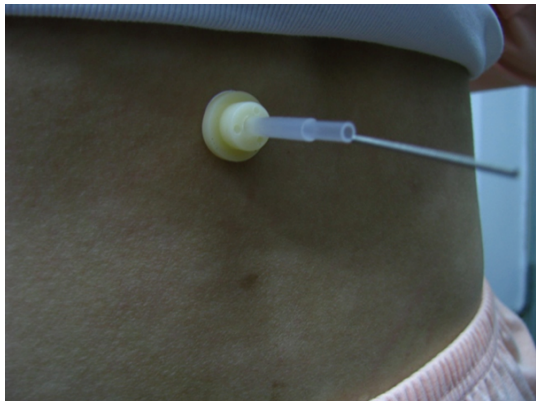

Figure 2: Sham acupuncture.

the handle for deqi after the needles are inserted. Since the device base is opaque, the subject is unable to tell whether the needle penetrates the skin or not (see Figure 1). The device is registered in the European Union as CE 0120 and in the US FDA as License No. 263.

2.7. Blinding and Point Selection. As the intervention must be performed by an acupuncturist and needle manipulation is prerequisite for deqi, the allocation concealment to acupuncturist is not feasible in this study. Thus, we applied a single-blind design in which both the volunteer participants and statisticians were blinded to group allocation till the final data analysis was finished. The selected point was Shenshu (BL 23) bilateral whose location followed the WHO standards [16]. The acupoints are located on the back; thus, the participants could not observe the needle and manipulation during the intervention. Therefore, we concluded that the blinding was effective in this study to all participants. See Figures 2 and 3.

2.8. Intervention Period and Procedure. The intervention consisted of two phases: sham needle intervention and real acupuncture. And there was a one-week washout interval

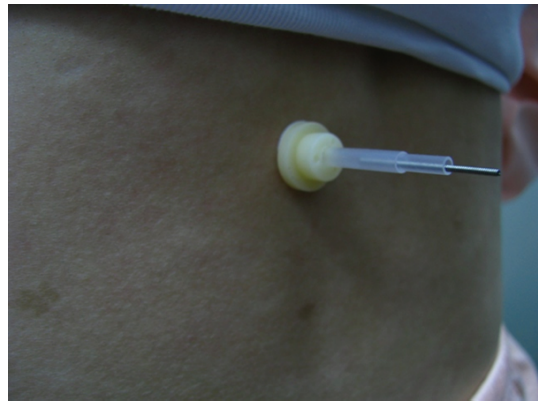

Figure 3: Real acupuncture.

between the phases to eliminate the residual effects in the preceding phase. A single phase was one week during which the participants received three sessions (20 minutes per session) of intervention every other day after being included and allocated to a group. In group A, the participants received real acupuncture at first and then sham needle intervention after the washout interval; in group B, the participants received sham needle intervention at first and then real acupuncture after the washout interval. The interventions were performed indoors with the average temperature of 25°C. After local disinfection by medical alcohol, the needles were inserted and manipulated for 30 seconds to induce deqi in both groups. The devices were retained in the acupoints for 5 minutes. All interventions were performed by an identical practitioner from the Acupuncture Department of Guangdong Provincial Hospital of Chinese Medicine. The intensity of pain and deqi sensation were evaluated in the end of both phases. The study procedure is illustrated in the flowchart (see Figure 4).

2.9. Outcomes for Evaluation. Both pain intensity and deqi sensation were assessed in this study. Pain intensity was measured on a visual analog scale (VAS). And deqi sensation was evaluated in two dimensions: the deqi feeling (including dullness, heaviness, numbness, radiating, and tingling) and the feeling of skin penetrated. A questionnaire was used for the assessment of deqi feeling, in which a positive response to any one of the perceptions including dullness, heaviness, numbness, radiating, and tingling would be considered as deqi. Because the deqi feeling is related to efficacy in real treatment while the feeling of skin penetrated is related to the concealment or the effect of blinding, they should be assessed separately. The outcome data were collected by patient-reported outcome (PRO) method, with the questionnaire being completed by the participants themselves with necessary instruction from the researchers.

2.10. Statistical Analysis. EpiData (version 3.1) was used for data entry and SPSS (version 16.0; SPSS Inc., Chicago, IL, USA) for statistical analysis. The analytic strategy included the descriptive analysis on demographic characteristics of the participants and the outcome of pain and deqi. The group

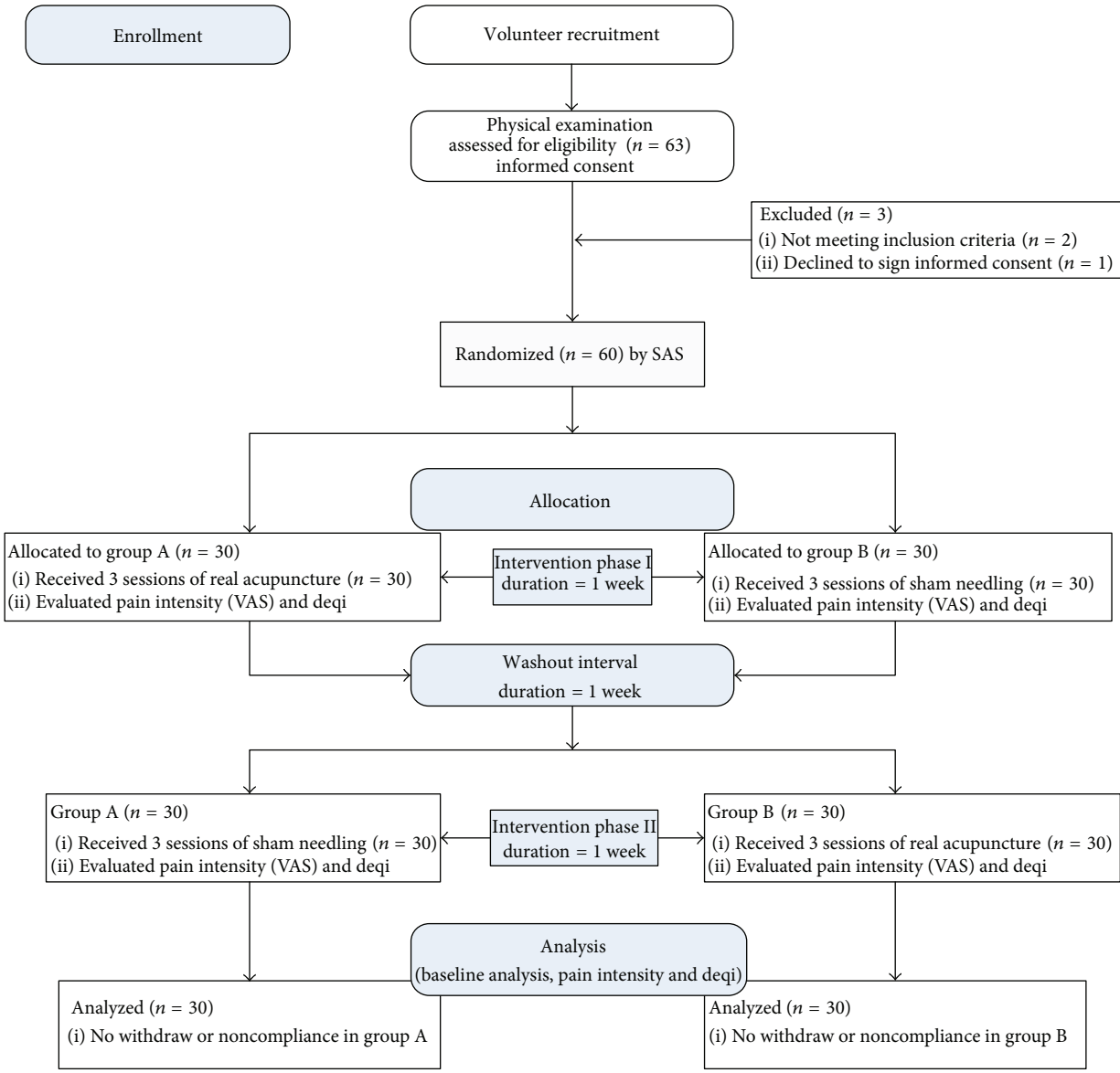

Figure 4: Flowchart of study procedure.

differences were tested by t-test for continuous variables, the Mann-Whitney test (two independent samples) or Wilcoxon test (two related samples) for continuous variables not complying with normal distribution, and the Chi-square test for categorical variables. The significance level is set at $\alpha = 0.05$, two-sided. The intention-to-treat (ITT) strategy would be applied if there were withdraws or noncompliance from the study.

3. Results

3.1. Volunteer Recruitment. Recruitment leaflets were distributed on the two campuses of Guangzhou University of Chinese Medicine for volunteer participants who were junior or senior student of Chinese medicine or acupuncture. The enrolled participants are given a physical examination by doctors from Guangdong Provincial Hospital of Chinese Medicine to confirm their healthy status. The participants were included only after they met the inclusion criteria and had signed an informed consent document. In the study, 63 volunteers were recruited. Two of them were later identified not meeting the inclusion criteria and one refused to sign the informed consent document. Hence, 60 were finally included in the trial and finished the observation without any withdraw. The participant flow is illustrated in Figure 4 of Section 2.8.

3.2. Baseline Demographic Data. A total of 63 participants were recruited in which 60 were eventually included and finished the study. There were 8 males and 22 females in Group A whose average age was 23.13 ± 0.62, and there were 4 males and 26 females in Group B whose average age was

Table 1: Baseline comparison of demographic data.

Comparison item	Group A ($n = 30$)	Group B ($n = 30$)	P value
Sex (%)			
Male	8 (26.7)	4 (13.3)	0.197*
Female	22 (73.3)	26 (86.7)	
Age			
Mean (SD)	23.13 (0.62)	22.93 (0.58)	0.201#

*Chi-square test, $\chi^2 = 1.667$.
#Mann-Whitney test, $Z = -1.277$.
SD: standard deviation.

Table 2: VAS score in intervention Phase I and Phase II.

	Mean (SD)		P value
	Group A	Group B	
Between group comparison			
Phase I	1.43 (1.61)	2.33 (1.89)	0.053*
Phase II	2.60 (2.29)	1.99 (2.02)	0.282**
Within group comparison			
P value	0.017#	0.690##	

*Independent-samples t-test, $t = 1.976$. **Independent samples t-test, $t = -1.087$.
#Paired-samples t-test, $t = -2.745$. ##Paired-samples t-test, $t = 0.580$.

Table 3: ANOVA test for crossover effects.

Source of variance	F	P value
Treatment method	4.140	0.046
Treatment sequence	1.736	0.193
Subject	3.441	0.687

Table 4: Report of deqi feeling.

Perception of deqi	Group A ($n = 30$)	Group B ($n = 30$)	P value
Between-group comparison			
Intervention Phase I			
Yes	19 (63.3)	11 (36.7)	0.039*
No	11 (36.7)	19 (63.3)	
Intervention Phase II			
Yes	12 (40.0)	16 (53.3)	0.301**
No	18 (60.0)	14 (46.7)	
Within-group comparison			
P value	0.143#	0.332#	

*Chi-square test, $\chi^2 = 4.267$, **Chi-square test, $\chi^2 = 1.071$.
#McNemar test.

Table 5: Report of skin penetrated feeling.

Perception of skin penetrated	Group A ($n = 30$)	Group B ($n = 30$)	P value
Between-group comparison			
Intervention Phase I			
Yes	21 (70.0)	23 (76.7)	0.559*
No	9 (30.0)	7 (23.3)	
Intervention Phase II			
Yes	25 (83.3)	23 (76.7)	0.519**
No	5 (16.7)	7 (23.3)	
Within-group comparison			
P value	0.424#	1.000#	

*Chi-square test, $\chi^2 = 0.341$, **Chi-square test, $\chi^2 = 0.417$.
#McNemar test.

22.93 ± 0.58. No statistical difference was found in sex and age between the two groups. (See Table 1).

3.3. Pain Intensity. The pain intensity caused by real needle insertion and sham needle pricking was measured by visual analog scale (VAS) in the end of each intervention phase. The ANOVA test for crossover design showed that only treatment methods contributed to the VAS difference in the study ($P = 0.046$). The between-group comparison showed the VAS scores had no statistical difference between groups in both Phase I ($P = 0.053$) and Phase II ($P = 0.282$). And in within-group comparison, the VAS score of Group A in intervention Phase II was higher than in intervention Phase I ($P = 0.017$), while the VAS scores in Group B had no statistical difference between Phase I and Phase II ($P = 0.690$). (See Tables 2 and 3).

3.4. Report of Deqi Feeling. Deqi is a subjective feeling which is described as a serial of sensations such as dullness, heaviness, numbness, radiating, and tingling. Thus we designed a questionnaire to inquire the participants whether dullness, heaviness, numbness, radiating, or tingling was perceived during the intervention based on their background knowledge and understanding. A positive response to any of the above sensations was considered as deqi. If all responses were negative, deqi was considered absent. In Phase I, 19 participants (63.3%) reported deqi in Group A compared to 11 participants (36.7%) in Group B, in which the difference was statistically significant ($P = 0.039$). In Phase II, 12 participants (40.0%) reported deqi in Group A compared to 16 participants (53.3%) in Group B, in which the difference was not statistical significant ($P = 0.301$). In within-group comparison between Phase I and Phase II, the reports of deqi had no statistical significance in both Group A ($P = 0.143$) and Group B ($P = 0.332$). (See Table 4).

3.5. Report of Skin Penetrated Feeling. Among the reports of skin-penetrated feeling, 21 (70.0%) participants in Group A and 23 (76.7%) in Group B gave a positive response in Phase I, and 25 (83.3%) participants in Group A and 23 (76.7%) in Group B gave a positive response in Phase II. The between-group difference was not statistically significant ($P = 0.559$ in Phase I & $P = 0.519$ in Phase II). In within-group comparison between Phase I and Phase II, the reports of skin penetrated feeling had no statistical significance in both Group A ($P = 0.424$) and Group B ($P = 1.000$). (See Table 5).

3.6. Safety Evaluation. The adverse events (AE) were local bleeding, numbness, and radiating on the acupoints being

needled. In this study, 5 cases of local bleeding were reported in Group A and other 3 cases were reported in Group B. The local bleeding was stopped within one minute when pressed by medical cotton. There were 9 complaints of local sustained numbness and radiating after the needle devices were withdrawn in Group A and 7 in Group B. The symptoms were effectively controlled within 30 minutes when applied with hot towels on the local skin.

4. Conclusion and Discussion

In this study, we designed a randomized, two-arm, single-blind, and crossover clinical trial to evaluate the deqi sensation of a noninvasive sham needle device and to explore the influence of deqi on placebo effect in RCTs with placebo control of acupuncture. The concealment and placebo effect of sham acupuncture have been assessed in a variety of studies outside China on subjects who were naïve to acupuncture and Chinese medicine [17] and who had acupuncture experience [18]. The currently notion is that the deqi sensation is more than pain [18], and it is a comprehensive acupuncture experience composed of perception of various dimensions. White et al. introduced the 17-item Southampton Needle Sensation Questionnaire to measure deqi which contains 7 items for pain sensations (i.e., "Aching deqi") and other 7 items for nonpain sensations (i.e., "Tingling deqi") [19]. Kim et al. developed the 19-item Acupuncture Sensation Questionnaire (ASQ) to measure deqi from real acupuncture experiences [20]. The similarity of these two questionnaires is that the sensations of deqi are both deconstructed to pain-related sensations and nonpain sensations despite the inconsistency in other aspects. Thus, it becomes the consensus on common understanding of deqi in the nearest decade. However, Deqi sensation is not simply pain but consists of a variety of acupuncture experiences and perceptions. The previous questionnaires only include the understanding and perceptions of Deqi by ordinary people, but they ignore the fact that Deqi is more than pain or unhappy feelings: it also directly affects the efficacy of acupuncture treatment. We thus organized this study in which participants were medical students of Chinese Medicine with profound understanding of Chinese medicine acupuncture. In the deqi assessment, the sensation was summarized into two questions: the overall feeling of deqi and the feeling of skin penetrated. The participants were required to make a decision based on their comprehensive knowledge of Chinese Medicine which covered all factors of deqi.

On the other hand, placebo device was advocated in acupuncture studies since 1995 [21]. An ideal placebo should comply with two principles: similarity in appearance and manipulation and production of no active effects [22]. Streitberger and Kleinhenz introduced the first sham device (Streitberger's device) in 1998 [23], but its placebo and concealment effect was challenged by later studies because the sham device was likely to be distinguished by subjects or even had superior effects over real acupuncture [24–26]. Park invented another sham device (Park Sham Device) in 2009 [27]. And it was considered as a credible sham control in both acupuncture naïve and experienced population [28]. Both Streitberger's device and Park Sham Device belong to noninvasive or nonpenetrating sham needle, which is composed of a blunt tip sham needle, a tube for needle insertion, and an opaque base sticky on the acupoint skin. The real or sham needle can be inserted through the tube and manipulate in the opaque base without being distinguished by participants. However, recent acupuncture trials in which sham needles were applied as placebo control still indicated noninferior efficacy of placebo acupuncture compared to real acupuncture [29, 30]. The outcome may attribute to the complexity of acupuncture treatment in which various factors contribute to the overall outcome; hence, the placebo devices are likely to affect actively except for their nonspecific (i.e., placebo) effect. These studies [17–20, 23, 27, 28] focused on evaluating the concealment of placebo device, but the issue that whether and to what extent the placebo devices affect actively was not specifically answered. Furthermore, how deqi sensations affect the treatment outcome and whether needle manipulation attributes to the efficacy are controversial issues in current studies.

Our work is to evaluate the deqi sensation stimulated by noninvasive sham needle device in college students of Chinese medicine. Deqi is a unique feeling induced by acupuncture, and it is believed that the perception of deqi is based on profound understanding and experience of Chinese medicine and acupuncture. Compared to ordinary people with acupuncture experience, our volunteer participants have been trained in Chinese medicine for at least two years; hence, their knowledge and experience are adequate to perceive deqi without concept deconstruction. In addition, pain is an inseparable component of deqi sensation and its intensity is related to both deqi and concealment; therefore, pain was quantitatively measured by VAS combined with the feeling of skin penetration as the assessment for concealment.

The result indicated that the noninvasive sham device produced more pain in intensity than real needle for its mean of VAS score was higher than real acupuncture in Phase I intervention though it is not statistically significant ($P = 0.053$). The ANOVA test for crossover study indicated only different treatment methods contributed to the VAS difference in the study ($P = -0.046$). The difference in VAS might also be affected by gender because more females were concluded in the study than men, and women are considered more sensitive to pain. For the assessment of deqi feeling, more participants reported deqi when they were treated and manipulated by real acupuncture. However, the volunteers could not distinguish the deqi feeling induced by real or sham needles when they were shifted to the other needle (i.e., real needle to sham needle or vice versa). The feeling of skin penetrated was similar in Group A and Group B, which implied good concealment of using noninvasive sham needles.

The study design limitation is the small sample size because no referred parameters are available from prior studies for healthy college students of Chinese medicine. If we use the VAS means and standard deviations as parameters for sample size calculation, in the significant level of $\alpha = 0.05$ and power of 0.8 ($\beta = 0.2$), the required sample

for each group is 61. Since healthy volunteers are difficult to recruit in clinical studies and the protocol compliance rate is 100% in this study, the data acquiring from this study provides valuable parameters for reference in future studies. Another limitation is that the study result is only appropriate to subjects with knowledge of Chinese medicine and acupuncture. The concept of deqi was not deconstructed into common life experience in this study; thus, it requires more profound understanding of acupuncture. The study participants were healthy college students; therefore, it cannot evaluate how deqi will affect the efficacy of acupuncture in real treatment. However, as deqi is considered an active factor for clinical efficacy, this study revealed that deqi is less likely to be evoked by noninvasive acupuncture, and tapping by sham needle on acupoints is felt even more painful than real acupuncture. These results will serve as valuable reference for future studies.

Conflict of Interests

The authors state that there are neither actual nor potential conflict of interests, including any financial or personal relationships with other people or organizations since the work was submitted.

Authors' Contribution

Zhao-hui Liang drafted and revised the paper in accordance with the 2010 CONSORT & STRICTA Guidelines, developed the statistical analysis strategy. Chang-cai Xie developed the study protocol. Zi-ping Li coordinated during the study. Xiao-ping Zhu submitted the protocol to ethics review and registered in the Chinese Clinical Trial Registry. Ai-ping Lu was the study's adviser in methodology. Wen-bin Fu was responsible for the study.

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Research Article

Effects of Deqi on Autonomic Balance in Adult Tinnitus Patients: Study Design of a Randomized Controlled Trial

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Background. Recent reports suggest that a proportion of tinnitus patients suffer from mental illness. Autonomic nervous system plays a useful role in tinnitus therapy since electrical vagal nerve stimulation (VNS) has been frequently used to alleviate tinnitus-induced depression in clinic. heart rate variability (HRV), which is reflective of autonomic nervous system function, has been proved to be modulated by acupuncture. In the present study, we aim to compare the effect of deqi sensation on heart rate variability in adult tinnitus patients. *Methods*. Thirty participants are randomly assigned to verum acupuncture (creating deqi) or shallow acupuncture (not creating deqi) at Baihui (Du-20), Shenting (Du-24), Tinghui (GB-2), Waiguan (SJ-5), and Zulinqi (GB-41) for 3 weeks. The primary outcome measure is heart rate variability, which is measured at the first acupuncture, as well as the last acupuncture. *Discussion*. Completion of this trial will help to identify the role of deqi sensation in acupuncture effect for tinnitus and reveal an autonomic modulation mechanism for acupuncture effect. *Trial Registration*. This trial is registered with International Standard Randomised Controlled Trial Number ISRCTN58013563.

1. Background

Tinnitus is generally defined as a perception of sound in the absence of an external acoustic stimulus. Subjective tinnitus affects approximately more than 600 million individuals worldwide [1, 2]. It has a prevalence of roughly 12–15% in the adult population [3–5]. The amount of distress in people suffering from tinnitus can be evaluated by validated tinnitus questionnaires. The imbalance of autonomic system leads to further increases in the sensitivity of the auditory system and reinforcement of the attentional filters, which makes tinnitus loudness and awareness more severe. This, in turn, exacerbates the level of stress and so on, making the tinnitus progressively worse over time [6]. A number of clinical trials have demonstrated the presence of psychopathological disorders and high depressive scores in tinnitus patients [7, 8]. For this reason, there may be a causal relationship between the molecular bases of these disorders. As a the neurotransmitter of the parasympathetic nervous system, acetylcholine (ACh) is likely to play a role in plasticity at many sites in the auditory system [9]. Animal models of tinnitus demonstrate changes in cholinergic mechanisms in auditory nuclei [10]. The cholinergic signaling is involved in many physiological functions and in some disease states such as anxiety and depression [11]. It is suggested that the limbic and autonomous nervous systems are largely responsible for troublesome tinnitus [12]. These findings in the literature suggest an association among ANS, depression, and tinnitus. Heart rate variability (HRV), as a simple and noninvasive quantitative marker of autonomic function [13, 14], has the potential to evaluate the autonomic status of tinnitus patients.

Acupuncture, as a particularly complementary and alternative medicine (CAM), has frequently been used to treat tinnitus [15, 16]. It can improve the symptoms of tinnitus by the

activating of endogenous opioid mechanisms and neuropeptides which stimulate specific brain structures [17]. Acupuncture can relieve the loudness and disturbing quality tinnitus immediately, and significantly improve the quality of life, tension and sleep [18]. During the verum acupuncture, needles create the specific needle sensation called "deqi" ("aching," "dull," "heavy," "numb," "radiating," "spreading" and "tingling") at specific acupuncture points [19]. Deqi is suggested to be the main mechanisms producing effects from acupuncture [20], by generating a release of spinal and supraspinal beta-endorphins, proinflammatory neuropeptides and an increase in peripheral circulation [21]. However, there is lack of adequate experimental data to indicate the relationship between deqi sensation and modulation effect of acupuncture on ANS [22]. Therefore, more evidences are needed to prove the specific effect of acupuncture. The aim of our study is to evaluate the effect of deqi on HRV in tinnitus patients.

2. Methods

We perform the study according to common guidelines for clinical trials (Declaration of Helsinki, International Conference on Harmonisation (ICH)/WHO Good Clinical Practice standards (GCP) including certification by an external audit). It will strictly follow the CONSORT statement to report high-quality study results. The trial protocol has been approved by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University (Ref: 201213). This trial was registered with ISRCTN at Current Controlled Trials (ISRCTN58013563).

2.1. Recruitment. Patients will be recruited in acupuncture clinic, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University with a target sample size of 30 subjects. The trial is executed from March 2012 to June 2013.

2.2. Inclusion Criteria. Patients who meet all of the following conditions will be considered for enrollment [23]:

(1) typical conditions of unilateral or bilateral tinnitus,

(2) aged 18–65, either sex,

(3) tinnitus duration of more than 3 months,

(4) not receiving any treatment last 1 month,

(5) normal language and intelligence ability to answer and fill in the questionnaire,

(6) better understanding of acupuncture, and good compliance to the research observation and evaluation,

(7) written and informed consent.

2.3. Exclusion Criteria

(1) Objectivity tinnitus (objective tinnitus is audible to the examining/auscultating physician),

(2) acute or intermittent tinnitus, history of Meniere disease, or tinnitus induced by middle ear/inner ear/small pons angle tumor,

(3) underlying disease or history: otitis media, tympanic membrane perforation, or eustachian tube function obstacle,

(4) acoustic neuroma, intracranial damage or use of any ototoxic drugs,

(5) severe dysfunction of heart, kidneys or liver,

(6) the serious original disease of hematopoietic system or endocrine system,

(7) serious aphasia, depression syndrome or mental disease.

2.4. Randomisation and Blinding. After participants complete a baseline evaluation, a research coordinator (Guang-Xia Shi) who is uninvolved with data collection randomly allocates them to either verum acupuncture group or shallow acupuncture group by using a computer-generated, blocked random-allocation sequence with a block size of 6. The random codes are only known by another researcher (Qian- Qian Li) who is not involved in treatment and statistical analysis.

The assignment is done in a single-blind manner, in which the patients are blinded to treatment assignment. In order to minimize the placebo effects, patients are informed in a manner suggesting that two different types of acupuncture treatment are compared. One type is traditional acupuncture, another is novel acupuncture, and the effect of both is uncertain. Similar strategies of informed consent have been used in most previous acupuncture trials [24]. HRV analysis and assessment of THI are performed by a researcher (Li-Li Han), who is blinded to patients' treatment respectively. During the intervention, acupuncturist and all the researcher personnel are segregated immediately after the treatment starts and are instructed not to exchange information with each other.

2.5. Interventions. This trial is a randomized controlled study. Participants will receive acupuncture for 3 weeks (Figure 1) (twice per week). All candidates go through a standardized interview and receive more information about the study and the treatments. They also undergo audiological testing of hearing thresholds, minimal masking levels, and loudness discomfort levels carried out by an audiologist in Tongren Hospital affiliated to Capital Medical University (Xin-Xin Fu).

Timepoints are as follow:

visit 1: screening,

visit 2: treatment initiation, participants will receive acupuncture for 3 weeks,

visit 3: 3 weeks later of first acupuncture, followup and treatment finish.

Patients who meet the inclusion criteria and none of the exclusion criteria are randomized to one of two treatment groups.

Group A will receive verum acupuncture (creating deqi sensation).

Group B will receive shallow acupuncture (not creating deqi sensation).

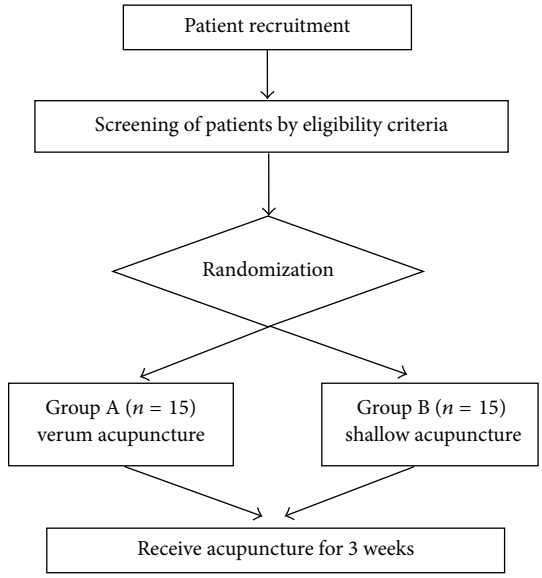

Figure 1: Flowchart.

Acupuncture points are selected as follow (Figure 2).

Patients are stimulated by 5 main acupoints: Baihui (Du-20), Shenting (Du-24), Tinghui (GB-2), Waiguan (SJ-5), and Zulinqi (GB-41). The acupoints are stimulated continuously by the true needles or the shallows for 20 minutes per session.

Acupuncture is performed with sterile needles by one therapist (Cun-Zhi Liu) with more than 22 years of experience and an acupuncture license from the Chinese medicine practitioner from the Ministry of Health of China. Treatment will be conducted over a period of 3 weeks, at a frequency of 2 sessions/week. No additional treatment is allowed.

2.6. Primary Outcome Measures. HRV indexes are measured using a digital 12 leads ECG-Holter machine (Mortara Instruments, USA). Within frequency domain, power in low frequencies (LF; 0.04–0.15 Hz), and in high frequencies (HF; 0.15–0.4 Hz) are calculated for each 5-minute density spectrum by integrating the power spectral density in the respective frequency bands. The HF/LF ratio also is analyzed [25]. HRV is measured at the first acupuncture, as well as the last acupuncture (Figure 3).

2.7. Secondary Outcome Measures

(1) Change of tinnitus severity according to the tinnitus questionnaire of Tinnitus Handicap Inventory (THI) [26]:

(1.1) F: functional subscale (11 factors),

(1.2) E: emotional subscale (9 factors),

(1.3) C: catastrophic subscale (5 factors).

Each question of the THI can be answered by the patient with either often (4 points), sometimes (2 point), or never (0 points) with a maximum total score of 100 indicating most severe suffering from tinnitus. The assessment is at baseline (before treatment initiation) and 3 weeks later of the first acupuncture.

(2) Participants also report adverse events induced by the acupuncture treatment, including discomfort or bruising at the sites of needle insertion, nausea, or feeling faint after each treatment. Answers concerning possible side effects related to the acupuncture treatment will be documented by using a standardised questionnaire at the end of treatment.

2.8. Data Analysis. We use paired t-tests and two-way ANOVA with one repeated measure to analysis the data of 30 tinnitus patients. Post hoc analyze is performed using Tukey test. The level of significance is defined as $P < 0.05$.

3. Discussion

This trial has been designed above to identify whether acupuncture could (verum acupuncture or shallow acupuncture) treat subjective tinnitus patients by modulating HRV, so as to explain the mechanism of acupuncture effects on tinnitus. If this questionnaire results provide evidence for the safety of acupuncture, more patients with these conditions may be encouraged to seek out acupuncture.

The present study aimed to help to draw more attention in acupuncture's potential for treating patients with tinnitus by autonomic regulation. Although a climate where acupuncture might be assumed to be ineffective exists [27, 28], there is inadequate evidence on which to base a judgment on acupuncture's effectiveness for tinnitus. Well-designed randomized controlled trials which can provide the acupuncture effect mechanism for tinnitus by scientific approach are needed.

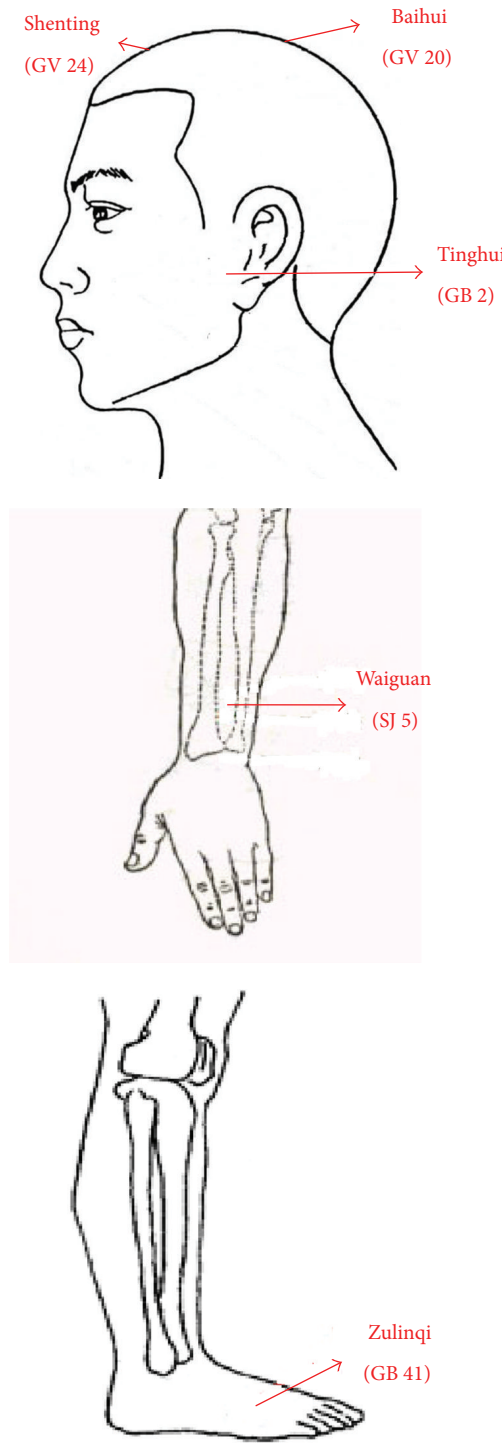

Figure 2: The points used in the trial.

Verum acupuncture is administered by twirling and lifting the needles until deqi occurred. One of the greatest challenges in acupuncture research is selecting an appropriate sham acupuncture control. There are several existing sham acupuncture methods including shallow needling on acupoint, shallow needling on nonacupoint and ritualized mock acupuncture. To avoide the difference of acupoint selection, shallow needling on acupoint is used as a control group in this trials. For the shallow group, the point selection is the same as the verum acupuncture group. However, the depth of needles inserted vertically to the subcutaneous level should be rigidly controlled over no more than 3 mm. Any sensation (deqi) or needle manipulation is prohibited in this group. Because the needles are inserted at the same points, the patients cannot

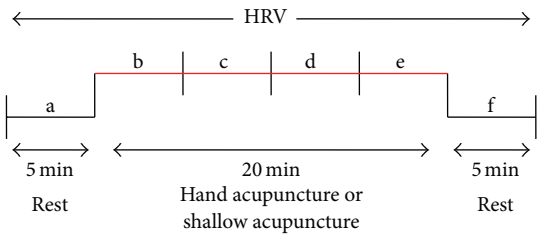

Figure 3: Sequence for heart rate variability (HRV) testing. The data before measurement phases (a), during (b–e), and after (f) were measured and statistically analyzed.

distinguish the shallow acupuncture from the real one on the vision.

Placebo effects of acupuncture are actively studied in many articles, and sham acupuncture is a representative method for an acupuncture placebo tool [29, 30]. But there is a lack of consensus on the most valid approach to establishing placebo acupuncture. Therefore, important aspects of the placebo acupuncture control need to be considered. In this trial, we will evaluate the effect of deqi on HRV and reveal the potential mechanism of acupuncture treatment for tinnitus.

Needling sensation has been considered important to acupuncture therapeutic effects [31]. Deqi sensation is assumed by many acupuncturists to be associated with a therapeutic effect and is often sought during needling [32]. Based on a hierarchical cluster analysis, a grouping of seven sensations is found to be associated with the category of deqi ("aching," "dull," "heavy," "numb," "radiating," "spreading," and "tingling") [19]. It has been determined that the changes in parasympathetic nervous activity were correlated with number of deqi sensations during acupuncture manipulation [33]. On the other hand, what degree does it affect the autonomic nerve is still unknown. It was concluded that at least a part of the effects of acupuncture was independent of the presence of a deqi sensation [34]. In this trial, we will compare the impact of needling at two different depths by HRV analysis and discuss the relationship of deqi phenomenon and acupuncture effect from the view of autonomic modulation.

Many patients mention that tinnitus has developed in a stressful life episode and that it is worsened by stressful situations [35]. In addition, tinnitus distress is related to autonomic changes in the sympathvagal balance [36]. However, there are few reports about the relationship between tinnitus and HRV, which was used as an objective noninvasive marker of the autonomic nervous system [37]. HRV monitoring is used to evaluate acupuncture-induced effects on the autonomic nervous system regulation [38]. In our study, the relations of HRV with tinnitus and HRV with acupuncture will be further discussed.

It should be acknowledged that our study has several potential limitations. First, the sample size is limited. Because there are few similar studies reported previously, we cannot calculate sample size on the basis of the differences of HRV modulated by verum acupuncture or shallow acupuncture in tinnitus patients. Second, shallow acupuncture may have some physiological effects, which is also a limitation of the study.

Trial Status

The trial is currently in the recruitment phase.

Conflict of Interests

The authors declare that they have no Conflict of interests.

Authors' Contributions

Cun-Zhi Liu conceived the study, and prepared the initial protocol. Lin-Peng Wang and Xin-Xin Fu made amendments to the protocol and participated in design of the trial protocol. Qian-Qian Li drafted the paper, and performed the measurements. Guang-Xia Shi and Lin-Lin Han performed the experiments. Na Hou is responsible for patients' recruitment. Li-Ying Liu participated in statistics analysis. All authors read and approved the final paper.

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Research Article

Influence of the Deqi Sensation by Suspended Moxibustion Stimulation in Lumbar Disc Herniation: Study for a Multicenter Prospective Two Arms Cohort Study

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Moxibustion stimulates the Deqi (Qi arrival) phenomenon. Many clinical observations have documented that the character of the Deqi was a composite heat-sensitive moxibustion sensation. In this prospective multicentre comparative observational nonrandomized study, 92 patients with moderate to severe LDH were included. This study consisted of two parallel arms (A: heat-sensitive moxibustion sensation group; B: nonheat-sensitive moxibustion sensation group). Moxibustion was applied in the following three acupuncture points simultaneously: Da Changshu (BL25), Wei Zhong (BL40), and A-Shi acupuncture point (tenderness). The adjusted mean total Modified-JOA score showed significant differences between the groups in the first week (10.32 ± 4.27 95% CI [$9.23 \sim 11.40$] versus control group 12.42 ± 5.02 [$11.62 \sim 13.69$], $P = 0.03$). The outcome in the second week also presented significant differences in both groups (7.62 ± 4.80 [$6.46 \sim 8.77$] versus 10.56 ± 4.75 [$9.35 \sim 11.76$], $P = 0.005$). Significant differences were also manifested in the follow-up period ($P = 0.007$). It can be inferred that the existence of the Deqi (heat-sensitive moxibustion sensation) phenomenon in the process of suspended moxibustion is closely related to the curative effect, and arrival of heat-sensitive moxibustion sensation could improve the clinical curative effect of moxibustion.

1. Background

Lumbar disc herniation (LDH) is one of the major chronic musculoskeletal diseases that are highly prevalent. In China, about 10%~15% patients with low back pain were diagnosed with LDH [1]. It seriously affects patient's quality of life (QoL) and leads to economic burden [2, 3]. Epidemiological studies from several countries showed that the prevalence of LDH frequently appeared in adults at the age of 30~55 [4]. LDH causes symptoms of sciatica and possible foot pain, numbness, or weakness. In most of the cases, a conservative attitude with different types of physiotherapy is preferred as the first choice [5, 6]. Most of patients with low back pain responded well to conservative therapy [7]. Absolute indications for surgery include altered bladder function and progressive muscle weakness, but these are rare. Therefore, many studies have already reported encouraging results in the treatment of LDH by acupuncture and moxibustion [8].

Moxibustion is a traditional Chinese method of treatment, which applies the heat generated by burning moxa (it is also called Mugwort or Moxa) to stimulate on the acupuncture points. Suspended moxibustion is commonly used, and it refers to application of the burning moxa stick on the acupuncture points at a distance. The results of a recent meta-analysis of six randomized controlled trials (RCTs) on moxibustion for LDH manifested that moxibustion presented a favorable effect on LDH symptom scores compared with that of the drug [RR = 1.91, 95% CI (1.01, 3.60)] [9].

According to traditional Chinese medicine (TCM), the Deqi is the key point to the clinical efficacy of acupuncture and moxibustion [10]. The Deqi is a term originated from *Huangdi Neijing,* also known as "Qi arrival." In the part of *Miraculous pivot, the chapter of nine needles and twelve sources* said: "The key point of acupuncture is the arrival of Qi, it ensures therapeutic effect. It resembles the wind over blows the cloud, soon the sky is clear." [11]. The Deqi's primary connotation is the endogenous Qi of regulation stimulated by acupuncture and moxibustion, which is closely related to the curative effect [12]. When Qi arrives at one part of the body, it can treat the diseases nearby.

Numerous studies have now shown that moxibustion stimulation stimulated a unique Deqi, heat-sensitive moxibustion sensation [13, 14]. In the process of moxibustion treatment, the researchers discovered that, when human body is in morbid condition, related acupuncture points were quite sensitive to moxa's heat and produced nonlocal or nonsuperficial heat sensation, such as penetrating heat, expanding heat, and transmitting heat [15]. This phenomenon resembles the one that occurs when the Deqi appears after moxibustion rather than local heat sensation and surface glow of the skin. The researchers named the phenomenon as heat-sensitive phenomenon of moxibustion or acupuncture point's heat-sensitive phenomenon, and it belongs to the Deqi phenomenon of moxibustion therapy [16].

However, there is lack of experimental data to indicate the difference of heat-sensitive moxibustion sensation (the Deqi stimulated by moxibustion) compared with conventional local superficial heat sensation (non-Deqi by moxibustion stimulation). For LDH especially, is it necessary for moxibustion to produce the phenomenon of obtaining Qi in order to improve the curative effect? Therefore, it would be valuable to know whether there is difference between the moxibustion sensations in the treatment of LDH. Therefore, we planned the rigorous multi centre prospective cohort study trial to investigate the difference.

2. Methods

2.1. Objective. The aim of this study is to determine the effectiveness of heat-sensitive moxibustion sensation and non-heat-sensitive moxibustion sensation in the treatment of patients with moderate to severe LDH in China.

2.2. Sample Size. The effective rate was used to determine sample size. There are few reports in the literature of clinical trials of control mode for LDH. Based on our earlier randomized controlled pretrial in the Affiliated Hospital of Jiangxi University of TCM, we believe that the effective rate for LDH is approximately 45% when adopting the non-heat-sensitive moxibustion sensation and should be increased to 75% when using the heat-sensitive moxibustion sensation. Based on 90% power at $P = 0.05$, 38 participants were included in each group to be calculated with the SPSS 13.0 programme. 20% loss was allowed to follow up a total of 46 participants were included in each group, with 92 participants in total.

Moreover,

$$n = \left\{ \frac{Z_{1-a}\sqrt{2pq} + Z_{1-\beta}\sqrt{p_1(1-p_1) + p_2(1-p_2)}}{p_1 - p_2} \right\}^2,$$
$$p = \frac{(p_1 + p_2)}{2} \quad q = 1 - p. \tag{1}$$

2.3. Design. The patients were referred by the doctors and acupuncturists from branch centers in Nanchang, Hefei, Nanjing, and Xian. Their patients were recruited at either outpatient service or inpatient department and had already made their own choice of moxibustion therapy. Thus, the acupuncture point's Deqi sensation towards manipulation of suspend moxibustion generated the groups to be compared. In trial group, patients felt the Deqi sensation when the acupuncture point was stimulated by moxibustion heat. In the control group, patients only felt local superficial heat sensation (non-Deqi sensation) when the acupuncture point was stimulated by moxibustion heat.

2.4. Participants

2.4.1. Recruitment. Patients were recruited in China for this nonrandomized prospective multicentre open comparative cohort study from November 27, 2009, to December 27, 2010. This trial protocol has been approved by local institutional review boards and ethics committees (code issued is 2008(11)) and follows the principles of the Declaration of Helsinki (Edinburgh Version 2000). Oral and written informed consent was obtained after verbal information about the study was provided by the physician.

2.4.2. Inclusion Criteria. Participants were included if they fulfilled the following conditions: (1) participants were diagnosed with LDH according to the guiding principles of clinical research on new drugs [17]; (2) participants were at the age of 18 to 65; participants suffered from moderate to severe LDH, according to the Modified-JOA criteria (>10 score). Standards of diagnosis were listed as follows: (1) pain occurred in lower back and radiated to the lower limb; (2) limitations of tender point; straight leg raising test and it's strengthen test are positive; (3) skin sensation, muscle strength, and tendon reflex had some changes; (4) changes in spinal posture; (5) X-lateral lumbar spine films showed scoliosis or lumbar lordosis; (6) CT suggestive of disc herniation. Participants were instructed to stop LDH symptomatic relief medication during the run-in and treatment periods and provided the usual care instruction for LDH.

2.4.3. Exclusion Criteria. Patients with any of the following conditions were excluded: (1) patients suffered from serious life-threatening disease, such as the heart disease and disease of brain blood vessels, liver, kidney, or hematopoietic system, and psychotic patients; (2) pregnant women or women in lactation; (3) patients suffered from a single nerve palsy or cauda

equina nerve palsy, patients suffered from muscle paralysis or rectum, and Patients presented bladder symptoms; (4) patients complicated with lumbar spinal canal stenosis and space-occupying lesions for other reasons; (5) patients complicated with lumbar spine tumors, infections, tuberculosis, and so forth; (6) patients complicated with moxibustion syncope and unwilling to be treated with moxibustion; (7) patients signed no informed consent.

2.4.4. Interventions and Comparison. Qualified specialists of acupuncture in TCM with at least five years of clinical experience performed the moxibustion in this study. All treatment regimens were standardized between four centers practitioners by means of video, hands-on training, and internet workshops. Both groups of patients were requested to receive no other treatments such as physical therapies, pain-killing medicines, or acupuncture treatment from other places.

In the two groups, 22 millimeter (diameter) × 120 millimeter (length) moxa sticks (made by Jiangxi Provincial TCM Hospital, China) were adopted. The patient usually lied in the comfortable supine position for treatment, with room temperature of 24°C ~ 30°C. Moxibustion was applied simultaneously on the following three acupuncture points: Da Changshu (BL25), Wei Zhong (BL40), and A-Shi Xue (tenderness). The suspended moxibustion was applied 3 centimetre, far from the surface of skin to search for the heat-sensitive moxibustion sensation.

2.4.5. The Heat-Sensitive Moxibustion Sensation Group. In this group, the three acupuncture points were brought mild warmth without burning by moxa sticks and manipulated until the patient reported the characteristic heat sensitization sensation that is commonly called Deqi. Patients felt comfortable in the moxibustion manipulation.

The following patients' sensation suggested the Deqi: penetrating heat sensation due to moxa heat, defined as the heat sensation conducted from the moxa local skin surface into deep tissue, or even into the joint cavity; expanding heat sensation due to moxa heat, defined as the heat sensation spreading the surrounding little by little around the moxa point; transmitting heat sensation due to moxa heat, defined as the heat sensation transferring along some pathway or direction, even to the ankle or hip conduction. In the course of manipulation, the therapist continued for 15 minutes in pertreatment session. Patients received the treatment two times/day in the 1st week (one time/day from the 2nd week) for a total of 18 sessions over 14 days.

2.4.6. The Non-Heat-Sensitive Moxibustion Sensation Group. Common practices were similar to the first group. Only one difference was that patients in this group felt local superficial heat sensation. No Deqi sensations were stimulated in this group.

2.4.7. Outcome Measure. The primary outcome in this trial was measured by Modified-JOA scale. The scale was proposed by Improvement Japanese Orthopaedic Association and was known as the modified edition of JOA Back Pain Evaluation Questionnaire [18]. This scoring system was previously validated [19]. The degree of LDH was divided into three levels: mild: <10, moderate: 10 to 20, and severe: >20. The outcome measured above was assessed before the treatment, 14 days of the last moxibustion session, and 6 months after the last moxibustion session.

2.4.8. Statistical Methods. The statistician was blinded from the allocation of groups. SPSS13.0 and SAS9.0 statistical software packages were used to analyze the data. Statistical analyses were based on the intention-to-treat (ITT) principle, including all patients with baseline values to receive treatment. All tests were exploratory and two-sided with a level of significance of 5%.

We used multilevel models in analysis of covariance (ANCOVA) or generalized estimating equations (GEE). In these models, physicians were considered random effect, and fixed effects were baseline value (continuous), duration of low back pain, patient's age and gender, body mass index (BMI), and Modified-JOA score (continuous). Results are presented as adjusted mean or proportioned with a standard error (SE) and/or 95% confidence interval (CI).

2.4.9. Adverse Events. We defined adverse events as unfavorable or unintended signs; however, symptoms or disease occurred after treatment was not necessarily related to the moxibustion intervention. Adverse events were analyzed descriptively by frequencies, percentages, and Chi-squared or Fisher's exact test (if feasible).

3. Results

3.1. Population and Baseline. Of 290 screened patients, 120 could not be included in the study, mainly because they did not meet all eligibility criteria (Figure 1). After searching for the Deqi, 112 patients experienced heat-sensitive moxibustion sensation; 58 patients had no Deqi sensation. Since a sample of 92 people was calculated in our trial, we selected 46 patients from each queue separately by random drawing.

After six months, data from 89 participants (44 in the trial group and 45 in the control group) were available. Reasons for missing follow-up data included refusal of further participation or being not contactable.

Patient preferences resulted in the following baseline differences: patients in the trial group showed more severe BMI scores, while the Modified-JOA score was higher in the control group. The females of the trial group were more than those of control group. For duration of low back pain, there were obviously differences among the two treatment groups (Table 1). These differences of baseline characteristics were similar to the patients who were still available to be assessed at the 7th month.

3.2. Outcome Parameters. After one week, the primary outcome parameter Modified-JOA score showed significant differences between groups: trial group 10.32±4.27 ((adjusted mean ± SE) 95% CI [9.23 ~ 11.40] versus control group

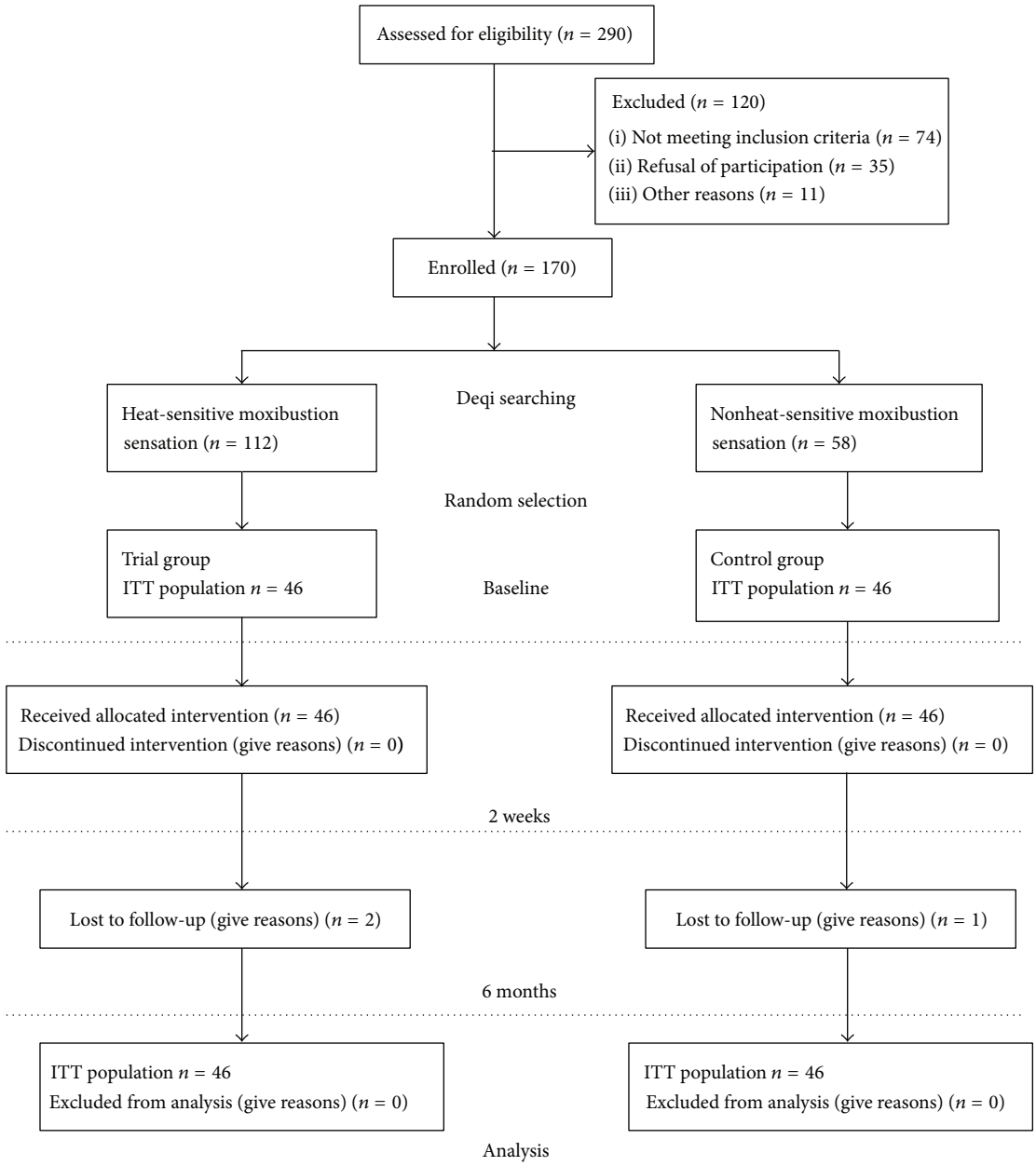

Figure 1: Flow diagram.

12.42 ± 5.02 [11.62 ~ 13.69], $P = 0.03$) (Table 2). Total Modified-JOA score was significantly lower in the trial group in the second week (7.62 ± 4.80 [6.46 ~ 8.77 versus 10.56 ± 4.75 [9.35 ~ 11.76], $P = 0.005$). Significant differences in total Modified-JOA score were observed between the groups, also evident during the follow-up period ($P = 0.007$).

3.3. Safety. No adverse events were reported for the 92 participants.

4. Discussions

The comparison of the trial group and control group in this study revealed differences that were statistically significant and clinically relevant in terms of efficacy in reducing Modified-JOA score. The relative change in the mean Modified-JOA score among the heat-sensitive moxibustion sensation group was 10.32 (SE 4.27), compared with 12.42 (SE 5.02) among the non-heat-sensitive moxibustion sensation group in the first week. In the second week, the trend of the differences was enlarged. In addition, significant differences in total Modified-JOA score were observed between the groups, which were also evident during the follow-up period.

To make the most of our knowledge, our study is the largest reported cohort study that compared effectiveness of heat-sensitive moxibustion sensation group with the non-heat-sensitive moxibustion sensation one in the treatment of patients with LDH. Both the evaluation of the results and

Table 1: Baseline characteristics of LDH patients.

Items	Trial group	Control group	*P* value
Age, mean (SD), years	45.65 (10.58)	44.51 (11.46)	0.62
Age > 60 year *n* (%)	12 (26.67%)	14 (31.11%)	0.64
Sex *n* (%)			0.0001
Male	11 (24.44%)	30 (66.67%)	
Female	34 (75.56%)	15 (33.33%)	
Duration of low back pain *n* (%)			0.0001
<1 months	5 (11.11%)	10 (22.22%)	
2–6 months	13 (28.89%)	12 (26.67%)	
7–12 months	6 (27.67%)	12 (26.67%)	
1–5 years	19 (42.22%)	5 (11.11%)	
>5 years	2 (4.44%)	6 (13.33%)	
BMI, mean (SD), kg/m′	25.23 (3.12)	23.24 (3.23)	0.003
Modified-JOA grade *n* (%)			0.21
Severe	30 (66.67%)	24 (53.33%)	
Moderate	15 (33.33%)	21 (46.67%)	
Modified-JOA score at baseline			
Total score mean (SD)	15.23 (4.41)	17.54 (4.57)	0.006

BMI: body mass index; Modified-JOA score: modified Japanese Orthopaedic Association score; SD: standard deviation; LDH: lumbar disc herniation.

Table 2: Comparison of modified-JOA scores.

Variable	Week 1		Week 2		Month 6	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Trial group	10.32	9.23~11.40	7.62	6.46~8.77	6.45	5.62~7.27
Control group	12.42	11.62~13.69	10.56	9.35~11.76	8.36	7.49~9.22
P value	0.03		0.005		0.007	

*Adjusted means or proportions and confidence intervals (CI) from multilevel models (ANCOVA or GEE) with fixed effects. All data are intended to treat. In both of the groups, $n = 46$. Modified-JOA score: modified Japanese Orthopaedic Association score; SD: standard deviation; LDH: lumbar disc herniation.

the statistical analyses were carried out in a blind fashion, in order to improve the objectivity and validity of the study outcomes.

We chose to take the Deqi sensation occurrence preferences into account, making randomization not possible. The groups were homogeneous, according to the baseline evaluation. In the trial group body mass index appeared to be higher compared with the trial group. Conditions according to the Modified-JOA score were less favorable. The gender ratios were different between the two groups. To take baseline differences into account, we adjusted our analyses for these factors. However, it is possible that other unknown and unmeasured factors might have influenced the results. Therefore, the nonrandomized design is a clear limitation of our study considering the internal validity of our results.

In this study, we investigated the relationship between the Deqi sensation and therapeutic effect according to moxibustion stimulation. For acupuncture needle, the needles are inserted into acupuncture points and stimulated until the Deqi is evoked. Multiple unique sensations were experienced by the patients around the applied part, such as suan (aching or soreness), ma (numbness or tingling), zhang (fullness/distention or pressure), and zhong (heaviness) [20]. From a physiological perspective, acupuncture is a modality of sensory stimulation, and the effects obtained are dependent on which sensory receptors are activated, the afferent activity setup, and the resulting activity in the central nervous system [21, 22]. However, the Deqi stimulated by moxibustion is different from the one simulated by acupuncture needle. When the Deqi appears during suspended moxibustion, the patient will have nonlocal or nonsuperficial heat sensation, such as penetrating heat, expanding heat, and transmitting heat. Our trial implemented moxibustion on acupuncture points of Da Changshu (BL25), Wei Zhong (BL40), and A-Shi Xue (tenderness). These acupuncture points were selected because they were commonly used in the treatment of LDH according to the theory of TCM [23–25] Therefore. However, few studies were reported to underlying the mechanisms of Deqi sensation in moxibustion.

The theory of TCM claims that the Deqi is essential to achieve the prospective therapeutic effects. And it was supported by our trial result. The effectiveness of the Deqi sensation might be more superior to the non-Deqi sensation in the treatment of LDH by moxibustion. In a word, it can be inferred that the existence of the Deqi (Qi arrival) phenomenon in the process of suspended moxibustion is closely

related to the curative effect, and arrival of heat-sensitive moxibustion sensation could improve the clinical curative effect of moxibustion.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

Rixin Chen and Mingren Chen obtained fund for the research project. Jun Xiong wrote the final paper. Tongsheng Su, Jianhua Sun, Meiqi Zhou, Zhenhai Chi, Dingyi Xie, and Bo Zhang contributed to the trial implemention. All authors read and approved the final paper.

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Research Article

Characterizing Acupuncture *De Qi* in Mild Cognitive Impairment: Relations with Small-World Efficiency of Functional Brain Networks

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As an intermediate state between normal aging and dementia, mild cognitive impairment (MCI) became a hot topic and early treatments can improve disease prognosis. Acupuncture is shown to have possible effect in improving its cognitive defect. However, the underlying neural mechanism of acupuncture and relations between *De Qi* and different needling depths are still elusive. The present study aimed to explore how acupuncture can exert effect on the reorganization of MCI and to what extent needling depths, associating with *De Qi* sensations, can influence the acupuncture effects for MCI treatment. Our results presented that MCI patients exhibited losses of small-world attributes indicated by longer characteristic path lengths and larger clustering coefficients, compared with healthy controls. In addition, acupuncture with deep needling can induce much stronger and a wide range of *De Qi* sensations both in intensity and prevalence. Acupuncture with deep needling showed modulatory effect to compensate the losses of small-world attributes existed in MCI patients while acupuncture with superficial needling did not. Furthermore, acupuncture with deep needling enhanced the nodal centrality primarily in the abnormal regions of MCI including the hippocampus, postcentral cortex as well as anterior cingulate cortex. This study provides evidence to understand neural mechanism underlying acupuncture and the key role of *De Qi* for MCI treatment.

1. Introduction

Alzheimer's disease (AD) accounts for 50–60% of all dementia [1], with incidence rates doubling every 5 years after the ages of 65. It is estimated that half of the population above 80 years old may have symptomatic AD and that this number will grow rapidly as life expectancy increases. As a prodromal stage of AD, mild cognitive impairment (MCI) refers to the clinical condition between the normal aging and AD.

MCI patients usually experience memory loss to a greater extent than one would expect for age, while they do not meet the criteria for AD [2]. However, it is reported that MCI has a high risk for AD progression and nearly 10–15% of them will convert to AD [3]. Early treatment is preferred to reduce burdens of patients' families, since the psychological and financial cost of AD is tremendous and rapidly rising. Patients often seek help through acupuncture hoping that such treatments might produce improvements in quality of life and delay cognitive decline [4, 5]. However, the underlying neural mechanism of acupuncture for MCI is still elusive. It is thus necessary and urgent to find out the modulatory effect of acupuncture on the treatment of MCI, which may provide opportunities for relatively early intervention of AD.

One research investigated the effect of acupuncture on cognitive performance of multi-infarct dementia (MID) rats by using neuroethology measurements [6]. They found

that acupuncture exerted a protective effect on cognitive impairment caused by cerebral multi-infarction in rats, and acupuncture has a specificity of cure. In addition, another randomized clinical trials have reported that electroacupuncture can exert favourable effects on activities of daily living, compared with drug therapy [7, 8].

Acupuncture improves cognitive function measured with MMSE compared with preintervention in eight patients with mild or moderate AD after 1 month of treatment [4]. However, most of previous studies have primarily focused on the relation between the acupuncture effects and the cognitive levels just by behavior measurements. One recent study clarifies the mechanisms of acupuncture in treating MCI and AD by using functional magnetic resonance imaging (fMRI). They found that, compared with the healthy control, acupuncture at Tai Chong (Liv3) and He Gu (LI4) can activate certain cognitive-related regions in both AD and MCI patients [9]. Considering that both AD and MCI are due to disconnections among several regions in a wide range of brain network, exploring the interregional connectivity within the whole brain networks, can further understand the modulated effect of acupuncture treatment for MCI.

According to the traditional Chinese medicine (TCM), acupuncture stimulation generally elicits *De Qi*, a composite of unique sensations interpreted as the flow of *qi* or "energy," which is essential for clinical efficacy. Exploring such key component from modern biomedical viewpoint is necessary for understanding the specific mechanism underlying acupuncture intervention for MCI. In the present study, we aimed to explore the relations between *De Qi* sensations induced by different needling depths of acupuncture and their differential modulated effects on the reorganizations of whole-brain networks using nonrepeated event-related fMRI techniques.

2. Methods

2.1. Subjects. Twelve aMCI patients were enrolled from the rehabilitation department of the Bao'an People's Hospital of Shenzhen (subjects' demographics shown in Table 1). MCI patients were diagnosed by a qualified neurologist using criteria for amnestic MCI [10], with mini-mental state examination (MMSE) scores >25 [11] and clinical dementia Rating (CDR) scale scores of 0.5 [12]. Twelve age-matched normal elderly were randomly selected from a community investigation of epidemiological research. All subjects were right handed according to the Edinburgh Handedness Inventory [13] and acupuncture naïve. Subjects were excluded if they had any significant medical, neurological, or psychiatric illness, or if they were taking medication or other substances known to influence cerebral function. After given a complete description of the study, all subjects signed the informed consent form. All protocols were approved by an ethic committee on human studies.

2.2. Experimental Paradigm. In this study, we adopted a novel experimental paradigm, namely, the NRER fMRI design to investigate the sustained effects induced by acupuncture administration [14]. For each group, the experiment consisted of two functional runs. At the beginning, a resting state (REST) scan was conducted for 6 minutes without any stimulation (Figure 1(a)). Then, the NRER experimental paradigm was conducted. Acupuncture was performed at acupoint KI3 on the right leg (Taixi, located on the medial border of the foot posterior to the medial malleolus, in the depression between the tip of the medial malleolus and Achilles tendon). This is one of the most frequently used acupoints and proved to have various efficacies in the treatments of dementia [15]. The needle was inserted vertically to a depth of 1-2 cm with deep needling (DA), but of 1-2 mm in superficial needling (SA). For both acupuncture DA and SA, we employed the NRER-fMRI design paradigm, incorporating 2 min needle manipulation, preceded by 1 min rest epoch and followed by 6 min rest (without acupuncture manipulation) scanning. All participants were not informed of the order in which these three runs would be performed and were asked to remain relaxed without engaging in any mental tasks. To facilitate blinding, they were also instructed to keep their eyes closed to prevent them from actually observing the procedures. According to participants' reports after the scanning, they affirmed keeping awake during the whole process. The presentation sequence of these three runs was randomized and balanced throughout the population, and every participant performed only one run in each day in order to eliminate potential long-lasting effect following acupuncture administration.

Acupuncture stimulation was delivered using a sterile disposable 38 gauge stainless steel acupuncture needle, 0.2 mm in diameter and 40 mm in length. Acupuncture administration was delivered by a balanced "tonifying and reducing [sic]" technique [16]. Stimulation consisted of rotating the needle clockwise and counterclockwise for 1 min at a rate of 60 times per min. The procedure was performed by the same experienced and licensed acupuncturist on all participants. As a concurrent psychophysical analysis, we used a verbal analog scale to ask participants to quantify the subjective sensations of acupuncture or deqi at the end of the acupuncture DA and SA runs. The sensations are all listed on the MGH acupuncture sensation scale (MASS), including aching, soreness, pressure, heaviness, fullness, warmth, coolness, numbness, tingling, throbbing, dull or sharp pain, and one blank row for subjects to add their own word(s) if the above descriptors did not embody the sensations they experienced

Table 1: Subject characteristics.

	Patients	Controls
N	12	12
Age (mean ± SD)	59.3 ± 3.3	60.6 ± 5.8
Sex (M/F)	1/11	4/8
Education (year)	2.3 ± 0.4	2.4 ± 0.5
MMSE score*	26.4 ± 0.9	29.8 ± 0.4
CDR	0.5	0

Education level was determined on a discrete scale with 3 levels: low = 1, middle = 2, and high = 3. Data are presented as mean ± SD. MMSE: mini-mental state examination. CDR: clinical dementia rating. *Statistically significant difference at the $P < 0.0001$ level.

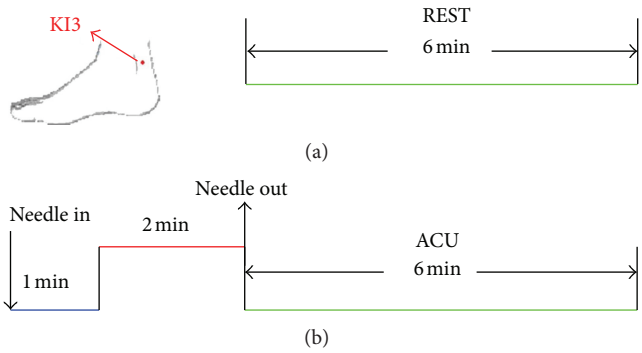


Figure 1: Experimental paradigm. (a) The paradigm for a resting state (REST) run lasting for 6 minutes. (b) The paradigm for acupuncture (ACU) for both DA and SA runs totally lasting for 9 minutes.

during stimulation [17, 18]. The intensity of each sensation was measured on a scale from 0 to 10 (0 = no sensation, 1–3 = mild, 4–6 = moderate, 7-8 = strong, 9 = severe, and 10 = unbearable sensation). Since sharp pain was regarded to result from an inadvertent noxious stimulation rather than acupuncture deqi [19], we excluded the subjects for further analysis if they experienced sharp pain (greater than the mean by more than two standard deviations). In this cohort, none of subjects experienced the sharp pain. No subject opted to add an additional descriptor in the blank row provided.

2.3. Data Acquisition and Preprocessing. Magnetic resonance imaging data were acquired using a Tesla Signa (GE) MR scanner. Head movements were prevented by a custom-built head holder. The images were parallel to the AC-PC line and covered the whole brain. Thirty axial slices were obtained using a $T2^*$-weighted single-shot, gradient-recalled echo planar imaging sequence (FOV = 220 mm × 220 mm, matrix = 64 × 64, thickness = 4 mm, TR = 2000 ms, TE = 30 ms, and flip angle = 77°). After the functional run, high-resolution structural information on each subject was also acquired using 3D MRI sequences with a voxel size of $1\,mm^3$ for anatomical localization (TR = 2.1 s, TE = 4.6 ms, matrix = 256 × 256, FOV = 230 mm × 230 mm, flip angle = 8°, and slice thickness = 1 mm).

For rest run, the data were preprocessed by removing the first 5 time points to eliminate nonequilibrium effects of magnetization. For acupuncture DA and SA, the postacupuncture resting state was adopted as the data sets for further analysis. All of data preprocessing procedures were conducted with the Statistical Parametric Mapping 5 (SPM5) (http://www.fil.ion.ucl.ac.uk/spm/). The images were corrected for the acquisition delay between slices, aligned to the first image of each session for motion correction, and spatially normalized to standard MNI template in SPM5 [20]. No subjects had head motions exceeding 1 mm movement or 1° rotation in any direction. The image data was further processed with spatial normalization based on the MNI space, resampled at 2 mm × 2 mm × 2 mm, and finally spatially smoothed with a 6 mm full-width-at-half maximum (FWHM) Gaussian kernel. The functional images were normalized to the Talairach stereotactic system. Finally, A band-pass filter ($0.01\,Hz < f < 0.08\,Hz$) was applied to remove physiological and high-frequency noise [21].

2.4. Anatomical Parcellation. After preprocessing, the fMRI data were segmented into 90 regions (45 for each hemisphere), using an anatomically labeled template [22] that has been widely used in previous neuroimaging studies via graph theoretical approaches [23–25]. For each subject, the representative time series of each region was estimated simply by averaging the fMRI time series over all voxels in the region.

2.5. Graph Construction. We calculated partial correlations between each pair of brain regions to reduce the indirect dependencies by other brain regions and to obtain a partial correlation matrix R [24]. Then, Fisher's transform was adopted to improve the normality of the partial correlation coefficients. Finally, a threshold (r) was related with the partial correlation coefficient (R_{ij}) to convert R to a binary graph. In this step, we set any R_{ij} whose absolute value was greater than r to 1 and others to 0. And a false discovery rate (FDR) procedure was performed at a q value of 0.05 to adjust for multiple comparisons [26]. When the same threshold was applied to the matrices of the three groups, the resulting graphs would be composed of different numbers of edges. Thus, the between-group differences in network parameters would not reflect the alterations of topological organizations precisely. To control this effect, the correlation matrix of each group was converted to a binary graph with the same number of edges [25, 27] or a fixed sparsity (S) defined as the number of edges in a graph divided by the maximum possible number of edges of the graph [28]. Because there is no gold standard to select a single threshold, we thresholded each correlation matrix repeatedly over a wide range of sparsity ($8\% \leqslant S \leqslant 36\%$) and calculated the parameters of the resulting graphs with different thresholds.

2.6. Small-World Analysis. Small-world measures of the functional connectivity of nervous systems involve clustering coefficients, C_p, and characteristic path length, L_p, [29]. C_p is the averaged clustering coefficient over all the nodes in the graph. The clustering coefficient of a node is the ratio of the number of existing connections among the neighbors of the node to the number of all possible connections. C_p measures the extent of local efficiency of information transfer of a network [29, 30]. L_p is the average of the shortest path lengths between any pair of nodes in the graph [29]. L_p was measured in this study by using a "harmonic mean" distance between nodal pairs in order to avoid nodal pairs with no connections in the original definition [31]. L_p measures the global efficiency of the brain network [32].

In order to determine whether the experimental networks have small-world attributes, a comparison must be made to random networks with the same number of nodes and average degree. Random networks with a Gaussian degree distribution will have clustering coefficients given by $C_p^{\text{rand}} = \langle k \rangle / N$ ($\langle k \rangle$ is the average degree of the network and N is

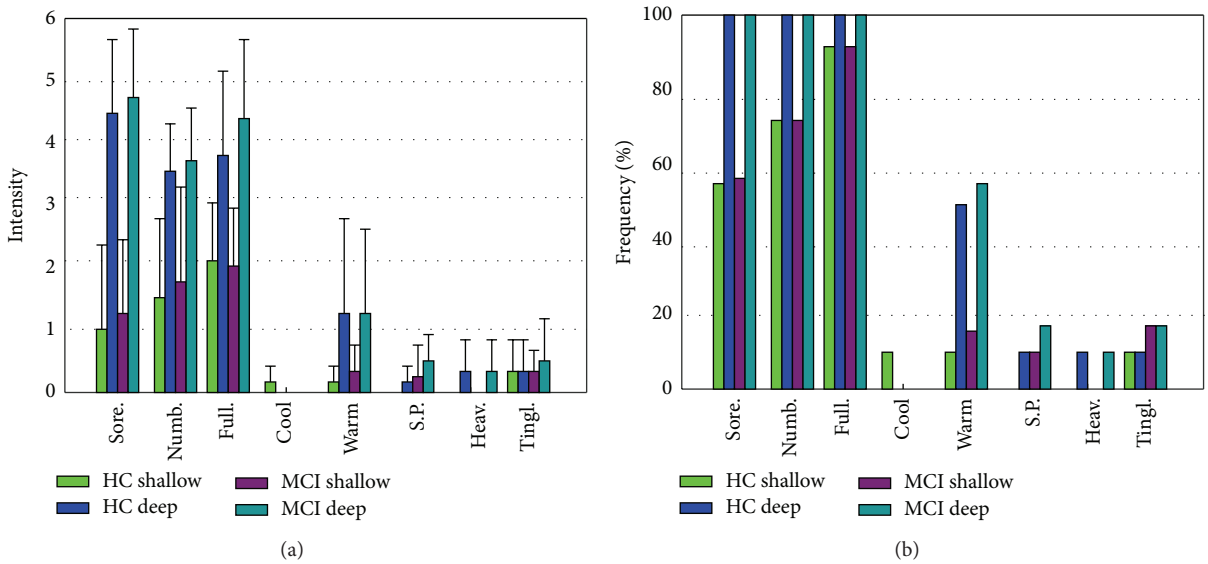


FIGURE 2: (a) The prevalence of deqi sensations. It was expressed as the percentage of the individuals in the group that reported the sensation (at least one subject experienced the seven sensations listed). (b) The intensity of sensations. It was expressed as the average score ± S.E. by measuring on a scale from 0 denoting no sensation to 10 denoting an unbearable sensation.

the total number of nodes) [30]. The path lengths of a random network are given by $L_p^{\text{rand}} = \ln N / \ln(\langle k \rangle)$ ($\langle k \rangle$ is the average degree of the network and N is the total number of nodes) [30]. A real network is considered to have the small-world topology if it meets the criteria: $\gamma = C_p^{\text{real}}/C_p^{\text{rand}} > 1$ and $\lambda = L_p^{\text{real}}/L_p^{\text{rand}} \approx 1$ [29].

2.7. Nodal Centrality. In this study, we considered the "betweenness centrality" of the nodes in the networks to investigate nodal characteristics. The betweenness B_i of a node i was defined as the number of shortest paths between any pair of nodes that run through node I [33]. We considered the normalized betweenness $b_i = B_i/\langle B \rangle$ ($\langle B \rangle$ was the average betweenness of the network) as in [28]. The brain regions with high values of b_i were considered to be the hubs of the brain networks.

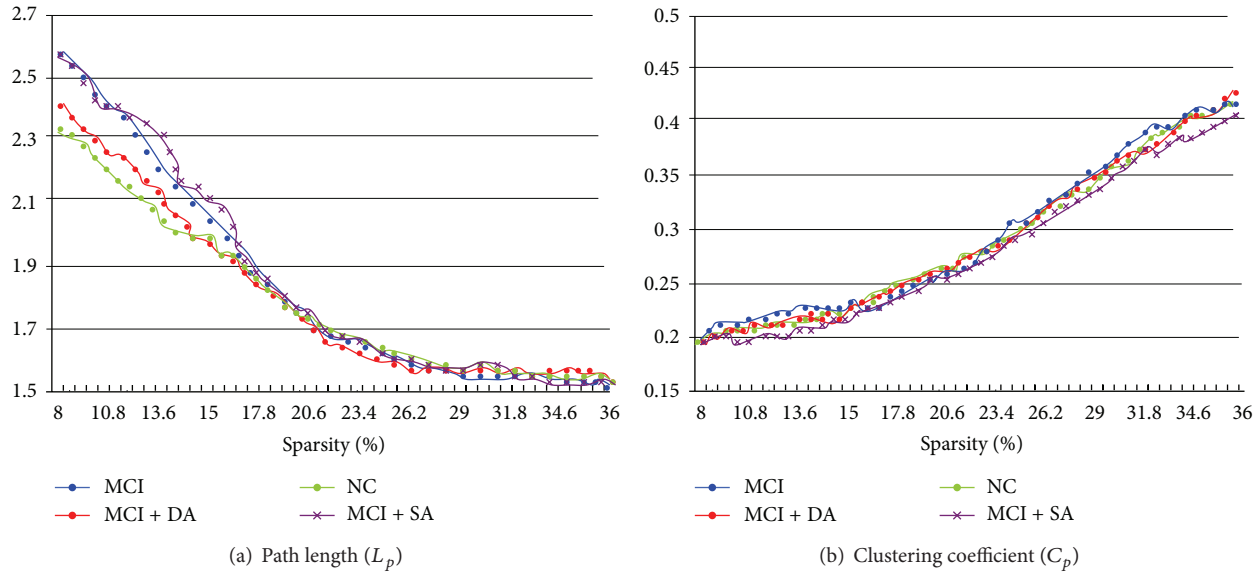
3. Results

3.1. Psychophysical De Qi Response. The prevalence of deqi sensations was expressed as the percentage of the individuals in the group that reported the sensations (Figure 2(a)). Differences did exist with respect to the type of sensations. In both the MCI and HC groups, the soreness, numbness, fullness, warmth, and heaviness were found to be more frequent for DA than that of SA. Whenever for the DA or SA condition, warmth and tingling were found to be more frequent in the MCI group than HC group.

The intensity of sensations was expressed as the average score ± S.E. (Figure 2(b)). Differences did also exist with respect to the type of sensations. In both MCI and HC groups, the sensations of soreness, numbness, fullness and warmth were found to be stronger for DA than for SA. For both conditions, a statistical analysis found no significantly difference between the MCI and HC groups in regard to the intensity of these sensations.

3.2. Small-World Attributes for MCI with Different Acupuncture Needling Depth and Healthy Controls. Our results demonstrated the small-world attributes of the resting state network in the MCI patients and healthy controls. We also found that the small-world attributes also emerged during the postacupuncture resting state for both DA and SA. The λ and γ of the networks presented the function of sparsity. As the sparsity increased, the λ increased while the γ for all the networks fell down. Different from the matched random networks, all of the networks for the MCI and healthy controls demonstrated small-world architectures as they all had almost identical characteristic path lengths ($\lambda \approx 1$) but were more locally clustered ($\gamma > 1$) over a wide range of sparsity ($8\% \leq S \leq 36\%$). At the low level of the sparsity, the γ of MCI networks was the largest in the three groups, while the λ of MCI networks was the smallest. Both measures of DA and SA for MCI patients' networks were intermediate between the MCI and healthy control groups. Notably, the small world attributes for DA in MCI patients were almost relatively similar to the healthy controls.

To further compare the nature of small-world attributes for MCI and healthy controls as well as DA and SA intervention effects on MCI patients, we evaluate clustering coefficients, C_p, and characteristic path lengths, L_p (Figure 3). We found that the L_p decreased while the C_p increased as a function of sparsity in all the groups. Both L_p and C_p in the MCI networks were the greatest. Additionally, these values of DA for MCI networks were intermediate between MCI and healthy controls. Our findings that the L_p increased



(a) Path length (L_p)

(b) Clustering coefficient (C_p)

Figure 3: Characteristic path lengths and clustering coefficients of the whole-brain networks in MCI, DA for MCI, SA for MCI as well as healthy control subjects.

in DA for MCI compared with MCI suggested that deep acupuncture enhanced the compensatory of the loss in small-world attributes for treatment effects.

3.3. Nodal Characteristics Changes for MCI versus Healthy Control and MCI with Different Needling Depths. The changes of the betweenness centrality between MCI and healthy control, SA for MCI and MCI, as well as DA for MCI and MCI were evaluated. Compared with healthy controls, MCI patients showed centrality decreases in the brain areas of the precuneus and posterior cingulate cortex (PreCN/PCC), fusiform gyrus (FG), hippocampus, superior parietal cortex, and angular gyrus, while the centrality increases were in the brain areas of the superior frontal gyrus, ventral medial PFC (vmPFC), and lateral prefrontal cortex (LPFC) (Table 2). Compared with MCI patients, acupuncture with deep needling for MCI patients showed the centrality increased mainly in the PreCN/PCC, hippocampus, postcentral cortex as well as the anterior cingulate cortex (ACC). Compared with MCI patients, acupuncture with superficial needling for MCI patients presented the increased centrality mainly in the premotor cortex and postcentral cortex.

Table 2: Brain areas showing significant difference in nodal centrality.

Regions	Normalized betweenness, b_i	
	MCI	Healthy controls
A. Nodal centrality changes for MCI versus healthy controls		
Decreased nodal centrality		
PreCN/PCC	0.9536	3.5475
Fusiform gyrus	0.2843	1.7431
Hippocampus	0.3302	1.8622
Superior parietal cortex	0.8539	2.9568
Angular gyrus	0.6735	1.7569
Increased nodal centrality		
Superior frontal gyrus	4.0174	0.1526
Ventral medial PFC	4.1528	0.1947
Lateral prefrontal cortex	3.9524	0.1751
B. Nodal centrality changes for MCI DA versus MCI		
Increased nodal centrality		
PreCN/PCC	2.1768	0.9536
Hippocampus	1.9244	0.3302
Postcentral cortex	2.1192	0.7852
Anterior cingulate cortex	3.1568	1.4679
C. Nodal centrality changes for MCI SA versus MCI		
Increased nodal centrality		
Premotor cortex	3.1894	1.1295
Postcentral cortex	2.7625	0.7852

Abbreviations: PreCN/PCC: precuneus and posterior cingulate cortex; PFC: prefrontal cortex.

4. Discussion

After search on the Pubmed, our study is the first report to illustrate that acupuncture with varying needling depths can induce distinct *De Qi* sensations accompanied by different modulatory effect on the reorganization of whole brain networks for MCI. The main findings of the present study were listed as follows: (i) acupuncture with deep needling can induce much stronger and a wide range of *De Qi* sensations both in intensity and prevalence, (ii) MCI patients exhibited losses of small-world attributes indicated by longer characteristic path lengths and larger clustering coefficients, compared with healthy controls, (iii) acupuncture with deep needling can exert modulatory effect to compensate

the losses of small-world attributes existed in MCI patients while acupuncture with superficial needling did not, (iv) acupuncture with deep needling can enhance the nodal centrality primarily in the PreCN/PCC, hippocampus, postcentral cortex, and anterior cingulated cortex. Most of these regions present decreased nodal centrality in MCI patients. By contrast, acupuncture with superficial needling just enhanced the nodal centrality in sensory-related cortex.

In clinical settings, acupuncturists focused on "*De-Qi*" feeling during the needling treatment. This sensation was generally experienced by the patients and also by manipulating feeling of the acupuncturist when it reaches the level of "*Qi*" in the body. *De Qi* has recently drawn the attentions of many scientific researchers, and some studies propose that no appreciable therapeutic effect is obtained under a certain stimulation level, which is determined by the appearance of a particular sensation known as *De Qi* [34, 35]. In the present study, we observed that acupuncture with deep needling can induce much stronger and a wide range of *De Qi* sensations both in intensity and prevalence of needling subjective sensations. Our finding is consistent with previous report that the intensity of *De Qi* plays a key role in the clinical efficacy underlying acupuncture. Furthermore, acupuncture with superficial needling depth cannot exert promising modulatory effects on stroke recovery and generally produced weaker subjective needling sensations. This preliminary evidence may provide solid clue to demonstrate that the beneficial effects of acupuncture relied on the accurate needling depths in order to induce sufficient individual feelings. Along the same lines, acupuncture-induced sensations were mainly generated from muscle and the activity of polymodal-type receptors in deep tissues may play an important role [36].

In comparison with MCI and healthy controls, we found that MCI has some losses in the attributes of small-word brain networks and the decreased node centrality primarily in the PreCN/PCC, FG, hippocampus, superior parietal cortex, and angular gyrus. The PreCN/PCC is the site of early metabolic abnormalities in MCI [37]. As the hub of the DMN, its altered resting-state activity seems to be a meaningful functional hallmark to distinguish aMCI from normal controls. In addition, we observed that there is coexistence of decreased node centrality in the PreCN/PCC and hippocampus. This result is consistent with previous studies that damaged connectivity between the medial temporal lobe and PreCN/PCC, as a result of MTL lesions, is thought to be responsible for PreCN/PCC abnormalities [38]. For comparison between before and after acupuncture intervention, results from acupuncture with deep needling for MCI patients showed the centrality increased mainly in the PreCN/PCC, hippocampus, postcentral cortex as well as the ACC. The results indicated that acupuncture has a promising beneficial effects on MCI recovery by enhancing the nodal centrality specially in the abnormal regions related to the disease in MCI patients, aiming to rehabilitate or participant in enhancing the function of the abnormal regions. Moreover, we also noted that acupuncture with needling depths can also enhance the nodal centrality of brain regions in the ACC which cannot show abnormal functional activity in the MCI patients. One explanation can provide a possible answer that such increased nodal centrality may be a compensatory mechanism underlying MCI recovery. This inference is consistent with previous studies that an increased recruitment of the frontal is observed to compensate in AD patients in memory task [39, 40].

The present study has some limitations. Firstly, we cannot choose the nonspecific acupoint as controls in the design paradigm. Selection of the study design for both clinical and study investigations is prerequisites to answering the research question of interest whether acupuncture really works compared with control group. In the present study, our aim focuses on the comparison of acupuncture effects on the MCI recovery by designing different needling depths, which primarily explore the different needling individual sensations by varying needling depths. Considering that it is still not known which aspects of the acupuncture treatment, such as the mode of stimulation or location of the acupuncture point, are specific to produce these physiological effects. Using multiple controls at once is an optimal choice to unveil the relative functional specificity of acupuncture as well as effectively control the intervention of subjective placebo effects. Secondly, we instructed all the participants to keep their eyes closed during the scanning run. However, one recent research from Van Dijk et al. has demonstrated that functional connectivity strength of brain network is influenced by tasks such that fixation and eyes open rest yielded stronger correlations in the networks examined against eyes closed rest or a continuous semantic classification task [41]. Therefore, instructing subjects simply to keep their eyes open is a practical condition in studies.

Conflict of Interests

There is no conflict of interests for any author.

Acknowledgments

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Research Article

Deqi Sensations of Transcutaneous Electrical Nerve Stimulation on Auricular Points

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Deqi sensation, a psychophysical response characterized by a spectrum of different needling sensations, is essential for Chinese acupuncture clinical efficacy. Previous research works have investigated the component of *Deqi* response upon acupuncture on acupoints on the trunk and limbs. However, the characteristics of *Deqi* sensations of transcutaneous electrical nerve stimulation (TENS) on auricular points are seldom reported. In this study, we investigated the individual components of *Deqi* during TENS on auricular concha area and the superior scapha using quantitative measurements in the healthy subjects and depression patients. The most striking characteristics of *Deqi* sensations upon TENS on auricular points were tingling, numbness, and fullness. The frequencies of pressure, warmness, heaviness, and soreness were relatively lower. The dull pain and coolness are rare. The characteristics of *Deqi* were similar for the TENS on concha and on the superior scapha.

1. Introduction

Deqi sensation, a psychophysical response, plays a key role in the clinical efficacy of acupuncture according to traditional Chinese medicine [1–4]. Recent neuroimaging fMRI studies also have demonstrated the neural correlates of *Deqi* sensation during acupuncture stimulation [5–8]. The exact components of *Deqi* sensation upon both manual acupuncture and electroacupuncture (EA) have been widely reported in clinical and experimental trials [3, 9–12]. In a survey with international acupuncture experts in 2006, MacPherson and Asghar reported that aching, dullness, heaviness, numbness, radiation, spreading, and tingling closely associate with acupuncture *Deqi* in patients [11]. In another study with 1095 patients, Park et al. found that subjects experienced distension, soreness, pulling, heaviness, tingling, and numbness during acupuncture procedures [12]. Our previous study on *Deqi* sensation of EA in healthy subjects also has revealed that the overall intensities and prevalence of individual sensations are fullness, numbness, soreness, tingling, heaviness, pressure, dull pain, warmness, and coolness in a decreasing order [10]. Overall, these researches of *Deqi* sensation focus on the acupuncture stimulation of the acupoints locating on trunk and limbs. Transcutaneous electrical nerve stimulation (TENS) has recently rapidly developed in the complementary and alternative medicine and it is popular as a kind of EA in acupuncture clinical practice [13, 14]. However, the characteristics of *Deqi* sensation of TENS on auricular points are seldom reported.

TENS on auricular points has been widely used to treat various disorders, for example, epileptic seizures and depression [15, 16]. However, the *Deqi* sensations of TENS on auricular points remain an ongoing area of research. In the present study, we attempted to characterize the *Deqi* sensations including frequency and intensity in individual sensation during TENS on auricular concha area and superior scapha (outer ear margin midpoint) in both healthy subjects and depression patients. This study was a part of the large project of transcutaneous vagus nerve stimulation (tVNS) at auricular concha area for treating major depression [15]. Based on the acupuncture sensation literatures and traditional Chinese medicine textbooks, the selected nine individual sensations

in this study were soreness, fullness, numbness, warmness, heaviness, coolness, tingling, pressure, and dull pain.

2. Materials and Methods

2.1. Subjects. In the present study, the *Deqi* data were collected as a part of the project of transcutaneous vagus nerve stimulation (tVNS) at auricular concha area for treating major depression. *Deqi* data were recorded during the brain fMRI imaging, which was to investigate the brain effect of tVNS on the depression patients at Guang An Men Hospital. It should be noted that fMRI data will be demonstrated in a separate paper. The hospital's ethics committee approved the research protocol. This study included 15 healthy subjects (18–30 years old, mean ± SD 24 ± 3, 8 M/7 F) and 16 depression patients (18–59 years old, mean ± SD 36 ± 13, 4 M/12 F). Subjects were screened to exclude drug abuse, history of head trauma with loss of consciousness, and contraindications for exposure to high magnetic field. All experimental procedures were explained to the subjects, and signed informed consent was obtained prior to participation in the study.

2.2. Stimulation Procedure. The participants were in their supine position in the MRI scanner. The auricular TENS was performed using a stand-alone electrical nerve stimulator, Huatuo (TENS-200, manufactured by Suzhou Medical Appliance Company, Jiangsu, China) connected with nonmagnetic fiber wires to two electrodes. The electrode was attached to the stimulation points with an adhesive tape. The points of TENS included the right auricular concha area (ACA) in both the healthy subjects and depression patients and the right superior scapha (outer ear margin midpoint) only in healthy subjects (Figure 1). The TENS stimulator was placed outside the scanner room. Before each TENS experiment, the stimulator was set at 20 Hz, and the individual threshold of stimulus intensity (mA) was determined, defined by the subjects as a maximum strong sensation that is just not painful and therefore could be well tolerated. Prior to the study, investigators instructed participants about possible *Deqi* sensations and required them to report *Deqi* sensations once they feel it.

2.3. Measurements of Deqi Sensations. Epochs of electric current delivery were continuous, lasting for 6 minutes. At the end of the procedure, the participant was questioned by another researcher in the team with a prepared questionnaire if each of the *Deqi* sensations (soreness, fullness, numbness, warmness, heaviness, coolness, tingling, pressure, and dull pain), sharp pain, or any other sensations occurred during the whole process and to rate its intensity on the scale of 0–10 (1–3 mild, 4–6 moderate, 7–9 strong, and 10 unbearable) [9, 10].

2.4. Statistical Analysis. Statistical analysis was performed with the SPSS software package 19 (Chicago, Illinois). Two sample paired t-tests were performed to compare the best tolerated electric current during TENS between ACA and the superior scapha in the healthy subjects. The paired chi-square tests were performed for comparing the frequencies of individual *Deqi* sensation between two experiments in the healthy subjects. On the other hand, Wilcoxon signed ranks tests were used for the comparison of the intensities in two tests for the healthy group. Independent samples t-tests were performed to compare the best tolerated electric current in the ACA between the healthy and patients' groups. The Fisher exact probability tests were used to compare the frequencies of individual *Deqi* sensations during TENS on ACA between the healthy and patients' groups. Mann-Whitney U tests were used to compare the intensities of individual *Deqi* sensation in these two groups.

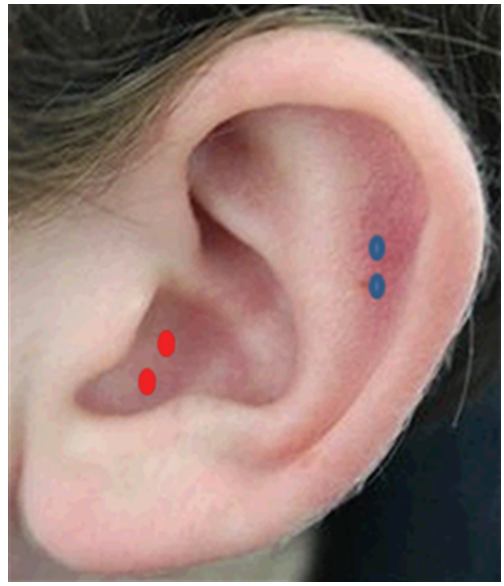

Figure 1: Locations of TENS on the auricular surface. Red spots mean auricular concha area (ACA) and blue spots mean the superior scapha.

3. Results

3.1. The Best Tolerated Electric Current during Auricular TENS. In the healthy subjects, no significant difference was found in the average amplitude of electric current between TENS on ACA (6.47 ± 0.54 mA) and the superior scapha (6.87 ± 0.41 mA) ($t = -0.685$, $P = 0.505$).

The average amplitude of electric current during TENS on ACA in the depression patients was 5.93 ± 0.36 mA. No significant difference was found between the depression patients and healthy subjects during TENS on ACA ($t = 0.824$, $P = 0.417$).

3.2. Prevalence of Deqi Individual Sensations during Auricular TENS in the Healthy Subjects and Depression Patients. The frequency of individual sensation during auricular TENS varies in both healthy subjects and depression patients. However, similar frequencies of tingling, numbness, fullness, pressure, warm, heaviness, soreness, dull pain, and coolness were demonstrated in the healthy subjects for ACA and the superior scapha ($P > 0.05$) (Table 1, Figure 2).

Sixteen depression patients during auricular TENS on ACA experienced tingling, numbness, fullness, soreness,

Table 1: Prevalence of individual *Deqi* sensations during TENS in healthy subjects and depression patients.

	Healthy subject ($n = 15$)		Depression patients ($n = 16$)
	Auricular concha area	Superior scapha	Auricular concha area
Soreness	2	3	4
Fullness	4	3	5
Numbness	9	11	6
Heaviness	2	1	1
Pressure	3	3	2
Tingling	14	14	16
Warmness	3	4	4
Coolness	0	0	0
Dull pain	0	1	0

The paired chi-square tests were performed for comparing the frequencies of individual *Deqi* sensations between the paired TENS points in the healthy subjects ($P > 0.05$). The Fisher exact probability tests were used to compare the frequencies of individual *Deqi* sensations during TENS on auricular concha area between the healthy subjects and depression patients ($P > 0.05$).

Table 2: Intensity of individual *Deqi* sensations during EA in healthy subjects and depression patients.

	Healthy subject ($n = 15$)		Depression patients ($n = 16$)
	Auricular concha area	Superior scapha	Auricular concha area
Soreness	0.67 ± 0.54	1 ± 0.47	0.88 ± 0.44
Fullness	0.67 ± 0.32	0.8 ± 0.47	1.19 ± 0.51
Numbness	2.27 ± 0.62	2.73 ± 0.65	1.56 ± 0.55
Heaviness	0.33 ± 0.23	0.2 ± 0.2	0.37 ± 0.37
Pressure	0.47 ± 0.28	0.47 ± 0.29	0.25 ± 0.17
Tingling	4.27 ± 0.64	4.27 ± 0.61	4.81 ± 0.31
Warmness	0.60 ± 0.34	0.60 ± 0.32	0.69 ± 0.36
Coolness	0	0	0
Dull pain	0	0.13 ± 0.13	0

Wilcoxon signed ranks tests were used to compare the intensities of individual *Deqi* sensation between the paired TENS points in the healthy subjects ($P > 0.05$). Mann-Whitney U tests were used to compare the intensities of individual *Deqi* sensation during TENS at auricular concha area between the healthy subjects and depression patients ($P > 0.05$).

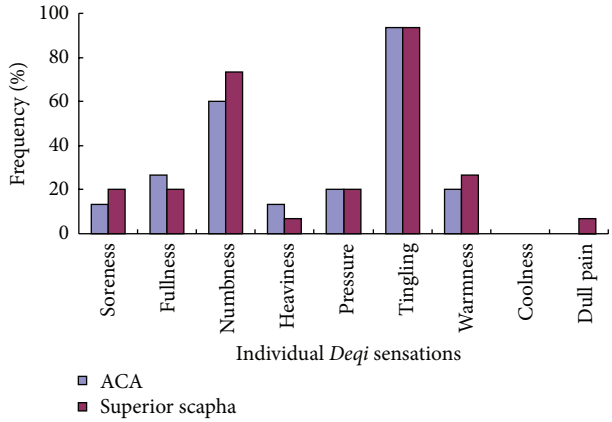

Figure 2: Comparison of the frequency of the individual *Deqi* sensations between TENS on ACA and the superior scapha in the healthy subjects. Tingling, numbness, and fullness were the most common sensations on both ACA and the superior scapha. No significant difference was found between the paired point in the healthy subjects ($P > 0.05$).

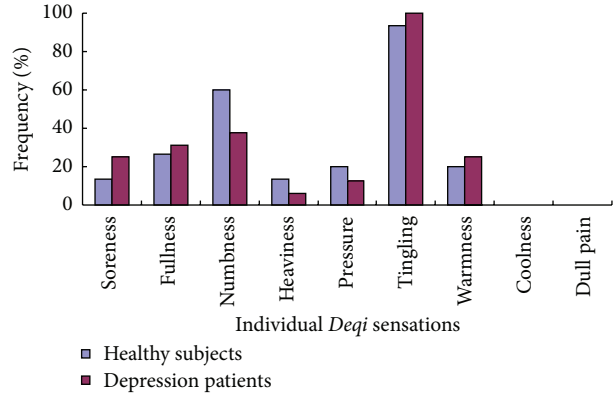

Figure 3: Comparison of the frequency of the individual *Deqi* sensations during TENS on ACA between healthy subjects and depression patients. Tingling, numbness, and fullness were the most common sensations in both healthy subjects and depression patients. No significant difference was found in the individual *Deqi* sensations during auricular TENS on ACA between healthy subjects and depression patients ($P > 0.05$).

warm, pressure, and heaviness. None experienced coolness and dull pain (Table 1).

No significant difference was found in the nine individual *Deqi* sensations during auricular TENS on ACA between healthy subjects and depression patients ($P > 0.05$) (Figure 3).

3.3. Intensity of Individual Deqi Sensations during Auricular TENS in the Healthy Subjects and Depression Patients. In the healthy subjects, no significant difference was found in the intensity of tingling, numbness, fullness, heaviness, pressure, soreness, dull pain, and warmness between auricular TENS on the two points ($P > 0.05$) (Table 2, Figure 4).

For auricular TENS on ACA, no significant difference was found in the intensity of pressure, numbness, tingling, heaviness, fullness, soreness, and warmness between the healthy subjects and depression patients ($P > 0.05$) (Table 2, Figure 5).

4. Discussion

Deqi sensation is a psychophysical response upon acupuncture characterized by a spectrum of different needling sensations which include aching, pressure, soreness, heaviness, fullness, warmth, coolness, numbness, tingling, and dull pain [2, 4, 9–11]. A number of researches have been studying

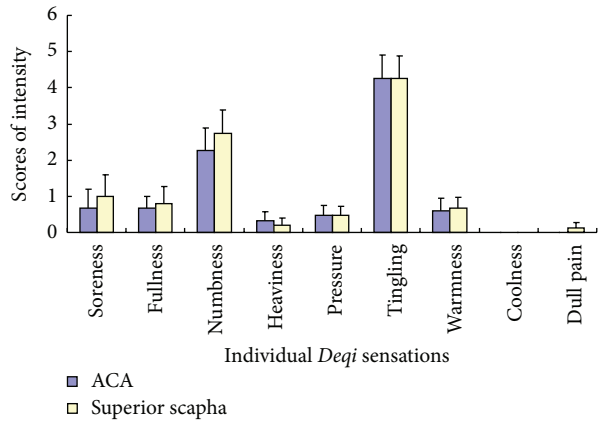

Figure 4: Comparison of the intensity of the individual *Deqi* sensations between TENS on ACA and the superior scapha in the healthy subjects. Tingling and numbness had the greater intensities on both ACA and the superior scapha. No significant difference was found between the paired point in the healthy subjects ($P > 0.05$).

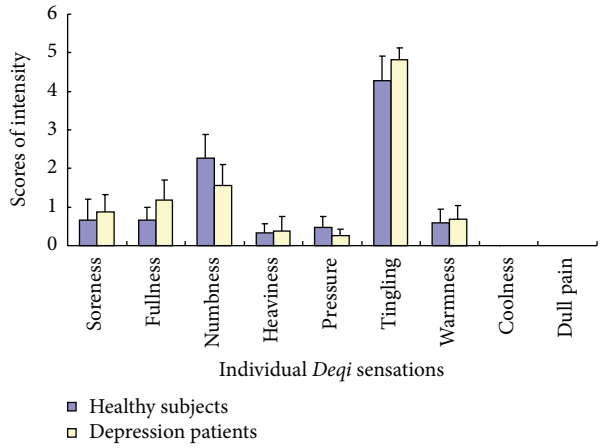

Figure 5: Comparison of the intensity of the individual *Deqi* sensations during TENS on ACA between healthy subjects and depression patients. Tingling and numbness had the greater intensities in both healthy subjects and depression patients. No significant difference was found in the individual *Deqi* sensations during auricular TENS on ACA between healthy subjects and depression patients ($P > 0.05$).

the characterizations of *Deqi* sensations of acupuncture on the acupoints locating at trunk and limbs by penetrating the skin with needles [2, 3, 9–12]. Some studies including ours have been investigating the *Deqi* components using the quantitative measurements [2, 9, 10]. Auricular TENS instead of penetrating has been widely used to treat various disorders like drug addiction, cigarette addiction, mood disorders, obesity, pain, and many other conditions in clinical practice by stimulating points on the ear [15, 16]. However, the characteristics of *Deqi* upon auricular TENS are unclear. In the present study, we investigated the frequency and intensity of *Deqi* individual sensations using the quantitative measurements.

The salient characteristics of *Deqi* upon auricular TENS were tingling, numbness, and fullness. Among these nine individual sensations, the three *Deqi* sensations had both most common prevalence and greater intensities in both healthy subjects and depression patients. The results were consistent with that of EA, which is a form of acupuncture where a small electric current is passed between pairs of acupuncture needles. Leung et al. [17] found that tingling was the predominant *Deqi* sensation deriving from EA. In our previous study using the same quantitative measurement, we found that numbness, fullness, and soreness were the most common sensations during EA on acupoints of ST36, ST28, GB34, CV4, CV12, PC6, and PC7 [10]. TENS is the stimulation with electrodes on the skin instead of insertion of acupuncture needles, and the types of afferent fibers activated by surface electrodes on acupoints correspond to those of EA [18]. EA and TENS are thought to dominantly activate myelinated fibers (Aβ and Aδ), which is responsible for the numbness and fullness [19, 20].

In a study of manual acupuncture, Hui et al. found that the most common individual sensations were soreness, tingling, and numbness [9]. Soreness is less common in the auricular TENS, though it is one of predominant *Deqi* sensations during penetrating the skin with needles. It is well accepted that soreness is correlated with stimulation of small myelinated Aδ and unmyelinated C fibers instead of Aβ fibers [19, 20].

In the present study, we analyzed the difference of individual *Deqi* sensation between auricular TENS on ACA and the superior scapha in the healthy subjects. No significant difference was found in the prevalence, intensity, and the amplitude of electric current of any individual *Deqi* sensation. It was consistent with the overlapped nerve innervations of the stimulation locations [21]. The ACA is innervated by the auricular branch of vagus nerve and the great auricular nerve. The superior scapha is innervated by the great auricular nerve. The great auricular nerve provides sensory innervations for the skin over both surfaces of the outer ear regions. The posterior branch communicates with the smaller occipital, the auricular branch of the vagus, and the posterior auricular branch of the facial. The overlapping nerve innervations may be responsible for the similar *Deqi* sensations.

This study was a part of the project of transcutaneous vagus nerve stimulation (tVNS) at ACA for treating major depression [15]. Auricular TENS on ACA has been used to treat depression in clinical practice. In the present study, we also compared the difference of the *Deqi* characteristics of TENS on ACA between the healthy subjects and depression patients. No significant difference was found in the prevalence, intensity, and the amplitude of electric current of any individual *Deqi* sensation. However, the results and the clinical significance need to be further investigated in large cohorts.

5. Limitation

The present results should be explained with caution. The sample size in this study is relatively small. The preliminary results of *Deqi* characterizations on auricular TENS need to be further confirmed by a larger sample size. Moreover,

the role of *Deqi* response during auricular TENS in the clinical outcome needs be further investigated.

6. Conclusions

The most striking characteristics of *Deqi* sensations upon auricular TENS are tingling, numbness, and fullness. The frequencies of pressure, warmness, heaviness, and soreness are relatively lower. The dull pain and coolness are rare. The characteristics of *Deqi* are similar for the auricular TENS on ACA and on the superior scapha.

Acknowledgments

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Research Article

A Longitudinal Study of the Reliability of Acupuncture Deqi Sensations in Knee Osteoarthritis

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Deqi is one of the core concepts in acupuncture theory and encompasses a range of sensations. In this study, we used the MGH Acupuncture Sensation Scale (MASS) to measure and assess the reliability of the sensations evoked by acupuncture needle stimulation in a longitudinal clinical trial on knee osteoarthritis (OA) patients. The Knee injury and Osteoarthritis Outcome Score (KOOS) was used as the clinical outcome. Thirty OA patients were randomized into one of three groups (high dose, low dose, and sham acupuncture) for 4 weeks. We found that, compared with sham acupuncture, real acupuncture (combining high and low doses) produced significant improvement in knee pain ($P = .025$) and function in sport ($P = .049$). Intraclass correlation analysis showed that patients reliably rated 11 of the 12 acupuncture sensations listed on the MASS and that heaviness was rated most consistently. Overall perceived sensation (MASS Index) ($P = .014$), ratings of soreness ($P = .002$), and aching ($P = .002$) differed significantly across acupuncture groups. Compared to sham acupuncture, real acupuncture reliably evoked stronger deqi sensations and led to better clinical outcomes when measured in a chronic pain population. Our findings highlight the MASS as a useful tool for measuring deqi in acupuncture research.

1. Introduction

Deqi (obtaining qi) is a core concept in traditional Chinese acupuncture theory [1, 2] that describes the physiological link between the stimulation of acupuncture needles and the energy meridians running through the body [2–5]. The term deqi encompasses numerous sensations (e.g., soreness, heaviness), the complete range of which is debated [6–8].

Traditional ancient acupuncturists believed that deqi was comprised of sensations and/or experiences of both the patient receiving the treatment and the acupuncturist administering the treatment [7–9]. Modern acupuncturists and researchers, however, have emphasized the patient's sensations rather than the acupuncturist's experience during needling [10–13]. One challenge in investigating these acupuncture sensations is that perception of deqi is subjective and the specific sensations associated with deqi may vary significantly both between and within individuals, which calls for the development of a systematic measurement of deqi sensation. To overcome this barrier, in recent years, investigators have started to use different scales to measure deqi sensation [2, 10–16] and have investigated the association between deqi sensation and therapeutic effects [13, 17, 18].

It is generally believed that deqi sensation is crucial for effective acupuncture treatment, a belief rooted in traditional Chinese acupunture theory [2]; however, the link between these sensations and improvements in clinical outcomes remains unclear [19, 20]. Previous studies investigating the relationship between deqi sensations and clinical outcomes are contradictory [21–24]. It is important to note that most

studies use deqi as a general construct [25] and that none of these studies explored the association between clinical outcomes and specific, quantified sensations [21–24]; rather, these studies investigated the difference between traditional Chinese acupuncture (with deqi) and sham acupuncture (with no or minimal deqi sensation). In a previous study in healthy subjects, we developed an acupuncture sensation scale [13] to measure the sensations evoked by electroacupuncture, manual acupuncture, and sham acupuncture. This scale has subsequently been revised, renamed, and used in other acupuncture research studies including the present study [2, 26]. In our previous study, we found that numbness and soreness were significantly associated with analgesia to experimental heat pain [13]. Nevertheless, few studies have systematically measured and characterized deqi sensations in a patient population longitudinally and explored the association between quantified deqi sensations and clinical outcomes.

In the present study, we longitudinally investigated acupuncture treatment-evoked deqi sensations in a chronic pain population using the Massachusetts General Hospital (MGH) Acupuncture Sensation Scale (MASS) and explored the association between deqi sensations and changes in clinical outcomes related to knee pain. More specifically, knee osteoarthritis (OA) patients were randomized into one of three treatment groups: high-dose acupuncture treatment (application of six acupuncture points), low-dose acupuncture treatment (application of 2 acupuncture points), and sham acupuncture (Streitberger placebo acupuncture needles on 6 nonacupoints). We employed a tapered longitudinal treatment design [21], such that each patient received 6 acupuncture treatments over the course of 4 weeks (2 treatments per week for the first 2 weeks and one treatment per week for the last 2 weeks). Deqi sensations were measured using the MASS twice during each treatment. And after the six-session acupuncture treatment period, the Knee injury and Osteoarthritis Outcome Score (KOOS) was also administered to investigate changes in knee pain and function following treatment with either real or sham acupuncture.

2. Materials and Methods

2.1. Subjects. The Institutional Review Board at the Massachusetts General Hospital approved all study procedures. All subjects provided written informed consent at the beginning of the study and were debriefed at the end of the study.

2.2. Patient Recruitment and Inclusion Criteria. Acupuncture naïve patients aged 40–70 with a diagnosis of chronic painful osteoarthritis (OA) in the right and/or left knee were recruited for this study, as previous studies have indicated that acupuncture is an effective treatment for patients with chronic knee pain [21–23]. Investigators excluded acupuncture-experienced subjects to minimize the possibility of subjects distinguishing sham from real acupuncture, serving to assist in blinding the subjects to their assigned treatment group. Patients were recruited from the Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH).

Subjects were included if they met the Kellgren-Lawrence scale for radiographically grading knee OA [27–29] as grade 2 or 3. Those with severe knee OA were excluded. Other specific inclusion and exclusion criteria were designed to allow for the retention of a relatively homogenous clinical population; subjects were excluded for any interventional procedure for knee pain within 6 months prior to enrolling in the study, intent to undergo surgery during the time of involvement in the study, knee pain due to other causes such as inflammation or malignancy, diagnosis of rheumatoid arthritis or other pain disorders that may refer pain to the leg, medications or disorders that would put patients at heightened potential for adverse outcome, and presence of MRI contraindications (e.g., cardiac pacemaker, metal implants, claustrophobia, and pregnancy). All OA patients had an endogenous knee pain intensity rating (average in the last week) of >2 on a 0 to 10 scale at the first visit.

2.3. Experimental Design. To maintain consistency within our sample of patients who had both unilateral and bilateral knee pains, we only treated one knee for each subject. For those subjects with bilateral knee pain, the knee with the highest pain ratings was treated. Subjects were stratified by knee and randomized into one of the three groups: high-dose real acupuncture (6 acupoints), low dose real acupuncture (2 acupoints), and high-dose sham acupuncture (6 nonacupoints with Streitberger placebo needles) (see Figure 1).

2.4. Blinding. At the time of consent, all patients were informed that they would receive one of three modes of acupuncture treatment and that there was an equal chance of receiving each mode of treatment. Using specially designed placebo needles (described below) and acupuncture-naïve subjects, we were able to keep all subjects blinded to acupuncture mode (real versus sham acupuncture). Subjects were not told how many needles would be used in the high- versus low-dose acupuncture groups. All clinical outcomes detailed below were measured by research staff, also blinded to treatment condition; thus, the study was single blinded (patients and research staff were blinded; acupuncturist was not blinded).

After an initial screening session, each subject engaged in a total of 6 acupuncture-treatment sessions, completing the MASS form twice within each session. Treatments 1, 3, and 6 occurred approximately 15 minutes into a scan session in which the patient was lying in a 3 Tesla Tim Trio magnetic resonance imaging scanner (Siemens, Erlangen, Germany) while functional imaging data was acquired. The remaining treatments were administered in a behavioral testing room with patients reclined in a chair. All acupuncture treatments were completed within four weeks.

2.5. Acupuncture Administration. High- and low-dose acupuncture groups differed only in the number of acupoints stimulated. In the high-dose group, 6 needles were inserted at 6 acupoints (see Figure 2(a)), and each point was stimulated 4 times. In the low-dose group, 2 needles were inserted, and each point was stimulated a total of 12 times. The total length

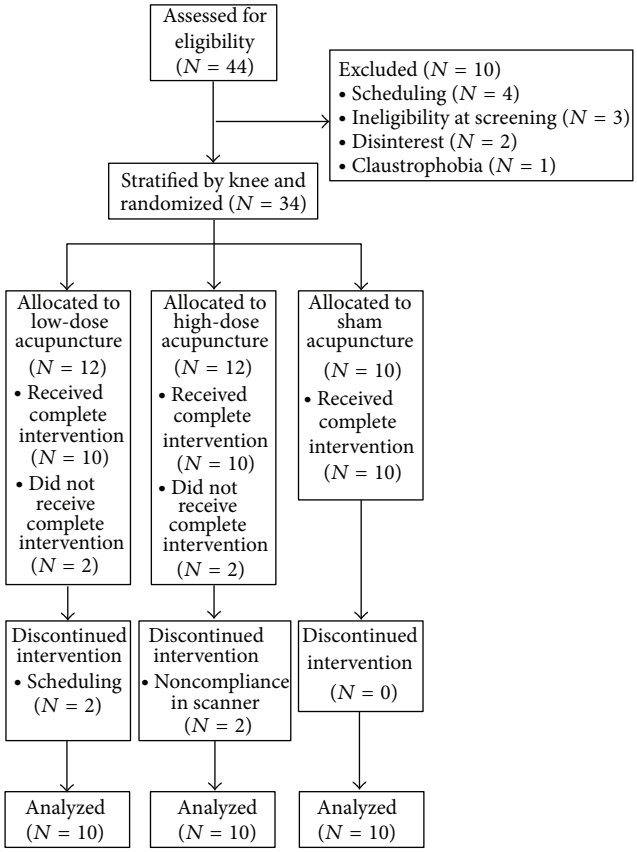

Figure 1: Consort diagram indicating the number of patients enrolled, dropped, and completed, by group.

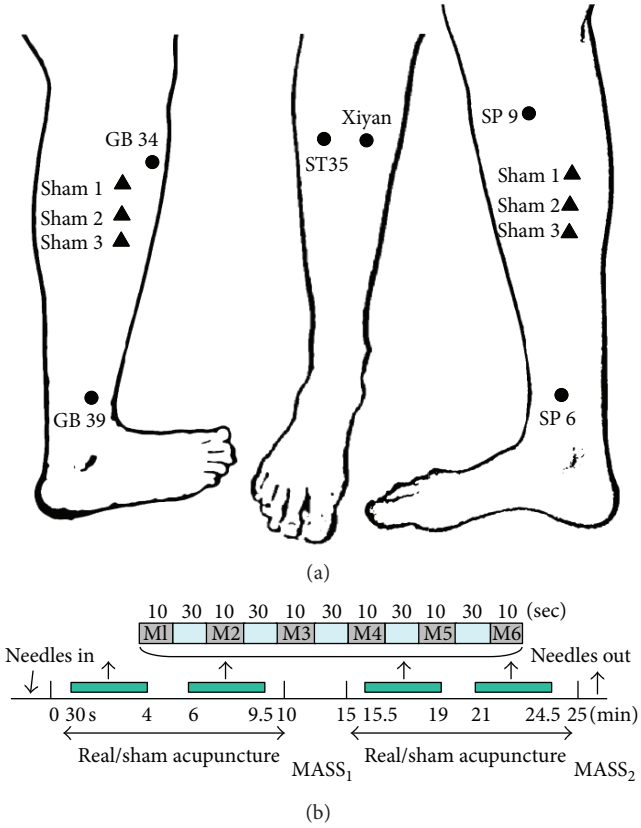

Figure 2: Standardized acupuncture protocol. (a) Real and sham acupuncture points. Low-dose real acupuncture was applied on ST35 and Xiyan (extra point). High-dose acupuncture group was applied to four additional points: GB34, SP9, GB39, and SP6. Six sham acupuncture points were used for the sham acupuncture group. (b) Acupuncture stimulation paradigm for both real and placebo acupunctures, indicating the timeline of intermittent needle stimulation during each acupuncture treatment. Six 10-second periods of manual needle rotation (M) were separated by 30 seconds of rest. The manual stimulation series (M1–6) was repeated a total of 4 times, twice prior to administering the first MASS, and an additional 2 times prior to the second MASS.

of the treatment remained constant across all treatment groups. All other treatment parameters, as described below, were held constant (Figure 2(b)).

Each acupuncture treatment session for subjects in both the real and the sham acupuncture groups was about 25 minutes in duration and was carried out by the same licensed acupuncturist. For all treatments, the acupuncturist located the acupoints on the leg, disinfected each point with isopropyl alcohol, and then placed a small plastic ring over the point, securing the ring with a thin strip of sterile plastic tape. This ensured patient blindness to the actual site of needle insertion and thus blindness to whether the treatment was real or sham. For all patients, a predetermined number of acupoints (either 2 or 6) were stimulated in a predetermined order for a total of 24 stimulations (Figure 2(b)).

2.5.1. Real Acupuncture Treatments. For the low-dose acupuncture group, real acupuncture was applied to ST35 and Xiyan (extra point) (see Figure 2(a)). These two acupuncture points are well documented for treating knee pain according to traditional Chinese acupuncture [9, 30]. Both points, located near the knee, have been used in previous clinical trials of OA patients [21–23].

The high-dose acupuncture group received treatment at four additional points including GB34, SP9, GB39, and SP6 (see Figure 2(a)).

For consistency, leg position, acupoint location, and needling parameters (1-2 cm depth, approximately 120 rotations per minute, 90° insertion angle, and moderate deqi sensations on a 0–10 scale) were kept constant across groups. Needles were rotated at each point for 10 seconds with 30-second breaks between each point (see Figure 2(b)). All points (either 2 or 6 acupoints) were stimulated one point at a time and were stimulated in a predetermined order. In the high-dose group, needles were manipulated in the order of GB34, SP9, ST35, Xiyan (extra point), GB39, and SP6. The specific starting acupoint was randomized across patients, but within patients, the starting point was held constant across sessions.

2.5.2. Placebo Acupuncture Procedures. Placebo acupuncture was applied at six nonacupoints using Streitberger placebo needles specially designed for subject blinding [13, 31–35] using a paradigm identical to the real acupuncture treatment. These sham needles are visually indistinguishable but differ from regular needles by virtue of their blunt, retractable tip. Instead of penetrating the skin, the point of the Streitberger needle retracts up into the shaft when the acupuncturist presses it against the skin. This sham device has been validated by studies showing that subjects cannot distinguish between real and sham needling [13, 31, 32].

Six sham points were used during placebo acupuncture: sham point 1 was located 1.5 cun posterior and inferior to GB34, sham points 2-3 were located 1.5 cun and 3 cun inferior to sham point 1, sham point 4 was located 1 cun posterior to the midpoint of K9 and K10, and sham points 5-6 were located 1.5 cun inferior and superior to the sham point 4 separately (see Figure 2(a)). All sham points were located on the lower leg where no meridians pass through. Placebo treatment administration was similar to high-dose acupuncture administration with regard to the number of acupoints.

2.6. Clinical Outcomes

2.6.1. Knee Injury and Osteoarthritis Outcome Score (KOOS). The Knee injury and Osteoarthritis Outcome Score (KOOS) [36] was used to measure clinical outcomes. The KOOS is comprised of 5 subscales, each of which produces an outcome score. These subscales include pain, other symptoms, function in daily living (ADL), function in sport and recreation, and knee-related quality of life (QOL). Based on previous studies, subscale scores of the KOOS related to pain, function in daily living, and function in sport and recreation were selected as the primary outcome of the present study [21]. Other subscores were used for exploratory analyses. Trained research assistants, blinded to treatment mode, administered the KOOS to all patients at baseline (within one week of the first treatment) and at the final (sixth) treatment. For each subscale, a normalized score was calculated, where 0 indicated the most extreme symptoms/pain and 100 indicated no symptoms/pain [36].

2.6.2. Massachusetts General Hospital Acupuncture Sensation Scale (MASS). The Massachusetts General Hospital (MGH) Acupuncture Sensation Scale (MASS) [2] is the revised version of the Subjective Acupuncture Sensation Scale that has been used in previous studies in healthy subjects [13]. This scale includes 12 descriptors (soreness, aching, deep pressure, heaviness, fullness/distension, tingling, numbness, sharp pain, dull pain, warmth, cold, and throbbing) that are considered to be associated with acupuncture treatment and one supplementary field for subjects to describe the acupuncture sensation in their own words [2]. Subjects were asked to rate the intensity of each sensation on a scale from 0 to 10, where 0 is none and 10 is unbearable. This scale was created through a collaboration of acupuncture researchers at the MGH Martinos Center and has been used by acupuncture researchers since 2007 [26, 37]. The MASS has subsequently been translated and validated in Chinese [38].

All subjects were asked to rate their acupuncture sensations using the MASS twice during each treatment. Subjects were asked to report the average sensation across all of the needles used for their treatment (either 2 or 6, depending on the group). Prior to the first treatment, the acupuncturist gave all subjects a brief description of deqi, as subjects were acupuncture naïve upon enrollment. Each subject was told the following: "The MGH Acupuncture Sensation Scale lists 12 of the sensations commonly reported by people who receive acupuncture. Different patients experience different sensations, and you might not experience all of the sensations. If you feel a sensation that is not listed here, you may write in the sensation you feel and indicate how intensely you felt that sensation." The MASS was used to measure average sensations *during* needle stimulation across each 10-minute treatment period. After the first block of intermittent acupuncture stimulation (see Figure 2(b)), subjects were asked to indicate the extent to which each of the 12 descriptors described their subjective acupuncture experiences. Subjects were asked to repeat this assessment again after the second 10-minute block of intermittent stimulation.

The MASS index is a measure that describes the overall magnitude of deqi sensation experienced during treatment. Using previously described methods [2], the index was calculated by ranking all of the sensations by self-reported intensity ratings (0–10) and then assigning a weight to each sensation based on rank.

2.7. Data Analysis. Statistical analyses were performed using SPSS 18.0 Software (SPSS Inc., Chicago, IL, USA). Variance in baseline characteristics, intensity ratings of each individual sensation, the overall sum of all sensations, and the MASS index across treatment modalities were analyzed using a one-way ANOVA and post hoc t-tests ($P < .05$) and were corrected for multiple comparisons. All confidence intervals (CIs) are reported at the 95% confidence level.

The MASS index, a weighted average of the intensity of sensations elicited, was calculated using previously published methods [2]. In brief, for each administration of the MASS (12 per subject), the deqi sensation descriptors (soreness, aching, etc.) were ordered from the highest to the lowest subjective intensity rating. As previously suggested, ratings of sharp pain were excluded from the MASS index calculation, as sharp pain is not always considered a deqi sensation. Using exponential smoothing, a weighted average (MASS index) was calculated.

The internal consistency reliability of the MASS scale was computed and results are presented as Cronbach's alpha. Measures of the test-retest reliability of each individual sensation, the overall sum of all sensations, and the MASS index were computed using intraclass correlation coefficients. To compare how frequently each sensation was rated ≥1 on a scale from 0 to 10 across the 3 groups, a chi-square test for independence was conducted for each sensation. For each chi-square test, we compared the number of people who reported that sensation at least once throughout the 6 treatments across the three groups.

Factor analysis was performed using the principal component extraction method to segment acupuncture

Table 1: Baseline characteristics.

Mean ± SD	All	High dose	Low dose	Sham
N	30	10	10	10
Gender	13 Females	2 Females	7 Females	4 Females
Age	57.5 ± 8.3	60.1 ± 8.9	58.30 ± 8.6	54.1 ± 7.3
Duration (treated knee, years)*	10.5 ± 8.3	9.8 ± 7.4	5.7 ± 6.0	16.22 ± 8.3
KOOS pain	55.94 ± 14.10	58.61 ± 12.99	53.09 ± 9.39	56.11 ± 19.15
KOOS symptoms	52.98 ± 16.17	57.14 ± 19.12	48.21 ± 10.68	53.57 ± 17.82
KOOS ADL	63.58 ± 15.34	66.03 ± 11.83	61.18 ± 13.83	63.53 ± 20.34
KOOS sport†	29.48 ± 22.92	30.00 ± 18.11	31.16 ± 19.06	28.50 ± 30.92
KOOS QOL	38.75 ± 15.25	41.88 ± 16.94	38.13 ± 13.96	36.25 ± 15.81

Significant main effect of group (high versus low versus sham) indicated by *; †indicates $N = 29$ due to one missing KOOS subscale score (low-dose group).

sensations (MASS) into meaningful clusters. Component extraction was based on eigenvalues greater than 1.0 with no specifications for a fixed number of factors to extract. A Varimax rotated solution with 25 maximum iterations for convergence was analyzed. Factors were loaded with a cut-off value of 0.4 (representing 16% variance). Pearson's correlations were applied to examine the potential relationship between osteoarthritis treatment outcomes (KOOS) and the perceived intensity of select sensations identified by the principal component analysis (PCA).

3. Results

Forty-four (19 females) acupuncture naïve patients aged 43–70 with a diagnosis of chronic painful osteoarthritis in the right and/or left knee enrolled in the study. Of the 44 patients who enrolled, 30 (13 females) completed all study procedures. Ten of the 14 patients who did not complete all study procedures dropped out prior to the first treatment due to ineligibility at screening (3), scheduling conflicts (4), claustrophobia (1), and lack of interest (2); the remaining 4 patients who underwent at least one acupuncture treatment session dropped out for the following reasons: scheduling conflicts (2, low-dose group) and inability to adhere to study requirements in scanner (2, high-dose group) (see Figure 1).

3.1. Clinical Outcomes. Of the 30 patients who completed all study procedures, 20 were treated on their right knee, and 10 were treated on their left knee. Baseline characteristics are detailed in Table 1. One subject in the low-dose acupuncture group did not complete the KOOS subscale for function in sport; thus, for all analyses including the KOOS function in sport variable only complete datasets ($N = 29$) were used.

Repeated measurements analysis of pre- and post-treatment knee pain across three groups revealed a significant effect of time (baseline versus endpoint) on the KOOS subscales for pain ($F(1, 28) = 9.661$, $P = .004$, and 95% CI [2.75, 13.34]), function in daily living (ADL) ($F(1, 28) = 8.310$, $P = .007$, and 95% CI [2.61, 13.92]), and function in sport ($F(1, 28) = 6.145$, $P = .0019$, and 95% CI [2.04, 21.41]). A trend was observed for the interaction between group and time on the KOOS pain subscale score ($F(2, 27) = 2.709$, $P = .085$) but not for either function in daily living ($F(2, 27) = 2.178$, $P = .133$) or function in sport ($F(2, 26) = 2.047$, $P = .149$) (see Figure 3(a)). Post hoc tests indicated no significant differences between the high- and low-dose real acupuncture groups for pain ($P = .612$), function in daily life ($P = 1.0$), and function in sport ($P = 1.0$).

To increase power in our analysis, we combined the two real acupuncture groups (high and low dose) to compare real acupuncture ($N = 20$) to sham acupuncture ($N = 10$). The results indicated a significant interaction between acupuncture mode (real versus sham) and time (baseline versus endpoint) on our primary outcomes: the KOOS subscale scores for pain ($F(1, 28) = 5.596$, $P = .025$) and function in sport ($F(1, 27) = 4.252$, $P = .049$). In addition, we found that our secondary outcome (KOOS subscale score for quality of life (QOL)) showed significant improvement in the real acupuncture group after treatment compared with the sham group ($F(1, 28) = 4.682$, $P = .039$) (see Figure 3(b)).

3.2. Acupuncture Deqi Sensations. In this study, subjects reported deqi sensations at 2 different time points in each treatment session: after the first 10-minute acupuncture stimulation period and again after the second 10-minute acupuncture stimulation period (see Figure 2(b)). In total, 30 subjects completed 6 treatment sessions, and all but one subject completed the MASS twice per treatment. For one subject, the second deqi assessment was missing from 3 treatment sessions. For the internal consistency reliability analysis of the MASS, only complete data sets were used. For all other analyses, the first and second administrations of the MASS in each treatment were averaged for each sensation.

3.2.1. Internal Consistency Reliability of the MGH Acupuncture Sensation Scale (MASS). The Cronbach's alpha reliability of the 12 items in the MASS was calculated for each administration of the MASS (twice per treatment session) and ranged from 0.856 to 0.948 (see Table 2 for complete list of Cronbach's alphas).

3.2.2. Test-Retest Reliability of Deqi Sensation across Different Treatment Modes. Intraclass correlation analysis showed that patients rated soreness, aching, deep pressure, heaviness, fullness/distension, tingling, numbness, sharp pain, dull pain, warmth, and throbbing reliably across all 6 sessions (ICC

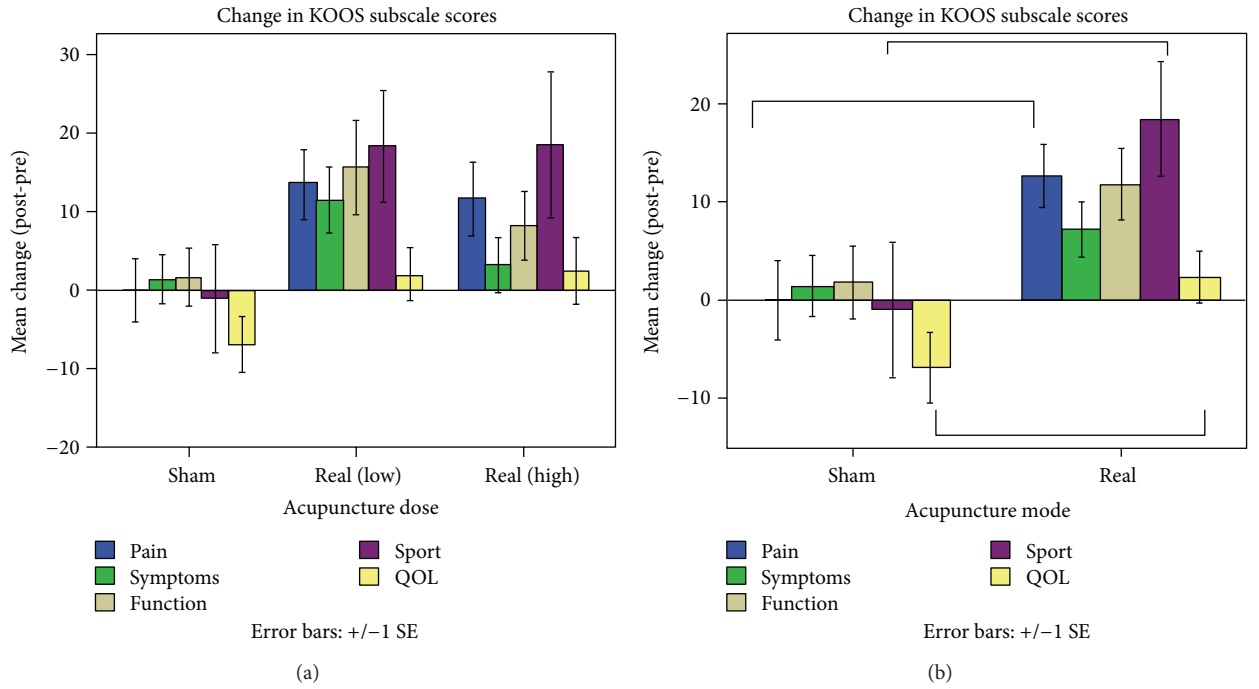

Figure 3: Changes in KOOS subscale scores from baseline to endpoint. Improvement in each of the 5 domains is indicated by a positive value. (a) The interaction between group (high versus low versus sham) and time (baseline versus endpoint) showed a trend for the KOOS pain subscale ($F(2, 27) = 2.709$, $P = .085$) but not for either function in daily living ($F(2, 27) = 2.178$, $P = .133$) or function in sport ($F(2, 26) = 2.047$, $P = .149$). (b) The interaction between group (real versus sham) and time (baseline versus endpoint) was significant for the KOOS subscale scores for pain ($F(1, 28) = 5.596$, $P = .025$), function in sport ($F(1, 27) = 4.252$, $P = .049$), and quality of life (QOL) ($F(1, 28) = 4.682$, $P = .039$).

Table 2: Internal consistency of the 12-item MGH acupuncture sensation scale (MASS).

	Administration 1	Administration 2
Treatment 1	.891	.909
Treatment 2	.948	.963†
Treatment 3	.913	.856
Treatment 4	.868	.880†
Treatment 5	.893	.907†
Treatment 6	.875	.878

All measures of the internal consistency of the MASS administered to 30 subjects are reported as Cronbach's alpha; $N = 29$ due to missing data set indicated by †.

ranged from .928 to .768). In short, 11 of the 12 sensations on the MASS were rated reliably with the exception of cold (ICC = .078, $P = .37$), and heaviness was rated most reliably across all sessions (ICC = .928, $P < .001$).

Further analysis of each treatment group indicated that, in the high-dose acupuncture group, heaviness (ICC = .88, $P < .001$) was rated the most reliably. In the low-dose acupuncture group, deep pressure (ICC = .943, $P < .001$) and fullness/distention (ICC = .943, $P < .001$) were rated the most reliably. In the sham acupuncture treatment group, numbness was rated most reliably (ICC = .932, $P < .001$). None of the treatment groups reliably rated the cold sensation. Both the sum score and the MASS index were highly reliable across all subjects and within each group (see Table 3 for complete list of all intraclass correlation coefficients).

3.2.3. Intensity of Sensations. Across all 30 patients, the sensations that were rated with the highest intensity in response to treatment included soreness, dull pain, and sharp pain. Those rated at the lowest intensity included cold and warmth. Descriptive statistics for each sensation are listed in Table 4.

After Bonferroni corrections for multiple comparisons ($P < .0038$), intensity ratings of soreness ($F(2, 27) = 7.74$, $P = .002$) and aching ($F(2, 27) = 7.55$, $P = .002$) differed significantly across treatment groups (high versus low versus sham). Post hoc comparisons of soreness and aching demonstrated that there was no significant difference between the high- and low-dose real acupuncture groups and that those subjects in the sham group reported significantly less soreness and aching as compared to the high-dose ($P = .01$ and $P = .05$, resp.) and low-dose ($P = .003$ and $P = .002$, resp.) acupuncture treatment groups. Reported intensity ratings for each individual sensation are depicted in Table 4.

To further elucidate the differences between real and sham acupuncture, data from the low- and high-dose acupuncture groups were pooled to increase power. After correction for multiple comparisons ($P < .0038$), sensations

Table 3: Test-retest reliability of deqi sensations.

	All	High Dose	Low Dose	Sham
Soreness	.889 (<.001)	.721 (.002)	.925 (<.001)	.688 (.004)
Aching	.913 (<.001)	.726 (.002)	.922 (<.001)	.777 (<.001)
Deep pressure	.903 (<.001)	.808 (<.001)	.943 (<.001)	.821 (<.001)
Heaviness	.928 (<.001)	.88 (<.001)	.926 (<.001)	.769 (<.001)
Fullness/distention	.921 (<.001)	.831 (<.001)	.943 (<.001)	.872 (<.001)
Tingling	.839 (<.001)	.848 (<.001)	.795 (<.001)	.81 (<.001)
Numbness	.861 (<.001)	.839 (<.001)	.837 (<.001)	.932 (<.001)
Sharp pain	.768 (<.001)	.486 (.069)	.812 (<.001)	.761 (.001)
Dull pain	.845 (<.001)	.583 (.026)	.874 (<.001)	.871 (<.001)
Warmth	.74 (<.001)	.664 (.007)	.661 (.008)	.894 (<.001)
Cold	.078 (.37)	.467 (.08)	−.052 (.493)	−.15 (.559)
Throbbing	.792 (<.001)	.774 (<.001)	.601 (.02)	.876 (<.001)
Other	.681 (<.001)	−.75 (.508)	.641 (.011)	.741 (.001)
Sum	.907 (<.001)	.792 (<.001)	.922 (<.001)	.901 (<.001)
Mass index	.907 (<.001)	.764 (.001)	.927 (<.001)	.902 (<.001)

All test-retest reliability analyses reported as intraclass correlation coefficients (P value).

Table 4: Comparison of intensity ratings and MASS Index across acupuncture treatment groups.

	All	High Dose	Low Dose	Sham
Soreness*	1.29 ± 1.21	1.69 ± .86	1.89 ± 1.47	.28 ± .34
Aching*	1.09 ± 1.14	1.25 ± .8	1.83 ± 1.4	.2 ± .3
Deep pressure	1.05 ± 1.13	1.1 ± .98	1.51 ± 1.53	.55 ± .57
Heaviness	.80 ± 1.12	.67 ± .94	1.54 ± 1.42	.2 ± .25
Fullness/distention	.71 ± 1.04	.68 ± .86	1.25 ± 1.42	.18 ± .38
Tingling	1.21 ± 1	1.61 ± 1.21	1.26 ± 1	.77 ± .64
Numbness	.70 ± .87	.82 ± .89	.96 ± 1.01	.33 ± .61
Sharp pain	1.43 ± 1.05	1.9 ± .84	1.63 ± 1.25	.76 ± .71
Dull pain	1.35 ± 1.1	1.55 ± .78	1.85 ± 1.38	.65 ± .73
Warmth	.48 ± .59	.4 ± .63	.66 ± .54	.38 ± .62
Cold	.06 ± .15	.06 ± .13	.11 ± .22	.02 ± .04
Throbbing*	.63 ± .81	1.13 ± 1.1	.63 ± .53	.15 ± .32
Other	.19 ± .34	.08 ± .19	.12 ± .19	.37 ± .49
Sum score*	10.99 ± 9.3	12.95 ± 7.55	15.22 ± 11.9	4.82 ± 3.79
MASS index*	1.62 ± 1.13	1.96 ± .84	2.10 ± 1.38	.80 ± .62

Values presented as mean ± standard deviation. Significant differences between acupuncture mode (real versus sham acupuncture) after correction for multiple comparisons indicated by ∗.

of soreness ($P < .001$), aching ($P < .001$), and throbbing ($P = .003$) were rated significantly more intensely in the real acupuncture group compared to the sham acupuncture group.

The average total MASS score (sum of the intensities of each sensation) differed significantly across the acupuncture treatment groups (high versus low versus sham) ($F(2, 27) = 4.21$, $P = .026$). Similarly, the MASS index, or overall perceived sensation of acupuncture, differed significantly across the acupuncture treatment groups ($F(2, 27) = 5.03$, $P = .014$). Those who received sham acupuncture had a significantly lower MASS index and total MASS score than those who received either high-dose ($P = .04$ and trend $P = .1$, resp.) or low-dose ($P = .02$ and $P = .03$, resp.) acupuncture treatments. No significant difference was observed between high- and low-dose acupuncture groups for the MASS Index ($P = .949$) or the total MASS score ($P = .617$).

3.2.4. Frequency of Sensations. A chi-square test for independence indicated that there was a significant effect of acupuncture dose (high versus low versus sham) on the number of individuals reporting soreness (χ^2 (2, $N = 30$) = 6.24, $P = .044$) and that there was a trend for aching (χ^2 (2, $N = 30$) = 5.96, $P = .051$) and fullness/distension (χ^2 (2, $N = 30$) = 5.83, $P = .054$). Further comparisons between acupuncture modes (real versus sham) indicated that there was a significant effect of acupuncture mode on frequency of

Table 5: By sensation, the number of individuals in each group who reported the sensation at least once across a total of 6 treatment sessions (assessed twice per treatment).

	All	High dose	Low dose	Sham
Soreness*	25	10	9	6
Aching*	21	9	9	5
Deep pressure	27	9	10	8
Heaviness	20	7	7	6
Fullness/distention*	18	8	7	3
Tingling	26	10	8	8
Numbness	20	7	7	6
Sharp pain	28	10	10	8
Dull pain	28	10	10	8
Warmth	17	5	8	4
Cold	8	3	3	2
Throbbing	18	7	7	4
Other	11	2	4	5

Sensations with significantly different frequencies across groups (real versus sham acupuncture) are denoted with a $*$.

reporting soreness, aching, and fullness/distension ($P < .05$). The total number of individuals reporting each sensation is listed in Table 5.

A one-way ANOVA comparing the total number of sensations reported by each subject across treatment groups (high versus low versus sham) revealed a trend in the effect of acupuncture dose ($F(2, 27) = 2.68$, $P = .087$). Further comparison of the real and sham acupuncture treatment groups using an independent sample t-test (equal variances not assumed according to Levene's test for equality of variance) showed that those who received real acupuncture reported significantly more sensations during treatment ($t(25.37) = -2.65$, $P = .014$) compared to the sham acupuncture group. Subjects who received real acupuncture reported an average of 5.79 ± 3.27 (mean $\pm$ SD) sensations during each treatment, while those who received sham reported experiencing 3.12 ± 2.19 sensations.

3.2.5. Principal Component Analysis. To further investigate the clustering of deqi sensations, principal components analysis (PCA) with Varimax rotation of components and Kaiser normalization was applied to the acupuncture sensations for all subjects. Two components with eigenvalues greater than 1.0 were identified, accounting in total for 77.4% of the variance. In this analysis, we used a factor loading cutoff of 0.4. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was .824, and Bartlett's test of sphericity was significant (χ^2 (66) = 385.65, $P < .001$) indicating that the data were suitable for factor analysis. While some variables loaded on a single factor, other variables loaded on both factors, providing evidence of the complex nature of some of the sensations (see Table 6). The variables loading onto a single factor can be characterized either by deep pressure sensations (heaviness, fullness/distension, dull pain, and cold) or sensations related to "spreading sensations" (tingling, throbbing).

Table 6: Results of principal component analysis.

Variable	Factor 1	Factor 2
Heaviness	.90	—
Fullness/distension	.87	—
Dull pain	.81	—
Cold	.81	—
Deep pressure	.75	.55
Soreness	.75	.40
Aching	.75	.55
Numbness	.60	.56
Sharp pain	.54	.71
Warmth	.42	.49
Throbbing	—	.95
Tingling	—	.85

Due to the similarity between high- and low-dose acupuncture with regard to intensity of sensations, we grouped the subjects receiving real acupuncture (both high and low dose) and added acupuncture mode (real or sham acupuncture) as a variable in our model to determine whether any of the sensations elicited were related to a single mode of acupuncture. The results of the PCA using acupuncture mode as an additional variable identified three components with eigenvalues greater than 1.0, accounting for a total of 82% of variance (see Table 7). The KMO measure of sampling adequacy was .824, and Bartlett's test of sphericity was significant (χ^2 (78) = 396.50, $P < .001$), again indicating that, after including acupuncture mode, the data were still suitable for factor analysis. Again, variables related to localized deep pressure sensations loaded onto the first factor, and variables related to spreading sensations loaded onto the second factor. Two complex variables (aching and soreness) loaded onto the third factor with acupuncture mode, providing further evidence that aching and soreness are associated with acupuncture mode (real versus sham).

3.2.6. Relation to Clinical Outcomes. To explore the relationship between acupuncture sensations and clinical outcomes, we performed Pearson's correlation analyses on the MASS index and KOOS subscales across all three groups. Results showed that there were no significant correlations between the overall perceived intensity of sensations (MASS index) and changes (baseline versus endpoint) in any of the subscales of the KOOS. For exploratory purposes, we also performed a PCA to model whether specific sensations were related to each subscale of the KOOS. For the pain and QOL subscales, two components were identified with eigenvalues greater than 1.0 with a factor loading cutoff of 0.4, and for symptom, ADL and sport, three components were identified. For each of the KOOS subscales, the KMO measure of sampling adequacy ranged from 0.802 to 0.819, and all Bartlett's tests of sphericity were significant ($P < .001$) indicating that the additional variables were suitable for factor analysis. Changes in both pain and QOL loaded onto a factor with tingling, throbbing, and sharp pain. For changes in function in daily living and in sport, the acupuncture sensations loaded onto

Table 7: Results of principal component analysis with acupuncture mode (real versus sham) included as an additional variable.

Variables	Factor 1	Factor 2	Factor 3
Heaviness	.90	—	—
Fullness/distension	.88	—	—
Deep pressure	.78	.54	—
Cold	.78	—	—
Dull pain	.77	—	—
Aching	.70	.485	.42
Soreness	.66	—	.56
Numbness	.64	.58	—
Warmth	.52	.60	—
Sharp pain	.50	.64	—
Throbbing	—	.91	—
Tingling	—	.80	—
Acupuncture mode (real versus sham)	—	—	.81

two different factors, and the KOOS subscale score loaded onto a third factor with a negative correlation with warmth. For changes in symptoms, the KOOS subscale score did not load onto a component with any of the sensations, indicating that it did not covary with any of the sensations (see Table 8 for the results of the PCA with each KOOS subscale included as an additional variable).

Post hoc tests were conducted to verify the associations indicated by the PCA between the MASS sensations and each subscale of the KOOS that loaded together. This exploratory analysis revealed a significant correlation between the intensity of the throbbing sensation and endpoint QOL subscale of the KOOS controlling for baseline QOL score ($r = .477$, $P = .009$) as well as the intensity of the tingling sensation and the QOL subscale score at endpoint controlling for baseline QOL ($r = .368$, $P = .049$). No other comparisons were significant when Pearson's correlations were tested.

3.3. Blinding. At the end of the study, all subjects were asked to complete a set of final questions to assess how well subject blinding was maintained throughout the study. Ninety percent ($N = 27$) of the subjects believed that the needle was inserted into the skin in every session. The 3 subjects who believed that the needle was not inserted were in the real acupuncture (low dose) group.

4. Discussion

In this longitudinal clinical trial, we investigated the descriptive nature of deqi in knee OA patients. We found that in real acupuncture treatment, soreness, deep pressure, dull pain, and sharp pain were the most frequently reported sensations. The intraclass correlation analysis indicated that most of the sensations on the MASS (with exception of cold) were reported reliably across different treatment sessions, implying that the deqi sensation can be reliably measured within subjects using scales such as MASS in a chronic pain population.

In this study, the average deqi sensation was of relatively weak intensity compared to previously reported acupuncture sensations [26, 39]. For the present study, the average intensity for each sensation was between .06 and 1.89, compared to our previous studies, where average intensity of each sensation was between 0 and 4 [26] and between 0.1 and 3.7 [39]. We believe that this may be due to the age of patients in the present study (58 ± 8.3) compared to studies conducted in healthy, young subjects (29 ± 7 [26] and 26.4 ± 4.9 [39]). We speculate that one difference between these populations is that the peripheral nervous system in these older patients may not be as sensitive as other younger populations. Additionally, we note that there are differences in the specific acupoints needled and the disorder treated in this study compared to previous studies, which may also influence the intensity of the sensations reported.

In this study, knee OA patients across all treatment groups tended to report soreness, deep pressure, tingling, dull pain, and sharp pain, among others, all of which are typical deqi sensations based on traditional Chinese medicine. Compared with real acupuncture, sham acupuncture using a placebo needle evoked very mild sensations, implying that superficial stimulation may be associated with different subjective sensations than deep tissue stimulation. This is consistent with previous studies that reported greater deqi sensations in real compared to placebo acupuncture [20]. In the present study, soreness and aching were reported as significantly more intense in the real acupuncture group compared to the sham acupuncture group.

Our results showed that sensations were equally reliable in the low-dose real acupuncture group as they were in the sham acupuncture group, but less reliably in the high-dose real acupuncture group. This may be due to the fact that subjects were asked to report their average sensations across all of the needles, and the number of needles differed between groups. For the low-dose acupuncture group, subjects reported the average intensity of each sensation across two needles; however, for the high-dose acupuncture group, subjects reported the average intensity of each sensation across all 6 needles, which is a complex task that could add additional variability to the data. For the sham acupuncture group, subjects reported fewer sensations in total, meaning that there was less room for variability in the repeated report of sensations.

Overall, the most reliably rated sensation was heaviness, and the least reliably rated sensation was coldness. We suspect that the reliability of the sensations may be related to the disorder studied (in this case, knee OA). Some experts believe that the exact deqi sensations elicited are specific to the physical conditions or the properties of the disorder [6]. It is not surprising that cold sensations were rated the least reliably because they were also rated the least frequently. Sensations such as coldness are generally included in acupuncture sensations scales because coldness and warmth are two of the earliest sensations described in the ancient literature and are symptom specific [2]. For some disorders that present with symptoms such as fever, acupuncture can produce cold sensations to counterbalance these symptoms. The knee OA patients in our study did not tend to report these symptoms

Table 8: Results of principal component analysis with the KOOS subscales included as additional variables.

	Pain		Symptom			ADL			Sport			QOL	
	1	2	1	2	3	1	2	3	1	2	3	1	2
KOOS	—	.65	—	—	.96	—	—	−.84	—	—	−.74	—	.76
Soreness	.81	—	.76	—	—	.78	—	—	.80	—	—	.83	—
Aching	.87	—	.76	.53	—	.76	.54	—	.76	.54	—	.86	—
Deep pressure	.88	—	.77	.53	—	.72	.57	—	.70	.55	—	.87	—
Heaviness	.95	—	.91	—	—	.84	—	—	.83	—	—	.93	—
Fullness distension	.93	—	.88	—	—	.81	—	—	.79	—	—	.91	—
Tingling	.47	.72	—	.85	—	—	.82	—	—	.81	—	.46	.73
Numbness	.76	—	.62	.55	—	.54	.57	—	.53	.56	—	.78	—
Sharp pain	.74	.50	.56	.70	—	.59	.68	—	.62	.67	—	.73	.51
Dull pain	.87	—	.82	—	—	.82	—	—	.82	—	—	.86	—
Warmth	.59	—	.45	.47	—	—	.55	.52	—	.54	.69	.56	—
Cold	.73	—	.81	—	—	.87	—	—	.88	—	—	.75	—
Throbbing	—	.84	—	.95	—	—	.94	—	—	.92	—	—	.86

during the acupuncture treatment. We speculate that this may be the reason for few patients reporting cold sensations.

The characterization of deqi sensations is useful for highlighting the differences between real and sham acupuncture experiences. Using a principal component analysis (PCA), we were able to segment the acupuncture sensations into meaningful categories. The results of this study indicate that deqi sensations on the MASS fall into one and/or two categories. One category of sensations we observed includes those sensations related to localized deep pressure. Sensations such as heaviness, fullness/distension, dull pain and cold are common traditional Chinese acupuncture sensations and have previously been reported in relation to deep tissue stimulation [40]. The other category of sensations identified by the PCA includes those sensations related to "spreading sensations" (such as tingling and throbbing). Both of these components are important factors in traditional Chinese acupuncture. The remaining sensations loaded onto both factors and can be viewed as a combination of the two factors. These results are in line with previous studies which have found that certain acupuncture sensations with similar characteristics tend to cluster together [9, 10].

Using the PCA, we were also able to conduct an additional analysis to identify which of the acupuncture sensations might be related to acupuncture mode (real versus sham acupuncture) and to clinical outcomes (KOOS). The present study suggests that patients in the real acupuncture groups report sensations such as soreness and aching significantly more intensely compared to patients in the sham acupuncture group. Exploratory component analyses indicated that tingling and throbbing may be associated with improvements in clinical outcomes.

Researchers continue to debate whether certain sensations or the perceived intensity of those sensations are related to clinical outcomes [17, 20–24]. In this study, we found that real acupuncture, which produced stronger deqi sensations, could also produce significant improvement in pain and function compared with sham acupuncture. This result is consistent with previous studies that indicate that stronger deqi sensation can produce better clinical outcomes [21, 22, 24]. In exploratory analyses, we found that tingling and throbbing were related to clinical outcomes. It is important to note, however, that these analyses are highly exploratory in nature due to small sample size and are not corrected for multiple comparisons. Specific investigation of the relationship between clinical outcomes and deqi sensations is needed to further confirm these findings.

In an earlier study by Takeda and colleagues, researchers investigated the effect of real and sham acupunctures on osteoarthritis (OA) and found that the experience of deqi can be used as a predictor for significant improvement [17]. In four subsequent OA studies comparing the effect of real acupuncture treatment to sham (minimal depth needling) acupuncture, three studies [21, 22, 41] found that real acupuncture produced significantly better therapeutic effects than sham acupuncture. The fourth study [23] showed no significant difference between real and sham acupuncture treatments and further concluded that "deqi sensation[s] do not result in marked effect," which calls into questioning "whether deep needling with stimulation and deqi sensation is superior to shallow needling."

One potential limitation of this study is the small sample size. We believe, however, that this data will provide the basis for a power analysis of larger clinical trials in the future.

5. Conclusion

In the present longitudinal treatment study, we found that patients with knee OA reliably reported sensations such as heaviness, fullness/distension, aching, and deep pressure that are in coherence with the traditional Chinese acupuncture theory. Compared with sham acupuncture, real acupuncture tends to produce stronger deqi sensation and better clinical outcomes. Soreness and aching were implicated as the two key sensations that differentiate real acupuncture with needle insertion from superficially stimulated acupuncture.

Elucidation and characterization of the deqi sensation among patients population may shed new light on our understanding of the mechanism of acupuncture treatment.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Review Article

Visualized Characterization for Cerebral Response of Acupuncture Deqi: Paradox Underway

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Acupuncture as an oriental natural healing therapy with prolonged history has been extensively utilized in the management of great numbers of disorders. Deqi, a renowned acupuncture needling sensation, is profoundly regarded as the predictor and also the prerequisite of a preferable acupuncture treatment efficacy. Till now, there is still no consistency being reached towards the mechanism of acupuncture Deqi as a result of the discrepancy for publicly acknowledged evidence. Recent visualized research on Deqi using modern technologies has demonstrated possible central mechanism towards it. However, there is a conspicuous paradox underway in the research of cerebral response to acupuncture Deqi. This paper provided a view of up-to-date studies using visualized tools to characterize the brain response to acupuncture Deqi, such as functional magnetic resonance imaging (fMRI) and positron emission tomography/computed tomography (PET/CT). The paradox was extruded to highlight certain reasons from a TCM view. It is hypothesized that acupoints located at different dermal sites, state of participant, and needling manipulation can all contribute to the current paradox. Hence, further studies on acupuncture Deqi should pay more attention to the strategy of experiment design with generalized measurement, valid sham control methods, and more to subjects in diseased condition.

1. Introduction

In clinical practice, acupuncture is widely accepted as an oriental natural healing therapy with prolonged history and thus has been extensively utilized in the management of great deals of disorders both physically and functionally. The clinical effect of acupuncture has been greatly validated [1–4] and its potential mechanism is at the same time partially elucidated from different levels in recent decades, for instance, acupuncture analgesia [5–9]. Deqi, a renowned acupuncture needling sensation, is profoundly regarded as the predictor and also the prerequisite of a preferable acupuncture treatment efficacy [10]. This concept and belief has been imprinted in mind and highly esteemed to canonical principle in ancient times by both acupuncturists and patients ever since the very origin of traditional acupuncture in China.

As a subject adoring experience, the importance of Deqi in acupuncture is inheriting generation by generation in China. For supporting this point, there are always no less than of plentiful evidences in old times far away and at present. As the very initial classic of acupuncture in TCM, *Neijing* or *Huangdi*'s classics of internal medicine leaves us with a clue to its *Ling shu* (*Spiritual Pivot*) part, that is, "the essence of acupuncture is *Qizhi* (Qi arrival, another term commonly used as an alternative to Deqi in ancient times [11, 12]), it's always closely accompanied with satisfactory clinical efficacy". Similar descriptions can be identified in the other part of *Neijing*, *Su Wen* (*Plain Questions*). In following ages, several symbolic works in acupuncture history also put emphasis for Deqi on the significance of acupuncture, like *Jin Zhen Fu* (*Ode to the Gold Needle*), and *Biao You Fu* (*Ode to clear Obscurity*) both embedded in *Zhen Jiu Da Cheng* (*Great Compendium of Acupuncture and Moxibustion*), *Medical Abecedarium* (*Yi Xue Ru Men*), *Zhong Guo Zhen Jiu Xue Shi (History of Chinese Acupuncture), Chinese Acupuncture Therapy* (*Zhong Guo Zhen Jiu Zhi Liao Xue*) written by Cheng Dan An, *Scientific Acupuncture Therapy* (*Ke Xue Zhen Jiu Zhi Liao Xue*) [11], *Zhong Guo Zhen Jiu Da Quan* (*Great compendium of Chinese acupuncture*) [13], and so forth. According to descriptions of the above books,

the typical descriptors of Deqi sensation of a patient are soreness, numbness, distention, heaviness, and dull pain [14]. From a historical aspect, acupuncture Deqi refers not only to the sensation a patient may feel during an acupuncture treatment procedure but also to the acupuncturist's personal simultaneous finger feeling [15, 16]. To our knowledge, the most interesting and remarkable characteristic of acupuncture Deqi from the acupuncturist's view is a vivid metaphor as "fish bite the hook" in one's finger. As in the recent literature, little has been mentioned about the role of an acupuncturist's perception of Deqi, and the preponderance of acupuncture works underline various sensations that yield from acupuncture Deqi in a patient of both healthy and unhealthy conditions. Researchers in nowadays commence to question the credibility and importance of an acupuncturist's awareness of Deqi as to the clinical efficacy. However, we believe that it is nevertheless still disputable to assert whether acupuncture Deqi is monophasic or bipolar sensation.

At present, modern neuroimaging technologies are regarded as valid tools and have been widely applied to investigate the central mechanism of acupuncture effect. Deqi plays a central role in acquisition of acupuncture efficacy and thus recent CNS mechanism researches on acupuncture paid enormous attentions to it. In order to quantify the characteristics of acupuncture Deqi sensations, Kong and colleagues amended and modified the Subjective Acupuncture Sensation Scale (the SASS) to MGH Acupuncture Sensation Scale (MASS) for a precisely quantification of Deqi, and they also found close correlation between acupuncture analgesia for experiment-induced thermal pain and SASS rating of numbness and soreness instead of other Deqi descriptors such as stabbing, throbbing, tingling, and heaviness, in a pilot study comparing manual, electrical, and sham acupuncture efficacy [11, 17]. Hui et al. demonstrated in their works that the prominent components for characterizing acupuncture Deqi are aching, soreness, and dull pain; thus, according to the innervation of differed somatosensory conductance, it resulted in the conjecture that wide spectrum of myelinated and unmyelinated nerve fibers may play a noticeable role in the physiological response to acupuncture Deqi, particularly the slower conducting ones in the tendinomuscular [18]. But till now there is still no consistency being reached towards it as a result of the discrepancy for a publicly acknowledged standardized measurement. Furthermore, the main controversy is concentrated on the characterization of acupuncture Deqi with visualized approaches [19–26] along with behavioral manners [11, 18, 27–30], while most of these studies were performed on healthy subjects.

Based on this, in this paper we aim to provide a view to sum up-to-date studies using visualized tools to characterize the brain response to acupuncture Deqi, such as fMRI and PET/CT. The main body of the content was separately reviewed according to the differed points of view associated with the brain area state during the elicitation of acupuncture Deqi. Moreover, we would like to exhibit our suggestions for perspective studies in acupuncture Deqi. It is therefore expected by us that paradoxes and issues underlying current Deqi studies as we summarized in this paper could enhance the basis of understanding towards acupuncture Deqi, which consequently may supply better view angle to perform more influential Deqi studies focusing on cerebral response. In all, we hope that these studies may potentially contribute as solid evidence to support a more widespread usage of acupuncture both nationally and internationally.

2. Searching Strategy and Material Identification

As this paper focused on the cerebral reaction of acupuncture Deqi, hence we searched PubMed for articles in English language by both key words in title/abstract, "Deqi" AND "functional magnetic resonance imaging" or "fMRI," "Deqi" AND "proton emission tomography-computed tomography" or "PET-CT," "Deqi" AND "single photon emission computed tomography" or "SPECT," "acupuncture sensation" AND "functional magnetic resonance imaging" or "fMRI," "acupuncture sensation" AND "proton emission tomography-computed tomography" or "PET-CT," and "acupuncture sensation" AND "single photon emission computed tomography" or "SPECT." Totally, there was 23 articles retrieved. Within them, 7 articles were excluded for overlapping and 2 were eliminated for not a neuroimaging study (one article about expert opinion on Deqi and the other one only about behavioral index of Deqi sensations). As last, there was 14 articles included in the processing of review.

3. Deactivation or Activation: Paradox Underway

fMRI and PET/CT are two common methods used in central mechanism study for acupuncture Deqi. On one hand, fMRI technology takes advantage of signal change of the blood-oxygenation level-dependent (BOLD) fMRI to reveal the hemodynamic response to measure the activity of brain tissues. That is to say, the signal intensity of BOLD fMRI reflexes the degree of blood O_2 consumption by neural activity. BOLD signal increase generally demonstrates the redistribution of blood to activated brain zones with greater O_2 demand which is regularly known as "blood stealing" or "physiological steal" [31]. On the opposite, negative BOLD signal often represents the neuronal deactivation or inhibition [32–34]. On the other hand, PET/CT and SPECT (single photon emission computed tomography) share similar paths to observe brain function. Through channels of rCBF, localized cerebral blood volume and metabolic rate of radionuclide in local brain region can be detected to indicate the condition of brain [35]. Mostly, FDG (fluorodeoxyglucose) is a frequent utilized tracer in PET study. Similarly, signal increase majorly indicates the high metabolism or blood flow in related brain and vice versa. Both fMRI and PET/CT are measures to evaluate the condition of brain functional activity. Indication of their signal change might share similarities with each other, and thus we to some extent regarded them as comparable.

In studies discovering the cerebral response by means of modern technologies, there is a stark paradox emerging

regarding the state of certain brain regions participating in the response evoked by acupuncture Deqi. Besides peripherally characterizing acupuncture Deqi, Hui and colleagues conducted series-related studies and demonstrated that acupuncture Deqi in three acupoints evoked preponderant deactivations of several brain regions pertaining to LPNN (limbic-paralimbic-neocortical network), amygdala, and hippocampus [19, 20, 22, 36, 37]. In conspicuous contrast to this, other researchers discovered marked increase or activation of brain signals or brain activity responding to acupuncture Deqi. Hsieh et al. performed a PET study on acupuncture analgesia and found out that activation of the hypothalamus might characterize acupuncture Deqi in a commonly used analgesic acupoint, LI4, which was likewise utilized in Hui's study [38]. This finding is in consistency with a study revealed that Deqi sensation mainly resulted in marked activation of relevant brain areas covering Brodmann areas 6, 8, 19, 21, 28, 33, 35, 37, and 47, and parahippocampal gyrus, lentiform nucleus, claustrum, and red nucleus by carrying out a single-photon emission computed tomography (SPECT) on healthy subjects receiving acupuncture stimulation at TE5 [39]. In this part, we would demonstrate the above paradox underway in terms of brain response to acupuncture Deqi from the aspect of either deactivation or activation.

3.1. Deactivation Characterized Cerebral Response to Acupuncture Deqi. Recent research put emphasis on patient's subjective perception of acupuncture Deqi. In central mechanism exploration on acupuncture effect by method of visualized imaging technologies, specific brain areas responding to an activation or deactivation manner to acupuncture stimulation at fixed acupoints are firmly believed to serve as evidence to the effect of acupuncture. Studies on acupuncture analgesia demonstrated that acupuncture affected nociceptive matrix both specifically and nonspecifically, which entwined with the effect of expectations on the patient for pain relief [40]. Wu et al.'s fMRI study that tryed to shed light on the CNS mechanism of acupuncture analgesia demonstrated that analgesic acupoints (ST36, LI4) stimulation that elicited Deqi sensation might evoke deactivation of rostral part of the anterior cingulate cortex (ACC), amygdala formation, and hippocampal complex, though these areas were not the overall interaction of the brain with Deqi [41, 42]. That seemed quite not sufficient for the explanation of acupuncture Deqi mechanism, for the potential involvement of the subcortical gray structures and cerebellum. The structural basis of the CNS in response to acupuncture Deqi is commonly accepted as the limbic-paralimbic-neocortical network to date [19, 22, 36, 43].

Deactivated brain regions above involving the limbic systems are in agreement with Hui's finding on Deqi for the same acupoints. With stimuli at LI4, a frequently used analgesic acupoint, the prominent fMRI signal decrease was shown in the limbic system and several subcortical gray structures, including nucleus accumbens, amygdala, hippocampus, parahippocampus, hypothalamus, ventral tegmental area, anterior cingulate gyrus (BA 24), caudate, putamen, temporal pole, and insula. In subject with pain in replacement of acupuncture Deqi as well as superficial tactile control stimulation, the main signal change is not deactivated [19]. Other pieces of their series studies also implicated that other brain structures took part in the cerebral response to acupuncture Deqi. In another study stimulating ST36, multifaceted neural activities of the cerebrocerebellar and limbic system were modulated through differed level of acupuncture Deqi. Pure Deqi subjects demonstrated concerted attenuation of signal intensity in the limbic and paralimbic structures of cortical and subcortical regions in the telencephalon, diencephalon, brainstem, and cerebellum. But, in contrast to this, for subjects suffering from sharp pain together with acupuncture Deqi, the signal interspersed in the entire cerebrocerebellar and limbic systems was mostly increased. A hypothesis was proposed that the unique Deqi sensation leading to a deactivation dominated cerebral response might work in conflict with sharp pain, and their interaction with each other is in a dynamic equilibrium. Attention and anticipatory anxiety modulated brain response was also observed as deactivation for ventromedial prefrontal cortex abreasted with Deqi. In superficial tactile control, activation of the somatosensory cortices was induced just the same as that in pure Deqi subjects [22]. Identical finding was also demonstrated in other researchers' work [25, 44]. Hence, cerebral activities evoked by Deqi stimuli could be regarded as a multiple dimensional factor-guided response. Certain factors contributing to the peculiar cerebral response might include the unadorned substantial Deqi effect, attention, and anticipatory anxiety effect as well as tactile stimulation. To some extent, the magnitude of the deactivation of LPNN and the cerebellum is relatively minor, generally 1% [22], compared to 2%–4% of that in visual evocation [45]. Because the deactivation of LPNN caused by attention is less extensive than that of Deqi, then the demand of attention might be incomplete to explain the comprehensive signal attenuation of the entire brain. Their further study demonstrated that acupuncture may modulate the anticorrelated functional cerebral network to mediate its actions, and that the effect is relying on the psychophysical response [20, 24]. In another study carried out by Fang et al., similar salient response pattern was identified for Deqi produced by other points (*Taichong* (LV3), *Xingjian* (LV2), and *Neiting* (ST44)) other than Hui's points. It was deeply speculated that the involvement of these brain regions forming the Deqi responsive neural circuit and sole to the processing of pain in affective and cognitive angle as well as in modulation and integration of emotion, memory, autonomic, endocrine, immunological, and sensorimotor may act as potent evidence to support the idea that acupuncture Deqi is beneficial to the condition of being anxious, noxious emotions accompanied with pain [43]. Hence, it seems like stimulating different acupoint to achieve Deqi may to some extent produce similar brain response. Possible explanations were postulated in Section 4.

Napadow et al.'s study further compared manual acupuncture with electroacupuncture of varied frequencies and clarified that the limbic system was central to acupuncture effect of various acupuncture modalities, instead of merely manual acupuncture-induced Deqi [46]. EA with 2 Hz or 100 Hz with acupuncture Deqi achieved

could, respectively, increase the fMRI signal of the limbic system as well as the manual acupuncture, though difference did exist in the brain areas such as both sides secondary somatosensory cortex, left inferior parietal lobule, and left dorsolateral prefrontal cortex. Relevantly, though without Deqi achieved, Han compared 2 Hz EA stimulation-induced brain area activation with that of 100 Hz for analgesic effect and demonstrated a frequency-dependent different, but overlapped, brain network. This may further supplement that different acupuncture modalities either with or without Deqi might yield different central response [47]. Duration of acupuncture Deqi may change the psychophysical feeling as well as the extensiveness and mode of central response. Li et al. showed that long duration (180 sec) manual acupuncture Deqi could enhance the deactivation mode and expand the extent of deactivated brain regions compared to short-term stimulation (30/60 sec) [48]. Thus, the central responsive domain and intensity of Deqi may be a time dependent and accumulative contributing factor to acupuncture therapeutic effects. An other study also demonstrated that acupuncture Deqi induced cerebral response with marked similarities of BOLD regardless of deep or superficial needling method [37]. It is therefore believed that these findings may further support the clinical practice for optimizing acupuncture modalities.

3.2. Activation Characterized Cerebral Response to Acupuncture Deqi. Brain areas involved in pain processing and perception are well aware typically such as SI (primary somatosensory cortex), SII (second somatosensory cortex), IC (insula cortex), thalamus, ACC, and PFC (prefrontal cortex) [49]. Amongst them, IC and SII are main interacting components of the sensory-discriminative dimension of pain, while ACC, thalamus, PFC, and posterior parietal cortices mainly compromise arousal and selective attention/orientating components of the attentional network for pain [50]. Regarding acupuncture Deqi, activation of several brain areas on the other hand in very few subjects was also presented in *Hui's* studies. For instance, subjects experiencing pain with nil Deqi sensation, or sharp pain with Deqi (mixed sensation) in acupuncture stimulation procedure exhibited activation dominated signal change of brain activity, and the brain areas involved were anterior cingulate gyrus (BA24), caudate, putamen, anterior thalamus, and posterior insula [19], which are frequently reported in correlation with pain perception. Thus, activation of these areas was interpreted as the mechanism of pain perception instead of Deqi. A trend similar to the above mentioned was noticed in the group of superficial tactile stimulation control. The overt activated brain region is the somatosensory cortex. From the aspect of cerebral network, acupuncture Deqi was demonstrated to regulate the default and somatosensory brain network to obtain an analgesic effect [51, 52] and also to modulate a larger spatiotemporal extent of spontaneous activities in the salient interoceptive-autonomic network, contributing to potential actions in the endogenous pain-modulation circuits and homeostatic control mechanisms [53]. Importantly, acupuncture Deqi's specific functional effect on CNS may leave over long-term influence through large-scale functional brain network [54].

There are also increasing numbers of studies disputing that acupuncture Deqi should induce evidently large activation of brain regions. Other studies manifested that classic acupuncture with Deqi could activate ACC, insula, cerebellum, superior frontal gyrus, medial and inferior frontal gyri, and amygdala which are in common with those activated by acute and chronic pain [55–57]. It indicates that the effect of acupuncture Deqi may regulate or even normalize the pain matrix of brain regions to a rectified status. Wu et al. shared the same view that acupuncture with Deqi achieved may activate structures as hypothalamus and nucleus accumbens of the descending antinociceptive pathway [41].

Despite these frequently administrated acupoints as ST36, LI4, and LV3 in Hui's studies, by achieving Deqi at other acupoints, a tendency of increasing activation over somatosensory-motor cortices, thalamus, anterior cingulate cortex, and insula areas was noticed with increasing EA parameters and Deqi response [42]. In a study on Deqi for Yuchi (LI11), the primary and secondary somatosensory area (SI, SII) and thalamus were observed to be activated by acupuncture Deqi signal, and postulation showed that the pathway of Deqi went via the stimulated-side thalamus into project to the stimulated-side S1. Several structures associated with emotion, sensation, memory perception, endocrine, and autonomic system activities were dragged in together to make Deqi considerably influential to emotional system, autonomic nerve system, and internal secretion system [58]. Besides, through activation of the sensorimotor cortices (BA 3, 4, 6, and 7) by Deqi, acupuncture also has been demonstrated to potentially amend the motor function of patients undergoing stroke by stimulating GB34 (traditionally used to recover motor function after several disabling diseases) in healthy patients [59]. Acupuncture has been demonstrated to be therapeutically beneficial to stroke patient not only for motor function recovery, but also for sensory rehabilitation. A study indicated acupuncture stimulation at LI4 accompanied with LI11 activated somatosensory cortex of stable somatosensory stroke patient. The somatosensory area was thought to be involved in mediating recovery from stroke via functional plasticity [60]. Zhang et al. attested in an fMRI study that stimulation of ST36/SP6 and GB34/BL57 in the same spinal segment yielded activation dominated response in some corresponding brain areas. Specifically, ST36/SP6 was able to activate orbital frontal cortex and deactivate hippocampus, while activating dorsal thalamus and inhibiting those of primary motor area and premotor cortex in GB34/BL57 [61]. Gareus et al. tried to determine whether or not a traditionally renowned vision-related acupoint could ignite the visual cortex; to their surprise, although the finding has shown inactivated BOLD response to visual cortex by Deqi in GB37, it did indicate the existence of clusters of activated voxels with significant activations in insula cortex, parietal operculum, parietotemporal cortex, inferior parietal lobule, superior colliculi, cuneus, middle occipital gyrus, and cingulate gyrus [62]. On the other hand, studies using other technologies of neuroimaging also connote similar activation in acupoints other than these commonly used in

Hui's work. For instance, Chen et al.'s study of PET imaging has shown increased glycometabolism in Brodmann areas 6, 8, 19, 21, 28, 33, 35, 37, and 47, the parahippocampal gyrus, lentiform nucleus, claustrum, and red nucleus while the TE5 was punctured and Deqi was achieved [39]. Similarly, Yoo and colleagues found that acupuncture manipulation on PC6 inducing Deqi, in comparison to the sham acupuncture and tactile stimulation conditions, selectively activated left superior frontal gyrus, anterior cingulate gyrus, and dorsomedial nucleus of thalamus [63]. This finding is consistent with that of another study using PET technologies [64]. Hence, the varied dermal sites for needle stimulation could in a certain way lead to the paradox of brain response to Deqi underway.

As to different states of participantion, it also may result in the activated cerebral response to Deqi as reported in some studies. Activation of hypothalamus was also reckoned to be crucial to acupuncture Deqi in addicted patients and chronic pain as Carpal tunnel syndrome with stronger psychophysical feeling harvested in comparison with healthy subject [65, 66].

4. Discussion

Therefore, based on the summarization of neuroimaging investigation to acupuncture Deqi, it could be concluded that the paradox of visualized presentation of acupuncture Deqi-induced brain response is underlied in both fMRI and PET/CT studies. The main divergence is the pattern of brain respsonse evoked by acupuncture Deqi. According to some studies, the preponderance of cerebral interaction with acupuncture Deqi is in a manner of deactivation in the LPNN brain system; on the contrary, other studies grasped the point that the prominent response of the brain to acupuncture Deqi is the activation in certain brain areas. The reasonable for this paradox is proposed as follows.

4.1. Explanation from Physiological Angle for Paradox in Deqi. Deqi as a key indicator of superior acupuncture efficacy is capable of evoking multifaceted cerebral response entwined with specific psychophysiological feeling. Several brain regions get involved in the acupuncture Deqi with certain responsive manner of activation or deactivation, such as the LPNN, cerebrocerebellar integration, and somatosensory cortex. Moreover, acupuncture stimulation with Deqi obtained may also participate in the normalization of the nociceptive brain network which is commonly regarded as the basis of pain perception regardless of acute or sharp pain. Previously, large majorities of studies have also demonstrated the mechanism of acupuncture analgesia from the viewpoint of peripheral nervous system [5–9, 67]. Four different kinds of endogenous opioids have been identified and attested to be mainly binding to the analgesic effect of acupuncture. Correlated to this finding, certain pathway from acupuncture analgesia effect has been formed. Mechanic signal of needling was sensed and transduced by sensorimotor sensor into psychophysical signal, which was then carried upwards by the excited Aβ/Aδ and C afferent fiber [68–70] to the posterior spinal horn to further project into the brain via the spinal ventrolateral funiculus. Many brain nuclei composing a complex CNS network are involved in the processing of acupuncture analgesia. The Arc-PAG-NRM-spinal dorsal horn pathway is crucial to mediate acupuncture analgesia through the participation of the opioid peptides and their receptors (μ-, δ-, and λ-receptors) [68]. However, specific Deqi sensations have been dominantly characterized by studies as aching, soreness, and dull pain, which is prominently in close relationship with slow conducting Aδ and C fibers. Thus deeper muscle layers with rich innervation of slow conducting fibers play an essential role in acupuncture Deqi though with all level nerve fibers participating [18].

4.2. Explanation from TCM Acupuncture Angle for Paradox in Deqi. In this paper, we demonstrated a considerable paradox existing underway in the neuroimaging research that tries to characterize acupuncture Deqi with visualized tools. The chief issue is encompassing the mode of response of brain regions in relevance to acupuncture Deqi. Some studies reported deactivation as the dominance and distinctive characteristic of Dei elicited cerebral response, while other debated activation to be that of Deqi. Inferring from the view of TCM, reasons are speculated and illustrated by us in this paper as followes.

(1) Acupoints located at different dermal sites possess varied abilities in function. From the aspect of TCM, meridians are internal and external linkage for viscera; different meridians are one-to-one corresponding to the internal organs. Acupoint on their circulating pathways can be utilized to modify abnormality of human body. Subsequently, their discrete function might cause different responsive brain regions, or similar reactive brain area with different modes. Furthermore, different acupuncture points are always believed to function subtly differently based on TCM theory. However, in real world practice, the peculiar treatment efficacy of certain meridian cannot be activated without relevant acupuncture point stimulation achieving Deqi. For instance, GB37 is traditionally applied to treat eye disease for the belief of its correlation with vision; neuroimaging studies also demonstrated specific activation of the visual area in brain by stimulating at it [71, 72]. Similar specificity has also been demonstrated in other points [73–75]. Thus, in previous studies on Deqi, one responsible factor for the paradox that could be posited is that different acupoints with their own unique efficacy could cause efficacy-related brain response which are certainly different in terms of pattern, mode, and intensity and as a result might contribute to the diversity of brain response to acupuncture Deqi. Therefore, it is understandable that acupoint with different body location and nerve innervation could induce varied cerebral response mode.

(2) State of participant is an influential factor to different brain response modes. As we mentioned in the above context, the bulk of the neuroimaging research on acupuncture Deqi was carried out on healthy subjects (HS). However, subjects in diseased condition may exhibit distinctive brain mapping in comparison with HS. For example, Zeng and colleagues demonstrated that in patients with functional dyspepsia, there is significant difference from that of HS. Certain brain

areas that are key to determine the severity of symptom are the ACC, insula, thalamus, MCC, and cerebellum [76]. TCM doctors always emphasize the role of patient's condition in choosing optimal treatment methods. Basically, according to the description of *Neijing*, in the process of inducing acupuncture Deqi, the states of acupuncture receiver, in terms of excess or deficiency or both, are always vital to achieve a robust Deqi phenomenon. It is that people in an excessive state are mostly easier to get Deqi, while people in a deficient condition may hardly experience a Deqi effect. The differed cerebral response shall result from this probably. Based on their condition in difference, suitable modality of TCM as individualized treatment approach [77] will be prescribed for patient. On the other level, acupuncture classics also clarified that different health conditions may experience Deqi sensations varied from each other [11], and this may subsequently lead to the possible difference of cerebral response to Deqi. Therefore, it can be indicated that the incompatible responding manner of certain brain areas was potentially resulting from the varied health condition of patient.

(3) Needling manipulation may change the effect of clinical treatment and cerebral response. According to the textbook of Acupuncture and Moxibustion Administration Method, acupuncture needling manipulation can be generally categorized into the reinforcing skills and reducing skills, basically for relevant excess or deficiency body condition. These manipulations always include mechanic actions as lifting, thrusting, rotating, and stirring [14]. Mechanic stimuli of different nature apparently could lead to relatively special nerve activated and get specific sensation produced. This is in contraindication to a former opinion that mentioned that acupuncture Deqi with both superficial and deep needling produced similar activation and deactivation, rather than reinforced manner receiving deep needing as expected. A possible reason can be inferred from their report about the blending of Deqi with sharp pain (acute pain). In the deep needling group especially, there was a relatively high score of sharp pain together with Deqi sensation. As the sharp pain is deemed to act oppositely to Deqi and may reduce or weaken the magnitude and level of responsive pattern of brain regions, it is plausible that there are similarities for both deep and superficial needling. Thus, the presentation of cerebral response may in contradicted. Essentially, the sharp pain was confirmed as noxious stimuli for Deqi sensation, for it was posited that it was negative factor to neutralize the Deqi-induced therapeutic effect [22].

4.3. Suggestions for Future Deqi Studies. Based on the aforesaid reasons as issues for current research, we would like to express our opinion and offer our suggestion for forthcoming acupuncture Deqi research. As a result of the absence of experiments for subjects with disease, firstly we suggest conducting further studies on patients with control arm as HS and those with large population are needed to elucidate the acupuncture Deqi-induced cerebral effect [78]. Secondly, it is still necessary for researchers to form a workshop and hence to remodify the current nongeneralized quantitative measurements. The tool to quantify Deqi is very essential for characterizing the psychophysical traits of Deqi. Only with standardized acupuncture Deqi quantification we could set an equivalent baseline for the comparison with brain reaction mode and cerebral location of Deqi and nil Deqi. Thirdly, the design of a credible sham control is really important to qualify the nature of acupuncture Deqi. In order to acquire more reliable results, the methodological design is key to study of Deqi. Generalized manipulation methods and also placebo control means are also needed to attest the pure Deqi effect. Hence, forthcoming studies on acupuncture Deqi should pay more attention to the strategy of experiment design with generalized measurement, valid sham control methods, and more to subjects in diseased condition.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

Jie Yang and Ming-Xiao Yang contributed equally to this paper.

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Review Article

Characterization of Deqi Sensation and Acupuncture Effect

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Acupuncture stimulation elicits deqi, a composite of unique sensations. According to traditional Chinese medicine (TCM), deqi experienced by patients is often described as *suan* (aching or soreness), *ma* (numbness or tingling), *zhang* (fullness, distention, or pressure), and *zhong* (heaviness) and is felt by the acupuncturists (needle grasping) as tense, tight, and full. It is believed that deqi may be an important variable in the studies of the mechanism and efficacy of acupuncture treatment. In recent years, great efforts have been made to understand deqi, which include a couple of questionnaires to qualify and quantify deqi sensations, neuroimaging studies of deqi and acupuncture, physiological mechanisms of deqi, and the relation between deqi and clinical efficacy. However, many problems need to be resolved, and more researches are required to be made in the future.

1. Introduction

Acupuncture is a medical intervention in which needles are used to stimulate certain points generally called acupoints on the body. Traditional Chinese medicine (TCM) indicates that acupuncture stimulation elicits deqi, a composite of unique sensations. It is regarded that the application of acupuncture through stimulating certain acupoints is to activate the *qi* and blood of meridians and collaterals and to regulate the function of internal organs so as to prevent and treat diseases in TCM theory. Therefore, deqi, which literally means "the arrival of vital energy," is a prerequisite for clinical effects, also an important judgment of the exuberance and decline of meridian *qi* and the prognosis of disease [1]. In addition, it may be of great importance to understand acupuncture mechanisms [2].

In recent years, evocation of deqi has been paid increasing attention in clinical trials of acupuncture, but the physiological mechanisms that produce deqi effect are still not well understood. Few investigators have made explicit efforts to describe deqi from both the patients' and the acupuncturists' perspective and to examine the relationship between deqi and therapeutic effect. Researches in this field focus more on the clinical characterization of the deqi, qualitative and quantitative measurements of deqi, and physiological mechanisms of deqi effect.

2. Characterization of Deqi during Acupuncture Treatment

Deqi is commonly translated as "needle sensation," sometimes as "arrival of *qi*" or "needling response." The current view holds that there is no significant difference between them. However, some have different understandings of these three words. Needling sensation is mainly meant subjective feelings and perceived responses of patients and acupuncturists; arrival of *qi* is a healing process, which activates the antipathogenic *qi* to expel the pathogens; the needling response suggests the final aim of acupuncture [3]. Deqi is usually used to describe the subjective sensations felt by the patients during acupuncture treatment, but the view is not shared by all, and some argue that deqi comprises not only the patients' sensations but also the acupuncturists' senses. Furthermore, there are few people suggesting that deqi also includes propagated sensation along meridians and the externally visible physical signs due to acupuncture treatment [4].

2.1. Characterization of Deqi Felt by the Patients. Over the past decades, researchers have put more weight on the patients' rather than the acupuncturists' experience during needling. This may be due in part to the rising popularity of new acupuncture modalities such as electroacupuncture [1]. Multiple sensations around the acupoints experienced by the patients are often described as *suan* (aching or soreness), *ma* (numbness or tingling), *zhang* (fullness/distention or pressure), and *zhong* (heaviness) in the literature according to TCM [5]. Besides, pain, which is experienced occasionally, has not been well characterized [6]. Dull pain is considered as deqi and beneficial to treatment, while sharp pain is not deqi and harmful [7]. Patients experience deqi very differently because of conditions of constitution or the therapists' manipulation, such as the direction, angle, and depth of needling [8, 9]. Nevertheless, some studies have shown that the sensations are similar between subjects, irrespective of their constitution, expectation, or cultural background [7, 10]. Recently, a study taking cultural differences into account shows that Chinese patients enjoy deqi experience whereas Americans do not [7]. No significant difference is found in the needling sensations among different acupoints [6]. Deqi sensation appears to be qualitatively and quantitatively different between manual and electrical stimulation. Aching is the most predominant deqi sensation of the former, whereas the latter is tingling [11].

2.2. Characterization of Deqi Felt by the Acupuncturists. Although the most popular view focuses mainly on patients' sensation, *Huangdi Neijing* (Huangdi's canon of medicine), one of the four great classics in TCM, states that deqi should be felt by the acupuncturists who also need to concentrate in order to hold it [12]. The increased resistance of the needle is felt by the acupuncturists (needle grasping) as tense, tight, and full like "a fish biting onto the bait" [13] or arrival of *qi* like "a bird flying" [14] as described in the ancient literature. Needle grasping is considered to be associated with clinical efficacy although little data is available [15].

2.3. Physical Signs due to Acupuncture Treatment. Another important feature of deqi is that it often spreads or radiates from the point of its elicitation, which is called "propagated sensation along meridians" (PSM) or, more commonly, "propagated sensation along channels" (PSC) [16], which is explained as the flow of *qi*. PSC is observed to "jump" between adjacent meridians through geographic information system, suggesting a close connection between PSC and classical meridians [2]. There are not obvious differences between acupoints for the distance of sensation transmission [6]. Sometimes, it may manifest like skin redness, gooseflesh, or localized red or white lines along the meridians of the body surface [4].

Although the characterization of deqi is mentioned, respectively, in the previous section, the patients' sensations and the acupuncturists' senses are closely linked. When the acupuncturists feel tense or tight, the patients usually experience soreness, numbness, fullness, or heaviness at the same time. Under the circumstances that the *qi* has not arrived, the patients have no special sensation or response and acupuncturists feel slow, slipping, or empty. It has been vividly described in classical prose named "*biao you fu*" [13]. Now most researchers agree with the explanation of the phenomenon just as the following. Acupuncture through stimulating certain acupoints may contract intraspindle muscle and then produce myoelectricity. Secondary impulse reaching to central brain produces the patients' needling sensation, and the contraction of local muscle fibers through needle body to needle handle causes the deqi sensation of acupuncturists' hands.

3. Qualitative and Quantitative Measurements of Deqi

Deqi may be an important variable in studies of the efficacy and mechanism of acupuncture treatment. Some attempts of developing deqi questionnaires (Table 1) have been made to measure deqi sensation. However, there is still no consensus for a method or instrument to qualify and quantify deqi sensation despite efforts towards this goal.

3.1. Deqi Questionnaires Discriminating Deqi from Pain. Vincent and colleagues started this work a couple of decades ago. To monitor needling sensations, Vincent et al. [17] condensed the McGill Pain Questionnaire [18] to 20 adjectives describing deqi by applying expert consensus. Park et al. modified the Vincent scale by adding five sensations based on the comprehensive literature review, including both pain and deqi sensations. These sensations primarily came from pain questionnaires and did not focus specifically on deqi [10].

Acupuncture needling evokes two sensations: pain and deqi. Pain is usually caused by penetrating the skin, whereas deqi is possibly caused by stimulating deeper structures at acupoints [19]. Sharp pain is believed to result from inadvertent noxious stimulation rather than deqi, as evidenced by distinct differences in hemodynamic response by fMRI [20]. Therefore, it is important to discriminate deqi from pain. MacPherson and Asghar [8] further examined the Park questionnaire using a "Delphi process" to separate the deqi sensation and pain. Based on a hierarchical cluster analysis, a group of seven sensations was found to be associated with the category of deqi, and a group of nine sensations was associated with the category of acute pain. Later on, the Southampton Needle Sensation Questionnaire (SNSQ), developed by White and colleagues [21], was shown to be a valid, rigorous, soundly grounded, and patient-centered measurement and to enable the discrimination between pain and deqi sensation. Pach et al. [22] tried to create a German version of the SNSQ in order to measure deqi in subjects receiving different forms of acupuncture and to evaluate the translated questionnaire. However, for the language and cultural differences, factor structure of the original questionnaire could not be reproduced with the German version of the SNSQ in an experimental setting. The above-mentioned questionnaires did not involve interviews with patients to ask them to describe what sensations they perceived when they

Table 1: The common questionnaires in deqi assessment.

Scale	Year	Group	Feature
Vincent questionnaire	1989	Vincent et al. [17]	The sensations primarily coming from pain questionnaires
Park questionnaire	2002	Park et al. [10]	
Macpherson questionnaire	2006	MacPherson and Asghar [8]	Separating the deqi sensations and pain
SNSQ	2008	White et al. [21]	A valid, rigorous, soundly grounded, and patient-centered measurement, enabling the discrimination between pain and deqi
German version of SNSQ	2011	Pach et al. [22]	For the language and cultural differences, the original questionnaire could not be reproduced
SASS	2005	Kong et al. [23]	One supplementary row was left blank for subjects to describe perceptions in their own words
MASS	2007	Kong et al. [1]	Including 12 descriptors, one supplementary row to describe perceptions, and two supplementaries (Acupuncture Sensation Spreading Scale and Mood Scale)
C-MMASS	2012	Yu et al. [24]	Chinese version of the MASS with "sharp pain" removed
Mao questionnaire	2007	Mao et al. [25]	Including 11 needling sensations, an open-ended question of additional deqi sensations, the situation of PSC, and 5 specifically designed items
Deqi composite	2007	Hui et al. [9]	An approach proposed for reducing the complex sensation profile of deqi to a single value
Kou questionnaire	2007	Kou et al. [26]	Evaluating 5 deqi sensations and anxiety using VAS

received acupuncture, which appeared to be the major design flaw.

3.2. Deqi Questionnaires with Patients' Interviews. To address the complexity involved in accurately assessing deqi, Kong et al. created a scale entitled "Subjective Acupuncture Sensation Scale (SASS)" in 2005 [23] when launching a study on acupuncture analgesia in 2000. Nine sensations mainly based on the traditional literature were listed on the scale. What is more was that one supplementary row at the end of the nine descriptors was left blank for subjects to describe perceptions in their own words. Using this instrument, it was possible to show significant correlations between the feeling of numbness as well as soreness and the analgesic effect of acupuncture. After deliberating with other acupuncture research groups, Kong et al. modified the SASS to make it useful to a wider range of research projects, which was called "MGH Acupuncture Sensation Scale (MASS)" [1]. The scale included twelve descriptors modified to form a more comprehensive set of sensations, one supplementary row (describing perceptions in their own words), and two supplementaries ("Acupuncture Sensation Spreading Scale" and "Mood Scale"). Yu et al. developed a Chinese version of MASS, namely, Modified MASS-Chinese (C-MMASS), a valid and reliable instrument for the assessment of needle sensations in Hong Kong Chinese people receiving electroacupuncture. "Sharp pain" was removed from C-MMASS [24]. Mao et al. [25] developed a questionnaire and conducted a descriptive survey, including eleven needling sensations, an open-ended question of additional deqi sensations, and a survey of asking about situation of PSC. Five items were specifically designed with response options ranged from "completely disagree" to "completely agree" to capture the patients' attitudes and beliefs about needling sensations. The common characteristics of deqi and its migratory nature could be described through the questionnaire.

3.3. Other Scales. Furthermore, Hui et al. explored "deqi composite," an approach proposed for reducing the complex sensation profile of deqi to a single value, which would facilitate more straightforward comparisons between subjects, acupoints, or stimulation techniques [9]. This index could be used as a covariate in the future exploration of the hemodynamic response of the brain to acupuncture demonstrated by fMRI and its correlation with the efficacy of acupuncture in clinical practice. Kou et al. confirmed that Visual Analogue Scale (VAS) was an objective and reliable way to quantify deqi sensation [26]. The questionnaire was given to subjects to evaluate deqi sensations, including numbness, pressure, heaviness, warmth, and radiating paraesthesia, respectively. A separate VAS to measure their levels of anxiety during the treatment was also included. The results showed that acupuncture significantly induced higher VAS values for numbness, pressure, warmth, and radiating paraesthesia but not for heaviness than the placebo. However, the results were not able to clearly distinguish the deqi sensation over each individual acupoint.

Though there are several ways to qualify and quantify deqi sensation, an international standard questionnaire is still needed to accurately describe deqi. The questionnaires are needed to be designed more comprehensively, including

the acupuncturist senses as well as the physical signs under the condition of a consistent definition of deqi. It might also be necessary to rethink the measurement of deqi with questionnaires. Such a measurement could be used in clinical trials for different diseases, making it possible to use specific sensations to predict the outcome of treatments and strengthen our understanding of acupuncture mechanisms. For the construct which is sensitive to cultural and ethical background, or strong subjectivity of deqi itself, perhaps the idea of an international standard questionnaire has to be rejected before. The development of such a questionnaire might have to go through the whole process.

4. Neuroimaging Studies on Deqi Sensation and Acupuncture Effect

Modern neuroimaging has provided revolutionary tools to monitor the dynamic response of the whole brain to acupuncture with specific regional localization. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies on acupuncture at commonly used acupoints have demonstrated the limbic system and paralimbic, hypothalamus, and subcortical gray structures as the important components in mediating the acupuncture effects and deqi [23, 27, 28].

Over the past decade, Hui et al. have built a database of fMRI scans of the brain response to acupuncture at multiple acupoints, LI4 (*hegu*), ST36 (*zusanli*), and LV3 (*taichong*) in healthy adults [20, 29, 30]. Their studies showed that acupuncture deqi evoked deactivation of a limbic-paralimbic-neocortical network, which encompassed the limbic system as well as activation of somatosensory brain regions. Importantly, Hui et al. consistently observed distinct patterns of limbic network hemodynamic response in the brain, mainly deactivation in deqi and activation in sharp pain. The findings were consistent with previous reports [8, 21, 31]. Hsieh et al. showed via PET that elicitation of deqi resulted in a significant increase of blood flow in the hypothalamus and insula with an extension to the midbrain when compared with minimal or no stimulation after needle insertion at LI4 [32]. Napadow et al. found that perceptions from acupuncture were preferentially processed by the dorsomedial prefrontal cortex through continuously monitoring rating of acupuncture sensations during fMRI. Deqi fostered acupuncture analgesia through focusing attention and accentuating the bodily awareness which in turn could enhance antinociceptive mechanisms within the central pain network [33]. Lai et al. revealed a significant difference in activated brain areas and brain metabolic changes when deqi was achieved by proper needle manipulation in SJ5 (*waiguan*) using PET in healthy volunteers. These studies mostly focused on healthy subjects, and the cerebral changes in patients who received acupuncture and the pathological conditions were rarely explored [34]. And for all we know, there was a study which showed that the activation of the hypothalamus was more robust in the heroin addicts than that in the healthy subjects during acupuncture. The deqi scores of the heroin addicts were significantly higher than those of the healthy subjects [35].

Hui et al. observed signal decreases in hypothalamus and nucleus accumbens with acupuncture deqi at both LI4 and ST36. But others reported increasing signals, using fMRI for acupuncture at both ST36 and LI4 [36] and using PET for acupuncture at LI4 [32]. Differences were also found among acupoints, with LI4 showing more prominent response than other commonly used acupoints, which may provide scientific support for why LI4 was frequently employed in clinical practice to a certain extent [37]. In comparison of modulation effect in the limbic-medial prefrontal network, there was a little stronger signal in ST36 than in CV4 (*guanyuan*) by using fMRI, which also indicated acupoint specificity [38]. It was proposed that the magnitude of signal change observed in acupuncture deqi was small, generally less than 1%, compared with the 2–4% activation by visual stimulation or other sensory tasks reported in the literature [39]. The smaller response suggested that acupuncture, unlike noxious insults and pharmacological agents, might act within physiological limits. This could explain in part why acupuncture treatment generally caused fewer side effects than medications, particularly potent analgesics.

5. Physiological Mechanisms of Deqi

In combination with techniques, basic scientific studies have begun to elucidate the physiological mechanism that produces deqi effect. In previous studies, researchers [40] have found that stimulation of vessels, nerves, muscles, tendons, and periostea could evoke variable sensations thus producing varying effects in the central nervous system and human body. Predominantly, stimulation of nerve branches produced numbness; stimulation of muscles produced soreness and distention; and stimulation of blood vessels produced pain. It was also demonstrated that many of the deqi sensations were conveyed by different nerve fiber systems without reaching the threshold of overt noxious simulation. Aching, soreness, distension, heaviness, warmth, and dull pain were conveyed by the slower conducting Aδ and C fibers, whereas numbness was conveyed by the faster conducting Aβ fibers in the skin [41, 42]. Deqi was also suggested to relate to activation of high-threshold ergoreceptors in muscle [43].

Deqi can help in regulating the blood flow with a certain degree of meridian specificity by using speckle laser blood flow scanning technology [44]. Sandberg et al. indicated that the intensity of deqi resulted in pronounced increase in both skin and muscle blood flows using photoplethysmography [45]. It was also proved that deqi had close correlations with the decrease in blood flow velocity while acupuncture on SP3 (*taibai*) [46]. Irnich et al. performed a trial comparing sham acupuncture to laser acupuncture. The results suggested that deqi may be caused by central processes of awareness rather than the redlight itself provoking deqi sensations directly within the skin [47]. Comparing placebo and deqi acupuncture, it was found that after acupuncture, the former showed a universal increase of transcutaneous CO_2 emission, while the latter showed a significant increase

of transcutaneous CO_2 emission specifically at acupoints located on the same meridian [48]. It was also observed that the greater acupuncture intensity is, the greater modifications of neurophysiological parameters are [49].

6. Relation between Deqi and Clinical Efficacy

According to TCM, deqi sensation is believed to be related to clinical efficacy. Manipulation and retaining the needle may strengthen the deqi sensation and improve clinical efficacy in some degree. Now, no studies to our knowledge have systemically investigated the relationship between different aspects of deqi and treatment effects.

Deqi is suggested to be the main mechanism producing effects of acupuncture [35, 50], for example, by generating a release of spinal and supraspinal beta-endorphins, proinflammatory neuropeptides, and an increase in peripheral circulation [51]. fMRI studies have also found a positive correlation between a subject's psychophysical and hemodynamic responses that strong deqi sensations induce strong deactivation of the limbic system, which result in clinical beneficial effect [20, 30].

However, for the clinical trials, there is still opposite evidence. Enblom et al. found that verum acupuncture, eliciting deqi, was not more effective than sham acupuncture in reducing emesis in cancer patients receiving radiotherapy [52]. White et al. indicated that the presence and intensity of deqi, using the subscale of the Park questionnaire, had no significant influence on the pain relief for the treatment of osteoarthritis of the hip and knee [53]. As we all know, now there is still no strict randomized controlled clinical trial to prove the necessity of deqi to acupuncture. The current conclusion is just based on TCM theory and clinical experience.

Traditional Chinese acupuncture intentionally elicits deqi sensations in patients and regards them as signs of treatment efficacy, but this is not true for all forms of acupuncture. Other styles, such as traditional Japanese acupuncture and wrist-ankle acupuncture, avoid inducing needling sensations in patients. For these forms of acupuncture, treatment effect may be related only to the acupuncturist's perception of deqi or not related to deqi at all—measured entirely in terms of symptom relief.

7. Conclusion

Deqi is of great importance to clinical effects and mechanisms of acupuncture treatment, which also need quite a lot of efforts to deeply understand although a few progress has been made. For the subjectivity of deqi, how to understand deqi more scientifically and objectively is more critical. Acupuncture is effective for many diseases, while unclear mechanisms limit its development. Deqi should be further explored in future clinical trials, and more researches are required to understand the underlying mechanisms.

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Research Article

Acupuncture De Qi in Stable Somatosensory Stroke Patients: Relations with Effective Brain Network for Motor Recovery

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Acupuncture has been widely used for treating stroke and De Qi may play an important role. In spite of its acceptance, the neural mechanism underlying acupuncture for motor recovery is still elusive. Particularly, by what extent De Qi sensations can reliably predict the therapeutical acupuncture effect on the mediating recovery from stroke is urgent to investigate. Nine stroke patients were assessed by De Qi, neurological examination, and scanned with acupuncture stimuli across two time points at an interval of two weeks. And we adopted multivariate Granger causality analysis to explore the interregional influences within motor executive brain network during post-acupuncture resting state. Our findings indicated that acupuncture at GB34 can enhance the recovery of stroke mainly by strengthening causal influences between the ipsilesional and contralesional motor cortex. Moreover, centrality of some motor-related regions correlated with clinical variables and thus served as a predictor of stroke recovery. Along the same line, the centrality of these motor-related regions has also high relations with the De Qi sensation. Our findings suggest that De Qi having relatively stable reliability may be essential and used as a predictor to the therapeutic effectiveness of acupuncture for stroke recovery.

1. Introduction

Acupuncture is an ancient East Asian healing modality that has been in use for more than 2000 years. In the last decades, acupuncture has gained great popularity as an alternative and complementary therapeutic intervention in the Western medicine [1]. In this process, the boundaries between East Asian medicines and biomedicine/science are porous, negotiated to connect different medical traditions. De Qi, rooted in the central concept of the Traditional Chinese Medicine, was generally experienced by the patients and also by manipulating feeling of the acupuncturist when reaches the level of "Qi" in the body. Recently, researchers paid more attention to the patient's sensations rather than the acupuncturist's experience during acupuncture needling treatment [2–4]. However, consistent scientific investigation has found about neither histological nor physiological correlates for traditional Chinese concepts such as De Qi.

According to the Traditional Chinese Medicine approach, stimulating specific acupuncture points corrects imbalances in the flow of Qi through channels known as meridians. During a typical acupuncture session, many practitioners perform needle manipulation in order to achieve the De Qi response. De Qi is believed to be essential to the therapeutic effectiveness of acupuncture and is often used as a signal to acupuncturists that the proper amount of needle stimulation is being performed [4–8]. It is also proposed that the patient's response (De Qi) served as a basis for "dose" of acupuncture needling, which calls for a better understanding of both the qualitative and quantitative characterization of the De Qi sensation [9, 10]. One recent report investigated the characteristics of the "De Qi" response in acupuncture at different acupoints (ST36, LI4, LV3) and its association with distinct nerve fibers, compared with the conventional somatosensory or noxious stimuli. They indicated that aching, soreness, and pressure were the most

common sensations for different acupoints, followed by tingling, numbness, dull pain, heaviness, warmth, fullness, and coolness. And the sharp pain was regarded as inadvertent noxious stimulation. The most specific sensations of De Qi were aching, soreness, pressure and dull pain, in comparison with tactile stimulation control. Such complex composite of De Qi sensations indicated involvement of nerve fibers at all levels (myelinated and unmyelinated nerve fibers). Particularly, the deeper muscle layers with their rich supply of slow conducting fibers may play the key role in acupuncture. It is consistent with the findings that De Qi sensations are blocked after injection of procaine into the muscle beneath the acupoints. Following lumbar anesthesia, both De Qi sensations and electromyography were completely abolished [11]. This phenomenon inferred that acupuncture-induced sensations were mainly generated from muscle and the activity of polymodal-type receptors in deep tissues may play an important role [12]. Other researches find the relations of the functional effects of De Qi with the changes in skin resistance [12, 13], modification of different evoked potential parameters [14, 15], increases in the cortisone serum level [16], or remote functional modifications [17]. These findings partly provide a clue to demonstrate the De Qi with modern concepts in neurophysiology and bearing clinically relevance.

Given that De Qi plays a pivot role in the therapeutic effect of acupuncture, some researches attempted to find out whether De Qi has any objective neurological correlate with the aid of the neuroimaging techniques. One study showed that acupuncture-induced De Qi sensations without sharp pain primarily elicited widespread signal decreases in several brain areas, including the frontal pole, ventral medial prefrontal cortex, cingulated cortex, hypothalamus, reticular formation, and cerebellar vermis, whereas sharp pain elicited signal increases in several areas including the frontal pole and anterior, middle, and posterior cingulate [18]. They further inferred that acupuncture feeling, without sharp pain is related to analgesia and antistress and deactivate the limbic-subcortical regions. By contrast, acupuncture feeling mixed with the sharp pain is associated with needling stimulation in deep tissue with skin piercing and biochemical reaction to tissue damage, and thus the central effects of pain prevailed, exhibiting an integrated response with predominance of activation over deactivation in the cerebrocerebellar and limbic systems. Another research indicated that individual differences in the De Qi scores can modulate the degree to which the right anterior insula was activated only following the verum acupuncture at ST36, compared with sham control [19]. The anterior insula has been widely accepted as a relay station integrating the centrally processed sensory information (visceral and autonomic) for its reciprocal connections with multiple brain regions [20]. This region, particularly the right anterior part, also plays a critical role in the interoceptive awareness of both stimulus-induced and stimulus-independent changes in the homeostatic state [21, 22], which enables us to regulate the organism's current state by initiating appropriate control signals toward the extrapersonal stimuli. This observation may suggest a key role of De Qi in characterizing the central expression of acupuncture stimulation at ST36, which is relevant to its clinical efficacy in gastrointestinal analgesia.

However, most of previous studies adopted healthy subjects and explored the neural mechanism of De Qi sensations mainly derived from the activation pattern of brain. Since acupuncture plays a homeostatic role it may have a greater effect on patients with a pathological imbalance compared to healthy controls [23, 24]. The hypothesis underlying neurobiological mechanism of De Qi needs further investigations in the altered and/or dysfunctional brain networks in patients. In addition, current neuroimaging studies focus on the spatial distribution of brain activity patterns induced by acupuncture. In fact, the well-identified physical effects of acupuncture needling and its purported clinical efficacy suggest that acupuncture acts in maintaining a homeostatic balance of the internal state within and across multiple brain systems [25]. Exploring the interactions between interregional effective connectivity and De Qi sensations modulated by acupuncture may provide a clue to understand the organizations of neural pathways underlying De Qi. More importantly, the reliability and reproducibility pattern of BOLD signal changes presents a significant challenge for both evaluating the effect and interpreting the neural mechanism of acupuncture. Although this discrepancy may partly be derived from different acupuncture modalities, needling dose, and postprocessing methods, individual physiology states contributes largely to such discrepancy. In the present study, we aim to address the above issues adopting the stable somatosensory stroke patients as the study cohort and using the individual-based Granger causality brain network analysis, in order to test the functional neurobiology of De Qi with two separate fMRI scannings as an interval of two weeks. In other words, we would like to determine whether, in acupuncture, the greater the individual sensorial needling experience, the greater interregional connectivity density, or whether such hypothesis can be verified by multiple measurements.

2. Materials and Methods

2.1. Subjects. A total of 9 patients (7 Males, mean age: 57.7 ± 9.92 years), recruited from Beijing Dongzhimen Hospital, were diagnosed with right hemispheric striatocapsular infarction and stable ischemic stroke by MRI with unilateral upper-limb disability. The criteria for patients recruitment are listed as follows: (1) stable recovery stroke patients: >2 weeks and <12 weeks after the onset of stroke (first episode of stroke); (2) sufficient cognition to follow simple commands, (minimental state examination score) MMSE >21. Patients were excluded if they met any of the below criteria: (1) bilateral infarcts, (2) recurrent stroke, (3) any previous history of alcohol or drug abuse, (4) history of epilepsy or other neurological disease and psychiatric disorder, (5) serious cognitive deficits, comprehensive aphasia and (6) other MRI contraindications (such as claustrophobia, etc.). The topographic distribution of the somatosensory deficit and the anatomic reconstruction of the brain lesions were shown in Table 1. Another 8 age-matched and sexually matched

Table 1: Clinical and demographic data.

	Patient number								
	1	2	3	4	5	6	7	8	9
Age (years)	56	64	57	68	57	37	58	71	52
Gender	F	M	M	M	F	M	M	M	M
Localization of infarct	BG	IC	IC	CR	IC	IC	IC	IC	BG
Motricity Index	0	60	14	72	23	60	34	76	76
	11	64	14	72	23	60	34	76	—
Rankin Scale	4	1	2	2	4	2	3	2	2
	4	1	2	1	4	2	3	1	—
Barthel Index	35	95	60	90	60	85	65	90	85
	40	95	65	85	60	85	75	90	—
NIHSS	14	3	9	5	8	7	7	3	5
	8	1	9	2	8	7	7	2	—
MMSE	22	30	27	29	22	30	30	24	30
	23	30	30	28	24	30	30	27	—
Brunnstrom	I	IV	II	II	I	V	II	V	II
	I	IV	II	III	I	V	II	V	—
Asworth	0	1	1	0	0	2	2	0	0
	0	1	0	1	0	2	2	0	—

BG: basal ganglia; IC: internal capsule; CR: corona radiate; NIHSS: National Institute of Health Stroke Scale; MMSE: minimental state Examination.

normal subjects (6 Males, mean ag: 51.6 ± 4.8 year) who were also recruited from Beijing Dongzhimen Hospital served as healthy controls. Each of them has normal neurological examination; no history of epilepsy or other neurological disease, psychiatric disorder and other MRI contraindications (such as claustrophobia, etc.). All of the patients and the normal subjects are with right-hand dominance.

2.2. Clinical Assessments. Each patient underwent a series of clinical evaluations. Clinical outcomes measurements included the National Institute of Health Stroke Scale (NIHSS), Ashworth Scale for clinical measure of muscle spasticity, Brunnstrom for sequential motor recovery, Rankin Scale For stroke disability, and Barthel Index of Activities of Daily Living and Motricity Index. The anatomic reconstructions of the brain lesions are listed in Table 1. One patient had only taken part in the first scanning and the second clinical assessments and scanning.

2.3. fMRI Motor Task. During fMRI scanning, a simple finger movement was firstly served as stimulation for patients. A simple block design was performed in which 30-second baseline and 30-second stimulation alternated and lasted for 5 minutes and 30 seconds, with 10 seconds rest in the beginning. And the healthy subjects had the same MRI procedure as the patients (Figure 1).

2.4. Acupuncture Stimulation. A multiblock paradigm is generally used in acupuncture fMRI studies, which implicitly presumes the temporal intensity profiles of the certain event conforming to the "on-off" specifications. Since the acupuncture action is slow to develop and resolve [25], the temporal aspects of the BOLD response to acupuncture may violate the assumptions of the block-designed estimates. In addition, using several stimulation blocks in a short period of time, investigators may not be able to dissociate the long-lasting effects from other confounding changes, such as the effect of needle manipulation during the experiment [26]. In the current study, we adopted a new experimental paradigm, namely, the nonrepeated event-related fMRI (NRER-fMRI) design, to investigate such prolonged effects after acupuncture administration.

Acupuncture stimulation employed the NRER-fMRI design paradigm scanning, incorporating 1 min. needle manipulation, preceded by 1 min. rest epoch, and followed by 10 min. rest (without acupuncture manipulation) scanning (Figure 1). Acupuncture was performed at acupoint GB34 on the left leg (located in the lateral aspect of the posterior knee). According to the TCM, the first choice acupoint for stroke is located at the scalp. Considering both limitation of fMRI scanning and classic use, we selected Yangming channel for Wei syndrome. GB34 is one of the most frequently used acupoints and proved to have various efficacies in the treatments of hemiplegia and rehabilitation for motor functional deficit/impairment after stroke. Acupuncture stimulation was delivered using a sterile disposable 38 gauge stainless steel acupuncture needle, 0.2 mm in diameter and 40 mm in length. The needle was insered vertically to a depth of 2-3 cm, and the administration was delivered by a balanced "tonifying and reducing" technique. The stimulation consisted of rotating the needle clockwise and counterclockwise for 1 min. at a rate of 150 times per min. The procedure was performed by the same experienced and licensed acupuncturist on all participants. Every subject endured twice acupuncture

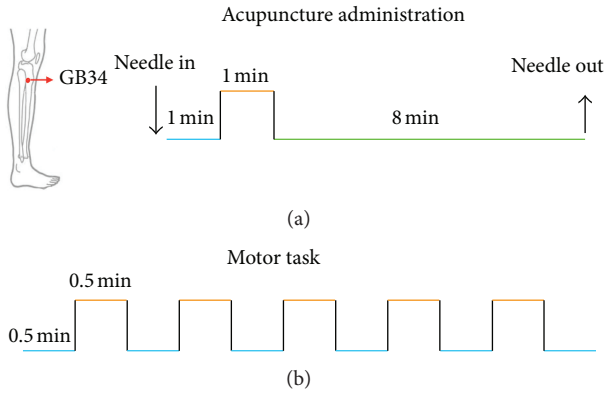


Figure 1: Acupuncture stimuli and motor task experimental paradigm.

stimulation scanning at an interval of two weeks, in order to test the reliability of the hypothesis.

At the end of each fMRI scanning, the subjects completed a questionnaire that used a 10-point visual analogue scale (VAS) to rate their experience (or "De Qi") of aching, pressure, soreness, heaviness, fullness, warmth, coolness, numbness, tingling, dull, or sharp pain they felt during the scan. The VAS was scaled at 0 = no sensation, 1–3 = mild, 4–6 = moderate, 7-8 = strong, 9 = severe, and 10 = unbearable sensation [16]. The questionnaire also had one blank row for subjects to add their own words if the above descriptors did not embody the sensations they experienced during the stimulation. Because sharp pain was considered an inadvertent noxious stimulation, we excluded the subjects from further analysis if they experienced the sharp pain (greater than the mean by more than two standard deviations). Among the sixteen participants, none experienced the sharp pain.

2.5. Imaging Data Acquisition and Analysis. The images were acquired on a 3T Siemens MRI Scanner. A custom-built head holder was used to prevent head movements. Thirty-two axial slices (FOV = 225 mm × 225 mm, matrix = 64 × 64, thickness = 3.5 mm) parallel to the AC-PC plane and covering the whole brain were obtained using a T2*-weighted single-shot, gradient-recalled echo planar imaging (EPI) sequence (T_R = 2000 ms, T_E = 30 ms, flip angle = 90°). Prior to the functional run, high-resolution structural information on each subject was also acquired using 3D MRI sequences with a voxel size of 1 mm^3 for anatomical localization (T_R = 1.9 s, T_E = 2.52 ms, matrix = 256 × 256, FOV = 250 mm × 250 mm, flip angle = 9°, and slice thickness = 1 mm).

All preprocessing steps were carried out using statistical parametric mapping (SPM5, http://www.fil.ion.ucl.ac.uk/spm/). The images were first slice-timed and then realigned to correct for head motions (none of the subjects had head movements exceeding 1 mm on any axis and head rotation greater than one degree). The image data was further processed with spatial normalization based on the MNI space and resampled at 2 mm × 2 mm × 2 mm. Finally, the functional images were spatially smoothed with a 6 mm full-width-at-half maximum (FWHM) Gaussian kernel. The statistics were color-coded and mapped in Talairach space.

For motor task, statistical analysis was performed in two steps. First, a single subject fixed effects model was used. The difference between the motor condition and the resting was estimated at each voxel by using the general linear model (GLM) and the parameter estimates for the covariate resulting from the least mean square fit of the model to the data were calculated. In the second-level analysis, the obtained individual t-maps were used in "random effect" group analysis framework by one-sample t-test for different groups. The statistical threshold was set at $P < 0.05$ (corrected for multiple comparisons).

2.6. ROI Definition. According to previous imaging studies on poststroke brain organization, motor execution areas rather than motor preparation areas play a key role [27]. We selected the regions of interest associated with the motor execution network from motor task by healthy controls ($P < 0.01$, FDR corrected). The regions of interest included regions, such as bilateral primary motor cortex, bilateral dorsolateral and ventrolateral premotor cortex, bilateral superior parietal lobule, bilateral basal ganglia, bilateral thalamus, anterior inferior cerebellum, left postcentral gyrus, and supplement motor area. In order to refine the accuracy of the ROIs, several procedures were conducted: the effect of intersubject anatomical variability was examined by defining ROIs in individual anatomical space, group-probabilistic anatomical map, as well as using the standard Talairach-Daemon-based atlas [28]. In order to obtain the group-probabilistic anatomical map, the individually drawn ROIs were registered to standard MNI space [28] and summed across all subjects

2.7. Effective Connectivity Networks Generated from mGCA. The entire time series of BOLD signal intensities from these selected ROIs during the PARS and PSRS, averaged across voxels within each ROI, were normalized across subjects (separately for different conditions) to form a single vector per ROI. The mGCA used the directed transfer function (DTF) [29], computed from a multivariate autoregressive model of the time series in the selected ROIs. In this study, we also adopted the weighted DTF with partial coherence in order to emphasize direct connections and inhibit mediated influences [30, 31]. To assess the significance of path weights, a null distribution was obtained by generating 2500 sets of surrogate data and calculating the DTF from these 2500 datasets [29, 30, 32]. The DTF value was compared with the null distribution for a one-tailed test of significance with a P value of 0.01 (corrected for multiple comparisons).

In order to better extract information on the temporal relations among the regions obtained from mGCA, a node interaction analysis was performed. In-degree of a node in a Granger causal connectivity network means the number of causal in-flow connections to the node from any of the other nodes. Out-degree of a node means the number of causal out-flow connections from the node to any of the other nodes in the network. We calculated "In + Out degree" for every node

within the DMN, respectively. The region was identified as the hub in the network if its sum of "In degree" and "Out degree" was at least one standard deviation (SD) greater than the average "In + Out degree" for all regions (i.e., sum > mean + SD).

2.8. Subjective Acupuncture Sensations Analysis. Because sharp pain was considered an inadvertent noxious stimulation, we excluded the subjects from the further analysis if they experienced the sharp pain (greater than the mean by more than two standard deviations). Among the thirty-two participants, none experienced the sharp pain. In order to quantify the total intensity of De Qi experienced by each individual, we employed the MGH Acupuncture Sensation Scale (MASS) index, defined as a weighted average of all sensations using an exponential smoothing [33]. This index is convenient to devise a single value to quantitatively summarize the full multivariate breadth and depth of acupuncture sensations.

3. Results

3.1. Psychological Analysis from De Qi Sensations. The prevalence of these sensations was expressed as the percentage of individuals in the group that reported the given sensations. A statistical analysis found significant difference between the stroke and healthy control with regard to the prevalence of these sensations ($P < 0.05$). For stroke patients, fullness and numbness were most common sensations, while fullness and aching were most common sensations for healthy controls. The intensity of sensations was expressed as the average score ± SE. The levels of sensations were kept low (mild to moderate), but statistically significant differences occurred in the average sensation intensity between the stroke patients (3.7 ± 1.2) and healthy controls (2.1 ± 1.4). In addition, the variability of De Qi between the first and second scanning at an interval of two weeks kept relatively stable for both intensity and prevalence ($P > 0.09$).

3.2. MGCA Mapping for Stroke Patients and Healthy Controls. A causal connectivity graph was constructed using the thickness of connecting arrows to indicate the strengths of the causal influences (shown in Figure 2). For stroke patients, the right premotor cortex, the right supplement motor area and the right anterior inferior cerebellum served as the hub, and were central targets during the post-acupuncture resting period. For normal controls, the central targets remain the same, while the brain network has more dense effective connectivities. Among causal influences of each node, the right premotor cortex projected the strongest inflow into the left premotor cortex, and also became even stronger than that of the normal controls. While, paths originating from the right motor cortex to bilateral basal ganglia and right superior parietal lobule became weak below the statistical significance level for stroke patients.

At an interval of two weeks, the interregional causal influence pattern kept relatively stable during the post-acupuncture resting epoch; however, the "in + out" degree in the right premotor cortex, right supplement motor area and the left postcentral cortex became much higher and more saliently for stroke patients. On the other hand, a trend towards a significant decrease was detected in the "in + out" degree in the right anterior inferior cerebellum and the right thalamus. Specifically, the causal interactions between the right premotor cortex and left premotor cortex attenuated in the stroke patients during the post-acupuncture resting period. However, the interregional causal influences among the ipsilateral motor cortices (the premotor cortex, the supplement motor area as well as the postcentral cortex) became even stronger. Path originating from the right ventrolateral premotor cortex projecting to the right thalamus as well as path from the anterior inferior cerebellum to the superior parietal lobule became decreased strengths.

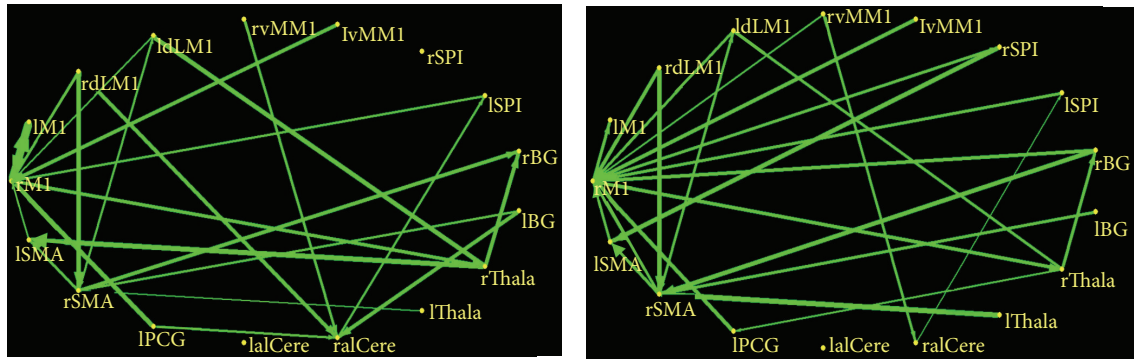
3.3. Relationship between Network Parameters and the Clinical Measures. To test relationships between the nature of regional centrality ("in + out degree of certain node") and neurological scales, we calculated the cross subject correlation between the "in + out" degree of certain node and the Motricity Index, Barthel Index, the National Institute of Health Stroke Scale, Ashworth Scale, Rankin, and Brunnstrom Scale (Figures 3 and 4). Our results presented that the centrality of the right premotor cortex indicated a significantly positive relation with the Motricity Index ($r = 0.74$, $P < 0.05$). By contrast, the centrality of the anterior inferior cerebellum showed the negative relation with the Motricity Index ($r = -0.82$, $P < 0.01$). Other correlations were not significant ($P > 0.08$).

3.4. Relationship between Network Parameters and MASS Index. To test relationships between the nature of regional centrality ("in + out degree of certain node") and De Qi sensations, we calculated the cross-subject correlation between the "in + out" degree of certain node and MASS (total intensity of De Qi sensations experience by each individual). Our results presented that the centrality of the right premotor cortex indicated a significantly positive relation with the MASS ($r = 0.72$, $P < 0.05$). By contrast, the centrality of the anterior inferior cerebellum showed the negative relation with the MASS ($r = -0.79$, $P < 0.05$). Other correlations were not significant ($P > 0.1$).

4. Discussion

The present study examined the relations of the De Qi sensations with the causal interactions within the motor executive brain network induced by acupuncture at GB34 for stable somatosensory stroke patients, compared with the healthy controls.

The aim of this study was to address (i) whether De Qi sensation induced by acupuncture at GB34 is associated with heterogeneous motor-executive pathway for stroke patients and healthy controls; (ii) by what way acupuncture-induced effect may enhance recovery for stroke patients by activating motor-related brain networks? (iii) by what extent De Qi sensations can reliably predict the therapeutical acupuncture effect on the mediating recovery from stroke?



(a) Stroke Patient (b) Healthy Control

Figure 2: Multivariate Granger causality connectivities among selected ROIs ($P < 0.01$, corrected for multiple comparisons) for both stroke patients and healthy controls during the postelectroacupuncture resting state. Relative strengths of path weights (in arbitrary units) were indicated by the width of arrows. M1: premotor cortex; dlM1: dorsolateral premotor cortex; vMM1: ventrolateral premotor cortex; SPl: superior parietal lobule; BG: basal ganglia; Thala: thalamus; aICere: anterior inferior cerebellum; PCG: postcentral gyrus; SMA: supplement motor area; l: left; r: right.

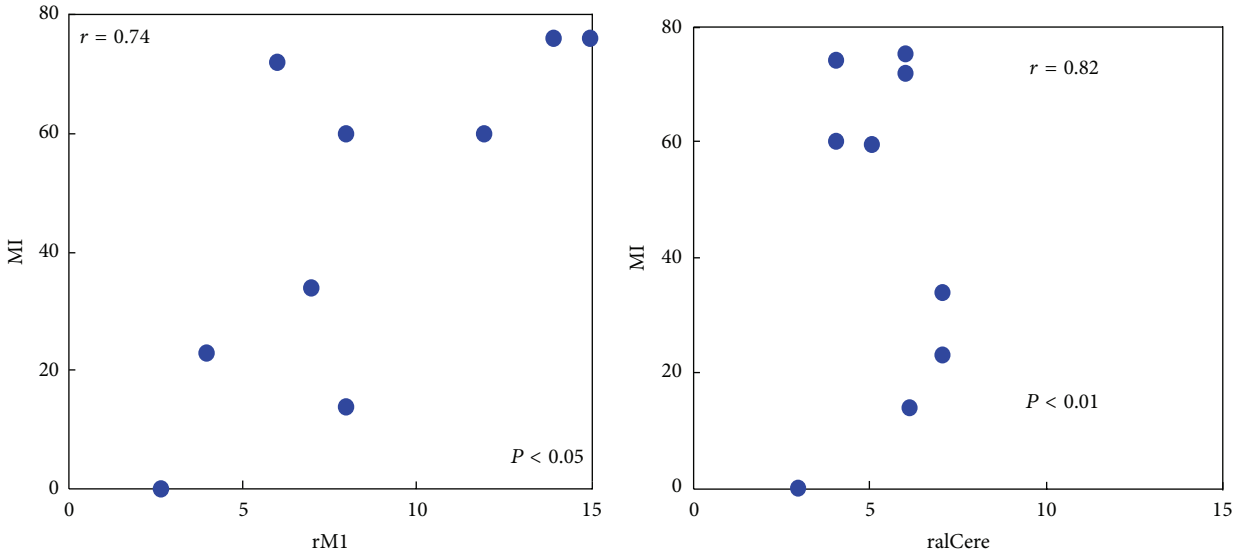


Figure 3: Cross subject correlation between the "in + out" degree of brain areas and Motor Index (MI) for stroke patients. For stroke patients, the MI and "in + out" degree of the right premotor cortex (rM1) presented the significantly positive relation ($r = 0.74$, $P < 0.05$, $n = 9$), while the significant negative correlation was mainly exhibited in the "in + out" degree of the anterior inferior cerebellum ($r = -0.82$, $P < 0.01$, $n = 9$).

Our findings demonstrated that acupuncture at GB34 can enhance the recovery of stroke mainly by strengthening the causal influences between the ipsilesional motor cortex and contralesional motor cortex. Moreover, the centrality of some motor-related regions correlated with clinical variables and thus served as a predictor of stroke recovery. Along the same line, the centrality of these motor-related regions has also high relations with the De Qi sensation. Collectively, our findings suggesting that De Qi has relatively stable reliability may be essential and used as a predictor to the therapeutic effectiveness of acupuncture for stroke recovery.

Most neuroimaging studies have focused on the spatial distribution of neural responses and more or less harness the exploration of brain networks underlying acupuncture. In addition to functional connectivity, effective connectivity between different regions is both important and essential in detailing working mechanisms of the brain's functional architecture underlying acupuncture effect. The resultant modeled primarily concern with the directions of neural interactions and how one neural system exerts influence over another. Granger causality has been highlighted in recent years, and is proved suitable for the study of directionality in neuronal interactions through assessment on neurophysiologic data in both the frequency and time domains [34–36]. It is assumed that the autoregressive prediction of the first time series at present time could be improved by including

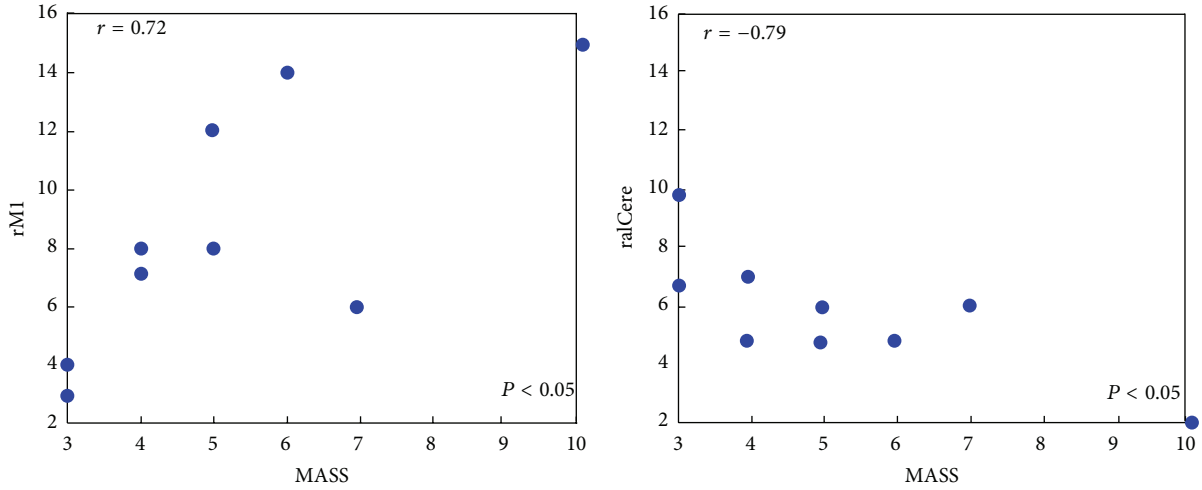


Figure 4: Cross subject correlation between the "in + out" degree of brain areas and MGH Acupuncture Sensation Scale (MASS) for stroke patients. For stroke patients, the MASS and "in + out" degree of the right premotor cortex (rM1) presented the significantly positive relation ($r = 0.72$, $P < 0.05$, $n = 9$), while the significant negative correlation was mainly exhibited in the "in + out" degree of the anterior inferior cerebellum ($r = -0.79$, $P < 0.05$, $n = 9$).

the past information of the second time series if the second time series has a causal influence on the first. The MGCA mapping showed that delayed effects of acupuncture exert distinct modulatory causal influence on motor-executive brain networks.

Acupuncture at GB34 can induce more enhanced bidirectional causal influence between the ipsilesional and contralestional premotor cortex for stroke patients, compared with the healthy controls. Accumulating evidence suggested that the outgrowth of enhanced connections may compensate for impaired neural pathways connecting important nodes after the motor pathway stroke. Cortical regions in the intact hemisphere are thought to be important in supporting motor function of the paretic hand after stroke. Contralesional premotor cortex is more active during the movement of the affected hand after stroke compared with that in healthy controls [37, 38], particularly for more impaired patients [39] with greater corticospinal tract disruption [40]. One research from animals has also indicated increased connections from the premotor cortex to the somatosensory cortex in a monkey with an ischaemic lesion to motor cortex [41]. This can be interpreted to indicate that stimulation of acupoints, used therapeutically, may enhance recovery from stroke selectively through improving the effective connectivities between these areas, which are generally thought to be involved in mediating recovery from stroke via functional plasticity. On the other hand, we also found that at an interval of two weeks, acupuncture at GB34, can induce decreased bidirectional causal influence between the ipsilesional and contralestional premotor cortex for stroke patients, compared with the first acupuncture administration. It is partly consistent with previous studies that neural activity in ipsilesional and contralesional cortical areas was pathologically increased when stroke patients moved their paretic hand, and that overactivity usually decreases over time, concomitant to clinical recovery [42, 43]. Another research also indicated that increased activation in the intact hemisphere is prominent in patients with poor motor recovery [40], and its also simply reflect the removal of transcallosal inhibition from the damaged hemisphere [44]. Our findings demonstrated that acupuncture at GB34 comply with the reorganization of brain networks and enhance the recovery of stroke patients.

Notably, we found that the De Qi sensations induced by acupuncture at GB34 have relative relations with the regional centrality of motor-executive brain networks which can be used as the predictor for the motor recovery of stroke patients. Particularly, as patients demonstrated recovery from stroke, gradual increases in regional centrality were presented in the ipsilesional primary motor areas while the opposite change was seen in ipsilesional anterior inferior cerebellum. One research focusing on the acupuncture effect for facial muscle recovery has demonstrated that stronger intensity of De Qi was associated with better therapeutic effects including reduced disability and better quality of life [45]. Abundant evidence indicated that the increasing importance of ipsilesional primary motor areas as a key node is attributed to the recovery of stroke patients [46, 47]. Specifically, there is a general trend for the centralization of brain activity towards the primary motor area of lesion hemisphere as the time delayed. On the other hand, the centrality of the right anterior inferior cerebellum attenuated by acupuncture at GB34 after an interval of two weeks, which is also significantly correlated with the degree of individual motor ability. It is already proved that the large involvement of the ipsilesional cerebellum in the acute phrase of stroke is partly due to the overuse of the unaffected limbs and may result in the more focusing on this region. As the time passed and improving the motor ability of the affected limbs, the node centrality of the ipsilesional anterior inferior cerebellum is attenuated. This

hypothesis can also be verified by the negative correlations between the regional centrality of this area and behavior recovery index. As a whole, acupuncture can provide beneficial effect on the recovery of stroke patients from subcortical lesions by coordinating the reorganization of motor-related brain network and enhancing the converging of certain regions, which is also predicted by the De Qi sensations experienced by patients enduring acupuncture treatments.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

L. Bai and F. Cui contribute equally to this work.

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Review Article

Factors Contributing to *De Qi* in Acupuncture Randomized Clinical Trials

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De qi is a core concept of acupuncture and is necessary to produce therapeutic effect. In 2010, *de qi* has been received as a term in the official extension of the CONSORT Statement. However, there are few articles that discuss which factors have influences on obtaining *de qi* in clinical trials. This paper aims to explore these factors and give advice on trial design in order to optimize *de qi* in acupuncture RCTs.

1. Background

One of the fundamental characteristics of traditional Chinese acupuncture is the "obtaining of *qi*," more commonly known by the pinyin *de qi*. The *de* component means "obtain," and the *qi* component is often translated as "vital energy" [1]. Commonly, the term *qi zhi* has been used for the same phenomenon, which indicates "arrival of *qi*." Both concepts originated from the classic book of traditional Chinese medicine (TCM) named *Huang Di Neijing* (also translated as *Yellow Emperor's Inner Classic of Internal Medicine*), which is the first comprehensive literature of TCM and treated as the authoritative guideline for Chinese medication and acupuncture until present day [2].

De qi is considered by many acupuncturists to be a fundamental component of acupuncture since the early classical texts. *Neijing* (*Lingshu* Chapter 1) states "For acupuncture to be successful, the *qi* must arrive (*qi zhi*). Acupuncture's effects come about like the clouds blown away by the wind" [2]. A more famous saying from the acupuncture poem *Biao You Fu* (Ode to Clear Obscurity) reads "If the *qi* comes quickly, the effect will be quick. If the *qi* comes slowly, the effect will be bad" [3]. Consistently with the classics, recent studies also provide evidence in support of this *de qi* phenomenon and indicate a statistically significant correlation between *de qi* and treatment efficacy [4, 5].

According to the theory of TCM and acupuncture experts, *de qi* is a composite of variable sensations experienced by both the patient and the administering acupuncturist [6, 7]. Typically, the acupuncturist would perceive *de qi* as heaviness or tension on the needle while stimulating it. In response to being punctured, the patient would perceive a sensation of soreness, numbness, heaviness, distension around the point, or even a sensation travelling to a specific place [3, 8].

The randomized controlled trial (RCT) is considered the gold standard to provide evidence for a treatment's efficacy [9, 10]. To improve and standardize reporting quality of RCTs, the CONSORT Statement was published in 1996 and received extensive applications [11]. Subsequently, extensions to CONSORT have been developed to cover the reporting of nonpharmacological treatments and pragmatic trials [12–14]. Since there are acupuncture-specific aspects to reporting not covered by these extensions, the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) was published in 2001 and its revision was added as an official extension of CONSORT in 2010 [15]. In these guidelines, *de qi* was listed to be a necessary part in acupuncture interventions. However, on the STRICTA checklist, there is a lack of articles discussing which terms in this list have significant or potential influences on obtaining *de qi*, and thereby how to effectively utilize *de qi* to create valid acupuncture RCTs.

This paper aims to explore these terms and give advice on their design methods in acupuncture RCTs.

Given that there is a broad diversity of acupuncture styles (e.g., traditional Chinese medicine, Japanese, Korean, Western, Five Element, ear acupuncture, etc.), this paper will focus only on traditional Chinese acupuncture due to the nature of the authors' clinical and research experiences.

1.1. Acupoints Selection. Acupoints vary in their ability and characteristic to produce *de qi*. Hui et al. found that among three commonly used acupoints LI4 (*Hegu*), ST36 (*Zusanli*), and LV3 (*Taichong*), LI4 showed the most prominent response in the frequency and intensity as well as the largest number of *de qi* sensations [16]. Cheng reported that acupoints on the head and extremities are more inclined to achieve *de qi* when compared with acupoints on the trunk [17]. Recent electrophysiologic studies explained these differences as a consequence of different nerve innervations and tissue structures around acupoints [17–19]. For example, they stated that stimulation to the trunk acupoints elicits somatic autonomic reflex at the spinal level whereas stimulation to the extremity acupoints elicits a somatic autonomic reflex at the brain level [19]. However, literature has pointed out that in comparison with daily practice, the needle sensation in experimental research is often required to be very strong in order to demonstrate a therapeutic effect [20]. Given the wide variety of acupoints' characteristics, acupuncture practitioners in future research should be flexible instead of seeking intense sensation of *de qi* blindly on every single acupoint. Excessive needle stimulation is prone to produce discomfort and noxious effects [21]. From another aspect, when selecting acupuncture points for noneffective control groups, those located in trunk or other thick body regions with fewer nerve fibers are considered to be the ideal choice. These acupoints are deemed to rarely elicit *de qi* and therefore produce only minor or no unexpected therapeutic effects.

In a study by Vincent et al., patients were asked to assess their needle sensations after acupuncture intervention when needles were applied to acupuncture points and nonacupuncture points (sham acupoints) [22]. The results showed no significant differences in needle sensations between acupuncture points and nonacupuncture points for any locations. Studies that shared similar results may be due to their inappropriate selection for sham acupoints. According to research about the nature of meridian and acupoint, we have recognized that acupoints are not as small as needle tips [23]. However, the upper range of them has not yet been established. Consequently, when selecting sham acupoints, the optimal distance away from real acupoints remains controversial. Sham acupoints which are too close to real ones may be included in the effective range of real acupoints and erroneously induce *de qi* in the control group. In order to provide more evidence for sham acupoint selection, further studies on the nature of meridian and acupoint range are required.

1.2. Depth of Insertion. The depth of insertion is another term that is directly related to the production of *de qi*. Park et al. applied acupuncture at four different depths including the epidermis, corium, fascia, and muscle [24]. Their results showed that only when punctured into the muscle can acupuncture produce statistically significant needle sensations (*de qi*). It has been demonstrated that many of the *de qi* sensations are conveyed by different nerve fiber systems. For example, sensations including aching, soreness, distension, heaviness, warmth, and dull pain are conveyed by the slower conducting $A\delta$ and C fibers, whereas numbness is conveyed by the faster conducting $A\beta$ fibers [25, 26]. Since these fibers are more densely distributed in the tendinomuscular layers [27], only acupuncture manipulation inserted into this depth could elicit valid *de qi* sensations. Based on these findings, superficial acupuncture without penetrating the skin is considered to be an ideal sham acupuncture intervention that effectively and easily blinds patients as well as avoids *de qi*.

1.3. Needle Stimulation. As major patterns of acupuncture manipulations, it has been confirmed that manual acupuncture and electroacupuncture (EA) produce different types and intensities of *de qi* sensations. For example, Leung et al. found that "aching" is the predominant *de qi* sensation derived from manual acupuncture whereas "tingling" is the predominant *de qi* sensation derived from EA [28]. One possible reason of this difference is that EA had different modulatory effects on the brain cortex from those by manual acupuncture [29]. It has been proven that different manual stimulation techniques (e.g., lifting-thrusting and twirling rotating) and variations in the direction, angle, and depth of needle insertion can affect the outcome of acupuncture treatment [30, 31]. However, there is no widespread agreement on how strong or which *de qi* sensations and needle stimulations should be used for a therapeutic effect.

Laser acupuncture usually serves as a contrast of therapeutic acupuncture, in the control group. Compared with a metal needle, laser acupuncture does not pierce skin and has always been considered to have no therapeutic effect as well as no evocation of *de qi*. However, in some study reports published in 2012, researchers have demonstrated that subjects with laser acupuncture also experienced *de qi* [32–34]. On the basis that *de qi* is the sign of acupuncture efficacy these studies signify that using laser acupuncture as an intervention in the control group may cause underestimation of acupuncture effects.

1.4. Practitioner Background. *De qi* is not only a fundamental sign of effective treatment, but also influences the speed of and potential for recovery [2, 5, 8]. Different technical processes of acupuncture insertion and stimulation lead to different characteristics of *de qi* and therefore different treatment results. As the person that conducts all of these manipulations, the acupuncturist is the vital determinant about the evocation and intensity of *de qi*. Hence it is essential to report pertinent information about the acupuncturist providing treatment including qualifications or affiliations and years in acupuncture practice, as well as any other experiences that may be relevant to the trial. Relevant differences (if any) in the qualification, training, and experience of the participating acupuncturists should be highlighted. Since the level

of reporting has historically been poor, recent reviews of acupuncture trials have stressed the need to extensively document these characteristics [35, 36]. The eligibility criteria for acupuncturists should also be explained, as these will influence the homogeny of the trial results. Training for the acupuncturists before the trial is necessary and important for achieving uniform manipulations of needle insertion and stimulation to be conducted during the trial. Where there are known to be potential variations between practitioners, selecting a random sample of practitioners will reduce expertise bias and help improve the applicability of the results [37].

2. Discussion

The STRICTA checklist clearly states that, in acupuncture RCTs, eliciting of *de qi* as well as the difference between the responses required in the protocol and those actually obtained should be reported in the Results section [15]. But there is no mention in the statement of how to assess whether *de qi* was attained. The majority of acupuncture clinical studies only mention *de qi* at intervention design without any assessments or reports to describe whether the subjects and acupuncturists actually obtained *de qi* [36]. Since different experiences of needle sensations may be associated with different outcomes, it is absolutely essential that *de qi* is carefully considered. This is especially so given that these RCTs are evaluating the therapeutic effects of acupuncture with *de qi* being an important variable. The complexity of ensuring that similar levels of *de qi* were experienced is a major challenge in our field. For this reason, attempts have been made to apply a scale to quantify the needle sensation.

A number of researchers have sought to establish a credible rating scale for *de qi*, such as the McGill Pain Questionnaire [22], Subjective Acupuncture Sensation Scale (SASS) [4], the Massachusetts General Hospital Acupuncture Sensation Scale [38], the Southampton Needle Sensation Questionnaire [39], and the *de qi* composite [16]. It should be noted that the existing scales and questionnaires do have limitations. Some experienced acupuncturists have stated that the scale descriptors do not tally with those given by their patients who often described more subtle sensation, such as a cool flow sensation, or sensations going from one point to another [40]. Furthermore, the terms in some scales are not clear for patients to understand. For example, some patients could not easily identify the difference between the term is "spreading" and "radiating" [40]. However, given that *de qi* sensations have been recognized as an important variable for different individuals, conditions, and needle stimulations, the use of *de qi* scales will be a promising way to facilitate the *de qi* sensation being controlled for in clinical and experimental studies. In addition, quantitatively calculated *de qi* sensations may offer a meaningful method to further interpret the findings of RCTs and increase validity. It is also recommended that future studies should assess *de qi* at each acupuncture consultation to reduce recall bias.

In TCM theory, the *de qi* felt by the acupuncture practitioner is as important as the *de qi* felt by the patient [6, 8, 41]. It is also reported that the practitioner's needle sensations are more objective than those of patients and are necessary for obtaining treatment results [42]. For some experts, *de qi* is an intuitive sensation that is affected by the condition of the patient or the anatomical location of the point and thereby hard to describe or assess in a quantitative or qualitative way. However, the practitioner questionnaire is considered to be a fairly reliable guide to the obtainment of *de qi* [43]. Even though there have been many attempts to assess the needle sensations experienced by the practitioner [44], a validated *de qi* questionnaire has not been developed. Further studies to develop tools assessing *de qi* based on the practitioner's feeling or senses should be conducted.

3. Conclusion

In recent years, although there has been increasing evidence from randomized trials and systematic reviews on the efficacy of acupuncture, the conclusions remain controversial. The lack of significant difference between real and sham acupuncture in RCTs may result from the omission of certain important components of acupuncture, especially the obtainment of *de qi*. According to the study reports of acupuncture, factors in the STRICTA statement including the point selection, needle stimulation, and depth of insertion will contribute to the achievement of *de qi*. Taking all these factors into consideration would have considerable implications for the design and interpretation of acupuncture clinical trials. Meanwhile, assessment of the *de qi* sensations for both patients and acupuncture practitioners may be conducive to ascertain and control the *de qi* sensations in future clinical and experimental studies.

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Review Article

Yes, There Is Deqi Sensation in Laser Acupuncture

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Deqi, a composite of unique sensations, is essential for clinical efficacy according to Traditional Chinese Medicine. It is described as a sensory perception of varying character and is mostly ascribed to metal needle acupuncture. However, it can also be elicited by different kinds of laser acupuncture stimulation. This short paper summarizes the current scientific status of deqi in laser stimulation. Different kinds of laser acupuncture are described in a comprehensive form, and the most interesting studies concerning deqi and laser acupuncture are presented.

1. Introduction

In relation to acupuncture research, the term "deqi" is described as a sensory perception of varying character [1]. However, deqi sensations can also be elicited without any cutaneous sensory input. Some authors conclude that deqi might be a central phenomenon of awareness and consciousness, and that its relevance should be taken into account, even in clinical studies [1].

The literature search in the commonly used database PubMed yielded the results demonstrated in Figure 1.

This review article summarizes the current scientific status of deqi in laser acupuncture in a comprehensive form and is aimed at motivating the readers to perform more research on this very interesting topic for acupuncture.

2. Different Kinds of Laser Acupuncture

Since ancient times, metal needles are the commonly used device for stimulating acupuncture points and eliciting a needle-specific deqi sensation. However, there are also new optical stimulation methods which were scientifically investigated for the first time by our research group within the last years [2]. These methods will be described in the following.

2.1. Violet Laser Acupuncture. Up to now, violet lasers are used only in special areas in medicine [3, 4], because it is a new and still expensive invention. In acupuncture research, violet laser was applied only in a few scientific investigations until now, which were published by our research group [5–10].

Violet laser needle acupuncture is a new optical method for stimulating different acupuncture points continuously and simultaneously. A wavelength of 405 nm, an output power of 110 mW, and a diameter of 500 μm were used for our experimental investigations. The system consists of 10 semiconductor injection laser diodes.

Each single needle can emit a different wavelength. We used a continuous wave mode (CW). Due to coupling losses, the output at the tip of the needle is about 100 mW. Irradiation usually lasts 10 min (600 sec), and therefore, optical power density was very high (range: kJ/cm^2) [9]. The violet laser needles are placed vertically at the skin and trigger painless but perceptible stimulation at the acupuncture point.

Violet laser acupuncture was made possible only due to latest inventions. Nakamura et al. [13] developed small, convenient blue and violet lasers which have not been available before. The acupuncture laser equipment used in our studies operates, as already mentioned before, at a wavelength of 405 nanometers. It is worth noticing that this wavelength is not in fact blue, but appears to the eye as violet, a color for which the human eye has a very limited sensitivity.

The violet laser does not have similar penetration depth in human skin as, for example, the red or infrared laser

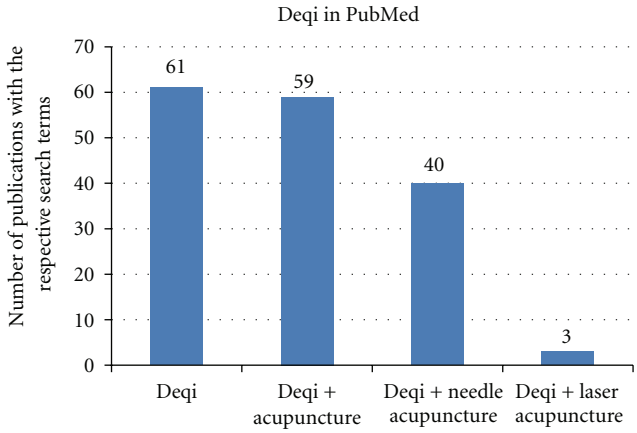

Figure 1: The PubMed literature search for the terms related to deqi. Note that, at the moment (Dec 3rd, 2012), there are only 3 articles mentioning deqi in connection with laser acupuncture [1, 11, 12].

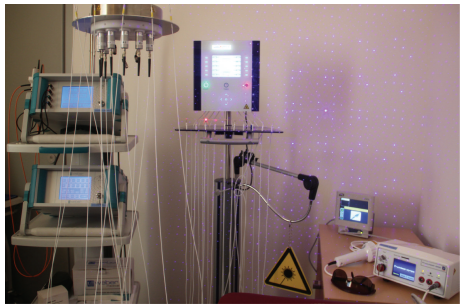

Figure 2: Different systems for laser acupuncture at the Medical University of Graz.

described in the next subsection (violet: approximately 2 mm versus red/infrared: 2-3 cm [5, 14, 15]); however, there is an evoked deqi sensation, which is a prerequisite for effective acupuncture stimulation [2].

2.2. Red and Infrared Laser Acupuncture. "The first bichromatic laser needles (685 nm and 785 nm) were developed at the University of Paderborn, Germany (Dr. Detlef Schikora), and the first clinical investigations were performed in Lauenförde, Germany (Dr. Michael Weber). The first scientific experiments and publications on this field of research started in 2002 at our Medical University in Graz, Austria [14, 16–20].

Multichannel laser needle acupuncture allows the simultaneous stimulation of individual point combinations (Figure 2) [14, 17]. Variations and combinations of acupuncture points according to TCM are possible on the body or at the ear and hand using Korean or Chinese hand acupuncture. The bichromatic laser needle method is based on systems with 8–12 separate semiconductor laser diodes and emission wavelengths of 685 nm and 785 nm. The system consists of flexible optical light fibers, which conduct the laser light with minimal loss to the laser needle. Thus, a high optical density can be achieved at the distal end of the laser needle. The intensity of the laser needles is optimized in such a way, so that the volunteer or patient does not immediately feel the activation of the needle (30–40 mW per needle; diameter 500 μm; duration 10 min; power density ~20 J/cm^2 per acupuncture point). More details regarding this method are described in previous studies and books [14, 19, 20] [2].

To the best of our knowledge, there are no studies concerning deqi and green laser or yellow laser. Green laser has a very low penetration depth and is suitable mainly for ear acupuncture or other superficial points. Yellow laser has not been used in acupuncture research up to now.

3. Deqi Sensation in Laser Acupuncture

Deqi is described by patients and volunteers as heaviness or like an electrical current running along the treated meridians. If red (685 nm) or infrared (785 nm) lasers are used, the patients normally do not notice when the laser is started. So, in the beginning of the treatment, they also do not feel any deqi sensation. Several minutes later (5–10 min), many patients report a pleasant warm and sometimes vibrating feeling in some treated areas [21].

In an experimental pilot study, we found that violet laser stimulation increases temperature (mean ~1.5°C) and microcirculation (mean ~20%) at the acupoint Hegu (LI.4) significantly and immediately (1 min) after stimulation onset [5]. The main interesting finding of our second publication concerning violet laser acupuncture was that heart rate decreases significantly within an interval of 5 min after violet laser stimulation onset at the acupoint Neiguan (PC.6) [2, 6]. Five interesting studies performed recently [7–10, 22] are also related to violet laser acupuncture.

According to Traditional Chinese Medicine, one must first obtain deqi sensation for acupuncture to be effective. In some studies, we could demonstrate that initial stimulation with a metal needle is stronger than the initial stimulation with a laser, but it fades earlier (it is like a spike). Laser needle stimulation is initially not as strong as the metal needle stimulation, but it continues to rise throughout the entire treatment—and it can also elicit deqi sensation [14, 21]. David Rindge, an oriental medical doctor and licensed acupuncturist, stated in *Acupuncture Today* [21]: "By the way, I have treated myself with laser needles, and I have felt this smooth deqi sensation, too."

In a research article published in Evidence-based Complementary and Alternative Medicine, Beissner and Marzolff [23] recently (2012) described sketches of acupuncture sensations of healthy volunteers after laser needle acupuncture. Since deqi can be subtle, they tried to reduce the confounding impact of external stimuli by carrying out the experiment in a floatation tank under restricted environmental stimulation. More than 80% of the subjects experienced deqi after laser acupuncture, that is, they described line-like or two-dimensional sensations, although there were some minor doubts that these were related to the laser stimulation [23].

One limitation of our studies is that we did not quantify deqi sensation, for example, as a percentage of how many people felt deqi in laser versus metal needle acupuncture up to now. It is clear, however, that the percentage will be much

smaller during laser acupuncture. At the moment, we also have no comparison of healthy volunteers versus patients on this topic.

Beside subjective and objective data that there is also a clear deqi sensation evoked by laser acupuncture, another related study published recently by our group is of particular interest [24]. In this study, we reported small, but reproducible human cerebral evoked potentials after bilateral, nonperceptible laser needle (658 nm, 40 mW, 500 μm, 1 Hz) irradiation of the Neiguan acupoint (PC6). These findings indicate that exposure to laser needle stimulation with a frequency of 1 Hz can modulate the ascending reticular activating system and can possibly act as further explanation for deqi-like sensations in laser acupuncture stimulation. Further investigations concerning this interesting topic of research are in progress.

Conflict of Interests

The author declares to have no conflict of interests.

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