Evidence-Based Complementary and Alternative Medicine

The Contribution of Mind-Body Practices to Emotional Health

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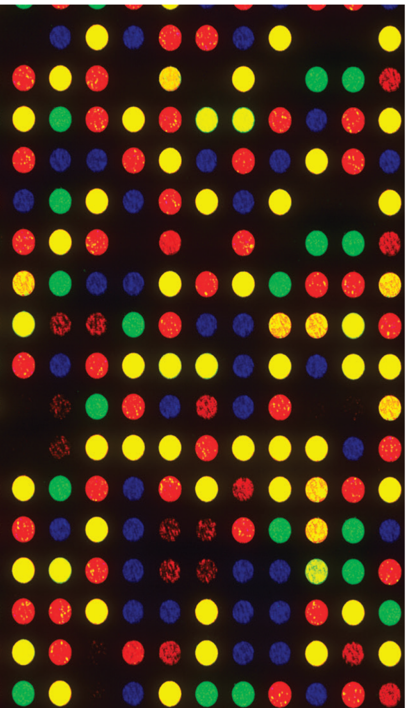
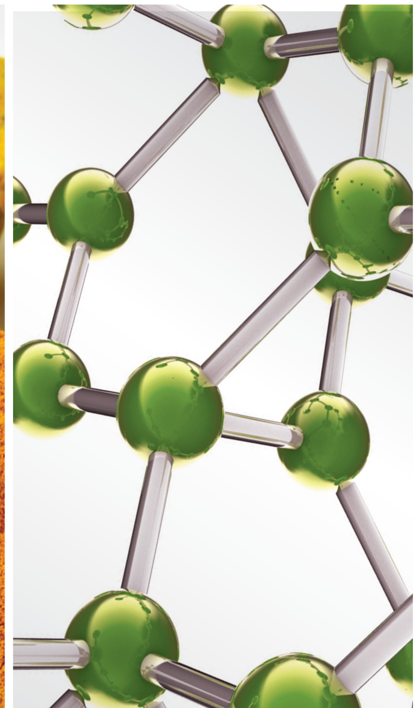
Guest Editors: Parco M. Siu, Ke Zhao, and Ruth Taylor-Piliae



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Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 1727479, 8 pages
https://doi.org/10.1155/2022/1727479

Research Article

The Effects of Foot Reflexology for Smoking Cessation on Brain Activities with Functional Magnetic Resonance Imaging (fMRI): A Pilot Study

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Received 12 May 2021; Revised 24 May 2022; Accepted 10 June 2022; Published 9 July 2022

Academic Editor: Vijaya Anand

Background. Foot reflexology is a treatment with the hypothesis that such massage stimulation on the feet may cause a therapeutic effect which should be helpful for smoking cessation. However, its mechanism of action in the brain of smoking people remains unknown. Functional magnetic resonance imaging (fMRI) is helpful for real-time brain activity detection. We aim to compare the brain activity effects of foot reflexology with fMRI between smoking and nonsmoking subjects. *Materials and Methods*. We divided participants into experimental (smokers) and control groups (nonsmokers). Both groups received similar foot reflexology under the fMRI examination. Then, we compared the mean response score in each brain area before and after foot stimulation among groups and between groups. *Results*. Five nonsmokers and fifteen smokers had completed the study. All participants were right-handed males, with a mean age of 38.6 years. The fMRI brain response in the areas correlated with foot stimulation, including the precentral gyrus of the frontal lobe and the postcentral gyrus of the parietal lobe, was present for all participants. The fMRI response outside the correlated area, including other parts of the frontal and parietal lobes, the temporal and occipital cortices, and the thalamus, was also found in all participants, but was not consistent. *Conclusions*. The fMRI of the brain is feasible and safe for demonstrating foot reflexology reactions. The response signal outside the correlated motor-sensory cortical area with foot reflexology may have clinical significance and may be helpful for smoking cessation. We suggest conducting a large-scale, randomized controlled trial to confirm these findings.

1. Introduction

Foot reflexology is a system of massage used to activate homeostasis, based on the theory that reflex points exist on the feet linked to every part of the body. It helps relieve pain and anxiety and improve sleep quality in patients with many diseases [1–3]. However, the mechanism of the reflexology is still uncertain [4]. Some previous studies suggested that foot massage at reflex points despite unilateral sole may activate the brain, as demonstrated in bilateral electroencephalographic changes [5, 6]. The reflexological stimulation at the reflex points on the soles activates the correlated somatosensory cortex and their reflex areas in the brain. Functional magnetic resonance imaging (fMRI) can demonstrate these significant effects [7].

fMRI brain is generally used for relevant sensorimotor task performance [8]. The most often used technique to detect the functional changes in the brain is blood

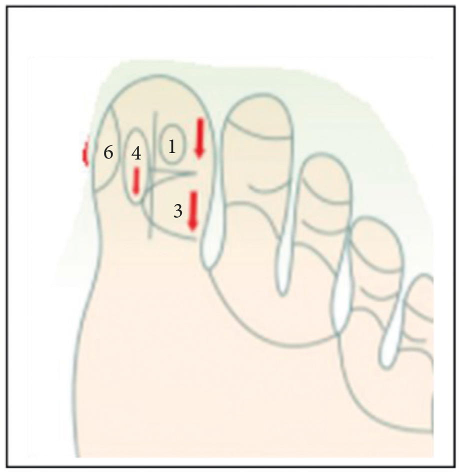

Figure 1: Three massage points.

oxygenation level-dependent (BOLD) fMRI [9]. Neurologists used BOLD fMRI to diagnose many neurological diseases, including sensory disorders [10]. fMRI brain could demonstrate the outside corresponded somatosensory activation during acupuncture [11]. A few previous studies reported the use of fMRI to detect brain activity in reflexology [7, 12]. A reflexologic expert recommended using fMRI as a surrogate marker of brain activity in patients treated with reflexology [13].

The World Health Organization stated that cigarette smoking had become one of the biggest public health threats the world has ever faced [14]. Less than five percent of smokers can quit without professional assistance [15]. Family and social support are the keys to success for smoking cessation [16]. Foot reflexology has been used in Thailand's tobacco control program for more than ten years. The community-based tobacco control program is becoming more and more widely used to help quit smoking in public health facilities, especially at the local level, including health-promoting hospitals. The successful smoking cessation rate rose to almost 50% with foot reflexology stimulation [17].

We conducted a pilot study to compare the brain activity effects of foot reflexology with fMRI between smoking and nonsmoking subjects.

2. Methods

This study is a double-blinded (participants and interpretation) clinical trial. We divided participants into experimental (smokers) and control groups (nonsmokers). Both groups do not know which group they are in (experimental or control group). In the fMRI test, the investigators will perform tests without knowing which group is the experimental or control group. The voluntary participants in the experimental group have had a habit of smoking regularly for at least one year. The study followed through in agreement with the Declaration of Helsinki (2008) of the World Medical Association. The Ethical Review Committee for Human Research, Faculty of Public Health, Mahidol University, approved the study (EC approval number: MOPH-2019-022, issued date: 30 Jan 2020).

The inclusion criteria were as follows: male, aged 20 years and over; the experimental group who were smokers, being a daily smoker who can either smoke the commercial or the domestic cigarette; the control group was nonsmokers; willing to give consent to study. The exclusion criteria were as follows: taking drugs affecting the central nervous system.

We performed the reflexological stimulation under the fMRI examination, where researchers applied the pressure with the right and left thumbs, respectively. Both groups received three plantar reflexological stimulation points (used to help quit smoking). Each point took 45 seconds for pressure application. We took 45-second breaks before the beginning of another pressure application on the same foot until the completion of all three points. Then, we switched the reflexological performance to the other foot. The total duration of the reflexological stimulation was approximately 10 minutes per participant.

The three massage points used in this study include the following (Figure 1):

(a) Above the hallux next to the toe index finger (area number 1)

(b) Inside of the hallux attached to the toe index finger (area number 2)

(c) The outer squares, both the top and bottom of the hallux (area number 3)

For quality control, only one reflexologist gave a treatment to prevent discrepancies between individuals (interpersonal error) on each day of data collection. The reflexologist gave a treatment to no more than five participants a day to prevent any individual discrepancies (intrapersonal error).

All fMRI measurements were performed using a Siemens MAGNETOM Skyra 3.0 Tesla scanner, high-resolution 3D T1 resolution, and an MPRAGE sequence-weighted structural image with a repetition time of (TR) = 1900 ms, echo time (TE) = 2.30 ms, field of view (FOV) = 230 mm, and 0.8 mm slice thickness for rapidly acquiring images. Echo planar imaging (EPI) was defined at TR = 3000 ms, TE = 30 ms, FOV 200 mm, 5.0 mm slice thickness, and spatial distortion of EPI

Table 1: The details of the MRI machine.

	TR (ms)	TE (ms)	Slice thickness	FOV (mm)	Acquisition matrix	Recon voxel size (mm)
MPRAGE (magnetization-prepared rapid gradient-echo)	1900	2.30	0.8	230	288 × 288	0.8 × 0.8 × 0.8
EPI (echo planar imaging)	3000	30	5.0	200	88 × 88	2.3 × 2.3 × 5.0
Gradient field mapping	737	4.92	3.0	320	64 × 64	5.0 × 5.0 × 3.0

Table 2: Demographic data.

No.	Age (years)	Underlying diseases	Smoking history	Type of cigarette	Smoking duration	Smoking intensity (cigarettes/day)	Carbon monoxide (ppm)
1	29	—	Nonsmoker	—	—	—	—
3	25	—	Nonsmoker	—	—	—	—
4	60	Hypertension	Nonsmoker	—	—	—	—
5	52	—	Nonsmoker	—	—	—	—
6	43	—	Nonsmoker	—	—	—	—
7	39	—	Smoker	Commercial cigarettes	24	5	3
8	59	Hypertension	Smoker	Commercial cigarettes	35	10	12
9	26	—	Smoker	Commercial cigarettes	12	5–6	2
10	25	—	Smoker	Commercial cigarettes	5	1–10	11
11	29	—	Smoker	Commercial cigarettes	14	1–2	2
12	30	—	Smoker	Commercial cigarettes	12	7	2
13	35	—	Smoker	Commercial cigarettes	20	10	6
14	25	—	Smoker	Commercial cigarettes	10	20	7
15	32	—	Smoker	Commercial cigarettes	12	10	14
16	43	Hypertension	Smoker	Commercial cigarettes	39	10	9
17	54	—	Smoker	Domestic cigarettes	33	>10	17
18	50	—	Smoker	Domestic cigarettes	34	20	24
19	38	—	Smoker	Domestic cigarettes	25	20	14
20	40	—	Smoker	Domestic cigarettes	26	10	10
21	46	—	Smoker	Domestic cigarettes	26	5	12

images was reduced using gradient field mapping; TR = 737 ms, TE = 4.92 ms, FOV = 320 mm, and 3.0 mm slice thickness were set, as shown in Table 1.

We collected demographic data and measured carbon monoxide in breath with a smokerlyzer dryer. We used syngo.via workstation software version VB30 for reading fMRI results.

The fMRI response signal was labeled as intense, positive, and negative, giving a score of two, one, and zero, respectively. We compared the mean response score in each brain area before and after foot stimulation among groups and between groups, using the t-test. A value of $p < 0.05$ was considered statistically significant.

3. Results

Among the 22 participants, we assigned six nonsmokers as a control group. We excluded one in the control group due to the low-quality fMRI resulting from currently taking anxiolytic drugs. Among the remaining 16 smokers assigned to the experimental group, one had a claustrophobic condition and refused to continue testing with MRI. Finally, five nonsmokers in the control group and 15 smokers in the experimental group remained for the study.

All participants in this study were male and right-handed. The left hemisphere was supposed to be dominant in all participants. The mean age was 38.6 years (37.4 years in

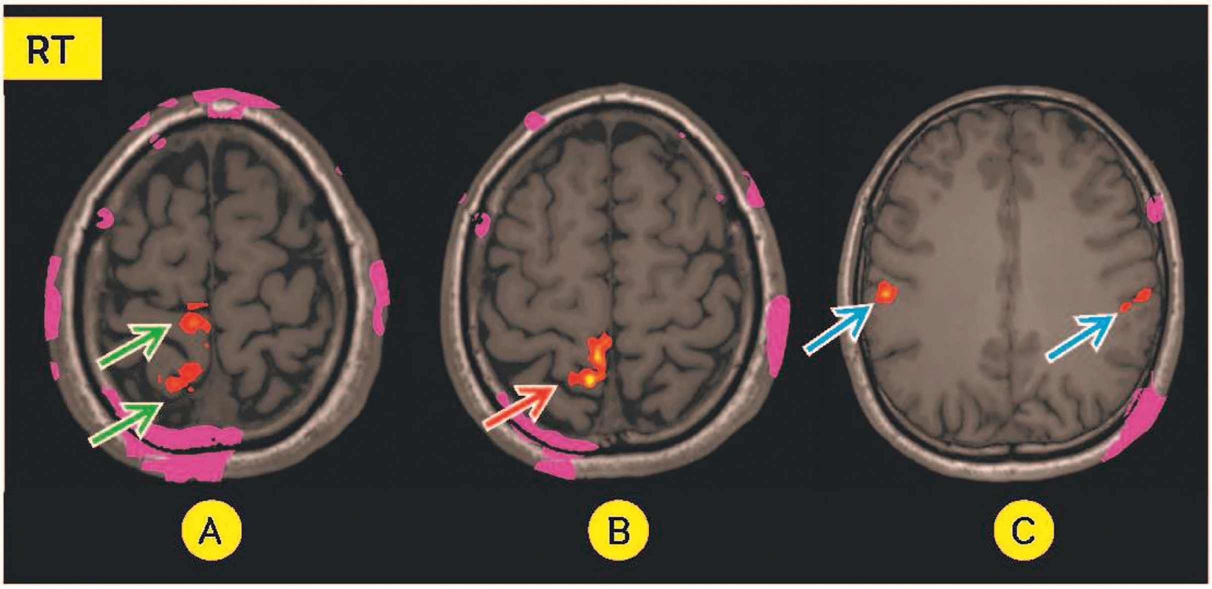

Figure 2: A 31-year-old smoking man. During massage on the left foot; intense signal at the right postcentral gyrus in B (red arrow), the present signal at precentral and postcentral gyri in A (green arrows), and the bilateral frontal lobes in C (blue arrows).

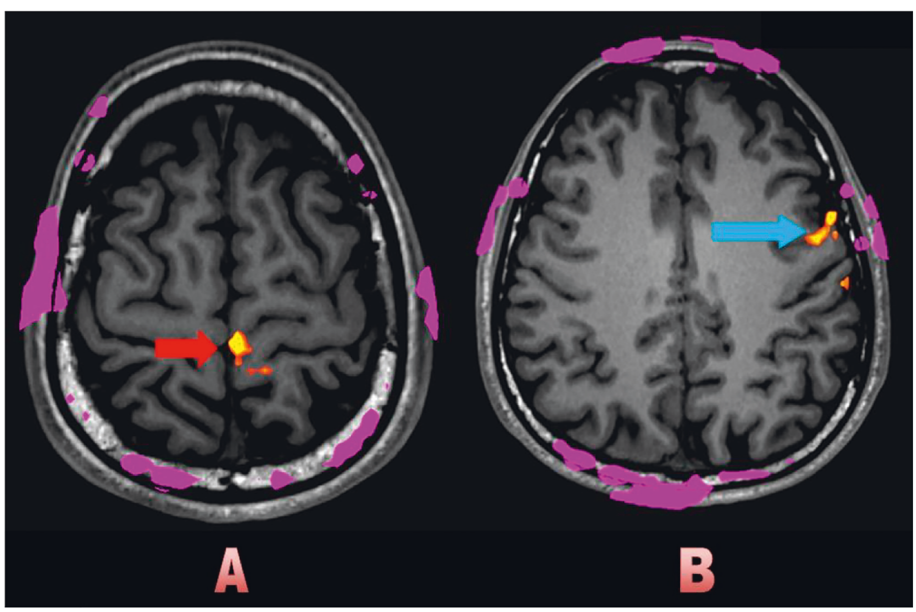

Figure 3: A 29-year-old nonsmoking man. During massage on the right foot; intense signal at the left precentral gyrus in A (red arrow), and the present signal at the left frontal lobe in B (blue arrow).

the experimental group and 38.8 years in the control group). One participant in the experimental group had hypertension. In comparison, two in the control group had hypertension and diabetes.

Table 2 shows the demographic data. According to the inclusion criteria, fifteen smokers in the experimental group had smoked for at least one year. Among the 15 smokers, five smoked domestic cigarettes (No. 17–21), and the rest smoked commercial ones (No. 7–16). The smoking duration ranged from 6 to 24 years averaging 16.2 years (standard deviation of 4.1 years). The number of cigarettes used per day ranged from 5 to 40 with an average of 21.9 (standard deviation of 10.7). Average carbon monoxide in breath ranged from 2 to 24 parts per million (ppm) with an average of 9.7.

When the ipsilateral foot gets massaged, the contralateral correlated cortex, such as the precentral gyrus of the frontal lobe and the postcentral gyrus of the parietal lobe (pre-and post-CG), basically expresses a present signal in the fMRI. The fMRI of the brain response in the area correlated with

Table 3: fMRI brain response during left foot stimulation.

Patient no.	Postcentral gyrus of the parietal lobe	Precentral gyrus of the frontal lobe	Other parts of the frontal lobe	Others parts of the parietal lobe	Occipital lobe	Temporal lobe	Postcentral gyrus of the parietal lobe	Precentral gyrus of the frontal lobe	Other parts of the frontal lobe	Other parts of the parietal lobe	Occipital lobe	Temporal lobe	Postcentral gyrus of the parietal lobe	Precentral gyrus of the frontal lobe
	Right hemisphere									Left hemisphere				
1	Present with an intense signal		Present							Present				
3	Present with an intense signal		Present				Present			Present				Present
4	Present		Present							Present				
5	Present with an intense signal	Present	Present							Present	Present			Present
6	Present		Present	Present			Present	Present		Present	Present			
7	Present with an intense signal		Present							Present				
8	Present with an intense signal	Present	Present						Present	Present				
9	Present	Present												
10	Present with an intense signal		Present	Present						Present	Present			
11	Present with an intense signal	Present	Present							Present				
12	Present	Present	Present							Present				
13	Present with an intense signal		Present							Present				
14	Present with an intense signal	Present	Present						Present	Present				
15	Present with an intense signal	Present	Present							Present				
16	Present		Present	Present						Present				
17	Present with an intense signal		Present	Present						Present	Present		Present	
18	Present	Present	Present							Present	Present			
19	Present	Present								Present				
20	Present with an intense signal	Present	Present							Present	Present		Present	
21	Present with an intense signal	Present	Present		Present					Present	Present		Present	Present

Table 4: fMRI brain response during right foot stimulation.

Patient No.	Right hemisphere: Postcentral gyrus of the parietal lobe	Precentral gyrus	Other parts of the frontal lobe	Other parts of the parietal lobe	Occipital lobe	Temporal lobe	Thalamus	Left hemisphere: Postcentral gyrus of the parietal lobe	Precentral gyrus of the frontal lobe	Other parts of the frontal lobe	Other parts of the parietal lobe	Occipital lobe	Temporal lobe	Thalamus
1								Present	Present	Present				
3	Present		Present	Present		Present	Present	Present with an intense signal	Present	Present	Present		Present	Present
4	Present		Present						Present	Present				
5			Present					Present	Present with an intense signal	Present				
6	Present		Present	Present	Present	Present	Present	Present		Present	Present			Present
7	Present							Present		Present	Present			
8			Present						Present	Present				
9	Present	Present												
10								Present	Present	Present				
11			Present	Present				Present		Present	Present			
12			Present					Present with an intense signal	Present	Present				
13							Present		Present				Present	Present
14			Present					Present with an intense signal	Present					
15			Present					Present with an intense signal	Present	Present				
16								Present	Present					
17				Present				Present with an intense signal		Present	Present			
18			Present	Present					Present	Present	Present with an intense signal			
19			Present					Present	Present	Present				
20			Present					Present with an intense signal	Present	Present			Present	Present
21	Present		Present		Present	Present		Present with an intense signal	Present	Present	Present		Present	Present

foot stimulation, including the precentral and postcentral gyri (pre-and post-CG), became intense or present for all participants (Figures 2(a), 2(b), and 3(a)). The signals became intense only at the right postcentral gyrus (sensory area) during left foot stimulation in 13 participants (Table 3). In comparison, the signals became intense during right foot stimulation at the left postcentral gyrus in seven participants (Table 4). We found the response outside the correlated pre- and post-CG, including other parts of the frontal cortex outside the precentral gyrus (Figures 2(c) and 3(b)), other parts of the parietal cortex outside the postcentral gyrus, occipital and temporal cortex, and thalamus, bilaterally (Tables 3 and 4). The fMRI response outside the correlated area in the cerebral hemisphere may lead to therapeutic effects.

4. Discussion

To the best of our knowledge, our study is the third report about the manifestations of the fMRI brain with foot reflexological stimulation [7, 12]. We find the activation signals outside the corresponding motor and sensory cortices, including the contralateral frontal, parietal, occipital, temporal cortices, and the thalamus with fMRI. The activation signals are inconsistent and various. Other brain reactions rather than the corresponding foot sensory areas detected by fMRI may imply that foot reflexology may affect other brain parts outside its motor and sensory territories. These fMRI manifestations are similar in both smokers and nonsmokers. Therefore, we cannot conclude whether these findings are positive phenomena for smoking cessation. The most well-known effects of foot reflexology are relaxation and pain relief [18]. We also do not know whether the positive results of foot reflexology on smoking cessation are its indirect consequences of relaxation.

The success rate of smoking cessation with bupropion, a standard medical treatment, is less than 50% [19]. The factors associated with successful smoking cessation are various [20]. Physicians usually provide patients with multimodal approaches to help them achieve absolute smoking cessation [21]. The successful smoking cessation rate of almost 50% with foot reflexology in a previous study is comparable to bupropion treatment but is much less expensive [17]. However, the mechanism of action from foot reflexology to the brain remains uncertain.

Due to lacking scientific evidence and unexplained mechanism of action, reflexology remains a nonstandard treatment. Healthcare professionals do not recommend reflexology for treating any medical diseases. Patients seeking reflexology may get delayed from the appropriate medical treatment. However, the relaxation effects and direct harmlessness are the advantages of reflexology. It is an excellent reason to apply reflexology in health promotion or disease prevention [22]. Due to its safety, reflexology has become an alternative treatment for pain relief and comfort during labor [23].

The limitations of our study include a small sample size, lacking smoking cessation outcomes, and no sham reflexology for comparison. The prospective randomized control trial of foot reflexology comparison with sham for smoking cessation programs using fMRI as a surrogate marker is suggested for further studies.

In conclusion, the fMRI of the brain is feasible and safe for demonstrating foot reflexology reactions. The response signal outside the correlated motor-sensory cortical area with foot reflexology may have clinical significance and may be helpful for smoking cessation. We suggest conducting a large-scale, randomized controlled trial to confirm these findings.

Data Availability

The fMRI raw data used to support the findings of this study have been deposited in the ResearchGate repository (DOI: 10.24203/ajas.v7i1.5743).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

PW contributed to the conception and design of the work, data collection, and drafting of the article; SM contributed to drafting and critical revision of the article and gave the final approval; MK and TK contributed to data collection; MK contributed to data collection and drafting of the article. All the authors, who have considerable contributions, approved the final manuscript. The corresponding author (SM) takes full responsibility for the contents of the paper.

Acknowledgments

This study was supported by the Center of Excellence in Stroke from Thammasat University and Tobacco Control Research and Knowledge Management Center (TRC) Research Funding.

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Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 9951693, 13 pages
https://doi.org/10.1155/2022/9951693

Research Article

Effects of Jie Yu Wan on Generalized Anxiety Disorder: A Randomized Clinical Trial

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Received 25 March 2021; Revised 30 January 2022; Accepted 14 March 2022; Published 8 April 2022

Academic Editor: Ruth Taylor-Piliae

Objective. To systematically assess the clinical efficacy of the *Jie Yu Wan* (JYW) formula in treating generalized anxiety disorder (GAD). *Methods*. A multicenter, prospective, double-blind, double-dummy, randomized controlled trial (RCT) was conducted at four hospitals in China. A total of one hundred thirty-three patients with GAD were enrolled from 2017 to 2019. This study aimed to evaluate the effects of a Traditional Chinese Medicine (TCM) JYW formula on GAD at eight weeks, with the use of Buspirone as the comparator. A stepwise dosing protocol was used (JYW: high dose 24 g/day, low dose 12 g/day; Buspirone: high dose 30 mg/day, low dose 15 mg/day) and the dose was adjusted depending on whether the treatment response of Hamilton Anxiety Scale (HAMA) score was less than or equal to 25% after one week. The primary outcome was a change in total score on the HAMA. The secondary outcomes included the Hamilton Depression Scale (HAMD), Clinical Global Impression (CGI) scale, and TCM Syndrome Scale. Adverse events were recorded using the Treatment Emergent Symptom Scale (TESS). Assessments were conducted at the baseline and 1, 2, 4, and 8 weeks. *Results*. A total of one hundred thirty-three participants were randomly assigned to the JYW group ($n = 66$) and the Buspirone group ($n = 67$). One hundred twenty-one patients (91%) completed at least one follow-up session. There were no significant differences between the two groups in terms of gender, age, disease course, HAMA, HAMD, CGI, and TCM Syndrome Scale scores at baseline (all $P > 0.05$). Repeated-measures analysis of variance revealed statistically significant time effects for the HAMA ($P = 0.002$), HAMD ($P = 0.018$), and CGI ($P = 0.001$) in both groups. Sensitivity analyses supported the credibility of the main results ($P > 0.05$). The group effect was not significant for the HAMA ($P = 0.43$), HAMD ($P = 0.27$), CGI ($P = 0.37$), and TCM Syndrome Scale ($P = 0.86$). Furthermore, there were no significant interaction effects between time and group in terms of the HAMA ($P = 0.47$), HAMD ($P = 0.79$), CGI ($P = 0.67$), and TCM Syndrome Scale ($P = 0.69$). After one week, 53 patients (80%) of the JYW group and 52 patients (78%) of the Buspirone group were adjusted to high doses. The interaction effect between time, group, and the dose was determined by repeated measures ANOVA test, and the HAMA score served as the outcome measure. The interaction effect between time and dose was statistically significant ($P = 0.04$), which shows that high-dose JYW (24 g/day) was more effective in decreasing patients' HAMA scores than low-dose JYW (12 g/day), and Buspirone had the same effect, which means that high-dose Buspirone (30 mg/day) was more effective than low dose. (15 mg/day). *Conclusions*. The conclusion of this study supports that JYW and Buspirone can effectively alleviate the anxiety symptoms of GAD patients, which are both effective and safe for treatment of mild to moderate GAD. Besides, high-dose JYW or Buspirone are more effective than low-dose, which is of great importance in assisting clinical medication choice.

1. Introduction

Generalized anxiety disorder (GAD) is a prevalent mental disease characterized by uncontrollable and excessive apprehension that persists in any environmental circumstance. Dominant symptoms include persistent nervousness, trembling, muscular tension, sweating, lightheadedness, palpitations, dizziness, and epigastric discomfort. [1] Epidemiological data indicate that the lifetime prevalence of GAD is 3.7–11%, and the 12-month prevalence rate is 1.8% [2–4]. GAD is a chronic, disabling, complex psychiatric disease that has a low rate of full remission, [4, 5] often having profound effects on quality of life and social function [6] and places a heavy financial and psychological burden on families and society [7, 8].

Available therapies for GAD include pharmacotherapy, psychotherapy, and combined treatment approaches. Prior to the 1980s, benzodiazepines represented the most prescribed medication for GAD. However, benzodiazepines are for short-term use only because of their adverse side effects (e.g., sedation, withdrawal symptoms). Antidepressant medicines such as sertraline (a selective serotonin reuptake inhibitor, SSRI) or venlafaxine (a serotonin-norepinephrine reuptake inhibitor, SNRI) are recommended when the symptoms of GAD cause significant functional impairment. However, their side effects may limit clinical applications. Buspirone is a non-benzodiazepine anxiolytic and 5-hydroxytryptamine (5-HT) 1A receptor agonist approved for treating GAD in adults, with fewer sedation or withdrawal symptoms. Its effectiveness and tolerance have been demonstrated in multiple, double-blind, placebo-controlled trials. However, it is not the preferred first-line therapy for GAD due to its delayed onset of action [9–11]. Therefore, it is necessary to explore other appropriate and safe therapeutic approaches for the treatment of GAD.

Traditional Chinese medicine (TCM), a treatment modality that has been used in China for several thousand years, has attracted increasing attention in anxiety therapy [12]. GAD belongs to the category of "visceral impatience" in TCM. The main causes are six excessive pathogenic factors: internal injury due to seven emotions, lingering illness, yin-yang disharmony, flaring of heart fire, damage of nutrient qi and yin fluid, and uneasiness affecting the spirit. The *Jie Yu Wan* (JYW), a Chinese patent medicine, was derived from the Gan Mai Da Zao decoction and Xiao Yao San, the famous TCM formulated to treat depression and anxiety. The JYW formula was prepared in the form of concentrated pills and comprised of 10 medicinal compounds: Paeoniae Alba, Bupleuri, *Angelica sinensis*, turmeric, Poria, lily, *Albizia julibrissin*, licorice, light wheat, and jujube. This medicine is approved by the China Food and Drug Administration (CFDA) for treating depression and anxiety with the CFDA ratification number of GuoYaoZhunZi-B20020101. Previous studies have shown that the antidepressant therapeutic actions of JYW are potentially mediated through the adjustment of 5-HT and noradrenaline (NE) levels and the attenuation of the monoamine oxidase activity of multiple brain areas including hypothalamus, hippocampus, and prefrontal cortex. Besides, JYW exhibited anxiolytic effects by increasing the time percentage in the elevated plus-maze and has no significant inhibitory effects on the central nervous system [13, 14]. Finally, previous clinical studies have also proved that JYW has shown remarkable efficacy on GAD with few side effects [15]. The abovementioned findings suggest that JYW may have a therapeutic effect on GAD. Thus, the primary aim of this study was to assess the efficacy and safety of JYW in the treatment of GAD, which may provide a potential clinical treatment option.

2. Materials and Methods

2.1. Study Design. This study was a randomized, prospective, double-blind, double-dummy, and multicenter clinical study. Five hospitals in China participated in this trial, and Beijing Anding Hospital is the leading unit. The participating hospitals included Tangshan Fifth Hospital, Zhumadian Mental Hospital, Hangzhou Seventh People's Hospital, and Xiamen Xian Yue Hospital. All experimental procedures and protocols were approved by the institutional ethics committee of the Beijing Anding Hospital ((2017)63-201772FS-2) and registered on the Chinese Clinical Trial Registry website (ChiCTR-IPR-17013058). Participants were recruited from outpatient and inpatient departments at each center. They were informed of the detailed information and potential risks of the study by verbal and written information. Patients provided written informed consent prior to participating in the study, and their personal information was treated as confidential by the study staff. Participants who met the inclusion criteria were randomly allocated to visit into a JYW group or a Buspirone group at a 1 : 1 ratio. A stepwise dosing protocol was used, the dose was adjusted depending on whether the treatment response of HAMA score was less than or equal to 25% after one week. Outcomes were measured at baseline, and weeks one, two, four, and eight.

2.2. Participants. All patients meeting the following criteria were eligible for inclusion in the study: (1) aged 18 to 65 years old; (2) met the International Classification of Disease-10 (ICD-10) criteria for a primary diagnosis of GAD; [16] (3) met the TCM diagnostic criteria for fire derived from the stagnation of Liver-QI, including emotional impatience, irritability, fullness in the chest and hypochondrium, dry mouth, bitter mouth, constipation, headache, conjunctival congestion, tinnitus, reddened tongue with yellow fur, and pulse number; (4) Hamilton Anxiety Scale (HAMA) score >14 points and ≤ 29 points at screening and baseline; and (5) informed consent form signed by the participant or legal guardian.

2.3. Exclusion Criteria. Patients who met any of the following criteria were excluded from the study: (1) presence of glaucoma, any serious internal disorder affecting vital organs (i.e., heart, liver, kidney, endocrine, acute blood diseases), or acute and chronic inflammatory disease (e.g., systemic lupus erythematosus, ulcerative colitis); (2) experiencing suicidal ideations, history of epilepsy (except for febrile convulsion in childhood), or alcohol or medicine dependence within the past year; (3) anxiety secondary to other mental or physical diseases; (4) pregnant or breastfeeding during the study period; (5) history of Buspirone allergy or other medicine allergies; (6) participated in any other investigational medicine studies or clinical trials within the past 30 days or having taken monoamine oxidase inhibitors or Buspirone in the past four weeks; (7) without a guardian or unable to follow the directions of the medication; and (8) HAMA score reduction rate >25% [17, 18] or Hamilton Depression Scale (HAMD)17 item score >7 between screening and baseline (3–7 days).

2.4. Randomization and Masking. A random allocation sequence was generated by a trained statistician using statistical analysis system (SAS) software (SAS Institute, Cary, NC). Participants who met the inclusion criteria were randomly allocated to visit into two groups (i.e., treatment or control group) at a 1 : 1 ratio. Each patient was assigned a bag used to distribute the medicines. It remained unchanged throughout the study. An individual not directly involved in the study carried out medicine blinding, labeling, and packaging. The blinding codes were preserved and protected separately by Beijing Anding Hospital and the manufacturing company. An emergency letter could only be opened in the case of a serious adverse event. Researchers responsible for screening and recruiting participants, dispensing medicines, and outcome evaluation were blinded to group allocation throughout the study. Statistical analyses were carried out by independent statisticians who were only aware of group codes and were blinded to group allocation. The treatment medicine and matching placebo had a similar appearance, weight, and taste to maximize participant blinding.

2.5. Interventions. As detailed above, study participants were assigned to one of two groups: a JYW group (JYW formula and Buspirone placebo) or a Buspirone group (Buspirone and JYW placebo). The JYW formula was prepared in the form of concentrated pills (total weight = 4 g) and comprised of 10 medicinal compounds: *Paeoniae Alba* (1.14 g), Bupleuri (0.86 g), *Angelica sinensis* (0.57 g), turmeric (0.57 g), Poria (0.69 g), lily (0.69 g), *Albizia julibrissin* (0.69 g), licorice (0.34 g), light wheat (0.86 g), and jujube (0.57 g). The JYW is a Chinese patent medicine that has been approved for marketing in China. The dosage of JYW was obtained from the historical records in ancient literature, which combined modern experimental techniques and multiple clinical trials, to define the clinically effective safe doses [13, 14]. The JYW formula and placebo were supplied by Tiansheng Taifeng Pharmaceutical Co., Ltd. (Lhasa, Tibet, China, GuoYaoZhunZi-B20020101). The Buspirone and placebo were supplied by Enhua Pharmaceutical Co., Ltd. (Xuzhou, Jiangsu Province, China).

A stepwise dosing protocol was used in this study: Low dose-JYW formula or placebo (4 g, t.i.d.) with Buspirone or its placebo (5 mg, t.i.d.); and high dose-JYW formula or placebo (8 g, t.i.d.) with Buspirone or its placebo (10 mg, t.i.d) [19]. In the first week, patients were assigned a low dose. If the decline in HAMA score was ≤25% of the baseline score, [15] then a double dose or high dose was selected as the second-week dose. Otherwise, the low dose was used (Figure 1). The doses of JYW and Buspirone have been based on the medicine instructions and the pre-experimental study [20, 21].

Medicines were prepackaged to facilitate administration and placed into envelopes along with information about the visit period, drug number, instructions for use, and storage conditions. Pharmacists who were not involved in the study were responsible for dispensing the medicines. Participants were given detailed verbal and written instructions about how to take the medicine. They were also asked to return the previous treatment cycle's medication and receive the next treatment cycle's medication at the end of each visit. Treatment was continued for eight weeks unless a severe adverse event occurred or a participant withdrew from the study. Antipsychotics, strategic and systematic psychological therapy, or other physical therapies such as electroconvulsive therapy, MECT, transcranial magnetic stimulation, and transcranial direct current stimulation were not allowed. Patients were permitted to take prescribed medicines for their somatic disease which were recorded in detail.

2.6. Adverse Event and Serious Adverse Event. Adverse events (AE) were assessed at each visit. An AE was defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with this study. All AE were considered into "possibly related," "probably related", or "definitely related." According to the following criteria: (1) Possibly related: The occurrence of AE may be caused by the medicine. It cannot be determined whether the AE was caused by other factors, such as concomitant medications or concomitant diseases. The occurrence of AE was logically related to the timing of investigational medicine use, so a causal relationship between events and medicine use cannot be ruled out. (2) Probably related: The occurrence of AE may have been caused by the use of the investigational medicine. The timing of events is suggestive, such as adverse effects that subside after drug withdrawal. It is unlikely that other factors explain the phenomenon, such as concomitant medications or concomitant diseases. (3) Definitely related: The type of AE has been considered to be a side effect of the investigational drug and cannot be explained by other factors, such as concomitant medications and concomitant diseases. The timing of events strongly suggests a causal relationship, such as the response to withdrawal and administered again.

For the AE that occurred during the study period, the symptoms, degree, time of occurrence, duration, treatment measures, and procedures should be recorded in the case report forms (CRFs), and the correlation between the AE and the medicines should be evaluated. The occurrence of any of the following conditions should be regarded as a serious adverse event: hospitalization, prolonging hospital stay, permanent disability, affect work ability, life threatening emergencies or death, and cause congenital

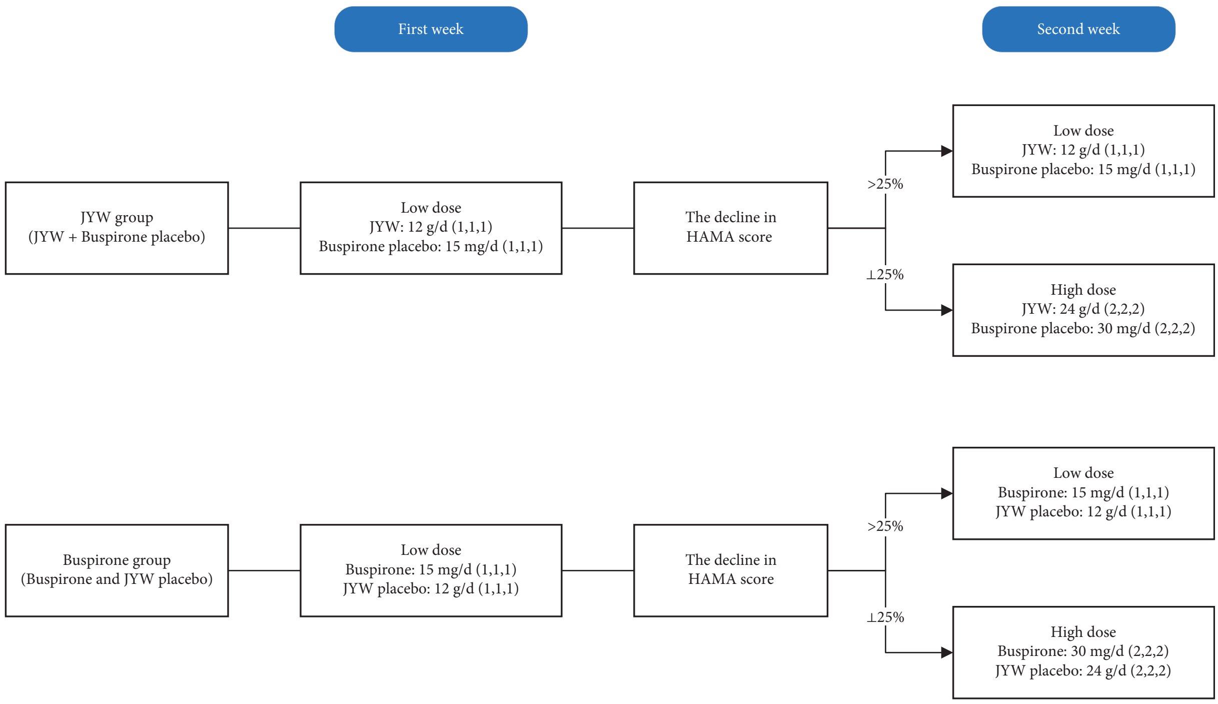

Figure 1: Detailed dose schedule. The number in () refers to the number of tablets taken in the morning, midday, and evening. 12 g/d, where "*d*" refers to day, not dose.

malformations, etc. All serious adverse events should be recorded in the serious adverse event report form.

AEs and SAEs were recorded at every study visit, using the treatment-emergent symptom scale (TESS). The researchers determined the correlation between adverse events and the experimental medicines.

3. Outcomes

Within 3–7 days screening period, all patients underwent a baseline evaluation, including demographic information (name, gender, age), medical history, physical and neurologic examination, and laboratory testing. Study day 1 was defined as the first day patients met enrollment criteria. Outcomes were measured at baseline and at weeks one, two, four, and eight.

The primary outcome was the change in HAMA score from baseline to 8 weeks. The HAMA is a 14-item diagnostic questionnaire used in the clinical and research setting to measure the severity of anxiety symptoms, involving two types of symptoms factors-psychic anxiety and somatic anxiety. The items are scored on a five-point scale (0 = not present to 4 = very severe). The total score is 0–56. It was divided into an absence of anxiety (0–6), possible anxiety (7–13), mild anxiety (14–20), moderate anxiety (21–28), and severe anxiety(29–56) [22]. The HAMA score has good reliability and acceptable validity to measure the severity of participants' anxiety [23, 24].

Secondary outcomes included changes in the HAMD, Clinical Global Impression (CGI) scale, and TCM Syndrome Scale. Depression severity was measured by using the 17-item HAMD scale. Evaluation criteria and methods were essentially identical to the HAMA's. The scale's seven-factor structure includes anxiety and somatization, weight, cognitive disorders, diurnal variation, block, sleep disorder, and hopelessness. [25] It has a high overall reliability as depressive outcome measure [26]. The CGI scale was used to assess the clinical efficacy of treatment. The scale was applicable across a broad range of psychiatric populations and consists of three items that assess the severity of illness, global improvement, and efficacy index [27]. The CGI has the characteristics of utility, sensitivity to change, and reliability in psychiatric research [28]. The TCM Syndrome Scale was developed by the Chinese medical team of experts. It contained over 90 items, assessing (n): mental symptoms (11), the head and face (7), the heart and chest (10), gastrointestinal symptoms (25), urologic symptoms (14), the reproduction system (10), and limb symptoms (11). In addition, two other TCM syndrome characteristics (i.e., tongue coating and pulse) are recorded as part of the scale. We used the two-round Delphi method to reach consensus. (See additional file for the process of the Delphi method). The evidence of reliability was conducted with the reliability coefficient of Cronbach's alpha ($\alpha = 0.935$), which means that reliability of this questionnaire is high. The main safety parameters included routine blood tests (i.e., red blood cell (RBC), hemoglobin (HB), white blood cell (WBC), and platelet counts), routine urine tests (i.e., urine protein, urine sugar, WBC, RBC), a urine pregnancy test (when screening female patients), blood biochemistry tests (i.e., alanine aminotransferase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), serum creatinine (Cr), and glucose and electrocardiograms (ECGs), which were carried out at baseline and the end of the 8 week intervention.

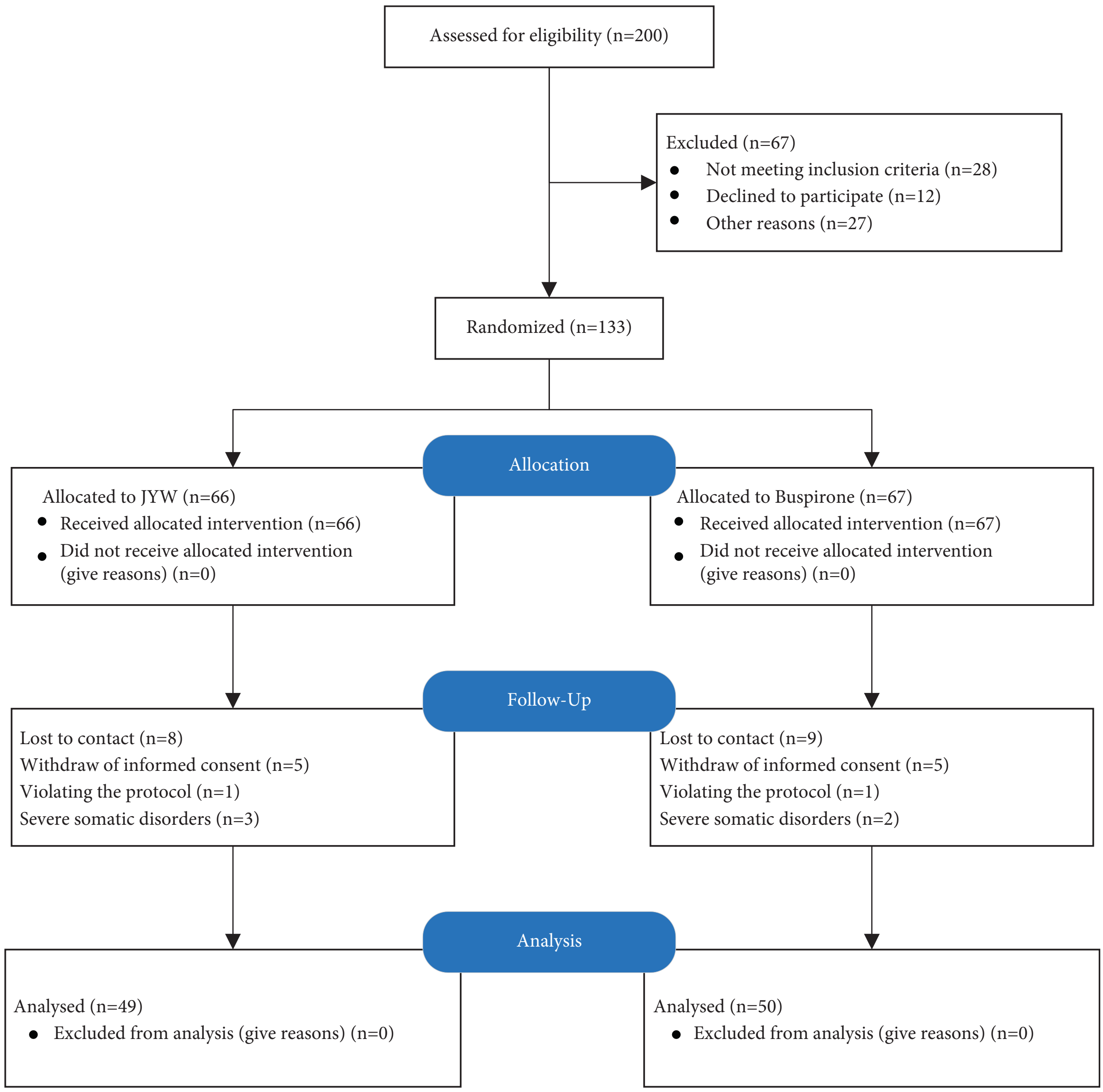

Figure 2: Study flowchart.

4. Statistical Analysis

Initially, the primary aim of the trial was to investigate the clinical efficacy of JYW in treating GAD, as stated in our protocol paper [19] and on ChiCTR-IPR. Base on the prior study, the response rate was 75% of Buspirone [29] and a response rate of 90% for JYW was assumed [15, 30, 31]. A prior power analysis was conducted with PASS Software version 15.0.5 (https://www.ncss.com/software/pass/), using an alpha of 0.05, a power of 0.8, and small to medium effect size (0.43) to determine the sample size. The sample size calculated was 83 for each group. Considering a dropout rate of 20%, a total of 200 participants were finally required.

Analyses and reporting were carried out in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines. [32](Table S1) CRF data were entered into EpiData 3.0 by two independent researchers in a double-blinded manner. Data were first examined for accuracy and consistency of data entry. A statistician blinded to the allocation of groups analyzed the data using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, N.Y.). Continuous variables were presented as means $\pm$ standard deviations (SDs), while categorical variables were presented as frequencies or percentages. Baseline data were compared between the two groups using *t*-tests (normally distributed data), nonparametric tests (non-normally distributed data), and Chi-square tests. Repeated-measures analysis of variance (ANOVA) was used to evaluate primary and secondary outcomes. The significance of differences between the two methods was evaluated by noninferiority tests. Sensitivity analysis is mainly used to evaluate the robustness of the primary outcomes. Sensitivity

Table 1: Demographic and baseline data ($x \pm s$).

	JYW ($n = 66$), n (%)	Buspirone ($n = 67$), n (%)	t/x^2	P
Age	46.96 ± 12.31	45.55 ± 10.84		
<30	8 (12.12%)	5 (7.5%)	0.70	0.49
30–50	28 (42.42%)	35 (52.23%)		
>50	29 (43.94%)	27 (40.29%)		
Gender				
Male	22 (33.33%)	21 (31.34%)	1.03	0.60
Female	44 (66.67%)	46 (68.57%)		
Race				
Han	65 (98.48%)	64 (95.52%)	−0.58	0.56
Minorities	1 (1.5%)	2 (3%)		
Educational level				
Primary education or less	6 (9.1%)	8 (12.94%)		
Secondary education	32 (48.48%)	34 (50.75%)	0.33	0.74
Tertiary education	28 (42.42%)	25 (37.31%)		
Duration	0.5 (0,1.85)	0.67 (0,2.08)		
≤12 months	36 (54.55%)	36 (53.73%)		
12 < months < 25	16 (24.24%)	15 (22.39%)	−0.71	0.48
25 < months < 36	6 (9.1%)	5 (7.5%)		
>36 months	8 (12.12%)	11 (16.42%)		
Baseline HAMA[a]	18.95 (4.07)	19.09 ± 3.92		
14 ≤ HAMA ≤ 21	51 (77.27)	47 (70.15)	−0.57	0.57
21 < HAMA ≤ 29	15 (22.73)	20 (29.85)		
Baseline HAMD[a]	6.79 ± 1.26	6.87 ± 1.39	−0.41	0.68
Baseline CGI[a]	3.73 ± 0.97	3.80 ± 0.83	−0.77	0.67
Baseline TCM syndrome[a]	102.42 ± 38.12	99.52 ± 42.39	0.50	0.62

[a]Data are presented as n (%) or mean (SD). Duration: the disease duration of GAD.

analysis was conducted using t-test with four-week HAMA scores as the dependent variable and time as the independent variable. [33]The efficacy analysis was performed according to the intention-to-treat principle (ITT) and conducted on the Full Analysis Set (FAS), which comprised of all randomized participants. The main analysis data set comprised all randomized participants that took their assigned drug on at least one occasion. Missing data were imputed by using the Last-Observation-Carried-Forward (LOCF) method. Statistical significance was defined as $P < 0.05$.

5. Results

5.1. Comparison of Baseline Data. A total of 133 eligible patients were randomly allocated into a Buspirone ($n = 67$) and JYW ($n = 66$) group from January 1, 2017, to August 31, 2019. All patients completed the baseline assessment, 121 (91%) patients completed at least one follow-up evaluation, and 99 (75%) patients completed the 8-week treatment period. The proportions of patients attending each follow-up visit were similar in both groups. Data from 34 patients were imputed using the LOCF method (Figure 2).

Overall, 99 patients completed the study, with 49 in the JYW group and 50 in the Buspirone group. Participants were well matched for age, sex, race, and education level (Table 1). The mean (SD) age of patients was 46.25 years (SD = 11.57); the majority patients were female (67.42%) and Han race (97.72%). 75 (56.81%) patients with a duration less than 12 months, and 19(14.39%) patients with a duration more than 36 months. The mean HAMA score was 19.02 (SD = 3.98), with 89 (67.42%) patients scoring between 14–21 and 44 (33.33%) patients exceeding a score of 21 (Table 1).

5.2. Change of the HAMA Score in Two Groups. Due to attrition and missing data, 99 patients were included in the analysis of the primary outcome. The mean of 8-week HAMA scores were 6.67 (SD = 4.04) in patients allocated to the JYW group and 8.22 (SD = 4.63) in patients allocated to the Buspirone group. The change in HAMA scores of the two groups during the experimental period is shown in Table 2. Repeated-measures ANOVA revealed a significant time effect (F (1.76,170.37) = 300.36, P = 0.000), but no significant group effect (F (1.00,97.00) = 0.78, P = 0.38), and interactive effect between groups and time (F (1.76,170.37) = 0.94, P = 0.38) (Table 2, model1).

Data from all participants were included in the efficacy analysis, according to the ITT principle, therefore, 133 participants were included in the FAS set analysis. The mean of 8-week HAMA scores were 9.21 (SD = 6.69) in patients allocated to the JYW group and 10.28 (SD = 4.68) in patients allocated to the Buspirone group (Table 2, model 2). We found that the results were consistent.

Sensitivity analyses were performed using t-test analysis to assess the stability of the results, using four-week HAMA scores as the dependent variable and time as the independent variable. The results of this analysis confirmed the results of the primary analysis (Table 2, models 3).

Patients who had less than 25% reduction in HAMA scores on day 7 were adjusted to high dose according to the

Table 2: Primary outcome analyses (the HAMA total score).

	n	JYW, mean (SD)	*n*	Buspirone, mean (SD)	*F*	*P*
Model 1	49		50			
Baseline		18.8 (3.73)		19.14 (3.66)		
1 week		16.31 (3.60)		16.58 (3.83)		
2 weeks		13.37 (4.00)		13.72 (4.82)		
4 weeks		10.31 (4.56)		11.06 (5.02)		
8 weeks		6.67 (4.00)		8.14 (4.62)		
Time effect		. . .		. . .	300.36	0.001
Group effect		. . .		. . .	0.78	0.38
Group ∗ time[a]		. . .		. . .	0.78	0.38
Model 2	66		67			
baseline		18.95 (4.07)		19.09 (3.92)		
1 week		16.65 (4.15)		16.58 (4.07)		
2 weeks		14.14 (4.72)		14.85 (5.31)		
4 weeks		11.91 (6.09)		12.58 (6.02)		
8 weeks		9.21 (6.70)		10.28 (4.68)		
Time effect		. . .		. . .	193.54	0.001
Group effect		. . .		. . .	0.55	0.46
Group ∗ time[a]		. . .		. . .	0.49	0.57
Model 3	53	10.79 (5.60)	54	11.00 (5.15)	−0.20	0.84
Model 4	53	10.79 (5.59)	54	5.3 (5.15)	5.27	0.001

Data are presented as mean (SD). The adjusted proportional difference can be interpreted as the difference in scores between the randomized groups, expressed as a proportion (or percentage). Model 1: primary analysis model, includes data for participants who completed the entire study ($n = 99$). Model 2: ITT analysis conducted on the FAS ($n = 133$). Model 3: sensitivity analyses ($n = 108$). Model 4: noninferiority test and analysis ($n = 108$). [a]Interaction effect between group and time.

study protocol (Figure 1). 53 patients (80%) of the JYW group and 52 patients (78%) of the Buspirone group were adjusted to high dose after one week. There was no statistically significant difference in the rate of attrition between the groups at baseline. The interaction effects between time, group, and dose were analyzed by multivariate analyses, using time as within-subjects factor, and dose and group as between-subjects factors. There was a significant time effect (F (1.71,195.10) = 12.02, $P < 0.001$), and the interaction effect between time and dose was statistically significant (F (1.71,195.10) = 3.38, P = 0.04), showing that high-dose had a significant better compared to low dose. However, no significant differences were found between JYW and Buspirone (F (1.71,195.10) = 1.34, P = 0.26).

Noninferiority analysis was conducted to verify the efficacy of JYW in treatment of GAD was not inferior to Buspirone. According to the previous studies and the guidance method of noninferiority test, the noninferiority margin of Buspirone was 5.7 [34, 35]. The score of JYW group remained unchanged, and the *t*-test was carried out ($P < 0.001$). The result indicated that JYW was noninferior to Buspirone (Table 2, model 4).

The time trend effect was estimated by using a repeated-measures ANOVA model, with time as the independent variable. The plot clearly showed a decreasing time trend effect in both two groups. Although the decrease in the HAMA score in the JYW group during the intervention was greater than in the Buspirone group, the two groups showed no evidence of interaction effect (Figure 3).

5.3. Change of the HAMD, CGI, and TCM Syndrome Score in Two Groups. Table 3 displayed the index change in the two groups before and after treatment, involving HAMD, CGI, and TCM syndrome. The adjusted proportional difference in HAMD scores across eight weeks was 3.14 (95% CI = 2.73–3.54). After eight weeks of treatment, there was a significant time effect in HAMD scores (F (2.16,282.51) = 90.79, $P = 0.018$]. We observed the similar results for the CGI. Specifically, the adjusted proportional difference in CGI scores across four weeks was 2.23 (95% CI = 2.09–2.36) and a significant time effect in CGI scores (F (1.96,256.82) = 146.16, P= 0.001). Differences in TCM Syndrome Scale scores did change over time (F (1.71,224.54) = 156.81, $P = 0.001$). There was no group effect for HAMD (F (1.00,131.00) = 0.71, $P = 0.27$), CGI (F (1.00,131.00) = 0.26, $P = 0.37$), and TCM Syndrome Scale (F (1.00,131.00) = 0.01, $P = 0.86$). We did not observe any significant interaction effects between time and group for HAMD (F (2.16, 282.51) = 0.22, $P = 0.79$), CGI (F (1.96,256.82) = 0.31, $P = 0.67$), or TCM Syndrome Scale (F (1.71,224.54) = 0.65, $P = 0.69$) (Table 3).

5.4. Comparison of the Incidence of Adverse Reactions between Two Groups. Based on the Council for the International Organization of Medical Sciences (CIOMS), adverse events with a frequency ≥10% were classified as very common and with a frequency ≥1% but <10% were classified as common. 5 very common adverse reactions occurred in the Buspirone group: dry mouth (18%), insomnia (14%), constipation (12%), weight gain (12%), skin symptoms (12%). Insomnia (12%) was the only very common adverse reaction that occurred in the JYW group. 14 common adverse reactions occurred in the Buspirone group. Specifically, the incidence rate of nasal congestion, sweat, nausea, and vomiting, diarrhea, tachycardia, loss of weight, and headache was 2%; the incidence rate of excitement, a hematological abnormality,

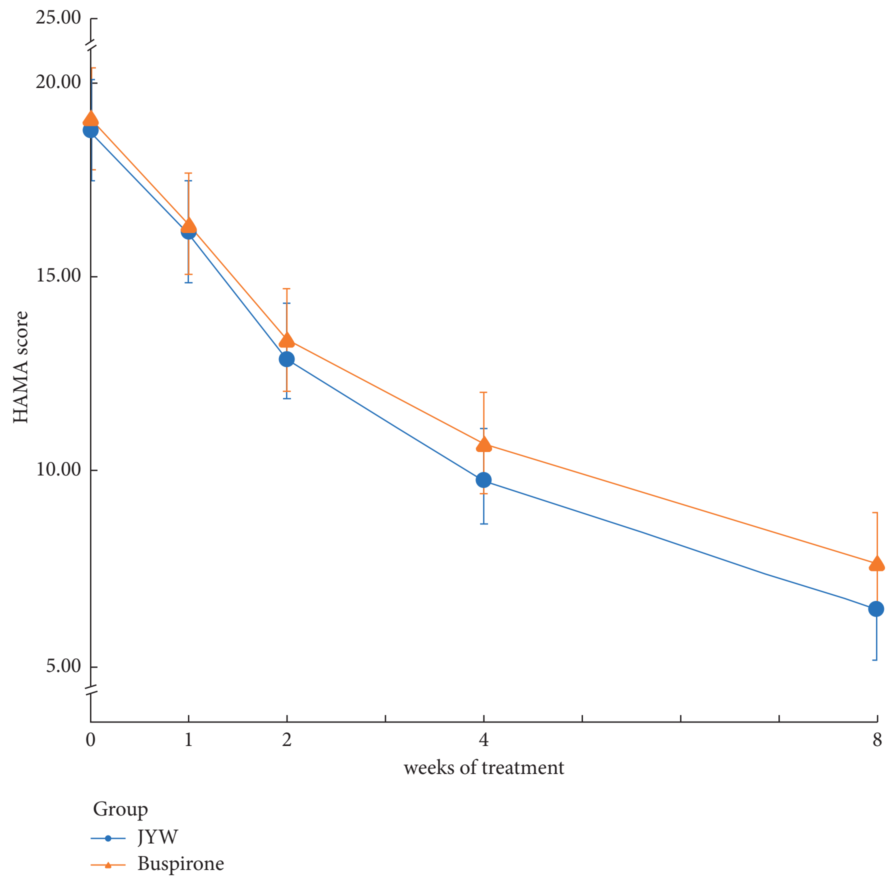

Figure 3: Changes in score from baseline on HAMA over time. The time trend effect was estimated using a repeated-measures ANOVA model, with time as the independent variable. The abscissa axis indicates weeks of treatment. The baseline, 1,2,4, and 8 weeks' time points are displayed. The ordinate shows the mean HAMA scores of every time point.

myotonia, and anorexia was 4%; the incidence rate of sleep and blurred vision was 6%, and the incidence rate of liver function was 8%. 15 common adverse reactions occurred in the JYW group. Specifically, the incidence rate of excitement, a hematological abnormality, tremor, dry mouth, nausea and vomiting, diarrhea, hypotension, weight gain, skin symptoms, and headache was 2%; the incidence rate of tremors hypokinesis, liver function, constipation, and increased saliva was 4%; and the incidence rate of depression was 6%. A chi-squared test was used to analyze the TESS results. The difference between the two groups was statistically significant at eight weeks ($P = 0.021$), which means that the side effect of JYW was less than the Buspirone. The most obvious are the nervous system ($P = 0.02$) and the cardiovascular system ($P = 0.047$), which showed that the adverse reactions of the nervous system and the cardiovascular system in JYW group were mild. Systems incidence rate of adverse reactions in the JYW group was significantly lower compared with that in the Buspirone group (Table S2).

6. Discussion

To the best of our knowledge, this was the first randomized controlled trial (RCT) that compared the effectiveness of JYW and Buspirone for the treatment of GAD. The majority of enrolled patients presented with mild to moderate GAD. Outcomes included HAMA, HAMD, CGI, and TCM syndrome. The results indicated that the antianxiety effects of JYW was noninferior to Buspirone. The HAMA score of the JYW group decreased over time ($P < 0.001$), which to be noninferior to Buspirone group at weeks 1, 2, 4, and 8 post-treatments. There were no significant differences between the two groups ($P > 0.05$). In addition, efficacy findings confirmed that high-dose JYW (24 g/day) had a higher significant of decrease patients' HAMA scores than low-dose JYW (12 g/day) ($P < 0.05$) and Buspirone had the same effect, which means that high-dose (30 mg/day) had a better effect than low-dose (15 mg/day) ($P < 0.05$). Our results showed that JYW was a new treatment approach that could improve mental health and physical symptoms in patients with mild to moderate GAD.

Findings from this trial demonstrate that JYW was not inferior to Buspirone with regard to clinical anti-anxiety efficacy in context, both are effective regimen for treatment of GAD. However, in terms of side effects, the cardiovascular and nervous system side effects in the JYW were relatively mild, which is expected to be more easily accepted by patients with GAD. Previous literature studies reported that the Buspirone may lead to the malignant syndrome [36], but no data were reported for JYW. Buspirone is a partial 5-HT1A receptor agonist. The mechanism of action for

Table 3: Repeated measures analyses of continuous secondary outcomes at weeks 1–8.

	JYW, mean (SD) ($n = 66$)	Buspirone, mean (SD) ($n = 67$)	F	P
HAMD				
Baseline	6.75 (0.20)	6.95 (0.20)		
1 week	5.88 (0.18)	6.12 (0.18)		
2 weeks	4.99 (0.23)	5.17 (0.23)		
4 weeks	3.91 (0.30)	4.46 (0.30)		
8 weeks	3.02 (0.29)	3.25 (0.29)		
Time effect	...	...	90.79	0.001
Group effect	...	...	0.71	0.40
Group ∗ time[a]	...	...	0.22	0.82
CGI				
Baseline	...	...		
1 week	3.42 (0.61)	3.45 (0.63)		
2 weeks	2.95 (0.62)	3.09 (0.85)		
4 weeks	2.56 (0.95)	2.60 (0.95)		
8 weeks	2.17 (1.13)	2.24 (1.14)		
Time effect	...	...	146.16	0.001
Group effect			0.26	0.61
Group ∗ time[a]	...	...	0.31	0.73
TCM syndrome				
Baseline	102.42 (38.12)	99.52 (42.39)		
1 week	89.94 (37.32)	89.43 (40.47)		
2 weeks	77.35 (37.65)	79.90 (42.81)		
4 weeks	67.53 (40.81)	68.60 (43.91)		
8 weeks	55.58 (42.83)	57.84 (44.72)		
Time effect	...	...	156.81	0.001
Group effect			0.01	0.94
Group ∗ time[a]	...	...	0.66	0.50

[a]Interaction effect between group and time.

Buspirone is well-characterized, which has a strong affinity for serotonin 5HT1a receptors [33]. In contrast, due to the variety components of JYW, the detailed mechanism behand JYW needs further investigation.

According to neurobiological studies, GAD may be associated with declines in cerebral blood flow and metabolic function, neuroanatomical impairments involving regions such as the amygdala and dorsolateral prefrontal cortex, neurotransmitter abnormalities, and altered adrenergic function. [37–40] Further, the immune-mediated inflammatory disease may induce the hippocampus, hypothalamus, medulla oblongata, brain stem, and other parts of the brain to dysregulate the release of histamine, serotonin, and other neurotransmitters, leading to anxiety or depression [41]. Another study mentioned that the level of inflammatory cytokines such as Interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP) in patients with GAD is different from the general population. [42] It affects the pathophysiological process and plays an important role in the immune regulatory response of GAD [43].

JYW is fabricated from the Xiao Yao San (XYS) and Gan Mai Da Zao (GMDZ) decoction. Preclinical studies have been conducted with these components in order to understand the potential mechanisms of action of XYS and GMDZ. First, animal experiments have demonstrated the potent antianxiety effect of XYS and GMDZ. Specifically, XYS improves anxiety or depressive-like behavior by modulating gut microbiota and immune function, regulating the Apelin-APJ System in the hypothalamus, and the structure of related brain regions. [44–47] The GMDZ decoction possesses anxiolytic-like effects in elevated plus-maze, light/dark box, and open field tests in mice, which are similar to those observed with diazepam and Buspirone. The mechanism of action may be related to the regulation of 5-HT, NE, the hypothalamic-pituitary-adrenal (HPA) axis, and γ-aminobutyric acid $_A$ (GABA $_A$) receptors [48, 49]. Second, JYW contains complex chemical compositions. Several studies of the pharmacological mechanism of herbs, including both animal experiments and clinical trials, support the antianxiety effects. Thus, some pharmacological lines of reasoning may explain the effects of JYW. For example, Radix Bupleuri extracts include in the prescription exhibited various biological activities (e.g., anti-inflammatory, neuroprotective, and immunomodulatory effects) [50] that can ameliorate depression symptoms by increasing serum levels of Nerve Growth Factor (NGF) and Brain-Derived Neurotrophic Factor (BDNF) [51]. The Radix Bupleuri and Radix Paeoniae Alba drug pair can significantly elevate the concentrations of 5-HT and NE in the hippocampal and cortical tissues [52, 53]. Several studies have found that extracts from the fractions of *Angelica keiskei*, the active constituent of *Curcuma longa*, and the flavonoid-rich ethanol extracts of licorice root have potential sedative and anxiolytic effects [54–56]. Various studies of Poria Coco's fungus have demonstrated its marked anti-inflammatory activity in different experimental models of acute and chronic inflammation [57]. Third, GAD belongs to the category of "visceral impatience" in TCM. The main causes are six excessive pathogenic factors including internal injury due to seven emotions, lingering illness, yin-yang disharmony, flaring of heart fire, damage of nutrient qi and yin fluid, and uneasiness affecting the spirit. Fire derived from the stagnation of Liver-QI is the most common type of GAD [58]. XYS and GMDZ decoction is a classic TCM prescription, first written by Zhang Zhong-jin, commonly used for the treatment of depression and lily disease. It should be noted that the clinical manifestations of depression or lily disease recorded by ancient texts were very similar to that of GAD (e.g., fidgeting and irritability, sleep disorder, headache and dizziness, expansion, fullness in both flanks). Previous research also has confirmed that these two prescriptions were safe and might effectively improve anxiety and TCM symptoms in patients with GAD, and improving sleep quality and quality of life [59, 60].

This study has several limitations. First, although several studies have suggested that TCM can regulate inflammatory responses, [61, 62] it is unclear whether JYW has a similar function. This study was conducted as a clinical investigation, we only used scale to evaluate reductions in anxiety symptoms. Further investigation in the biological mechanism of action is needed. Second, TCM contains complex chemical compositions. Thus, the pharmacological action of antianxiety prescriptions requires further research by using a multicomponent approach. Although animal experiments have confirmed that individual medicines in the prescription have potential antianxiety mechanisms, [49, 52] it is unknown whether JYW has the same mechanism of action. This needs to be explored further. Third, there were no differences between JYW and Buspirone in improvements in TCM syndrome. This contrasts with the findings of previous studies [59, 63] and might be a result of varying statistical methods and follow-up periods. Fourth, we were unable to obtain reliable efficiency rates since there were no prior RCTs of JYW for GAD. Thus, we estimate the required sample size was 200. Due to time constraints, the study was terminated prior to reaching this targeted sample size. Fifth, there was a relatively high dropout rate, including 10 participants who revoked consent, 2 participants who did not follow the study protocol, and 22 participants lost to follow-up for many reasons, such as the inconvenience and the longer distance, the insufficient efficacy, or patient recovered well and no require long treatment. Last, this research was conducted according to the prespecified protocol, and we followed the protocol thoroughly. According to the instructions, the Buspirone starting and recommended dose was 10–15 mg/d on the first week, the dose would be increased to 20–30 mg/d for the second week of the treatment period. Although many studies have shown that TCM has antidepressant or antianxiety effects [14, 46, 49], high dosages of TCM may be to achieve the same effects like western medicine in clinical practice. In order to raise the completion rates in the trial and avoid the dropout, we designed the adjustment time of the drug to be 1 week according to the clinical experience, not 2 weeks or 4 weeks. This problem should be considered and improve the therapeutic strategies when designing future trials.

Considering the abovementioned limitations, future research will be able to consider the following. For example, we plan to continue to recruit patients to increase our sample size in future studies. Inflammatory factors such as IL-6 and TNF are important regulatory factors in the development of GAD. It remains to be investigated whether JYW could relieve anxiety by regulating the inflammatory immune processes. Relevant research has been underway. Lastly, many omics technologies, such as transcriptomics, proteomics, and metabolomics, have been widely applied in medical research. They are potential tools to better understand the pathogenesis of GAD, the mechanisms of medicines, and uncovering more favorable approaches in TCM therapy. We will apply proteomics to further investigate the detailed mechanism of JYW action and the relationship between the dose and efficacy in future study.

7. Conclusions

The main conclusion of this study was that JYW and Buspirone can effectively alleviate the anxiety symptoms of GAD patients, which are both effective and safe for treatment of mild to moderate GAD. Not only that, high-dose JYW or Buspirone are more effective than low dose, which is of great importance in assisting clinical medication choice.

Data Availability

The data that support the conclusions of this study are available from the corresponding author Jia Hongxiao at any time upon reasonable request.

Disclosure

The funding agencies had no roles in study design, collection, analysis, and interpretation of the data, in the report's writing, and in the decision to submit the paper for publication.

Conflicts of Interest

The authors do not have any conflicts of interest to declare.

Authors' Contributions

X.L. and H.Z. drafted the manuscript and were responsible for data and interpretation. A.Z., D.W., H.G., N.D., Y.D,. and J.C. collected the data. S.Z. was responsible for the statistical analysis. F.S., R.M., and Y.J. were responsible for the language editing. H.J. is the guarantor and contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content. All authors had full access to the data in the study, are responsible for the integrity of the data and the accuracy of the data analysis, and read and approved the final version of the manuscript.

Acknowledgments

The authors thank everyone who helped with data collection. This study was funded using an investigator-initiated grant from Henan TaiFeng Pharmaceuticals Company and supported by Beijing Hospitals Authority Clinical Medicine Development of Special Funding (ZYLX202129), Beijing Hospitals Authority's Ascent Plan (DFL20191901), and Beijing Hospitals Authority Youth Programmed (QML20191901).

Supplementary Materials

The process of the Delphi method, the CONSORT 2010 checklist (Table S1), and the result of adverse reaction at eight weeks (Table S2) are provided as additional file. (*Supplementary Materials*)

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Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2021, Article ID 8600443, 12 pages
https://doi.org/10.1155/2021/8600443

Research Article

The Feasibility of Tai Chi Exercise as a Beneficial Mind-Body Intervention in a Group of Community-Dwelling Stroke Survivors with Symptoms of Depression

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Received 11 May 2021; Revised 8 October 2021; Accepted 15 October 2021; Published 2 November 2021

Academic Editor: Hualiang Jin

Depression is prevalent among one-third to two-thirds of acute and chronic stroke survivors. Despite the availability of pharmacotherapies and/or psychotherapies, depression persists, even for 5–10 years after stroke, reflecting limited treatment responses and/or adherence to this conventional care. Mind-body interventions are commonly used among adults to ameliorate depressive symptoms. Thus, the feasibility of Tai Chi, alongside conventional care, to manage poststroke depression was investigated using a single-group pre-post intervention design. Recruitment and retention, intervention adherence, safety, acceptability, and fidelity were assessed. Symptoms of depression, anxiety, and stress were assessed using standardized questionnaires, objective sleep was assessed via a research-grade triaxial accelerometer, and blood samples were taken to measure oxidative stress, inflammatory markers, and a neurotrophic growth factor using commercially available kits per manufacturer's protocol. Pre-post intervention changes were assessed using paired t-tests. We enrolled stroke survivors ($N = 11$, mean age $= 69.7 \pm 9.3$) reporting depression symptoms. After the intervention, we observed significant reductions in symptoms of depression (-5.3 ± 5.9, $p = 0.01$), anxiety (-2.2 ± 2.4, $p = 0.01$), and stress (-4.6 ± 4.8, $p = 0.01$), along with better sleep efficiency ($+1.8 \pm 1.8$, $p = 0.01$), less wakefulness after sleep onset (-9.3 ± 11.6, $p = 0.04$), and less time awake (-9.3 ± 11.6, $p = 0.04$). There was a 36% decrease in oxidative stress ($p = 0.02$), though no significant changes in the other biomarkers were found (all p values >0.05). Tai Chi exercise is a feasible intervention that can be used alongside conventional care to manage poststroke depression, aid in reducing symptoms of anxiety and stress, and improve sleep.

1. Introduction

Depression symptoms are widespread among acute and chronic stroke survivors with prevalence rates of 33–66% [1, 2]. Poststroke depression leads to increased disability and mortality rates, along with a higher risk for recurrent stroke [3–5]. Individuals with poststroke depression commonly experience anxiety, stress, and poor sleep [2]. At the biochemical level, stroke survivors with depression have significantly elevated proinflammatory cytokines compared to those without depression [6, 7]. This inflammatory response also disrupts neuroplasticity by decreasing serum brain-derived neurotrophic factor levels, which is predictive of depression [8–10]. While increased levels of oxidative stress are associated with greater depression among stroke survivors [11, 12]. Depression in poststroke patients is currently treated with pharmacotherapies, psychotherapies, or both. Despite the availability of pharmacotherapies and/or psychotherapies, depression persists, even for 5–10 years after stroke, reflecting limited treatment responses and/or adherence to this conventional care [13, 14]. Moreover, the use of pharmacotherapies to treat poststroke depression is associated with adverse events, such as recurrent stroke, seizures, delirium, and dizziness [15].

Mind-body interventions are commonly used among adults to ameliorate depressive symptoms. Tai Chi is a safe and promising mind-body exercise intervention to reduce depressive symptoms [16, 17]. Tai Chi integrates physical movements, breathing training, and mindful awareness [18]. For individuals with depression, Tai Chi provides the practical tools to manage or restructure behaviors and to cultivate autonomy (e.g., choosing to perform Tai Chi), competence (e.g., making progress/mastering Tai Chi movements), and relatedness (e.g., social connections developed through Tai Chi practice) to satisfy their basic psychological needs [19, 20]. In addition, Tai Chi can help sustain and better integrate the connection between mind and body. During Tai Chi practice, it allows the individual to quiet the mind by dwelling in the present and setting aside unnecessary negative emotions. Tai Chi focuses on releasing tension in the body, incorporating mindfulness and imagery into movement, increasing awareness and efficiency of breathing, and promoting overall relaxation of body and mind [21]. Thus, investigating the feasibility of Tai Chi, an established mind-body approach, alongside conventional care to manage poststroke depression is reasonable.

Self-Determination Theory (SDT) was used to guide the delivery of the Tai Chi intervention. SDT has been used for over three decades to direct health behavior change research [22, 23]. In this feasibility study, the intervention was specifically structured to fulfill the three basic psychological needs of autonomy, competence, and relatedness, as outlined in SDT [23, 24]. According to SDT, when these psychological needs are met, individuals benefit from better psychological health, such as less depression [19, 24]. In this study, our overall objective was to determine the feasibility of Tai Chi as a beneficial mind-body intervention, guided by SDT, in a group of community-dwelling stroke survivors with depression.

2. Methods

2.1. Study Design. In this feasibility study, a single-group pre-post intervention design was used. This study is reported in accordance with the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) statement [25].

2.2. Objectives. The objectives in this study are as follows: (1) determine the feasibility of recruitment and retention, intervention adherence, safety, acceptability, and fidelity of a Tai Chi exercise intervention among community-dwelling stroke survivors with depression and (2) describe changes in symptoms (depression, anxiety, and stress), sleep, and selected biomarkers associated with depression in stroke survivors after the intervention.

2.3. Participants. Potential participants were recruited from multiple sources, including flyers (placed at outpatient rehabilitation centers, senior centers, and neurosurgery/neurology offices), and presentations at stroke support groups and outpatient rehabilitation staff meetings. Interested stroke survivors contacted study staff, who screened for eligibility to safely participate, using the Patient Health Questionnaire (PHQ-9) to screen for depressive symptoms. Community-dwelling stroke survivors from all sex/gender, racial/ethnic and socioeconomic groups, aged 55 years and older, at least 3 months after stroke (stable condition after rehabilitation) [26], at least mild depressive symptoms (PHQ $9 > 5$) [27], moderate or less disability (Modified Rankin Scale score ≤ 3) [28], normal cognitive function (Mini-Mental Status Exam score ≥ 24) [29], and living in the greater Tucson, AZ area were eligible to enroll. Stroke survivors currently practicing Tai Chi greater than once/week, having severe hemineglect, hemianopia, or aphasia [30], a serious psychiatric disorder (e.g., schizophrenia), other serious medical condition [31, 32], or unable to provide informed consent were excluded. Because this is a feasibility study, we did not perform power and sample size calculations based on important or likely differences over time.

2.4. Ethical Issues. Approval to conduct the study was obtained from the appropriate Institutional Review Boards. The investigation was carried out according to the principles outlined in the Declaration of Helsinki. Study staff obtained written informed consent from all participants prior to data collection.

2.5. Intervention. The Tai Chi intervention protocol (one hour, three times per week for 12-weeks), which was used in our prior research among older adults with cardiovascular disease was implemented [33]. Moreover, this Tai Chi protocol has been used for over 10 years to instruct community-dwelling older adults with/without chronic illness, without safety issues or adverse events. Ms. Edna Silva, RN, an experienced Tai Chi Instructor (>25 years) provided the Tai Chi instruction in this study. The Tai Chi protocol included correct body preparation, standing meditation, and 24 basic movements. Participants were gradually taught the 24 basic movements from the Classic Wu style of Tai Chi (average two new movements per week). Weight shifting was incorporated into all movements, containing one or more of the five basic stances: (a) *parallel* (i.e., stand with feet hip width apart), (b) *empty* (i.e., step forward with one foot placing no weight on it), (c) *T-step* (i.e., turning one foot inward 45–60°), (d) *horse riding* (i.e., stand with feet double width of parallel step), and (e) *archery* (i.e., step forward with one foot, front leg bent with rear leg straight) [34]. During class, participants were asked to replicate the motions, postures, and movement speed of the Tai Chi Instructor. Each movement was broken into its components and practiced in many ways (e.g., using just legs, then just arms, and finally arms and legs together). Each session consisted of a 10-minute warm-up period, 40-minute Tai Chi exercise, and a 10-minute cool-down period. All classes were held at a community-based exercise facility with accessible parking. Each class began with a review of prior content. Participants were standing during classes, but chairs were set up to allow for brief rest periods. Participants were monitored closely for safety (e.g., foot placement) during the class by the Tai Chi Instructor and study staff.

Intervention delivery was guided by SDT, such as allowing participants to make their own decisions and express ideas/opinions (autonomy), learn new skills and instill a sense of accomplishment (competence), and interact with others to create/build meaningful connections (relatedness) [22, 35]. This was accomplished by using noncontrolling language and providing information, encouragement, and feedback within a supportive environment. In addition, the 8 "active ingredients" of Tai Chi as outlined in the Harvard Medical School Guide to Tai Chi [18] were incorporated during class. For example, the instructor describes/corrects the Tai Chi movements to ensure structural integration/correct body posture. In this study, we refined the Tai Chi intervention based on participant feedback and added a brief (5-minute) "circle sharing session" after each class, to allow each person to share how they were feeling, provide comments or ask questions. Each person had the opportunity to share or "pass," if they wanted. No movements were modified, though due to COVID-19, the Human Subjects Protection Program required us to end the Tai Chi intervention after 8 weeks, instead of the planned 12 weeks.

2.6. Outcomes. Study staff built a REDCap database to house all feasibility, symptom, and sleep data collected. Data were collected before and after the intervention by phone and entered directly into REDCap. Before and after the intervention, blood samples were collected by trained personnel and processed for plasma or whole blood and stored (−80°C) in aliquots in the Biological Sciences Laboratory in the College of Nursing at the University of Arizona, to assess selected biomarkers associated with poststroke depression.

2.7. Primary Outcomes

2.7.1. Recruitment. Recruitment was assessed as the proportion of respondents who remained interested in the study after information and screening [36]. Our goal was to recruit on average 5 stroke survivors per month for 4 months.

2.7.2. Retention. Retention included the number of participants that completed all aspects of the study (data collection before and after intervention and study intervention), as well as the reasons for attrition [36]. Our goal was at least 80% study retention, with reasons for attrition collected.

2.7.3. Intervention Adherence. Intervention adherence was calculated as the percent of Tai Chi classes attended out of those prescribed [36]. Our goal was at least 80% adherence with reasons for missing the prescribed classes recorded.

2.7.4. Intervention Safety. Intervention safety was assessed as the number of adverse events and serious adverse events occurring during the Tai Chi classes [36, 37]. Our goal was to have no safety issues or adverse events occur.

2.7.5. Intervention Acceptability. Intervention acceptability was assessed by having participants complete a short survey on the acceptability and satisfaction with Tai Chi after intervention [36]. On a scale from 1 to 10, participants were asked to rate their level of intervention acceptability (1 = least acceptable, 10 = most acceptable) and satisfaction (1 = least satisfied, 10 = most satisfied). In addition, they provided yes/no responses to six questions pertaining to classes being offered at a convenient time, difficulty following the instructor, gaining any personal benefit, if their health got better or worse, and if they would recommend the interventions to others. Our goal was at least 75% intervention acceptability.

2.7.6. Intervention Fidelity. Intervention fidelity was assessed using intervention scorecards that were developed for this study, based on the Behavioral Change Consortium's five-component model (i.e., design, training, delivery, receipt, and enactment) [38–40]. Our goal was 90% intervention fidelity using the scorecard.

2.8. Secondary Outcomes

2.8.1. Depression. Depression was assessed using the Center for Epidemiological Studies Depression scale (CES-D) [41] and Neuro-QOL (Quality of Life in Neurological Disorders) Depression Short Form (SF) [42]. The CES-D is widely used in research and clinical settings as a screening tool to detect depressive symptoms. The CES-D asks questions pertaining to how the respondent felt or behaved in the past week using a four-point Likert format (0 = none of the time, 3 = most of the time), with possible scores ranging from 0 to 60. Higher scores represent more depressive symptoms. A score of ≥16 using the CES-D is considered a clinical cut-point warranting further evaluation for depression [41]. Construct, convergent, and discriminate validity; high internal consistency; and good test-retest reliability of the CES-D among older adults and stroke survivors have been reported. The Neuro-QOL Depression SF was developed for use among adults living with neurological conditions, such as stroke, and asks how a person felt in the past week. The Neuro-QOL Depression SF contains 8 items, using a five-point Likert format (1 = never, 5 = always), with possible scores ranging from 8 to 40. Higher scores represent more depressive symptoms. Validity and reliability have been reported [43].

2.8.2. Anxiety. Anxiety was assessed using the Generalized Anxiety Disorder Assessment (GAD-7) [44] and the Neuro-QOL Anxiety SF [42]. The GAD-7 is a well-established scale used extensively in research and clinical practice. It contains 7 items and asks a person about problems they may have experienced in the past 2 weeks using a four-point Likert format (0 = not at all, 3 = every day). Possible scores range from 0 to 21, with higher scores indicating greater anxiety (mild = 5–9, moderate = 10–15, severe = >15). Psychometric testing has established construct, convergent, and criterion validity, with high internal consistency reported [44]. The Neuro-QOL Anxiety SF asks how a person felt in the past week. The Neuro-QOL Anxiety SF contains 8 items, using a five-point Likert format (1 = never, 5 = always), with possible scores ranging from 8 to 40. Higher scores represent more anxiety symptoms. Construct validity and high internal consistency have been reported [43].

2.8.3. Stress. Stress was assessed using the Perceived Stress Scale (PSS-10) [45]. The PSS-10 is a widely used, self-administered tool, designed for community samples with limited education. The PSS-10 contains 10 items and asks a person about situations they may have experienced in the past month as being unpredictable, uncontrollable, or overloaded using a five-point Likert format (0 = never, 4 = very often). Possible scores range from 0 to 40, with higher scores indicating greater perceived stress. Psychometric testing has established concurrent, predictive, and known-groups validity with high internal consistency and test-retest reliability [45–47].

2.8.4. Sleep. Sleep was assessed objectively with participants wearing an ActiGraph GT9X Link activity monitor (ActiGraph, Pensacola, FL, USA) on their waist for 1 week before and after intervention [48, 49]. The ActiGraph GT9X Link activity monitor is a research-grade triaxial accelerometer and has been validated to assess sleep in adult populations [48, 49]. The raw data was downloaded using the ActiLife software (version 6.13.4, ActiGraph, Pensacola, FL, USA) and converted into Excel files for use with sleep analysis. The Cole-Kripke sleep algorithm was applied to analyze the data with the Tudor-Locke "default" for sleep period detection. The protocol used in this study was validated in our prior research [50, 51].

2.8.5. Selected Biomarkers Associated with Poststroke Depression. Blood samples were collected from participants and were batch analyzed to measure oxidative stress, inflammatory markers, and a neurotrophic growth factor using commercially available kits per the manufacturer's protocol. At the time of plasma collection, a preservative, butylated hydroxytoluene (0.005% BHT) was added to an aliquot of the plasma sample. Positive controls were used (e.g., spike in known protein concentrations) to ensure assay validity. All data were reported in pg/mL for statistical analysis.

(1) Oxidative Stress. Oxidative stress was operationalized by measuring plasma superoxide dismutase (SOD) activity and 8-iso prostaglandin $F_{2\alpha}$ (8-isoprostane). SOD was measured using a colorimetric assay (Abcam, ab65354, Cambridge, MA) that assessed the inhibition activity of SOD in a sample. Samples were thawed on ice and the SOD assay was used according to manufacturer instructions. All samples were run in duplicate with an average coefficient of variation (CV) of 1.8%. All data are reported as a percent inhibition, reflective of SOD activity. A competitive ELISA assay (Cayman Chemical cat516351, Ann Arbor, MI) was used to measure plasma 8-isoprostane, a biologically active chemical and marker of oxidative stress. The BHT preserved plasma samples were stored at −80°C prior to use, and samples were thawed on ice prior to use. The assay was used according to manufacturer instructions and the range was reported as 0.8–500 pg/ml and sensitivity (80% B/B_0) of 3pg/ml. Plasma samples were purified using a solid-phase extraction cartridge (Caymen #400020) and N_2 gas according to manufacturer instructions and the assay was used according to manufacturer instructions with no deviations. All samples were run in duplicate with an average CV of 2.4%.

(2) Inflammatory Markers and Neurotrophic Factor. Concentrations of inflammatory markers tumor necrosis factor-alpha (TNF-α), interleukin- (IL-) 6, IL-10, and brain-derived neurotrophic factor (BDNF) were measured from serum samples. To measure TNF-α, IL-6, and IL-10, a serum aliquot was shipped on dry ice to Quanterix (Billerica, MA) for data collection using the Simoa® platform. The Simoa® platform was chosen because of its documented sensitivity to measure low concentrations of analytes [52]. Detection ranges for analytes were as follows: TNF-α (0~100pg/mL), IL-6 (0~140pg/mL), and IL-10 (0–50pg/mL). All samples were run in duplicate with an average CV of 10%. A Luminex platform was used to measure BDNF in serum samples using an assay kit (R&D Systems LXSAHM-0, Minneapolis, MN). All samples were run in duplicate with an average CV of 4%.

2.9. Statistical Methods. Descriptive statistics were calculated for all variables to ensure data quality (check distributions, examine outliers) and describe the sample. To determine recruitment and retention rates, along with intervention adherence, safety, acceptability, and fidelity, descriptive statistics were used and were reported as frequencies and percentages or mean ± SD. To describe changes in symptoms (depression, anxiety, and stress), sleep, and selected biomarkers between baseline and postintervention, paired *t*-tests and signed-rank tests were used. Data were analyzed using SAS statistical software (version 9.4, SAS Institute, Cary, NC, USA).

3. Results

3.1. Study Enrollment. A total of 26 stroke survivors were assessed for study eligibility, of which 9 did not meet the eligibility criteria and 6 declined study participation. A total of 11 stroke survivors were enrolled in the study. The flow of participants in the study including enrollment, group allocation, follow-up, and analysis is presented in Figure 1.

3.2. Description of Protocol Deviation. Due to COVID-19, the Human Subjects Protection Program required us to suspend further study recruitment efforts and to end the ongoing Tai Chi intervention after 8 weeks, instead of the planned 12 weeks.

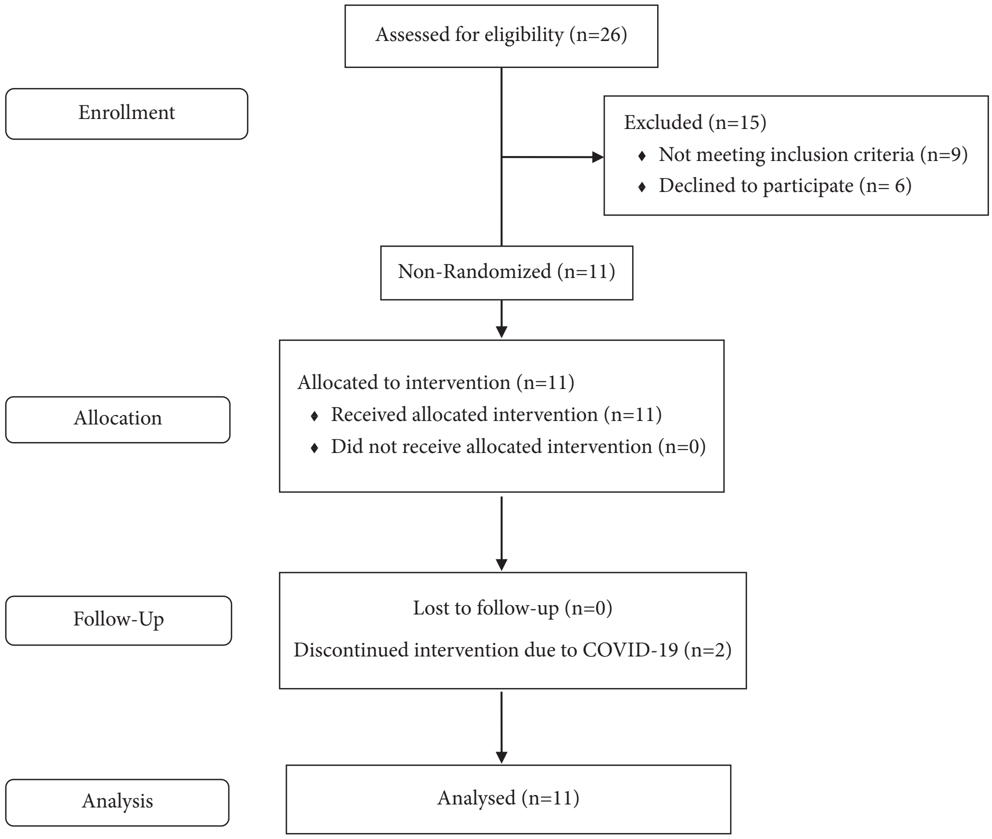

Figure 1: Trend flow diagram.

3.3. Recruitment Dates and Follow-Up. Participants were recruited for over 4 months from August to December 2019. Baseline data were collected in January 2020 with post-intervention data collected in March 2020, prior to COVID-19 closures.

3.4. Baseline Demographic and Clinical Characteristics. Participants were on average 70 years old, mainly retired (73%, $n = 8$), married men (55%, $n = 6$) with >13 years of education (91%, $n = 10$), reporting depression symptoms (CESD = 17.3 ± 11.4) with 55% taking antidepressant medications. The majority of participants reported having an ischemic stroke (82%, $n = 9$) with hemiparesis (55%, $n = 6$), but were able to walk 15 feet without assistance (91%, $n = 10$). Participants self-reported medical history included hypertension (64%, $n = 7$), arthritis (64%, $n = 7$), and prior cancer (36%, $n = 4$) (Table 1).

3.5. Primary Outcomes

3.5.1. Recruitment and Retention. Due to COVID-19, the Human Subjects Protection Program required us to suspend study recruitment efforts, and we were unable to meet our recruitment goal of enrolling 20 stroke survivors in the study. While a total of 17 stroke survivors were screened and met the eligibility criteria, 6 declined study participation, with an average recruitment rate of 2.8 participants/month over 4 months. Study retention was 100% ($n = 11$), with all participants completing all aspects of the study (i.e., data collection pre-post intervention and study intervention).

3.5.2. Intervention Acceptability, Safety, Adherence, and Fidelity. Participants' acceptability and satisfaction with the Tai Chi intervention were very high (Table 2). All participants (100%, $n = 11$) reported that the interventions were conducted at a convenient time that they gained personal benefits. Almost all (91%, $n = 10$) would recommend this intervention to others and felt that their health improved. There were no safety issues or adverse events during any of the Tai Chi classes. Participants had very high intervention adherence, attending on average 88% of scheduled classes, with 91% ($n = 10$) of participants attending ≥80% of the scheduled classes. The most frequent reasons for missing class were due to doctor's appointments ($n = 8$), feeling unwell ($n = 7$), or being out of town travel ($n = 5$). Using a scorecard, intervention fidelity was 90%, which was due to ending the Tai Chi intervention early after 8 weeks, as a result of the COVID-19 restrictions.

3.6. Secondary Outcomes

3.6.1. Changes in Symptoms of Depression, Anxiety, and Stress. At baseline, participants on average reported mild to moderate symptoms of depression (CES-D = 17.3 ± 11.4), anxiety (GAD-7 = 5.5 ± 4.8), and stress (PSS = 14.3 ± 7.6). After the Tai Chi intervention, we observed statistically

Table 1: Participant demographic and clinical characteristics ($n = 11$).

Variable	Mean ± SD or frequency (%)
Age	70.00 ± 9.30
BMI	25.45 ± 4.78
Males	6 (54.55%)
Education	
High school/GED	1 (9.09%)
Some college	3 (27.27%)
Bachelor	4 (36.36%)
Graduate	3 (27.27%)
Employment	
Retired	8 (72.73%)
Disabled	3 (27.27%)
Income	
<16K	3 (27.27%)
25~50K	3 (27.27%)
50~75K	1 (9.09%)
>75K	3 (27.27%)
Refused	1 (9.09%)
Race	
White	10 (90.91%)
Latino	1 (9.09%)
Marital status	
Married	6 (54.55%)
Widowed/divorced/never married	5 (45.45%)
Stroke type	
Hemorrhagic	2 (18.18%)
Ischemic	9 (81.82%)
Completed stroke rehabilitation	8 (72.73%)
Hemiparesis	6 (54.55%)
Walk 15 feet without assistance	10 (90.91%)
Uses assistive device	3 (27.27%)
Chronic conditions	
Arthritis	7 (63.64%)
Diabetes	1 (9.09%)
Heart disease	2 (18.18%)
High blood pressure	7 (63.64%)
Cancer	4 (36.36%)
Lung disease	1 (9.09%)
Kidney disease	2 (18.18%)
Tobacco use	1 (9.09%)
Antidepressant medication use	6 (54.55%)

Table 2: Intervention acceptability, satisfaction, safety, and adherence ($N = 11$).

Variable	Mean ± SD or frequency (%)
Acceptability*, mean ± SD	9.5 ± 0.97 (range: 7 to 10)
Satisfaction*, mean ± SD	9.0 ± 1.67 (range: 5 to 10)
Convenient time (%)	11 (100%)
Any difficulty (%)	4 (36.36%)
Gain benefits (%)	11 (100%)
Better health (%)	10 (90.91%)
Worse health (%)	0 (0%)
Recommend to others (%)	10 (90.91%)
Safety/adverse events (%)	0% ($n = 0$)
Adherence/class attendance (%)	88 ± 10.5 (range: 64–100%)

*Possible score range = 1–10 (1 = least, 10 = most).

significant changes in these symptoms, with less depression, anxiety, and stress reported (Table 3).

3.6.2. Changes in Objective Sleep. Participants were asked to wear an actigraph for 1 week before and after the intervention. Before the intervention, 91% of participants wore the actigraph ($n = 10$), with the majority ($n = 6$) wearing the actigraph for all seven days. Two participants wore the actigraph for 6 days including weekends, and one participant wore the actigraph for 5 days, excluding the weekend.

After the intervention, 82% of participants ($n = 9$) wore the actigraph, with the majority ($n = 8$) wearing the actigraph for all seven days, and one participant wearing the actigraph for 6 days including the weekend. After the Tai Chi intervention, we observed statistically significant changes in sleep with better sleep efficiency ($+1.8 \pm 1.8$, $p = 0.01$), less wakefulness after sleep onset (-9.3 ± 11.6, $p = 0.04$), and less time awake (-9.3 ± 11.6, $p = 0.04$) (Table 3).

3.6.3. Changes in Biomarkers Associated with Poststroke Depression. After the intervention, 82% of participants ($n = 9$) provided blood samples. We found a 36% decrease in SOD activity (ES = 0.75, $p = 0.02$) indicative of a decreased oxidative environment after intervention (Figure 2), though no significant changes in 8-isoprostane were observed. In addition, increases in IL-6 (ES = 0.59) and IL-10 (ES = 0.61) were observed, though these did not reach statistical significance due to the sample size. No significant changes in TNF-α or BDNF were found (all p values >0.05) (Figure 2).

4. Discussion

Among community-dwelling stroke survivors, Tai Chi exercise is a feasible intervention that can be used alongside conventional care to manage poststroke depression and may also aid in reducing symptoms of anxiety and stress and improve sleep. Recruitment of community-dwelling stroke survivors to participate in intervention studies is challenging, particularly among those with poststroke depression [53]. In this study, recruitment was impacted by COVID-19 closures, though our recruitment rates were similar to a recent intervention study to ameliorate poststroke depression [54]. Few studies have examined the effect of Tai Chi on poststroke depression [36, 37, 55], though they reported high study retention rates ranging from 85 to 90%, though less than the 100% retention in this study.

This study is the first to report on all four attributes of Tai Chi exercise feasibility among stroke survivors, namely, the intervention adherence, safety, acceptability, and fidelity. Intervention adherence in this study was high (88%), and similar to prior Tai Chi studies that examined the effect of Tai Chi on poststroke depression (85–92%) [36, 37]. Tai Chi is a safe form of exercise for stroke survivors, including those with hemiparesis or poststroke depression [36, 37, 56], though intervention safety or adverse events are frequently not reported [57–59]. While stroke survivors typically report

Table 3: Summary of symptoms and objective sleep by time point.

Variable	Time 1 ($N = 11$) mean ± SD	Time 2 ($N = 11$) mean ± SD	Time 2–Time 1 ($N = 11$) mean ± SD	p value*
Depression				
CES-D	17.27 ± 11.42	12.00 ± 8.51	−5.27 ± 5.92	**0.01 (0.03)**
Neuro-QOL depression SF	14.09 ± 7.73	10.82 ± 3.57	−3.27 ± 6.33	0.12 (0.11)
Anxiety				
GAD-7	5.45 ± 4.78	3.27 ± 4.29	−2.18 ± 2.40	**0.01 (0.02)**
Neuro-QOL anxiety SF	14.55 ± 6.89	10.45 ± 4.01	−4.09 ± 4.68	**0.02 (0.02)**
Stress				
PSS	14.27 ± 7.55	9.64 ± 7.90	−4.64 ± 4.76	**0.01 (0.01)**
Objective sleep#	Time 1 ($N = 10$)	Time 2 ($N = 9$)	Time 2–Time 1 ($N = 9$)	
Efficiency	93.67 ± 1.89	95.35 ± 2.38	1.81 ± 1.76	**0.01 (0.02)**
TST	8.87 ± 2.08	9.26 ± 2.36	0.52 ± 2.73	0.58 (0.65)
WASO	29.48 ± 8.58	21.00 ± 8.12	−9.34 ± 11.58	**0.04 (0.04)**
Number of awakenings	9.12 ± 3.91	6.94 ± 2.91	−2.55 ± 3.41	0.06 (0.05)
Length of awake time (minutes)	29.48 ± 8.58	21.00 ± 8.12	−9.34 ± 11.58	**0.04 (0.04)**

*Derived from paired t-test (signed-rank test), #derived from actigraph using the Cole–Kripke analysis method [83]. CES-D = Center for Epidemiological Studies Depression Scale; GAD-7 = Generalized Anxiety Disorder 7-item Scale; PSS = Perceived Stress Scale; SF = Short Form; Bold shows statistically significant p-value, derived from paired t-test (signed-rank test). sleep efficiency = total sleep time/time in bed × 100; TST = total sleep time; WASO = wake after sleep onset; time 1 = preintervention; time 2 = postintervention.

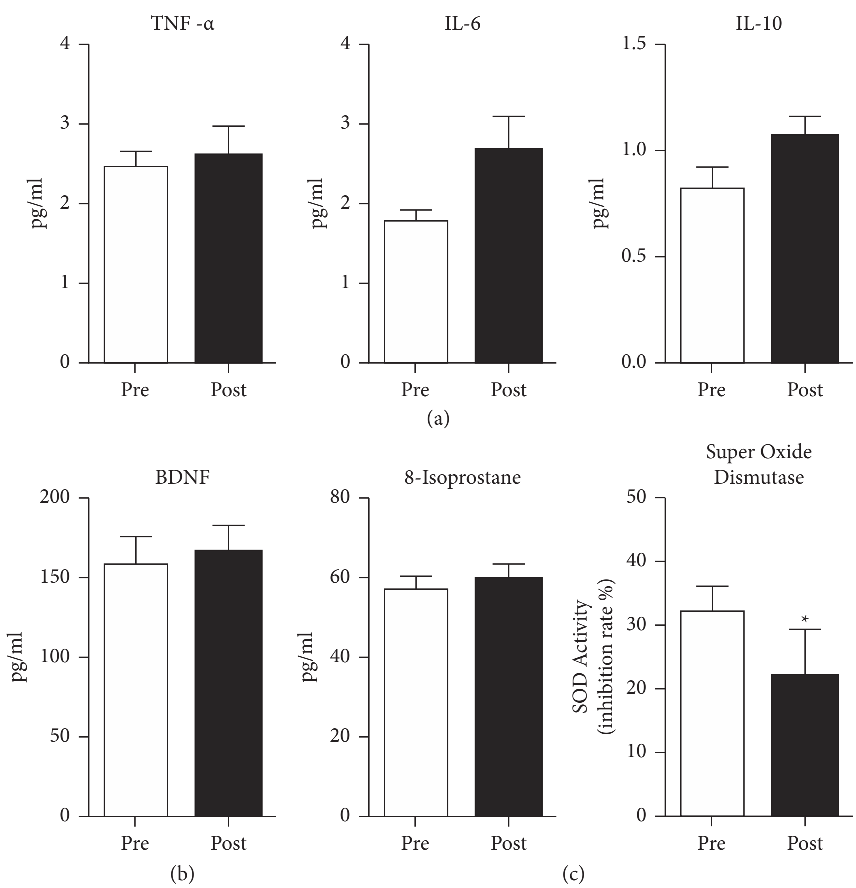

Figure 2: Changes in biomarkers associated with poststroke depression. Summary data of changes in serum biochemicals after Tai Chi intervention include inflammatory markers TNF-α, IL-6, and IL-10 (a), neurotrophic factor BDNF (b), and markers of oxidative stress 8-isoprostane and superoxide dismutase (c). Superoxide dismutase was significantly decreased after Tai Chi intervention ($^{*}p < 0.05$). Sample size = 9 for all biochemical assays with statistical analysis using paired t-test.

great enjoyment and satisfaction when performing Tai Chi [37, 56, 60], the acceptability or fidelity of Tai Chi interventions among stroke survivors are frequently not reported [58, 59].

After the Tai Chi intervention, we observed significant reductions in symptoms of depression, anxiety, and stress, along with better sleep. Among stroke survivors, prior studies have examined the effect of Tai Chi on symptoms of depression [36, 37, 55], but the effect of Tai Chi on symptoms of anxiety and stress was not reported. Our findings are consistent with prior studies, reporting less depression among stroke survivors after a Tai Chi intervention [37, 55] and a recent meta-analysis [61], though are in contrast to a Tai Chi intervention study among community-dwelling stroke survivors [36]. While depressive symptoms were assessed in that study [36], the primary outcome was an improvement in physical function and not all stroke survivors had symptoms of depression at baseline. Among stroke survivors, prior studies examining the effect of Tai Chi on sleep are limited and have primarily assessed subjective sleep quality [55].

After the Tai Chi intervention, we observed improvements in several biomarkers associated with poststroke depression. Several clinical trials have reported that the practice of Tai Chi has an antioxidant effect [62]. SOD is an important antioxidant enzyme, which catalyzes the dismutation of the superoxide anion into hydrogen peroxide and molecular oxygen. In this feasibility study, we found a 36% decrease in SOD activity indicating a decreased oxidative environment after the intervention. However, this finding is in contrast to a recent systematic review and meta-analysis [62], reporting an increase in SOD activity following a Tai Chi intervention. Our measurement of SOD quantifies enzyme activity, rather than absolute SOD concentrations. As a single measure of oxidative stress, our findings may be interpreted broadly and possibly in multiple ways. Traditionally and without a broader picture, elevated SOD activity may be interpreted as a biomarker of a low oxidative stress environment because of the consistent and constant conversion of reactive oxygen species to hydrogen peroxide and then to water by catalase and glutathione peroxidase [62, 63]. On the other hand, low SOD activity may result from a reduced oxidative stress environment (e.g., low demand results in low activity), less efficient enzyme activity that is often associated with age, or damage to SOD due to persistent or high levels of oxidative stress [64]. In the future and because determining the physiologic meaning of data based on a single measure is difficult, a more complete picture of the effects of Tai Chi on the oxidative stress environment could be obtained through multiple measures, for example by including measures of catalase and glutathione as well as SOD concentrations [63]. While we also collected data on 8-isoprostane, a biologically active chemical that results from oxidation of arachidonic acid by, for example, hydrogen peroxide, it is considered a quantitative index of lipid peroxidation [65]. In this dataset, SOD activity was significantly decreased; however, 8-isoprostane concentrations were unchanged. Therefore, it is difficult to elucidate the physiologic significance of the findings in this feasibility study.

Moreover, others have reported that the effects of exercise on oxidative stress (e.g., SOD activity) depends on several factors, including the exercise type (aerobic, nonaerobic), intensity (mild, moderate, vigorous), and frequency (sessions per week), as well as an individual's personal characteristics, such as age, gender, exercise capacity, and chronic health conditions [66, 67]. In this study, participants were, on average, 70-year-old stroke survivors with symptoms of depression. Also, there are different sampling methods (blood, saliva, urine) and indicators of oxidative stress (e.g., SOD, $F_{2\alpha}$ 8-isoprostane, catalase, and glutathione peroxidase) each with unique validation, stability, and reproducibility considerations [68], which may, in part, explain the differences in the findings obtained.

Several studies indicate that increased levels of oxidative stress and inflammatory biomarkers are common among persons with depression [69, 70]. Our findings are consistent with a prior systematic review examining the effect of Tai Chi on inflammatory markers [71], with mixed results found after the intervention. In this study, we observed increases in IL-6 (ES = 0.59) and IL-10 (ES = 0.61) though these did not reach statistical significance due to the sample size, while no significant changes in TNF-α or BDNF were found (all p values >0.05). IL-6 is a commonly investigated protein and a well-known biomarker of inflammation, stress, and depression, all closely interrelated, in both preclinical and clinical studies [72]. Moreover, IL-6 levels correlate differently among different depression subtypes, symptomology, and may be confounded by chronic inflammatory conditions that are often comorbid with ischemic stroke. Complicating our interpretation of IL-6 biomarker data further, prior research indicates that IL-6 exerts both pro- and anti-inflammatory properties [73, 74]. While IL-6 is generally regarded as having proinflammatory properties, research indicates it has many anti-inflammatory functions as well. This dichotomy of IL-6 functions indicates that it may be responsible for maintaining the balance between pro- and anti-inflammatory responses [73, 74]. Considering these limitations, higher levels of IL-6 have been observed among those with treatment-resistant depression, and among stroke survivors with depression [75, 76].

While IL-10 is studied less frequently than IL-6, others illustrate that IL-10 concentrations are also increased in patients with depression, compared to healthy controls [77] and similar to IL-6, they may be confounded by underlying inflammation and/or stress disorders. IL-10 may be produced by B-cells and Th2 cells of the adaptive immune system. Although IL-10 is broadly considered an "anti-inflammatory" cytokine, it also has known immunosuppressive and immunostimulatory effects that are disease dependent [78]. When considering serum or plasma biomarkers of neurological-based diseases such as IL-6 and IL-10, it must be acknowledged that serum or plasma cytokine levels may not reflect the brain microenvironment, but rather, might be overwhelmed by the systemic milieu [79]. On the other hand, when considering poststroke depression and recent evidence of a leaky glial scar during poststroke recovery in preclinical models [80–82], the brain and systemic milieu may be more intermingled than once appreciated. Despite prior research evidence linking depression, oxidative stress, and inflammatory biomarkers, many aspects remain to be explored in future larger studies with more rigorous study designs, and carefully chosen outcome measures that assess the mechanisms as well as the effects of Tai Chi on these biomarkers associated with poststroke depression.

4.1. Study Limitations. Since this was a feasibility study, several limitations should be noted. In this study, our primary outcome was to determine the feasibility of recruitment and retention, intervention adherence, safety, acceptability, and fidelity of a Tai Chi exercise intervention among community-dwelling stroke survivors with depression. A single-group pre-post intervention design was used, which was not powered to assess intervention effectiveness and there was no control/comparison group. While our secondary outcomes used standardized questionnaires to assess changes in symptoms of depression, anxiety, and stress; this self-report data may be subject to recall bias or socially desirable responses. Moreover, the changes in these symptoms may be due to the participants' poststroke recovery improvements. Also, the small sample size limits the generalizability of the results obtained from our objective measures of sleep and biomarkers associated with poststroke depression. Nevertheless, our results support the feasibility and acceptability of Tai Chi exercise for poststroke depression and provide useful information for developing a future large-scale trial.

5. Conclusions

Symptoms of depression, anxiety, and stress were observed among these community-dwelling stroke survivors along with suboptimal sleep. Among community-dwelling stroke survivors, Tai Chi exercise is a feasible intervention that can be used alongside conventional care to manage poststroke depression and may also aid in reducing symptoms of anxiety and stress and improve sleep. Further research is needed with rigorous study designs and larger samples before widespread recommendations can be made.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

This study was funded by the Laurence B. Emmons Research Award (Grant no. EMMRT-5330000, Taylor-Piliae, PI).

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Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2021, Article ID 5596111, 12 pages
https://doi.org/10.1155/2021/5596111

Research Article

On Mindfulness Training for Promoting Mental Toughness of Female College Students in Endurance Exercise

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Received 22 January 2021; Revised 19 July 2021; Accepted 18 August 2021; Published 25 August 2021

Academic Editor: Ruth Taylor-Piliae

Objective. The aim of this study was to examine the promoting effects of mindfulness training on female college students' mental toughness in endurance exercise. *Methods*. A cluster sampling method was used to select 60 female college students as subjects. Based on the body mass index (BMI), stratified randomization was used to divide them into the mindfulness-training group and the control group. Participants in mindfulness-training group had an 8-week mindfulness training, while participants in control group waited. Before and after training, Five Facet Mindfulness Questionnaire (FFMQ) and Connor–Davidson Resilience Scale (CD-RISC) were used for pretest and posttest, and paired t-test and covariance analysis were performed on pretest and posttest between-group data. *Results*. (1) Paired t-test results showed the posttest scores (26.67 ± 3.56; 20.97 ± 3.66; 126.53 ± 8.59) of the three dimensions of description, nonresponse and FFMQ total score of the mindfulness-training group were higher than the pretest scores (25.53 ± 3.74; 19.23 ± 3.59; 121.43 ± 6.78). Statistical significance was shown in their differences ($t = -2.25$; -2.70; -3.25, $p < 0.05$). However, there was no statistical significance in the pretest and posttest of control group. The covariance analyses showed the posttest scores of the mindfulness-training group in three dimensions of description, nonresponse, and FFMQ were higher than the posttest scores of the control group. Statistical significance was shown in their differences ($F = 6.55$; 6.08; 5.91; $p < 0.05$). (2) Paired t-test showed posttest scores (46.50 ± 5.93; 30.40 ± 3.75; 15.00 ± 2.34) were significantly higher than pretest scores (42.60 ± 7.68; 26.50 ± 4.32; 12.87 ± 2.51) in all dimensions of the mental toughness of the mindfulness-training group. Statistical significance was shown in their differences ($t = -3.135$, -4.765, -4.922, $p < 0.01$). However, there was no significant difference in the pretest and posttest scores in all dimensions of the mental toughness of the control group. The covariance analysis showed that the posttest scores of all dimensions of the mental toughness of the mindfulness-training group were higher than those of the control group, and the differences were statistically significant ($F = 11.133$, 12.101, 16.053, all $p < 0.001$). (3) Paired t-test showed that the posttest score of the mindfulness-training group on exercise intensity perception immediately after 800-meter endurance run (5.67 ± 2.61) was lower than the pretest score (7.03 ± 1.24) and the difference was statistically significant ($t = 4.18$, $p < 0.001$), while the difference was not statistically significant in the control group. The covariance analysis showed that the posttest score of the mindfulness-training group on exercise intensity perception was lower than that of the control group, and the difference was statistically significant ($F = 15.81$, $p < 0.001$). *Conclusion*. Mindfulness training improved the level of female college students' mindfulness and mental toughness in their endurance sports, while reducing the fatigue feeling of female college students in endurance sports.

1. Introduction

In recent years, "mindfulness" has been widely used as the third generation of cognitive behavioral therapy, which is a psychotherapy method to improve individual psychological flexibility and reduce empirical avoidance by accepting and changing the current state, such as mindfulness-acceptance-commitment [1]. Mindfulness affects cognition and emotion through psychological and behavioral regulation, including attention, memory, and emotional regulation, so as to reduce the occurrence of psychological disorders such as pain sensation and drug dependence [2], anxiety, and depression [3]. The core of mindfulness is to pay attention to and accept the current physical experience [4, 5]. It can reduce the individual's sense of pressure through emotional regulation (the processes by which emotional responses are modified to accomplish individual goals [6]) to improve subjective well-being. Mindfulness training focuses on breathing and body scanning to guide attention to the current experience and get rid of the influence of disturbing information. Guiding consciousness and attention are always maintained on the task object, and open and nonjudgmental acceptance of physical experience to avoid the influence of negative experience on emotion [7].

Mindfulness training, through psychological control and regulation, wakes up the ability of self-regulation of stress and emotion in concentration and attention. Its core is the self-regulation of attention and the psychological attitude of openness and acceptance, including continuous attention and acceptance of physical experience. It is in sharp contrast with avoidance, avoidance of negative experience, and memory [8]. In recent years, more and more studies have proved that mindfulness training plays a positive role in sports. For example, Feng and Si believe that mindfulness training improved the mindfulness level, attention level, and sports performance level of athletes [9]. Through case analysis and logical induction, Liu and Xu believe that there are many similarities between mindfulness training and traditional psychological counseling and training, which can provide a feasible basis for shooting athletes to carry out mindfulness training [10]. Mindfulness training promotes sports performance and reduces anxiety levels [11]. Compared with the traditional psychological training methods, it can more effectively reduce the negative effects of sports behavior and emotion, improve sports performance, and reduce emotional disorder. In sports [12], mindfulness training can improve the athletes' attention and their acceptance level of physical experience. It can also promote the physical feeling of athletes and reduce the negative emotional reaction of athletes [13]. Besides, mindfulness training can also improve the acceptance of pain stimuli [14]. The existing research mainly focuses on high-level athletes, and there are few reports on the influence and promotion of the general population, especially in endurance sports.

Endurance exercise refers to long-term single repetitive task exercise [15]. The aerobic endurance quality level promoted by it is closely related to cardiopulmonary function and is the basic part of physical fitness and an important factor in evaluating physical health. Lack of endurance quality is also the main factor affecting the physical health of Chinese students. However, under certain intensity, long-term repetitive, single endurance exercise will inevitably produce physiological feelings such as dyspnea, heart rate rise, lactic acid accumulation, muscle pain, and other psychological phenomena such as tension, anxiety, and depressive symptoms. Meanwhile, we should also mobilize and maintain attention to overcome the distraction in the process of exercise for a long time. Therefore, participating in endurance sports requires strong mental preparation to initiate an endurance task and keeping attention to the exercise task all the time. Surely, in addition to motivation, will, warming-up, and other influencing factors, strong mental toughness regulated by emotion and attention is also needed to initiate and maintain endurance sports behavior [16].

Early studies reported [17] that mental toughness in sports is the application of personality toughness to sports, which refers to the psychological ability to cope with the pressure in sports, suppress bad emotions, and finally achieve good results [18]. Mental toughness is not only affected by congenital inheritance but also a dynamic and applied developmental personality factor [19]. However, from the perspective of diversification, this paper studies the relationship between sports environment and mental toughness and integrates the sports situations-related concepts of cognition, self-confidence, concentration, and representation into the concept of sports mental toughness, forming the ecological orientation of sports mental toughness. So, it is possible to shape or develop sports mental toughness through psychological intervention [20]. Therefore, the sports mental toughness understood from the categories of cognition, emotion, and behavior can be cultivated and improved through the acquired intervention and training [21]. There is a significant correlation between mental toughness and emotional regulation and coping behavior in a certain situation. Higher mental toughness is significantly correlated with positive behavioral coping strategies such as psychological representation, sense of effort, thought control, and logical analysis [22]. The core of mindfulness is attention and acceptance of the current physical experience. By adjusting breath, body scanning, and attention regulation, consciousness and attention are always kept on the task object. Regulating cognitive, memory, attention, and emotions can help reduce negative emotions such as emotion disorder and anxiety symptoms, get rid of interference information, and improve attention.

Women are more likely to be affected by their emotions under stress. Emotional disorder, as an intermediary variable, is more likely to affect female behavioral inhibition, and experience avoidance is activated as a negative emotion regulation strategy to reduce the persistence of exercise behavior, thus resulting in posttraumatic stress disorder (PTSD) [23]. Therefore, women's sports behavior in endurance sports is more likely to be affected by mental toughness shown in emotions and attention. However, female college students without systematic professional training are more likely to have negative emotions and behavioral inhibition such as tension, anxiety, depression, and so on. Therefore, mental toughness is very important to the endurance sports behavior of female college students. The paper takes female college students from ordinary undergraduate colleges as the research object, through eight weeks of mindfulness training, to verify the promotion effect of mindfulness training on female college students in endurance sports.

2. Research Subjects

The calculation of the sample size is an important part of the research design. The determination of the sample size is based on a priori assumptions of effect size, significance level, and power force. The sample size is calculated by G * power 3.1. Assuming the effect size of 0.5 at a modest level, the significance level of 0.05 [24], and a power of 0.8 when performing a paired t-test of intra-group means, 34 participants are required per group. Assuming the preset effect size of 0.7, the significance level of 0.05, and a power of 0.8 when performing an independent sample t-test of intergroup means, the participants needed are still 34 each.

Using cluster sampling method, 67 female college students were selected from two natural classes of the same grade and major in an ordinary undergraduate college in the Central and Western China, with the average age of 19.54 ± 0.82, average height of 162.73 ± 5.36 cm, average weight of 55.47 ± 10.47 kg, and BMI 21.06 ± 4.26. According to the BMI index, 67 female college students were divided into 4 levels. Within each level, participants were divided into mindfulness group and control group by completely stratified randomization. The average age of the participants in the mindfulness group was 19.30 ± 0.77, and that of the control group was 19.76 ± 0.82. ($t = -2.378$, $p = 0.020$). The average height of participants in the mindfulness group was 162.06 ± 5.12 cm, and that of the control group was 158.72 ± 28.32 cm ($t = 0.676$, $p = 0.503$). The average weight of participants in the mindfulness group was 56.64 ± 11.00 kg, and that of the control group was 54.34 ± 9.95 kg ($t = 0.896$, $p = 0.374$). The BMI of the mindfulness group was 21.61 ± 4.42, and that of the control group was 20.52 ± 4.09 ($t = 1.041$, $p = 0.302$). There was no significant difference in BMI between the mindfulness group and the control group ($t = 1.067$, $p = 0.291$). There was no significant difference in age, height, weight, and BMI between the two groups. All the above can be seen in Table 1.

Table 1: Baseline characteristics of the mindfulness and control groups.

	Mindfulness intervention group ($n = 33$)		Control group ($n = 34$)		T-test	
	Mean	Std.	Mean	Std.	T	Sig. (2-tailed)
Age (years)	19.30	0.77	19.76	0.82	−2.378	0.020
Height (cm)	162.06	5.12	158.72	28.32	0.676	0.503
Weight (kg)	56.64	11.00	54.34	9.95	0.896	0.374
BMI (kg/m^2)	21.61	4.42	20.52	4.09	1.041	0.302

Note. BMI: body mass index.

3. Research Methods

Gross established an emotional regulation model in 2015, which believes that situation, attention, evaluation, and response form a closed loop, and their mutual influence forms a spiral upward [25]. This study believes that in addition to the closed loop formed by situation, attention, evaluation, and response, the emotional tendency generated by the response not only has a positive effect on behavior, which spirals upward but also has a negative effect on behavior and makes it spiral downward. The process model of emotion regulation behavior and mental toughness is shown in Figure 1.

The process model of emotional regulation behavior and mental toughness shows that when a situation occurs, individuals choose the situation according to their expectations and then direct their attention to their emotional goals through attention regulation, which determine the individual's evaluation of the situation through their cognitive changes. The response mechanism is then directed to experience, physiology, and behavior through emotion [25]. If both the experience and the physical sensation are positive, they will induce positive emotions, and if both are negative, they induce negative emotions.

When the positive emotion is generated, the behavior in the current status will increase, and the benign behavior experience is produced, which leads to cognitive reappraisal. Cognitive reappraisal can promote positive emotions in situations, attention, assessment, and response. Therefore, cognitive reappraisal can lead to the decline of negative emotional experience levels and the encoding of subsequent memory [26, 27]. When the negative emotion is generated, the behavior in the current status is reduced, and the negative behavior experience is produced, which leads to inhibition of expression. Inhibition of expression can bring about the decrease of positive emotion experience [28] and the increase of response of sympathetic nervous system [29], which will activate the amygdala and other brain regions where emotions are generated [30], resulting in negative memory [31]. Similarly, inhibition of expression will also lead to negative emotional experience in situation, attention, assessment, and response, thus resulting in negative emotional tendency. A virtuous circle formed by cognitive reappraisal will continuously promote the increase of benign behavior, and the behavior will continue, while mental toughness will increase as well. In contrast, the negative cycle formed by inhibition of expression will lead to negative emotions in the situation, attention, evaluation, and response. Thus, the behavior will be reduced or interrupted, resulting in experience avoidance, while mental toughness is reduced too. The method of mindfulness intervention is to regulate the negative cycle of expression inhibition in the situation, attention, evaluation, response, and emotion regulation tendency through mindfulness training so as to reduce the interruption of behavior and improve mental toughness.

3.1. Research Tools

3.1.1. The Five-Factor Mindfulness Scale (FFMQ). It is composed of 39 items in total, 5 dimensions: observation, description, conscious action, no evaluation, and no reaction. The internal consistency coefficient between the scores of the five dimensions and the total score of FFMQ is between 0.792 and 0.905. The five most representative dimensions of mindfulness include observation (attention and

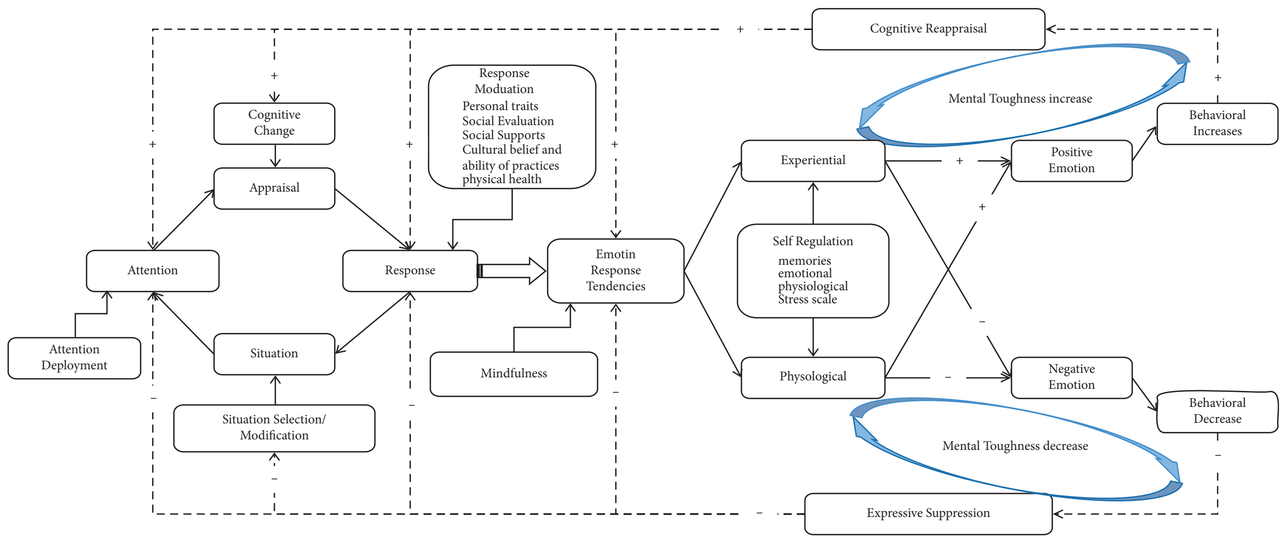

Figure 1: The process model of emotion regulation behavior and mental toughness. Partially quoted from [25]. Dotted line represents emotional regulation after the first round.

attention to various internal experiences and external stimuli), description (description and classification of observed phenomena through words), and conscious action (full involvement at the moment, attention to each experience consciously), no judgment (acceptance of the various experiences at the moment), and no response (no habitual, automatic response in the face of stimulation) [32].

3.1.2. The Psychological Toughness Scale. It is modified on the basis of the original Connor Davidson Resilience Scale (CD-RISC-25), including three dimensions: tenacity (It describes an individual's equanimity, promptness, perseverance, and sense of control when facing situations of hardship and challenges), strength (It focuses on the individual's capacity of recovering and becoming strong after setbacks and past experiences.), and optimism (It reflects the individual's tendency of looking on the positive sides of things and trusting one's personal and social resources. Therefore, this factor is labeled as optimism, measuring one's confidence in resisting adverse events). The Cronbach's α coefficient was 0.91 [33]. It has good reliability and validity and is widely used [34].

3.1.3. The Subjective Fatigue Scale. The "Rating of Perceived Exertion" (RPE) was used to monitor participants' internal training load. "Rating of Perceived Exertion" (RPE), which has a single item, was originally used in the field of medicine [35]. RPE is used in the sports and exercise sciences to indicate the psychological feedback of physiological exercise intensity. It is the psychological load effect of exercise intensity and reflects the influence of exercise behavior on cognition, attention, emotion, etc. [36]. Studies have proved that "self-perception of exertion" can be used to indicate and detect the intensity of exercise [35, 37]. The application of RPE in sports and exercise science is recomposed and applied by Foster [38]. There are many ways to divide the scale of RPE. Among them, the 0–10 CR-10, which is called Session-rating of perceived exertion Scale, is regarded as the most widely used. SRPE has been proved to be an effective method for evaluating training load [39–42]. The correlation between SRPE and objective index such as heart rate, blood lactic acid, and VO2max was $r = 0.62$, 0.57, and 0.64, respectively [43]. Liu et al. made appropriate modifications to the English version of the Rating of Perceived Exertion and translated it into Chinese [44]. Chen et al. verified the validity of the Chinese version of SRPE through the testing of football players. It is considered that the correlation between SRPE value after training and training load calculated by heart rate is between 0.75 and 0.91, so SRPE can effectively quantify and evaluate the training load of athletes [45].

3.2. Experimental Design. The experiment adopted a mixed experimental design of 2 (experimental group and control group) × 2 (pretest and posttest). Before the experimental intervention, the mindfulness group and the control group were asked to complete the scales of the Five-factor Mindfulness Scale and Psychological Toughness Scale, respectively, and 800-meter endurance running. Besides, all the participants were asked to form the Subjective Fatigue Scale within three minutes after the 800-meter endurance race test. All the work done above is taken as a pretest plan. Then the mindfulness group was given mindfulness intervention for 8 weeks, while the control group participated in class activities normally. After 8 weeks, the two groups were tested with the same scheme as the pretest. In order to eliminate the impact caused by the environment, the posttest was carried out at the same place and environment as the pretest, under conditions similar to the pretest as close as possible in temperature and time.

3.3. Mindfulness Training Program. In the study, the Mindfulness-Acceptance-Insight-Commitment (MAIC) training method developed by Si et al. was used [46], as seen in Table 2. Mindfulness training was implemented once a week for 90 minutes in 8 weeks. The course was based on the MAIC training method, with appropriate modifications to increase endurance exercises. The program aimed to train students to develop attention on the body, breathing sensation, sounds, visual objects, thoughts, and emotions. In addition to classroom training, students in the mindfulness group were required to do a daily practice of mindfulness breathing and body description. While in the control group, students were trained in a traditional physical training method by the same coach of mindfulness group in the same field and the same periods of the day, such as gymnastics shoulder elbow stand exercises, gymnastic swan balance training, swallow balance, stretching exercises, strength, and running exercises, etc.

3.4. Data Collection Methods. Before and after the intervention, the teacher organized the students into groups to finish the Five-Factor Mindfulness Scale (FFMQ), the Mental Resilience Scale (CD-RISC-25), the 800-Meter Endurance Run, and the Subjective Fatigue Scale, respectively. All the scales were distributed, filled in, and collected in person. The test results were input into SPSS software by a double-input method.

3.5. Statistical Processing. SPSS22 software was used for data sorting and statistics, and the measurement data were expressed by mean ± standard deviation. T-test was used for general data, paired sample t-test was used for intra-group comparison, and analysis of covariance was used for posttest intergroup comparison. Differences were considered statistically significant when $p < 0.05$.

4. Results and Analyses

4.1. Comparison of Mindfulness Levels. Before the intervention, there were no statistically significant differences between the mindfulness group and the control group in the pretest scores of mindfulness observation ($t = 0.218$, $p = 0.828$), description ($t = 0.368$, $p = 0.714$), conscious action ($t = -0.852$, $P = 0.398$), no evaluation ($t = 0.690$, $p = 0.49382$), and no reaction ($t = 0.691$, $p = 0.492$). Paired t-tests were performed on the pretest and posttest scores of the mindfulness group and the control group, respectively. It was found that the difference between the pretest and posttest scores of the control group was not statistically significant ($t = 0.160, -1.444, 0.368, 0.157, -1.346$, $p > 0.05$), while the posttest scores in the three dimensions of "description," "no reaction," and FFMQ total scores of mindfulness group were higher than those in pretest, and the difference between the pretest and posttest scores of the mindfulness group is statistically significant ($t = -2.246$, -2.695, -3.25, all $p < 0.05$). In the research, the posttest scores of five dimensions of mindfulness were taken as dependent variables, pretest scores as covariates, and the groups as fixed factors for the covariance analysis; it was found that the posttest scores of "observation," "no response," and FFMQ total score in mindfulness group were higher than those in the control group, and the differences between groups were statistically significant ($t = 6.55$, 6.080, 5.91, all $p < 0.05$). See Table 3 for an overview of paired t-test and covariance analyses of pre- and posttest scores of the mindfulness group and control group.

4.2. Comparison of Mental Toughness. Before the intervention, there were no statistically significant differences between the mindfulness group and control group in the pretest scores of mental toughness in three dimensions of tenacity ($t = 0.172$, $p = 0.864$), strength ($t = -0.936$, $p = 0.353$), and optimism ($t = -1.263$, $p = 0.212$). Paired t-tests were performed on the pretest and posttest scores of the mindfulness group and the control group, respectively, the result of which showed that the posttest scores of the mindfulness group in three dimensions of "tenacity," "strength," and "optimism" (46.50 ± 5.93), (30.40 ± 3.75), (15.00 ± 2.34) were higher than its pretest scores, respectively (42.60 ± 7.68), (26.50 ± 4.32), (12.87 ± 2.51), and the differences between the pretest and posttest scores of the mindfulness group were statistically significant ($t = -3.135$, -4.765, -4.922, $p < 0.01$) while the differences between the pretest and posttest scores of the control group were not statistically significant. In the research, the posttest scores of the mindfulness group in three dimensions were taken as the dependent variable, the pretest scores as the covariates, and the groups as the fixed factors, respectively; for the covariance analysis, it was found that the posttest scores of mindfulness group in three dimensions were higher than those in the control group, and the differences between groups were statistically significant ($t = 11.133$, 12.101, 16.053, all $p < 0.001$). See Table 4 for an overview of paired t-test and covariance analysis of the pre- and posttest scores of mental toughness in the mindfulness group and the control group.

The figures of mean scores of mindfulness group and control group in three dimensions of mental toughness showed intuitively that the posttest scores of the mindfulness group in three dimensions were significantly improved compared with its pretest scores and its posttest scores becoming much higher than the posttest score of control group too. Mean changes in the three dimensions of mental toughness are displayed in Figures 2–4 .

4.3. Comparison of Exercise Intensity Perception. Paired t-test was conducted on the pretest and posttest scores of the exercise intensity perception immediately after two 800-meter endurance runs in the mindfulness group and control group. Paired t-test showed that the posttest score of the mindfulness-training group on exercise intensity perception immediately after 800-meter endurance run (5.67 ± 2.61) was lower than the pretest score (7.03 ± 1.24) and the difference was statistically significant ($t = 4.18$, $p < 0.001$), while the difference was not statistically significant in the control group.

The results showed that compared with the pretest score, the posttest score of the mindfulness group on the exercise

Table 2: Contents of mindfulness training.

Week	Training subjects	Training contents
Week 1	Approaching mindfulness and preparation for mindfulness training	1. Introduce mindfulness to the participants. 2. Do a brief centering exercise
Week 2	Understanding mindfulness in practice	1. Practice mindful breathing 2. Do a body scan from head to toes.
Week 3	Attention regulation	1. Practice mindful breathing 2. Do 30 minutes of sitting meditation. 3. Listen carefully to possible sounds with mindfulness
Week 4	Acceptance	1. Practice mindfulness eating with raisins. 2. Taste water, an apple, or a banana with 7 steps: hold, look, touch, smell, release, swallow, and feel.
Week 5	Value and awareness	1. Gymnastic shoulder and elbow stand exercises, 2. Mindfulness stretching exercises.
Week 6	Commitment	1. Gymnastic swan balance training 2. Mindfulness walking
Week 7	Skills practice	1. Endurance training of double arms horizontal lift. 2. Mindfulness running exercises.
Week 8	Integrating training	Do systematically integrating mindfulness training

Table 3: Paired t-test and covariance analyses of pre- and posttest scores of mindfulness group and control group (Mean ± SD.).

	Paired t-test								ANCOVA		
	Mindfulness intervention group ($n = 33$)				Control group ($n = 34$)			p-value	F	P p-value	Partial η^2
	Pretest	Posttest	t	p-value	Pretest	Posttest	t				
Observation	24.70 ± 6.05	26.13 ± 4.37	−1.973	0.058	24.40 ± 4.49	24.32 ± 3.18	0.160	0.874	6.55	0.013	0.103
Description	25.53 ± 3.74	26.67 ± 3.56	−2.246	0.032	25.20 ± 2.25	25.83 ± 2.36	−1.444	0.160	1.376	0.246	0.024
Conscious action	27.80 ± 5.76	28.50 ± 3.89	−0.789	0.436	28.87 ± 3.72	28.68 ± 2.72	0.368	0.716	0.133	0.717	0.002
No evaluation	24.17 ± 3.47	24.27 ± 4.56	−0.135	0.893	24.80 ± 3.63	24.72 ± 2.92	0.157	0.876	0.008	0.928	≤0.001
No reaction	19.23 ± 3.59	20.97 ± 3.66	−2.695	0.012	18.63 ± 3.11	19.15 ± 1.80	−1.346	0.189	6.080	0.017	0.096
FFMQ total score	121.43 ± 6.78	126.53 ± 8.59	−3.25	0.003	121.90 ± 6.71	122.70 ± 5.50	−0.77	0.45	5.91	0.018	0.094

Table 4: Paired t-test and covariance analysis of the pre- and posttest scores of Mental Toughness in the mindfulness group and the control group (Mean ± SD.).

	Mindfulness intervention group ($n = 33$)			p	Control group ($n = 34$)			p-value	ANCOVA		
	Pre-test	Post-test	T		Pre-test	Post-test	T		F	p	Partial η^2
Tenacity	42.60 ± 7.68	46.50 ± 5.93	−3.135	0.004	42.27 ± 7.35	42.80 ± 6.02	−1.262	0.217	11.133	0.001	0.163
Strength	26.50 ± 4.32	30.40 ± 3.75	−4.765	≤0.001	27.53 ± 4.22	28.20 ± 3.71	−1.455	0.156	12.101	0.001	0.175
Optimism	12.87 ± 2.51	15.00 ± 2.34	−4.922	≤0.001	13.63 ± 2.17	13.77 ± 2.22	−0.724	0.475	16.053	≤0.001	0.220

Tenacity: Describing an individual's equanimity, promptness, perseverance, and sense of control when facing situations of hardship and challenge. Strength: Focusing on the individual's capacity of recovering and becoming strong after set back and past experiences. Optimism: Reflecting the individual's tendency of looking on the positive sides of things and trusting one's personal and social resources, measuring one's confidence in resisting adverse events.

intensity perception decreased significantly, and the difference was statistically significant ($p < 0.001$), while the control group slightly increased but not statistically significant. In the research, the posttest scores of exercise intensity perception as dependent variables, the pretest scores as covariates, and groups as fixed factors, respectively, for the covariance analysis, it was found that the posttest scores of the mindfulness group on exercise intensity perception were lower than those of control group, and the difference was statistically significant ($p < 0.001$), which can be seen in Table 5.

The means of exercise intensity perception showed that after the mindfulness training intervention, the fatigue of the 800-meter endurance running test in the mindfulness group decreased significantly compared with the control group and before the intervention. Mean changes of exercise intensity perception are displayed in Figure 5.

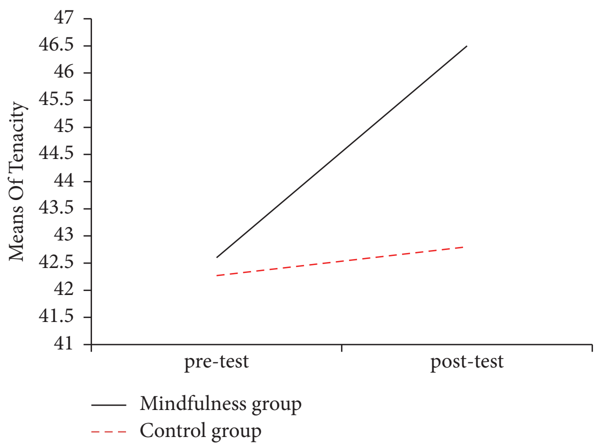

Figure 2: The mean scores of the tenacity of pre-and posttest in the mindfulness group and the control group.

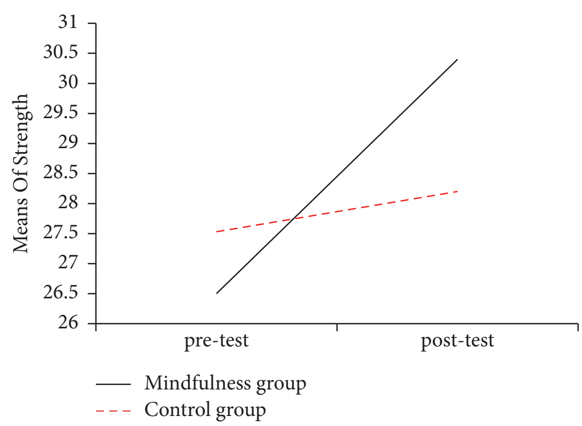

Figure 3: The mean scores of the strength of pre-and posttest in the mindfulness group and the control group.

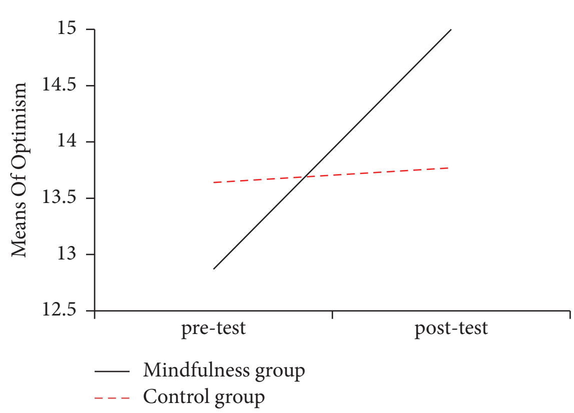

Figure 4: The mean scores of optimistic of pre-and posttest in the mindfulness group and the control group.

5. Discussion

In 2016, Abdul thought that mindfulness plays an important mediating role in the relationship between the mental toughness and athletic performance of college track and field athletes [47]. Walker's research on women hockey players in 2016 showed that mindfulness is not only significantly related to the overall mental toughness but also closely related to confidence, constancy, and control. Athletes with higher mindfulness levels reported higher control, constancy, and general mental toughness. It was believed the higher the mindful level, the higher the mental toughness level of the athletes [48]. Many previous studies have proved that mindfulness plays an important mediating role in the mental toughness of track and field athletes or long-distance runners, but no empirical research has been conducted. In this study, cluster sampling, stratified randomized block controlled experimental design was adopted, through 8 weeks mindfulness training experimental intervention, to verify the effect of mindfulness training on female college students' mental toughness in endurance sports. The results showed that the female college students who had received the mindfulness training had a significant improvement in the overall level of mindfulness and the scores of some dimensions. In the 800-meter endurance run test, they also showed better mental toughness than the performance before the intervention training and the performance of the control group as well; at the same time, mindfulness training also reduced college female students' exercise intensity perception and other negative physical feelings such as fatigue. Through empirical study, this research proves that mindfulness training has a promoting effect on college female students' mental toughness in endurance sports. The results further support Petrillo's research that mindfulness training, as a kind of psychological training, intervenes and improves mindfulness, sports anxiety-related worries, and long-distance runners' expectations [49]. Thompson believes that mindfulness training significantly improves the mindfulness and endurance performance of long-distance runners [50]. Nien believes that mindfulness training can improve college athletes' mindfulness level, endurance performance, and various cognitive functions, including executive functions [51].

In recent years, some scholars have proposed that cognition, self-confidence, concentration, representation, behavioral coping, and other factors related to sports situations should be included in the research field of mental toughness from a diversified perspective, forming a new concept and category of mental toughness. They believe that cognition, emotion regulation, and behavioral coping strategies play important roles in mental toughness [20]. The core of mindfulness is an open and nonjudgmental attention and acceptance attitude towards the current physical experience. Mindfulness training is a new generation of cognitive behavioral therapy for mental disorders, which regulates cognition, memory, and emotion by adjusting attention and acceptance attitude [52].

Mindfulness training is to guide consciousness and attention on the task object through adjusting breathing, body scanning, and attention regulation. Through the regulation of cognition, memory, attention and emotion, it can reduce the influence of exercise-related worries and exercise-irrelevant thoughts (two aspects of cognitive interference during sports) on sports. Besides, mindfulness training

Table 5: Paired t-test and covariance analysis of the pre- and posttest scores of exercise intensity perception in the mindfulness group and the control group (Mean ± SD).

	Mindfulness intervention group ($n = 33$)			p	Control group ($n = 34$)			p	ANCOVA		
	Pre-test	Post-test	T		Pre-test	Post-test	T		F	p	Partial η^2
Exercise intensity perception	7.03 ± 1.24	5.67 ± 2.61	4.18	≤0.001	7.07 ± 1.57	7.30 ± 1.49	−1.02	0.315	15.81	≤0.001	0.217

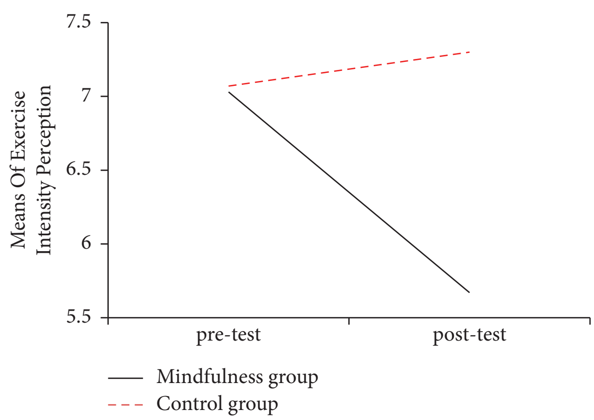

Figure 5: Diagram of the average scores of exercise intensity perception before and after the mindfulness group and the control group.

trained the participants to accept their physical experience openly and nonjudgmentally, avoid the influence of negative experiences on their emotions, reduce the exercise-related physical worries, and improve the self-cognition related to attention regulation and arousal regulation [53]. Mindfulness training uses breathing, body scanning, experiencing drinking and eating, walking, balance, running, and other body awareness control and adjustments to guide attention to stay focused on the task experience at the current moment so as to get rid of the influence of irrelevant attention and interference information on the process of endurance exercise, reduce the occupation of working memory capacity by irrelevant attention and interference information during long-term endurance exercise, and improve the working memory ability and the individual's concentration of endurance exercise tasks. At the same time, the regulation of consciousness and attention through mindfulness improves the individual's inhibition and control over previous negative experiences, reduces the negative impact of female college students' past negative experience of endurance sports on current endurance sports behavior, and improves the individual's executive function [54–56]. Through the open and nonjudgmental experience and attention on thoughts, emotions, and body feelings, new behavioral experience feelings are formed, thereby avoiding experience avoidance caused by previous negative experiences and memories. Therefore, mindfulness training can inhibit negative thoughts, emotions, behaviors, and the competition and interference of negative physiological reactions through conscious adjustment and prevent the influence of subconscious, automatic, and habitual thinking on endurance sports behavior so as to promote the individual's conscious perception of current behavior [57–59], which makes female college students inhabit negative coping strategies such as experience avoidance in the endurance running test, reduces the difficulty of starting the endurance exercise task, and prevents the endurance exercise task from being interrupted. This promotes mental toughness in endurance sports.

The individual's various negative physiological experiences and memories in the previous endurance exercises will increase the individual's painful feelings for the body. It can cause individuals to experience negative emotions such as tension, worries, depression when facing a current similar situation and lead to experience avoidance, even stress disorder, which is an important factor affecting female college students to participate in endurance sports. Therefore, Jones believes that individual Pain Catastrophizing mediates the relationship between mindfulness and endurance sports performance, which is an important factor affecting female college students' participation in endurance sports [60]. However, in addition to the physiological reactions of the body itself (accelerated heartbeat, dyspnea, and muscle pain) and the release of chemicals that cause pain during endurance exercise, the individual's perception of pain is also affected by the individual's judgment, expectations, and other emotions and cognition. Individual psychological differences, such as memory, coping strategies, and personality, can inhibit or enhance individual's perception of noxious activities [61]. Meta-cognitive beliefs about worry play an important role in the connection between pain behavior and pain catastrophizing. Positive cognitive beliefs about worry mediate the relationship between neuroticism and pain catastrophizing, while negative cognitive beliefs about worry mediate the relationship between pain catastrophizing and self-reported pain behavior [62]. Pain is variable, and an individual's emotion and cognition are components of pain perception. Therefore, the openness and nonjudgmental attitude towards physical experience is used in mindfulness exercises to cultivate and improve the individual's acceptance and tolerance of pain and other negative physical experiences [63, 64] so as to reduce the negative impact of negative experience on the current endurance sports task and the avoidance coping strategies, which has been proved in many studies in recent years [65–67]. Therefore, mindfulness training improves the individual's open and nonjudgmental acceptance of physical experience, which makes the individual accept, accommodate, and not reject kinds of pain in endurance sports, and improves the tolerance of pain in endurance sports, avoid negative coping such as experience avoidance in endurance sports, so as to improve the mental toughness in endurance sports.

Martin's survey of the sample of cyclists in 2018 found that mindfulness partially mediated a negative relationship between mental toughness and pain catastrophizing. Mindfulness is positively associated with mental toughness and negatively associated with pain catastrophizing [68]. This empirical study proves the theories and hypotheses above and proves that mindfulness training can reduce female college students' negative physical feelings of intensity, pain, and fatigue in endurance sports and improve their mental toughness in endurance sports.

6. Limitations and Future Perspectives

It is important to note that although reliable statistical findings have been observed, there are still some limitations in this study. The questionnaire was handed out and collected face to face, and all the subjects were required to fill in the questionnaire carefully, but it is not sure that all participants have given honest answers. In the process of the experimental intervention, a total of 90 minutes of training was conducted once a week for a total of 8 weeks in mindfulness training group. Besides, participants in the mindfulness group were asked to do 45 minutes of mindfulness training on their own every day, while the control group received a certain amount of traditional training every day. However, the individual's intensity of self-training cannot be controlled, so there are some differences, which may affect the results of the experiment. The research data relies on the individual's self-report rather than the observation of the individual's behavior (such as the degree of fatigue during exercise). So the social desirability of the individuals may affect the experimental findings to some degree. Furthermore, the sample size of the study is relatively small. Although it basically meets the requirements of the study, if the sample size is appropriately expanded, a more convincing effect size will be obtained. In future research, we will use more scientific experimental design and control to compare the effects of long-term and short-term mindfulness training on mental toughness in endurance sports. How different intensity, duration, and practice environments in mindfulness training affect individual's mental toughness will also be studied later.

7. Conclusion

The level of mental toughness in endurance exercise is the key factor that affects the participation and persistence of endurance sports, while cognition, attention, and emotion before and during the sports are all the factors affecting the persistence of endurance sports behavior. At the same time, endurance exercise may cause anxiety symptoms for low sports or sedentary people. Stubbs et al. conducted a cross-sectional study based on community data in 47 countries around the world and found that there was a significant positive correlation between low physical activity and anxiety symptoms [69].

The emotional states in these sports behaviors are the factors that cause experience avoidance behaviors and new emotional disorders such as anxiety and depression. Traditional psychological training develops internal state and self-control through cognitive behavior methods and techniques such as goal-setting, arousal-control, self-efficacy, and self-talk. However, more and more works of literature believe that trying to suppress negative internal experiences and thoughts will activate them on the contrary, which is the paradox effect of suppression [70]. Mindfulness-Acceptance-Commitment (MAC) proposes acceptance of the present experience, rather than changing, inhibiting, or controlling, which emphasizes attention and nonjudgement. Therefore, mindfulness training promotes the level of mindfulness of female college students through attention guidance and regulation by guiding breathing, body scanning, body movement, etc. The attention adjustment guidance awareness and attention are always maintained on the task object. Mindfulness training promotes the mindfulness level of female college students through attention guidance and regulation, including guiding breathing, body scanning, body movement, etc. Attention regulation guides awareness and attention on the task object consistently. Besides, through the regulation of cognition, memory, attention, and emotions, mindfulness training reduces exercise-related physical worries and the occupation of working memory capacity by some exercise-irrelevant thoughts so as to improve female college students' working memory ability and executive ability of endurance exercise tasks. Through the open and nonjudgmental experience and attention to the endurance sports task, female college students can have a new experience and avoid the experience avoidance caused by the previous negative experience. Therefore, mindfulness can improve the individual's tolerance to pain and other negative body feelings, avoid the negative coping behaviors such as experience avoidance in endurance sports, reduce the female college students' negative body feelings such as intensity feeling and pain, reduce the fatigue feeling of endurance sports, and improve the female college students' psychological resilience in endurance sports. Mindfulness improves the individual's tolerance for pain and other negative body sensations, avoids negative coping behaviors such as experience avoidance in endurance exercise, reduces the female college students' negative physical sensations such as intensity feeling pain and fatigue in endurance exercise, and improves their mental toughness in endurance sports at last.

Data Availability

The data are available upon request.

Ethical Approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and Ethical approval was obtained from the school's Academic research Council.

Consent

All the participants are given written informed consent.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2021, Article ID 5924040, 8 pages
https://doi.org/10.1155/2021/5924040

Research Article

Effectiveness of Progressive Muscle Relaxation, Deep Breathing, and Guided Imagery in Promoting Psychological and Physiological States of Relaxation

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Received 19 April 2021; Accepted 14 June 2021; Published 3 July 2021

Academic Editor: Ruth Taylor-Piliae

Research suggests that multiple forms of relaxation training (e.g., progressive muscle relaxation, meditation, breathing exercises, visualization, and autogenics) can help individuals reduce stress, enhance relaxation states, and improve overall well-being. We examined three different, commonly used approaches to stress relaxation—progressive muscle relaxation, deep breathing, and guided imagery—and evaluated them in a head-to-head comparison against each other and a control condition. Sixty healthy undergraduate participants were randomized to one of the four conditions and completed 20 minutes of progressive muscle relaxation, deep breathing, or guided imagery training that was delivered by recorded audio instruction. Baseline and follow-up assessment of psychological relaxation states were completed. Physiological relaxation was also assessed continuously using measures of electrodermal activity and heart rate. Results showed that progressive muscle relaxation, deep breathing, and guided imagery all increased the state of relaxation for participants in those groups, compared to participants in the control group. In each case, the increase was statistically significant and although the groups did not differ on relaxation before training, all groups were significantly higher on relaxation after training, as compared to the control group. Progressive muscle relaxation and guided imagery showed an immediate linear trend toward physiological relaxation, compared to the control group, and the deep breathing group showed an immediate increase in physiological arousal followed quickly by a return to initial levels. Our results lend support to the body of research showing that stress relaxation training can be effective in improving relaxation states at both the psychological and physiological level. Future research could examine stress relaxation techniques in a similar manner using designs where multiple techniques can be compared in the same samples.

1. Introduction

The present investigation seeks to better understand relaxation strategies by examining the efficacy of three different relaxation approaches in bringing about both psychological and physiological relaxation. Extant literature demonstrates the effectiveness of relaxation strategies, such as deep breathing, guided imagery, meditation, progressive muscle relaxation, and many other methods [1], but rarely are these strategies examined side-by-side in an experiment to evaluate relative effectiveness in promoting relaxation. It remains the case that we know only that many of these techniques are effective in promoting relaxation, not which techniques are most effective in bringing about relaxation. It is critically important that we better understand the most effective methods for increasing relaxation and the underlying self-regulation competencies because the relaxation response is directly and inversely related to chronic stress difficulties and poor mental and physical health [2–4]. The current study explores differences in the impact of progressive muscle relaxation, deep breathing, and guided imagery, as compared to a control condition, on psychological and physiological relaxation states in an undergraduate student sample. We chose to examine deep breathing, guided imagery, and progressive muscle relaxation because these three methods can be easily taught and practiced using a standardized audio recording, they are known to be effective, and they can realize almost immediate benefits. While we expect that all three methods will elicit relaxation responses, differences among the techniques are less clear and will be carefully examined in this comparative effectiveness research. We begin with a brief review of these techniques and then summarize our present aims.

1.1. Progressive Muscle Relaxation. Progressive muscle relaxation (PMR) is an actively engaging relaxation technique developed by Edmund Jacobson in the 1920s [5]. PMR involves participants actively contracting muscles to create tension and progressively releasing this [6]. The routine is repeated until participants acquire complete relaxation. This technique utilizes the principles of neuronal "top-down" and "bottom-up" processing to achieve results [7]. In "top-down" processing, participants use areas higher in the nervous system like the cerebral cortex and the cerebellum to contract muscles and gradually release the tension. In "bottom-up" processing, the holding and releasing of bodily tension produce proprioceptive stimulation from peripheral muscles that ascends to the brain via the spinal cord and the brainstem. With both stimulatory passages activated, PMR provides participants with quick and immediate relief.

The effects of this technique have been widely demonstrated in numerous studies. For instance, PMR can be useful in reducing stress. Pv and Lobo selected a simple random sample of 30 first-year nursing students, measured stress levels before and after PMR, and found a significant reduction in stress [8]. In another study with nursing students, PMR alleviated test anxiety [6], In this study, 49 students were randomized to a PMR treatment or control group, and both groups completed the Sarason Anxiety Questionnaire at baseline and completion of the experiment. The PMR treatment group received four 30-minute sessions of PMR. Although there was no significant difference before and after the experiment in the control group on test anxiety, a significant reduction in test anxiety was found in the treatment group.

Not only does PMR demonstrate stress-alleviating effects, but also it exhibits a positive influence on depression and anxiety. In one study, PMR was administered twice a day for five days to patients who had coronary heart disease [9]. The Hospital Anxiety and Depression Scale [10] was used to measure anxiety and depression. The results showed that PMR had a positive effect on reducing depression and anxiety in these patients. In another study, 50 hospitalized cancer patients were randomized into an experimental PMR group and a control group [11]. Patients in the PMR group showed reductions in anxiety as measured by the Generalized Anxiety Questionnaire, whereas patients in the control group showed no such improvements.

1.2. Deep Breathing. Deep breathing, which is also known as diaphragmatic breathing, is a technique that is based on the notion that mind and body integration produces relaxation [12]. The technique requires participants to contract the diaphragm, slowly inhaling and exhaling. Deep breathing appears to amplify blood oxygen levels, massages the inner organs located in or close to the abdomen, and possibly stimulates the vagus nerve [13].

Deep breathing has been shown to have a positive impact on various factors like stress, anxiety, and negative affect in numerous studies. For instance, in an experiment conducted in China, 40 healthy participants were recruited to investigate the effects of deep breathing on attention, negative affect, and stress [14]. Participants were randomized into control and experimental groups, both of which were measured on the variables of interest including attention, affect, and cortisol before and after the eight weeks of treatment conducted for 30 minutes every other day. Findings showed that over the course of deep breathing treatment, as compared to controls, participants increased sustained attention and decreased negative affect and cortisol levels.

Deep breathing is useful with multiple patient populations. A study of 4,793 presurgical patients was designed to investigate the benefits of using deep breathing and aromatherapy to reduce preoperative anxiety [15]. After deep breathing along with lavender aromatherapy, approximately 40% of the patients demonstrated a decrease in anxiety. Additionally, deep breathing has been shown to exert a positive influence on certain chronic conditions. In one quasi-experimental study, 32 patients with type II diabetes mellitus were trained on deep breathing and compared to untrained controls [16]. Deep breathing resulted in a significant decrease in Hamilton Anxiety Rating Scale scores for deep breathing trained participants, whereas untrained controls did not show any decrease in anxiety.

1.3. Guided Imagery. Guided imagery is a method for treating stress and anxiety in which one replaces disturbing memories with positive mental imagery [17]. This involves instructional guidance that invokes sensory experiences and behavioral and physiological responses. Sensory and contextual engagement are a key focus of this technique. The instructional guidance and the strong focus on the engagement of participants help gain greater perceptual detail of the images generated which creates a more realistic mental representation during the relaxation exercise [18].

Research supports the effectiveness of guided imagery in reducing stress and anxiety. In one study conducted to evaluate the effects of guided imagery on intraoperative anxiety for patients undergoing abdominal surgery under spinal anesthesia, guided imagery techniques were shown to significantly reduce anxiety [19]. In another study investigating the effects of 20 minutes of guided imagery on preoperative anxiety, guided imagery was shown to significantly reduce anxiety and cortisol levels [20]. Yet another study showed that hospital nurses working during the COVID-19 pandemic who were trained in guided imagery, as compared to controls, showed significantly greater decreases in death anxiety [17]. Other studies show the use of guided imagery outside of the medical setting. One study evaluating the use of nature-versus-urban-based guided imagery as an intervention for anxiety found a significant decrease in state anxiety amongst adults imagining both urban and natural settings [18], and the effect was strongest for nature-based guided imagery. Another study using guided imagery to facilitate self-forgiveness showed significant increases in self-forgiveness scores following seven five-minute sessions of guided imagery [21].

1.4. Multiple Methods. Studies have also been conducted that either combine or compare the effects of multiple methods of relaxation with one another. One study combined guided imagery, progressive muscle relaxation, deep breathing, mindfulness, exercise, aromatherapy, and yoga for nursing students during the course of one academic year to test for changes in anxiety [22]. This was a mixed-methods study, but quantitative analyses did not reveal significant changes in anxiety. Another study investigated the differences between PMR, guided imagery, and diaphragmatic breathing techniques on the quality of life for elderly individuals diagnosed with breast or prostate cancer [23]. Results of this study showed significant improvement following 45 minutes of training in quality of life and physical functioning after either of the three techniques were used. A study of undergraduates compared five minutes of deep breathing and progressive muscle relaxation to each other and other relaxation techniques such as the adapted dive reflex and the use of a weighted lap object for their effects on anxiety [7]. All of the separate techniques tested showed significant reductions in anxiety, but deep breathing and progressive muscle relaxation techniques appeared to be responsible for the greatest amount of anxiety reduction. Another study compared the use of PMR and guided imagery and its effects on stress, anxiety, and depression for pregnant women [24]. Participants in this study participated in two twenty-minute sessions of progressive muscle relaxation and guided imagery exercises. The combination of these techniques resulted in decreased stress and depression, but not anxiety.

1.5. Present Study. The existing research has provided a good evidence base to support the usefulness of multiple forms of stress relaxation techniques for the reduction of stress, anxiety, and depression and the improvement of quality of life, relaxation states, and positive mental health. Often these studies have examined specific patient or demographic populations and used clinicians to train individuals in these techniques. Equally often, the outcomes of interest are stress, anxiety, and depression, whereas the most direct outcome of interest, that is the state of relaxation, is commonly missing. Furthermore, not only are relaxation states not commonly assessed, but also when they are physiological parameters are not included in assessment, leaving a comprehensive picture of the efficacy of these stress relaxation states incomplete. Consequently, we sought to design an experiment comparing three of the more common stress relaxation techniques—PMR, deep breathing, and guided imagery—in healthy young undergraduates. We also sought to directly assess stress relaxation states and physiological manifestations of relaxation across a 20-minute relaxation session guided by a scripted audio instructional program. We hypothesized, based on existing literature, that each of the tested techniques would lead to both distinguishable psychological and physiological states of relaxation, as compared to controls.

2. Method

2.1. Participants. Participants included 60 undergraduate students who participated for extra credit in an undergraduate psychology course. Meta-analyses of several types of stress relaxation techniques show pooled effect sizes of moderate-to-large magnitude [3]. Using $\eta^2 = .06$ as a conservative estimate of effect size for the group by time interaction of our least powerful analysis, an alpha of .05, and required power of .90, 60 participants were required for this study. The majority were female (71.4%) and the average age was 19.64 (SD = 1.32; range = 18–23). Female/male proportions, $\chi^2 = 4.54$, $p = 0.21$, and average age, $F = .58$, $p = 0.63$, did not differ across the groups. Participants were recruited through an introductory psychology student pool. All participants provided informed consent prior to beginning the study, and the study was approved by the institutional ethics committee.

2.2. Measures

2.2.1. Psychological Stress Relaxation. The Smith Relaxation States Inventory-3 [25] was used as a self-report assessment of the effectiveness of the relaxation exercises. The Smith Relaxation States Inventory-3 consists of 38 items measuring 18 relaxation states and 3 stress states (somatic stress, worry, and negative emotion). Researchers can conceptualize the relaxation states in 5 categories: basic relaxation (sleepiness, disengagement, physical relaxation, rested/refreshed, and mental relaxation), core mindfulness (mindful acceptance, mindful quietness, mindful centeredness, mindful awareness, mindful awakening, and mindful innocence), mindful doing (trust, energized, and happy), mindful giving (thankful and loving, prayerful), and deep mindfulness (awe and wonder, deep mystery, and timeless, boundless, infinite, at one). Example items are “My mind is silent and calm,” “My body is physically relaxed,” and “I feel at peace.” Participants are asked to rate each item according to how they feel “right now” on a 6-point Likert scale of 1 (*not at all*) to 6 (*maximum*). The Smith Relaxation States Inventory-3 possesses good reliability and validity. [25] In the present study, the total score was used and demonstrated excellent internal consistency at both baseline and follow-up assessment ($\alpha s > .90$).

2.2.2. Psychophysiological Stress Relaxation. Psychophysiological measures of autonomic nervous system arousal were collected using the Biopac MP35 lab software and hardware (https://www.biopac.com). Biopac hardware and software is considered a gold-standard psychophysiological data collection system by some [26] and has been used in 4,440 studies that measured electrodermal activity and 10,400 studies that measured electrocardiographic activity [27]. The Biopac MP35 measured the participant's phasic changes in electrodermal activity (i.e., skin conductance) and heart rate (HR). Electrodermal activity was assessed at the first and second fingers of the nondominant hand. Heart rate was assessed using a standard triple-lead configuration where sensors were placed above each ankle and on the wrist of the nondominant hand. Psychophysiological data were continuously monitored and reduced to five-minute segments where the average value for each five-minute segment was used for analysis.

2.2.3. Controls. Age and sex (male/female) were collected as control variables.

2.3. Procedure. Sixty participants were randomly assigned to one of three stress relaxation groups (deep breathing, PMR, or guided imagery) or a control group. Participants arrived at the laboratory, were greeted by a researcher, and read and signed the informed consent. All sessions were conducted in the evening between 7:00 p.m. and 9:00 p.m., Monday through Friday, during the fall and spring semesters. Participants were asked to refrain from the consumption of alcohol, nicotine, and caffeine 12 hours prior to participation. Participants were connected to the Biopac MP35 hardware to begin monitoring baseline psychophysiological data and then completed the baseline relaxation self-report questionnaire. Participants then completed the appropriate 20-minute exercise for their assigned group. In the control group, participants were offered several popular news or sports magazines to read (e.g., TIME, Sports Illustrated). Participants in the PMR group learned how to tense and relax muscle groups to bring about a state of relaxation. Participants in the deep breathing group learned how to use their breathing to invoke relaxation by breathing deeply, slowly, and attending to their breath. Guided imagery participants learned how to use mental representations to bring about a state of relaxation. All relaxation exercises were taught by recorded verbal instructions that were developed and disseminated by Dr. Jonathon Smith [25]. Once the assigned exercise was completed, participants were disconnected from the psychophysiological recording equipment, completed the follow-up relaxation self-report questionnaire, were thanked for their participation, and were dismissed.

2.4. Analysis. Data were examined using descriptive statistics (means and standard deviations) and repeated measures analyses of variance. Physiological data was first reduced to 5-minute epochs and examined using repeated measures analyses of variance. Group by time interactions were the statistical test of interest, and in the presence of a group by time interaction, simple effects were examined. All analyses included age and sex (male/female) as control variables. Data met assumptions for statistical hypothesis testing, and statistical significance was set at $p < 0.05$.

3. Results

3.1. Psychological Results. Psychological changes in self-reported relaxation are displayed in Figure 1. Changes in levels of relaxation differed across the four groups, $F = 2.81$, $p = 0.048$, $\eta^2 = .14$. The control group (baseline to follow-up difference = 0.31, $p = 0.019$) showed a slight increase in relaxation from baseline to follow-up assessment, but this change was considerably smaller than that of the relaxation groups. The PMR (baseline to follow-up difference = 0.42, $p = 0.002$), deep breathing (baseline to follow-up difference = 0.68, $p < 0.001$), and guided imagery (baseline to follow-up difference = 0.79, $p < 0.001$) groups all showed statistically significant increases from baseline to follow-up assessment. While differences between the four groups were not statistically significant at the baseline ($ps > 0.118$), PMR (mean difference = 0.43, $p = 0.046$), deep breathing (mean difference = 0.54, $p = 0.014$), and guided imagery (mean difference = 0.54, $p = 0.015$) groups were significantly higher on follow-up assessment relaxation scores compared to the control group. None of the relaxation groups differed from one another on follow-up assessment relaxation scores ($ps > 0.621$).

3.2. Physiological Results. Physiological relaxation evidenced by changes in electrodermal activity is displayed in Figure 2. Changes in levels of electrodermal activity differed across the four groups, $F = 8.18$, $p < 0.001$, $\eta^2 = 0.31$. The control group, $F = 0.36$, $p = 0.837$, $\eta^2 = 0.03$, showed no changes in electrodermal activity throughout the relaxation exercise. Guided imagery, $F = 3.86$, $p = 0.008$, $\eta^2 = 0.23$, and PMR, $F = 13.40$, $p < 0.001$, $\eta^2 = 0.51$, groups showed linear decreases in electrodermal activity throughout the relaxation exercise. The deep breathing, $F = 7.46$, $p < 0.001$, $\eta^2 = 0.37$, group showed a curvilinear trend where levels of electrodermal activity initially increased in the first 15 minutes and then decreased over the last 10 minutes. Changes in levels of heart rate activity across the four groups only approached statistical significance, $F = 1.65$, $p = 0.084$, $\eta^2 = 0.11$.

4. Discussion

Findings from the present study show effectiveness of all three stress relaxation exercises in promoting both psychological and physiological relaxation states. In terms of psychological relaxation, all groups started at a similar level of relaxation, but following relaxation training, all three stress relaxation groups showed statistically significant

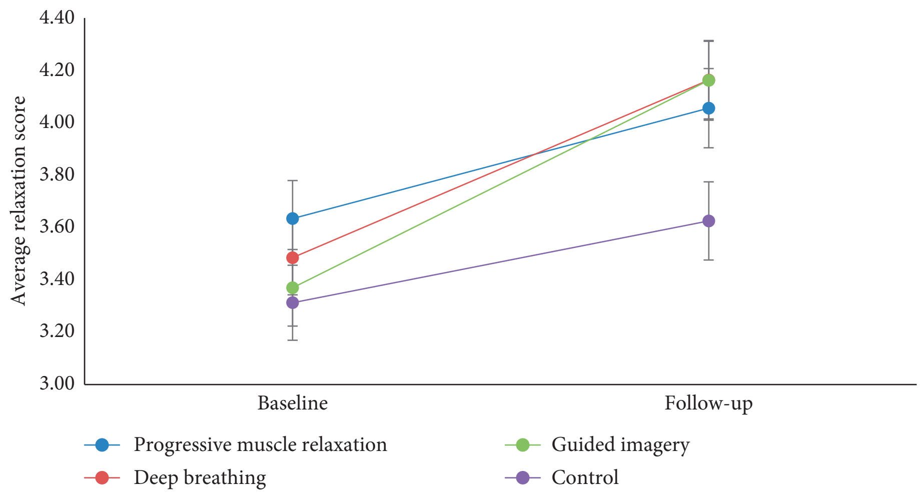

Figure 1: Baseline and follow-up levels of psychological relaxation states for participants in progressive muscle relaxation, deep breathing, guided imagery, and control groups. *Note.* Error bars represent standard errors.

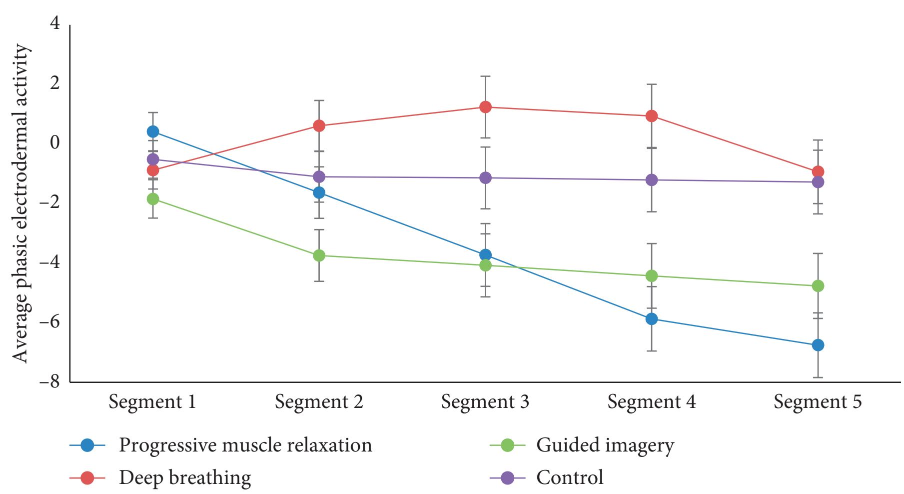

Figure 2: Changes in average phasic electrodermal activity (skin conductance) for participants in progressive muscle relaxation, deep breathing, guided imagery, and control groups. *Note.* Error bars represent standard errors. Segment 1 is a five-minute baseline.

increases in relaxation states. Levels of relaxation following the stress relaxation exercises were significantly higher for the relaxation groups as compared to the control group. After the exercises, none of the relaxation groups differed from one another. In terms of physiological states of relaxation, we found that guided imagery and PMR showed linear decreases in phasic electrodermal activity. The deep breathing group showed a curvilinear trend where levels of electrodermal activity increased in the first 10 minutes but in the final 10 minutes returned to their initial levels. Electrodermal activity did not change significantly in the control group, and no statistically significant or interpretable trends occurred in heart rate over the stress relaxation exercises or in the control condition.

These findings support and extend an existing body of findings showing that stress relaxation techniques can be effective in helping individuals to cope with stress and enhance well-being. For instance, with regard to PMR, our findings extend recent work showing that not only does PMR alleviate stress [8] and test anxiety [6] in nursing students and depression and anxiety in coronary heart disease [9] and cancer patients, [11] but it also induced psychological and physiological relaxation states in our student sample. Similarly, our guided imagery technique showed effectiveness in inducing states of both psychological and physiological relaxation, similar to the effects of guided imagery for surgery patients [19, 20], hospital nurses working during the COVID-19 pandemic [17], and healthy adults [18]. Of note is that the work of Felix and Ferreira [20] is a rare recent example of research that confirms the physiological effects of guided imagery, and we extend this finding from a patient sample to our sample of healthy transitional adults.

Our findings on the effectiveness of deep breathing for bringing about psychological relaxation are in line with other studies showing deep breathing to positively impact negative effect, stress, and cortisol [14], studies in medical patients showing decreases in anxiety for surgery patients

[19, 20], and individuals with chronic illnesses (e.g., diabetes) [16]. Interestingly, in work by Ma and colleagues [14], deep breathing yielded a net benefit for reduced cortisol levels, while our findings revealed a curvilinear trend—as the deep breathing session progressed, electrodermal activity increased until the approximate midpoint of the training exercise and then began to decrease. Perhaps, early in a training session, deep breathing has an immediate physiological stimulating effect which quickly gives way to a state of physiological relaxation felt in both the autonomic and neuroendocrine systems [28]. As some have argued, focusing too much on the inhalation of deep breathing could cause physiological arousal and, early in training, participants may not understand how to obtain maximal relaxation benefits from deep breathing where one focuses more on the exhalation, which invokes the parasympathetic nervous system [29].

Our study is one of only a few investigations that evaluates the effectiveness of different types of stress relaxation training against each other in a head-to-head comparison, whereas past studies have often investigated combined methods of stress relaxation. For example, in a study of nursing students by Moore and colleagues [22], guided imagery, progressive muscle relaxation, deep breathing exercises, mindfulness, exercise, aromatherapy, and yoga were utilized concurrently. Although the combined effects of multiple stress relaxation techniques may act in synergistic ways to bring about considerable additional relief above and beyond any single method, such studies are unable to isolate which contributing component is responsible for the effect. Other studies have been designed to directly compare the effectiveness of different stress relaxation techniques but, often, these studies [23, 24] have examined unique populations (i.e., elderly oncology patients, pregnant women) or have not found consistent evidence of differences between stress relaxation techniques [7].

Our study offers a direct comparison of three of the more commonly used stress relaxation techniques, finding that all three techniques are more effective in inducing relaxation than the control condition, but none of the three techniques is any better than the others. This holds true for psychological relaxation states but not for physiological states of relaxation, which were evoked more robustly by PMR and guided imagery. For deep breathing, we found an initial increase in physiological arousal, followed by a return to baseline levels, a pattern which may have emerged due to a limited follow-up period. Although it is conjecture, it may be that deep breathing requires a longer period of time to exert its benefits, and its effects may be comparable to PMR and guided imagery with a longer follow-up period. Yet, given the techniques we utilized and the time allotted, it appears that physiological relaxation may be best facilitated by PMR and guided imagery.

4.1. Limitations. Our novel findings must be considered in the context of some limitations, including our method of assessing sociodemographic characteristics. For instance, biological sex was measured with only "male" and "female" response options and although our college student population is quite homogeneous (e.g., 85% White, 75% on-campus work-study, no children), no data on employment, parental status, race, or income was collected. Next, although our study design offers the ability to draw causal conclusions about the effectiveness of stress relaxation techniques, only three techniques are evaluated, and many other stress-reduction strategies may be effective. For instance, mindfulness, autogenic training, and aromatherapy are common methods that have received enthusiastic support from the public and should be evaluated in head-to-head comparisons to assess effectiveness.

Although our study goes beyond many studies by including both psychological and physiological assessments, these could be expanded upon in future research. Measures of awe, contentment, and serenity and perceptions of space, self, and time could be added to psychological assessment, and measures of neuroendocrine functioning would be useful. It may be important to also assess neurophysiological functioning with fMRI, PET, or EEG technologies. Finally, while many studies of stress relaxation are conducted with objectively stressed populations (e.g., persons with chronic illness), our study aim was to examine whether stress relaxation methods could be effectively used to reduce stress in healthy, young college students. Yet, this approach also limits generalizability and additional work is needed to substantiate our findings in a diverse community and clinical samples.

5. Conclusions

Our study provides evidence of the effectiveness of three commonly used approaches—PMR, deep breathing, and guided imagery—for stress relaxation, confirming past research indicating their benefits for promoting both psychological and physiological states of relaxation and offering a head-to-head comparison of stress-reduction strategies. At the psychological level of analysis, our results suggest that PMR, deep breathing, and guided imagery offer good improvement in relaxation. At the physiological level of analysis, PMR and guided imagery offer good improvement in relaxation, but further work is needed to establish the benefits of deep breathing.

Several avenues of future work are possible, including examination of the effectiveness of relaxation strategies in (1) undergraduate versus graduate student populations, (2) minority groups, (3) the unemployed, and (4) groups with health disparities or poor access to healthcare. Relaxation interventions could also be implemented as a public health effort, to maximize relief at a population level. Future studies might also examine the curvilinear effect of deep breathing on physiological relaxation, using an extended follow-up period and additional measures (e.g., neuroendocrine assessment), to better understand both the immediacy and endurance of the effects of deep breathing on relaxation states. Initial arousal may be viewed as a means to an end if deep breathing proves to have lasting physiological benefits, whereas if the physiological relaxation benefits of deep breathing are fleeting and cyclic in nature, there may be a reason for greater scrutiny. Answering these questions will require longer time intervals of assessment, multimodal physiological assessment, and careful attention to linear and curvilinear patterns of response. Future research comparing stress-reduction strategies utilizing enhanced assessment and diverse samples is needed to better understand what stress relaxation methods bring about the most comprehensive and effective relief of the stresses that impact us.

Data Availability

Data are available upon request to the first author.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

The authors would like to thank Dr. Joel Schrock for his invaluable assistance and work on this project.

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Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2021, Article ID 5585239, 12 pages
https://doi.org/10.1155/2021/5585239

Review Article

TaiChi and Qigong for Depressive Symptoms in Patients with Chronic Heart Failure: A Systematic Review with Meta-Analysis

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Received 11 March 2021; Accepted 14 June 2021; Published 25 June 2021

Academic Editor: Parco M. Siu

Background. Depression is a debilitating comorbidity of heart failure (HF) that needs assessment and management. Along with mind-body exercise to deal with HF with depression, the use of TaiChi and/or Qigong practices (TQPs) has increased. Therefore, this systematic review assesses the effects of TQPs on depression among patients with HF. *Methods*. Randomized controlled trials (RCTs) that examined the effect of TQPs on depression in patients with HF were searched by five databases (PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, CINAHL, and China National Knowledge Infrastructure (CNKI)). With standardized mean difference (SMD) and 95% confidence intervals (95% CI), random-effects meta-analyses of the effect of TQPs on depressive symptoms were performed. *Results*. Of eight included RCTs, seven (481 patients) provided data for the meta-analysis. The pooling revealed that TQPs contribute to depression remission in HF (SMD −0.66; 95% CI −0.98 to −0.33, $P < 0.0001$; $I^2 = 64\%$). Its antidepressive effect was not influenced by intervention duration or exercise setting, but rather by ejection fraction subtype, depressive severity, and depression instruments. The beneficial effects were preserved when the study with the largest effect was removed. *Conclusion*. This study suggests that TQPs might be a good strategy for alleviating depressive symptoms in patients with HF. And rigorous-design RCTs, which focus on the identified research gaps, are needed to further establish the therapeutic effects of TQPs for depression in HF.

1. Introduction

Depression is a frequent comorbidity in patients with heart failure (HF) [1]. Data from meta-analysis have shown that patients with HF have a mean depression prevalence of 21.5%, 2 to 3 times the rate of the general population [2]. Depression often exacerbates symptoms of patients with HF, doubling the risk of mortality and other cardiac events among patients with HF [3]. It is also a strong predictor of future cardiac events related to HF, similar to traditional cardiovascular risk factors [4]. Therefore, routine screening for and treatment of depression is an urgent need for patients experiencing HF. It is also suggested by the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) HF guidelines [5, 6].

Review articles are now suggesting the therapeutic benefits of mind-body exercise on depression of varying severity [7–11]. Moreover, for patients with HF experiencing depression, interventions designed to improve both physical and psychological symptoms have been shown to reduce depression, increase physical function, and improve quality of life [12]. Thus, mind-body exercise may be the optimal therapy for depressive patients with HF.

TaiChi and Qigong are common mind-body exercises that originated in China. Each is an ancient Chinese healing art with a history of thousands of years [13, 14]. Qigong is an umbrella term covering a spectrum of mind-body exercises, such as Dao-Yin-Shu (physical and breathing exercise), Wu-Qin-Xi (five-animal play), Ba-Duan-Jin (eight-section health exercise), and Yi-Jin-Jing (changing tendons exercise) [15]. It is characterized by simple physical movements and is thought to be the grandfather to TaiChi, while TaiChi derives from Qigong and Martial Arts, involving more complex and choreographed movements [16]. Both TaiChi and Qigong employ slow and gentle physical movements, synchronized with breathing regulation and meditation to stretch the body, relax the muscles, coordinate breathing, and regulate attention and consciousness [17, 18]. Traditional Chinese medicine physicians believe that performing the meditative and synergistic dance-like movements of TaiChi and Qigong can promote Qi to flow harmoniously, thus promoting health and spirit [19].

Review articles and meta-analyses have demonstrated TaiChi's and Qigong's benefits on depression in the general population [10, 20], patients with chronic illnesses [9, 21–23], and patients with cardiovascular disease [24, 25]. Of note, TaiChi has served as a treatment for depression in many clinical trials, and evidence has shown that it is correlated with significant reductions in depression [18]. However, analysis for each illness has been limited to a handful of studies, precluding robust testing of whether the effects of TaiChi and Qigong differ by illness.

In recent years, many randomized controlled trials (RCTs) have reported the effects of TaiChi and Qigong among patients with HF, some of them reporting depression outcomes [26–33]. However, the results have been inconclusive, and convincing quantitative evidence to estimate treatment effects has been lacking. Therefore, this review evaluates the evidence from RCTs of TaiChi and Qigong on depression in patients with HF.

2. Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [34] and the Cochrane Handbook for Interventional Reviews [35]. The study protocol has been published in PROSPERO (CRD42018081982). We followed the methods of Chen et al. (2020) [36].

2.1. Search Strategy. PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, CINAHL, and China National Knowledge Infrastructure (CNKI) were searched from inceptions until October 23, 2019, without language restriction. Search terms were classified in three groups (Appendix 1: search strategy): condition (CHF, chronic heart failure and related terms), intervention (tradition Chinese exercise and related terms such as traditional exercise, mind-body exercise, Qigong, Taiji, Tai ji, Tai Chi, TaiChi, Liuzijue or Liu Zi Jue, or Baduanjin or Ba duan jin, or Wuqinxi or Wu Qin Xi, or Yijinjing, or Yi Jin Jing), and study type (RCT and related terms).

2.2. Study Selection. We applied the following selection criteria: (1) study design: RCTs reported in a full text; (2) participants: patients diagnosed with HF with or without restriction of left ventricular ejection fraction and in a stable phase of the disease; (3) interventions and control: RCTs comparing TaiChi and/or Qigong (TQPs) plus routine management (RM) with RM alone, or comparing TQPs plus RM with general exercise plus RM. RM included standard medical treatment, education, health guidance, or aerobic exercise. RCTs in which the intervention group was TQPs plus other traditional Chinese medicine therapies, such as acupuncture, Chinese herbal medicine preparation, were excluded; and (4) outcomes: depression or depressive symptoms measured by using patient-reported outcomes (PROs) or non-PRO assessment instruments.

After screening titles and abstracts from articles found in the searches, two reviewers (WJ, SL) retrieved potentially relevant full-text articles. These two reviewers independently assessed the eligibility of the full-text articles according to the selection criteria. Meanwhile, they resolved any discrepancies by agreement after rechecking the source articles or/and after discussion with a third reviewer (XC).

2.3. Data Extraction. One reviewer (WJ) extracted data with a standardized form from the included articles. A second reviewer (SL) checked the extracted data. Discrepancies were resolved by consensus after rechecking the source papers and further discussion with a third reviewer (XC).

The extracted data including study characteristics (e.g., title, author, publication year, and the use of randomization, allocation concealment, blinding and control, and country), participant characteristics (e.g., age, sex, sample size, New York Heart Association (NYHA) classification, and left ventricular ejection fraction (LVEF)), description of interventions (e.g., types of exercises, frequency, and durations) and controls, and instruments used to measure depression or depressive symptoms. Attempts were made to contact the original investigators regarding any missing data.

2.4. Risk of Bias Assessment. The trials' methodological quality was independently evaluated by two reviewers (WJ and SL) using the Cochrane risk of bias assessment tool. Discrepancies were resolved by agreement after rechecking the source papers and further discussion with a third reviewer (XC). Two reviewers assessed a quality rating for the following domains for each included trial as high risk, low risk, or uncertain risk of bias: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessors; (5) incomplete outcome data; and (6) selective reporting.

2.5. Data Analysis. The data from the included studies were analysed with RevMan 5.3 and STATA 12. Heterogeneity was assessed using a chi-square test (a P value <0.10 was considered indicative of statistical significance) and an I^2 statistic (where $I^2 > 30\%$, 50%, or 75% indicated moderate, substantial, and considerable heterogeneity, respectively). Then, data from each trial were pooled with a random effects model in order to provide the included studies with more uniform weight. Given that all variables in the included studies consisted of continuous data and that various instruments were used, we used standardized mean difference (SMD) with 95% confidence intervals (95% CI) to analyse the outcomes. For studies with more than 2 control groups [33], such as TQPs plus RM vs. general exercise plus RM vs. RM alone, the means and standard deviations (SDs) of the two controls were combined using the methods described in the Cochrane Handbook (Section 6.5.2.10). A P value <0.05 was considered statistically significant.

Sensitivity analysis was first conducted by removing each study individually to estimate the results' consistency, as well as to explore the heterogeneity contributed from each individual study. Thereafter, subgroup analysis was undertaken to investigate the role of the various study characteristics on the observed effect, as well as to identify any potential sources of heterogeneity [37].

For trials with missing information on the means or SDs of outcomes, data were first sought from the original investigators. If it was not available from the author, then imputations were performed using the statistical approaches recommended in the Cochrane Handbook. One study used the median and interquartile ranges (IQR) instead of means and SDs [31]; the medians were taken as a substitute for the means and the SD was approximated as SD = IQR/1.35. In another study, SDs were imputed from a reported confidence interval [28] with missing SDs. Publication bias was not assessed due to the limited number of studies (<10) included in each analysis.

3. Results

1480 records (PubMed ($n = 31$), EMABSE ($n = 64$), Cochrane ($n = 156$), CINAHL ($n = 29$), CNKI ($n = 1191$)) totally were retrieved from the database searches. After excluding duplicates, 999 potentially relevant abstracts were screened, and 934 were excluded for failing to meet the inclusion criteria. The remaining 65 full texts were read, and finally, 8 RCTs [26–33] were deemed eligible for this review. Figure 1 presents reasons for exclusion.

3.1. Characteristics of the Included Studies

3.1.1. Study Characteristics. Table 1 shows the main characteristics of selected studies. Eight RCTs (3 in Chinese [26–28] and 5 in English [29–33]) were published between 2007 and 2019. Regions of publication were the United States ($n = 4$) [30–33], Mainland China ($n = 2$) [26, 27], Taiwan ($n = 1$) [28], and the United Kingdom ($n = 1$) [29].

3.1.2. Participants. Sample size per RCT ranged from 16 to 113, with a total of 514 patients who were elderly (mean age: 65 to 68 yrs.). The percentage of males ranged from 50% to 88%. Most patients were in NYHA classes II and III, and with LVEFs <40%, while two trials included patients with LVEFs ≥ 40% [32, 33].

3.1.3. Intervention and Control. The majority of the trials used TaiChi ($n = 6$) [26, 27, 30–33], and the rest used Qigong (Chan-Chuang) [28] or TaiChi plus Qigong [29]. Exercise times lasted from 15 to 60 minutes per session. The length of exercise programs was either 12 weeks ($n = 5$) [26, 28, 30–32], 16 weeks ($n = 2$) [29, 33], or 24 weeks ($n = 1$) [27]. The exercises were center-based in 5 trials [29–33], and home-based in 3 trials [26–28]. The controls received the typical care, including medication and education advice in all trials and also received formal aerobic exercise training [32] or resistance band exercise [33].

3.1.4. Outcome Measurement Instruments. The included studies used various depression severity scales (Table 2). This included three depression specific scales: the Hamilton Rating Scale for Depression (HAM-D) [26, 27], the Beck Depression Inventory (BDI) [30–33], and the Hospital Anxiety and Depression Scale (HADS) [28]. The HAM-D was assessed by clinicians while BDI and HADS were self-rated scales. Two general instruments were used and depression was reported as subscale scores: the Symptom Checklist 90-Revised (SCL-90R) [29] and the Profile of Mood States (PMOS) full [31] and brief versions [32]. Both instruments were self-rated scales.

3.1.5. Depression Status. Based on the baseline mean scores and the reference cutoff points of the depression severity scales (Tables 1 and 2), participants were mildly depressed in four studies [28–30, 33] and moderately depressed in two studies [26, 27]. The other two studies using PMOS reported that 30% [31] and 37% [32] of the subjects had depression as a comorbidity, respectively. However, it was difficult to determine the average severity of the included participants as neither the classification nor the cutoff points of the PMOS scale were reported. Only one study applied clinically diagnosed depression as inclusion criteria for participants [26].

3.2. Methodological Quality of the Evidence. Table 1 presents the risk of bias assessments for individual studies (Appendix 3: risk of bias analysis). Five [26, 28, 31–33] out of eight RCTs described the methods of randomization. However, only two of the included trials [28, 33] reported allocation concealment details. Blinding of participants and personnel were judged as high risk of bias for most of the trials [26–30] due to the nature of the intervention. Blinding of outcome assessors was judged as high risk of bias for patient-reported scales. Two [26, 27] claimed that statisticians had been blinded. Most of the articles showed a low risk of incomplete outcome bias [26, 27, 29, 31–33]. Selective reporting bias was

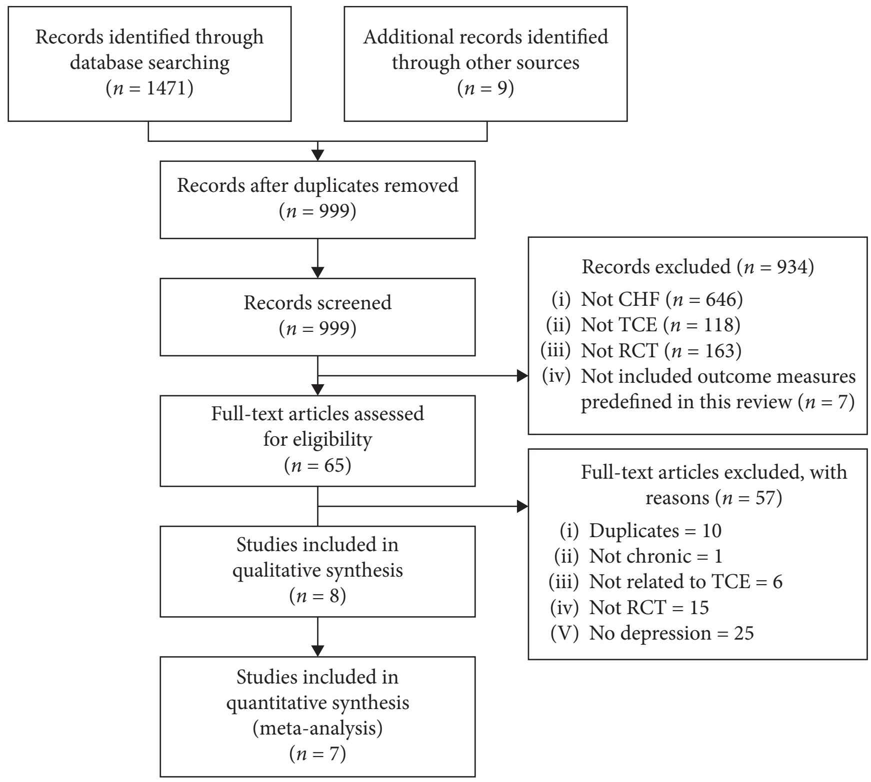

Figure 1: Search strategy and flow chart of the screened, excluded, and analysed articles. CHF: heart failure, TCE: traditional Chinese exercise, and RCT: randomized controlled trial.

unclear in most RCTs [26–31, 33] because neither protocol nor trial registration information was available.

3.3. Outcomes. One study, conducted by Redwile et al. (2012) [30], could not be incorporated into the meta-analysis because of the incomplete data presented. This study included 28 elderly patients (mean age 68 yrs.) undertaking 12-week center-based TaiChi training ($n = 16$) or typical care ($n = 12$). The author reported that patients in the TaiChi group had experienced reduced BDI total symptom scores from pre- to postintervention, compared to the controls. However, depression values were only provided at baseline, but not at the 12th week. The remaining 7 trials reported various outcomes, including measurements of symptoms and depression status, which were included in the quantitative synthesis.

3.3.1. Overall Effects. Pooling across the remaining seven RCTs (481 patients) provided evidence of a decrease in the depression symptoms with TQPs, but this analysis demonstrated substantial heterogeneity (SMD −0.66, 95% CI −0.98 to −0.33, $P < 0.0001$; $I^2 = 64\%$; Figure 2 ; Appendix 2: subgroup analysis (overall pooled effect)). Here a sensitive analysis was performed with one study removed at a time to explore potential sources of heterogeneity, as well as to assess whether the result could have been affected markedly by a single study. The result showed that Yeh et al.'s (2011) study [31] was removed, the statistical heterogeneity disappeared, and the pooled results continued to significantly favor the TQPs with smaller effects (SMD −0.54, 95% CI −0.74 to −0.33, $P < 0.00001$; $I^2 = 0\%$; Figure 2; Appendix 2: subgroup analysis (overall pooled effect)). However, omitting other studies altered neither effect estimates nor heterogeneity (Figure 3).

3.3.2. Subgroup Analysis. We conducted subgroup analysis to investigate the role of the various study characteristics on the pooled effects, as well as to provide estimates of treatment effects for clinically relevant subgroups.

(1) Participants' EF. The benefits of TQPs on depressive symptoms according to ejection fraction (EF) subtype were inconsistent (Figure 4(a); Appendix 2: subgroup analysis (EF subtypes)). The pooled results favored TQPs with increased effect size and remained significant for the heart failure with reduced ejection fraction (HFrEF) RCTs. However, when pooling the two trials including patients with both HFrEF and heart failure with preserved ejection fraction (HFpEF), an insignificant beneficial effect towards the TQPs was found.

(2) Depressive Severity. In the subgroup analysis for participants' depressive severity, the moderately depressed patients benefited more than the mildly depressed patients (SMD −0.76 versus −0.37; Figure 4(b); Appendix 2: subgroup analysis (depressive severity)). However, when pooling the two trials with unknown depression severity, the beneficial effects became insignificant.

Table 1: Characteristics of included studies.

Source (country)	Populations: NYHA subtype	Populations: Sample size (drop out) (I/C), #	Populations: Male (I/C), %	Populations: Age, yrs. (I/C) mean ± SD	Types of TQPs (time/frequency; duration)	Control	RM[a]	Depression severity: Instrument	Depression severity: Baseline mean (I/C)	Depression severity: Changes mean (I/C)	Risk of bias[b]
Barrow et al. (2007) [29] (UK)	II~III HFrEF	65 (32/33) (13 (7/6))	81%/82%	68.4 ± NA[c]/67.9 ± NA[c]	III. TaiChi & Qigong (55 mins/twice per week; 16 wks)	—	TDs	SCL-90R[d], DEP subscale	Mild 58.3/60.2	−6.8/−2.9 (neutral)[e]	Unclear; unclear; high; high; low; unclear
Redwine et al. (2012) [30] (US)	II HFpEF & HFrEF	24 (12/12) (4 (4/0))	83%/92%	72.6 ± 6.2/63.9 ± 12.0	I. TaiChi (60 min/twice per week; 12 wks)	—	TDs	BDI[d], DEP specific	Mild 8.0/9.2	NA/NA[c] (positive)[f]	Unclear; unclear; high; high; unclear; unclear
Yeh et al. (2011) [31] (US)	I~III HFrEF	100 (50/50) (4 (1/3))	56%/72%	68.1 ± 11.9/66.6 ± 12.1	I. TaiChi (60 min/twice per week; 12 wks)	Education	TDs; dietary, exercise advice	PMOS-full[d], DEP subscale	Unclear[g] 2.0/3.0	−2.0/1.0 (neutral)[e]	Low; unclear; unclear; unclear; low; high
Yeh et al. (2013) [32] (US)	I~III HFpEF	16 (8/8) (0)	50%/50%	68.0 ± 11.0/63.0 ± 11.0	I. TaiChi (60 min/twice per week; 12 wks)	Aerobic exercise[h]	TDs; dietary, exercise advice	PMOS-brief[d], DEP subscale	Unclear[i] 4.0/1.3	−1.7/+1.7 ($p = 0.05$)[e]	Low; unclear; low; low; low; unclear
Yuan et al. (2016) [26] (China)	II~III HFrEF	60 (30/30) (0)	57%/53%	66.3 ± 5.6/67.5 ± 3.8	I. TaiChi (20–40 min/5 times per week; 12 wks)	—	TDs; education; antidepressants	HAM-D[d], DEP specific	Moderate[j] 19.9/19.5	−5.6/−3.9 (positive)[e]	Low; unclear; high; low; low; unclear
Deng et al. (2018) [27] (China)	I~III HFrEF	113 (57/56) (2 (2/0))	54%/52%	64.7 ± 4.2/67.2 ± 4.9	I. TaiChi (40~60 min/≥5 times per week; 24 wks)	—	TDs; daily life advice	HAM-D[d], DEP specific	Moderate 22.6/21.3	−8.7/−2.1 (positive)[e]	Unclear; unclear; high; unclear; low; unclear
Redwine et al. (2019) [33] (US)	NA[d] HFrEF & HFpEF	45 (25/23/22) (7 (4/0/3))	92%/86%/87%	63.0 ± 9.0/67.0 ± 7.0/65.0 ± 9.0	I. TaiChi (60 min/twice per week; 16 wks)	−/resistance band[k]	TDs; usual care	BDI[d], DEP specific	Mild 9.6/8.0/11.9	−3.5/−1/−3.3 (positive)[f]	Low; low; unclear; unclear; low unclear
Cheng et al. (2018) [28] (Taiwan)	II NA[c]	91 (41/44) (9 (3/6))	72%/70%	62.2 ± 15.1/66.6 ± 12.7	II. Qigong (Chan-Chuang) (≥15 min/2~3 times per day; 12 wks)	—	TDs	HADS[d], DEP specific	Mild 7.2/7.3	−1.1/−0.2 (positive)[f]	Low; low; high; high; unclear; unclear

NYHY: New York Heart Association; I: intervention group; C: control group; SD: standard deviation; TQPs: TaiChi and/or Qigong practices; RM: routine management; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with perceived ejection fraction; NA: not available; wks: weeks; TDs: therapeutic drugs (prescribed according to heart failure management guideline); DEP: depression; SCL-90-R: Symptom Checklist-90-Revised; BDI: Beck Depression Inventory; PMOS: Profile of Mood States; HAM-D: Hamilton Rating Scale for Depression; HADS: Hospital Anxiety and Depression Scale. [a]Routine management provided as a consistent cointervention to both groups. [b]Risk of bias tool domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of patients and personnel; (4) blinding of outcome assessors for primary outcomes; (5) incomplete outcome data; (6) selective reporting, respectively. [c]LVEF was not measured. [d]Lower sum scores denote improvement. [e]Between-group comparisons. [f]Group-by-time interaction. [g]The classification or the cutoff points of the scale (PMOS) were not found, but 30% of the subjects had depression as a comorbidity. [h]Aerobic exercise: 60 min/twice per week. [i]The classification or the cutoff points of the scale (PMOS) were not found, but 37% of the subjects had depression as a comorbidity. [j]Clinically diagnosed depression according to the CCMD-3 classification scheme and diagnostic criteria of Chinese psychosis. [k]Resistance band training: 60 min/twice per week.

Table 2: Summary of the depression severity scales used in the included studies.

Instruments (no. of study)	Objective	Rater; number of item; rating scale	Categorization/cutoff
SCL-90R, DEP subscale ($n=1$) [29]	To reflect the psychological symptom patterns in 9 domains: somatization/obsessive-compulsive/ sensitivity/depression/anxiety/hostility/phobic anxiety/paranoid ideation/psychoticism	PRO; 90 items (DEP: $n=13$); 5-point scale (0~4)[a]	A T-score[b] ranging from 40 to 60 represents the normal range[c]
BDI, DEP specific ($n=2$) [30, 33]	To measure the severity of depression in adults and adolescents, two subscales include a cognitive-affective subscale and a somatic-performance subscale	PRO; 21 items; 4-point scale (0~3)[a]	0–13: minimal; 14–19: mild depression; 20–28: moderate; 29–63: severe[d] In nonclinical populations, scores above 20 indicate depression
PMOS-full, DEP subscale ($n=1$) [31]	To assess emotional states in 6 domains: depression/anxiety/fatigue/vigor/irritability/ confusion	PRO; 65 items (DEP: $n=15$); 5-point scale (0~4)[a]	Not found
PMOS-brief DEP subscale ($n=1$) [32]	Same as the full version	PRO; 30 items (DEP: $n=5$); 5-point scale (0~4)[a]	Not found
HAM-D DEP specific ($n=2$) [26, 27]	The “gold standard” for assessing severity of depressive severity	Clinician; 17 items; 5-point scale (0–4)[a] ($n=8$); 3-point scale (0–2)[a] ($n=9$)	0–7: normal; 8–16: mild; 17–23: moderate; 24–50: severe[e]
HADS DEP specific[f] ($n=1$) [28]	To assess anxiety and depression symptoms in medical patients	PRO; 14 items (DEP: $n=7$); 4-point scale (0~3)[a]	0–7: normal; 8–10: mild; 11–14: moderate; 15–21: severe[g] A cutoff of 8: clinically significant depression

PRO: patient-reported outcome; DEP: depression; SCL-90R: Symptom Checklist-90-Revised; BDI: Beck Depression Inventory; PMOS: Profile of Mood States; HAM-D: Hamilton Rating Scale for Depression; HADS: Hospital Anxiety and Depression Scale. [a]Higher scores indicate depressed. [b]The SCL-90-R scores are converted to standard *T*-scores (ranging from 30 to 80) by referring to the appropriate population-based norm tables provided by the test manual and a *T*-score of 50 represents the mean of the respective normal population. [c]Holi, M. (2003). Assessment of psychiatric symptoms using the SCL-90. [d]Jackson-Koku, G. (2016). Beck depression inventory. Occupational Medicine, 66 (2), 174-175. [e]Zimmerman, M., Martinez, J. H., Young, D., Chelminski, I., & Dalrymple, K. (2013). Severity classification on the Hamilton Depression Rating Scale. Journal of Affective Disorders, 150 (2), 384–388. [f]Although the anxiety and depression questions are interspersed within the questionnaire, it is vital that these are scored separately. [g]Stern, A. F. (2014). The Hospital Anxiety and Depression Scale. Occupational Medicine, 64 (5), 393–394.

(3) Depression Instruments. The pooled results were inconsistent across subgroups according to the depression instruments (Figure 4C; Appendix 2: subgroup analysis (depression instrument)). When pooling two trials in which the depression severity was evaluated by the clinicians, the beneficial effects from TQPs exceeded the overall effects (Figure 4(c): clinician; Appendix 2: subgroup analysis (depression instrument)). However, when pooling two trials in which patients self-rated their depressive severity using depression specific instruments (BDI and HADS), the beneficial effects from TQPs became smaller and insignificant (Figure 4(c): PRO/specific; Appendix 2: subgroup analysis (depression instrument)). Of note, when pooling the other three trials in which depressive severity was also self-rated by patients, but using nondepression specific instruments (PMOS and SCL-90R), the pooled results became significant again with a larger effect (Figure 4(c): PRO/nonspecific; Appendix 2: subgroup analysis (depression instrument)).

(4) Characteristics of TQP Programs. Generally, the pooled effects were not influenced by the characteristics of the TQP programs. There were similar pooled effect sizes in the *TaiChi* subgroup (Figure 4(d); Appendix 2: subgroup analysis (TQPs)). In addition, TQP program length (<12 weeks vs. >12 weeks) might not have influenced the pooled effect sizes (Figure 4(e); Appendix 2: subgroup analysis (length of TQP programs)). Furthermore, the effect sizes were also similar whether the TQPs were delivered at centers or were home-based (Figure 4(f); Appendix 2: subgroup analysis (TQP delivery settings)). As the sensitivity analysis showed that the study by Yeh et al. (2011) [31] was the main contributor to the heterogeneity (Figure 3), we removed this study and then repeated the subgroup analysis. This change solved the statistical heterogeneity and resulted in a mitigated pooled effect, but did not alter the (in)significance of the pooled results in the associated subgroups (dashed line in Figure 4).

3.4. TQP Safety and Overall Evidence. Patient dropout in the TQP groups was low, with most withdrawals being due to hospitalization or CHF exacerbation. We found no adverse events related to TQPs in the included studies.

4. Discussion

To our knowledge, this is the first systematic review to synthesize RCTs written in both Chinese and English languages that have explored the potential effects of TaiChi and Qigong on depression among patients with HF. Eight RCTs were included, and seven RCTs involving 481 patients with HF were evaluated in the meta-analysis. The results showed that practicing TaiChi and Qigong were associated with a significant reduction in depressive symptoms (SMD −0.66, 95% CI −0.98 to −0.33, $P < 0.0001$; $I^2 = 64\%$), and its

Study or subgroup	TQPs Mean	TQPs SD	TQPs Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, random, 95% CI
1.1.1 Overall								
1. Barrow 2007	51.5	9.5	25	57.3	9.5	27	13.8%	−0.60 [−1.16, −0.04]
19. Yeh 2011	0	1.5	50	4	3.7	50	16.3%	−1.41 [−1.85, −0.97]
20. Yeh 2013	2.3	2	8	3	3	8	7.4%	−0.26 [−1.25, 0.73]
22. Yuan 2016	14.25	2.32	30	15.59	1.52	30	14.6%	−0.67 [−1.20, −0.15]
31. Deng 2018	13.9	5.8	55	19.2	7.2	56	17.5%	−0.80 [−1.19, −0.42]
34 Redwine 2019	6.1	6	18	7.73	6	33	13.4%	−0.27 [−0.84, 0.31]
35. Zheng 2018	6.11	3.15	47	7.07	3.15	44	16.9%	−0.30 [−0.72, 0.11]
Subtotal (95% CI)			*233*			*248*	*100.0%*	*−0.66 [−0.98, −0.33]*
Heterogeneity: $tau^2 = 0.12$; $chi^2 = 16.80$, $df = 6$ ($P = 0.01$); $I^2 = 64\%$								
Test for overall effect: $Z = 3.97$ ($P < 0.0001$)								
*1.1.2 Overall**								
1. Barrow 2007	51.5	9.5	25	57.3	9.5	27	13.7%	−0.60 [−1.16, −0.04]
20. Yeh 2013	2.3	2	8	3	3	8	4.4%	−0.26 [−1.25, 0.73]
22. Yuan 2016	14.25	2.32	30	15.59	1.52	30	15.7%	−0.67 [−1.20, −0.15]
31. Deng 2018	13.9	5.8	55	19.2	7.2	56	28.4%	−0.80 [−1.19, −0.42]
34 Redwine 2019	6.1	6	18	7.73	6	33	12.8%	−0.27 [−0.84, 0.31]
35. Zheng 2018	6.11	3.15	47	7.07	3.15	44	24.9%	−0.30 [−0.72, 0.11]
Subtotal (95% CI)			*183*			*198*	*100.0%*	*−0.54 [−0.74, −0.33]*
Heterogeneity: $tau^2 = 0.00$; $chi^2 = 4.53$, $df = 5$ ($P = 0.48$); $I^2 = 0\%$								
Test for overall effect: $Z = 5.11$ ($P < 0.00001$)								
Test for subgroup differences: $chi^2 = 0.37$, $df = 1$ ($P = 0.54$); $I^2 = 0\%$								

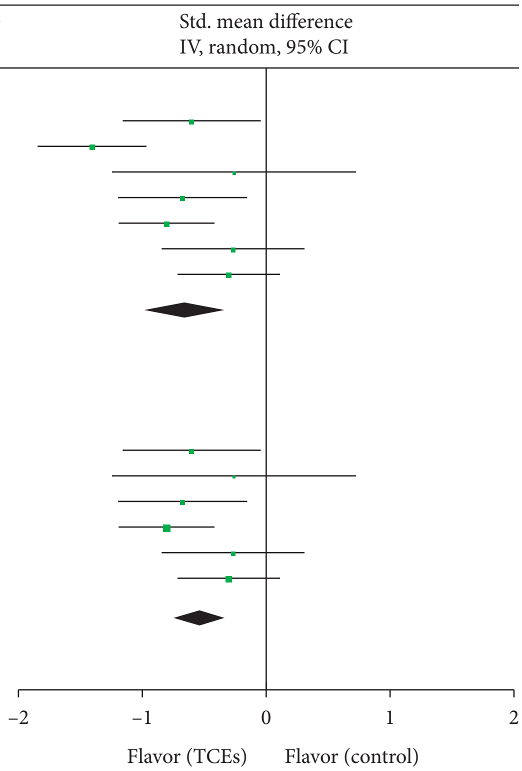

Figure 2: Meta-analysis results of overall pooled effects.

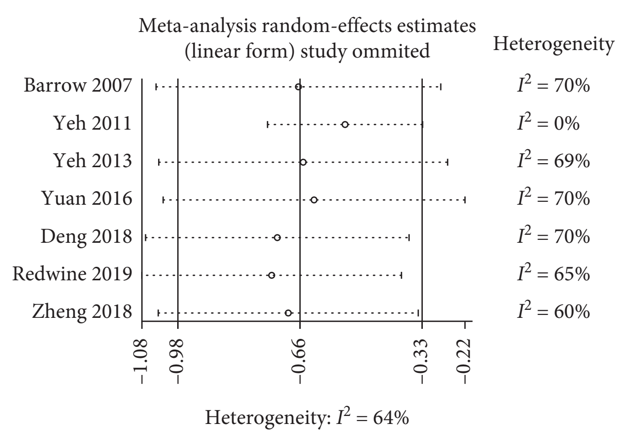

Figure 3: Influence of each individual study on the overall pooled effect estimate.

antidepressive effect was not influenced by intervention duration or exercise setting, but rather by EF subtype, depressive severity, and depression instruments. Significant effects were found for HFrEF (SMD: −0.89; 95% CI −1.25 to −0.53; $I^2 = 54\%$), moderate depression (SMD: −0.76; 95% CI −1.07 to −0.45; $I^2 = 0\%$), mild depression (SMD: −0.37; 95% CI −0.66 to −0.09; $I^2 = 0\%$), specific clinician-rated scales (HAM-D) evaluated depression severity (SMD: −0.76; 95% CI −1.07 to −0.45; $I^2 = 0\%$), and nonspecific self-rated scales (PMOS and SCL-90R) evaluated depression severity (SMD: −0.84; 95% CI −1.53 to −0.15; $I^2 = 73\%$); however, not for HFrEF and HFpEF, specific self-rated scales (BDI and HADS) measured depressive severity. In addition, the beneficial effects of TQPs were preserved when we removed the study with the largest effect (SMD −0.54, 95% CI −0.74 to −0.33, $P < 0.00001$; $I^2 = 0\%$).

Our review is consistent with other systematic reviews and meta-analysis supporting the fact that TaiChi and Qigong reduce depressive symptoms [9, 10, 21]. One review of 17 randomized controlled or nonrandomized trials found that TaiChi reduced depression by heterogeneous standardized effects of −0.66 (95% CI −0.29 to −1.03) among various populations [10]. Gu et al. [38] reviewed evidence on TaiChi in relation to various clinical outcomes including depressive symptoms among patients with HF, founding that TaiChi resulted in significant depression-reduction effects, compared to the control. However, this result was based on only two RCTs involving 112 participants from the USA, most of whom were white. Unlike these previous studies, our review provides a synthesis of the evidence on all types of TaiChi and Qigong with a focus on patients with HF. In addition, previous studies have suggested that emotional responses to TaiChi or Qigong may vary across cultures [39]. Through extensive literature search, our review included the most updated evidence from Mainland China, Taiwan, the USA, and the UK, covering a range of ethnic groups.

The mechanism whereby traditional Chinese Qigong attenuates symptoms of depression is probably multifactorial. An underlying philosophy of the practice is that any form of traditional Chinese Qigong has an effect on the cultivation of balance and the harmony of vital energy (Qi), which functions as a holistic, coherent, and mutually interactive system [18]. In terms of biological mechanisms, it

	Study characteristics	No. of studies	No. of patients	Standardized mean difference (95% CI)	I^2
	Overall effect estimate				
	- Total	7	481	−0.66 (−0.98 to −0.33)	64%
	- Total*	6	381	−0.54 (−0.74 to −0.33)	0%
A.	EF subtype				
	- HFrEF	4	323	−0.89 (−1.25 to −0.53)	58%
	- HFrEF*	3	223	−0.72 (−0.99 to −0.45)	0%
	- HFpEF	1	16	−0.26 (−1.25 to 0.73)	NA
	- HF (both)	2	142	−0.29 (−0.63 to 0.05)	0%
B.	Depressive severity				
	- Mild	3	194	−0.37 (−0.66 to −0.09)	0%
	- Moderate	2	171	−0.76 (−1.07 to −0.45)	0%
	- Unclear	2	116	−0.92 (−2.03 to 0.19)	77%
	- Unclear*	1	16	−0.26 (−1.25 to 0.73)	NA
C.	Depression instrument				
	- Subscale/PRO	3	168	−0.84 (−1.53 to −0.15)	73%
	- Subscale/PRO*	2	68	−0.52 (−1 to −0.03)	0%
	- Specific/PRO	2	142	−0.29 (−0.63 to 0.05)	0%
	- Specific/clinician	2	171	−0.76 (−1.07 to −0.45)	0%
D.	Type of TQPs				
	- TaiChi	5	338	−0.75 (−1.16 to −0.34)	66%
	- TaiChi*	4	238	−0.62 (−0.88 to −0.36)	0%
	- Qigong	1	91	−0.3 (−0.72 to 0.11)	NA
	- TaiCh&Qigong	1	52	−0.6 (−1.16 to −0.04)	NA
E.	Length of TQPs program				
	- 12 week	4	267	−0.7 (−1.28 to −0.12)	79%
	- 12 weeks*	3	167	−0.43 (−0.74 to −0.12)	0%
	- > 12 weeks	3	214	−0.62 (−0.92 to −0.31)	13%
F.	TQPs delivery setting				
	- Center-based/outside China	4	219	−0.69 (−1.29 to −0.08)	75%
	- Center-based/outside China*	3	119	−0.41 (−0.79 to −0.04)	0%
	- Home-based/China	3	262	−0.59 (−0.91 to −0.28)	36%
	*Remove Yeh 2011				

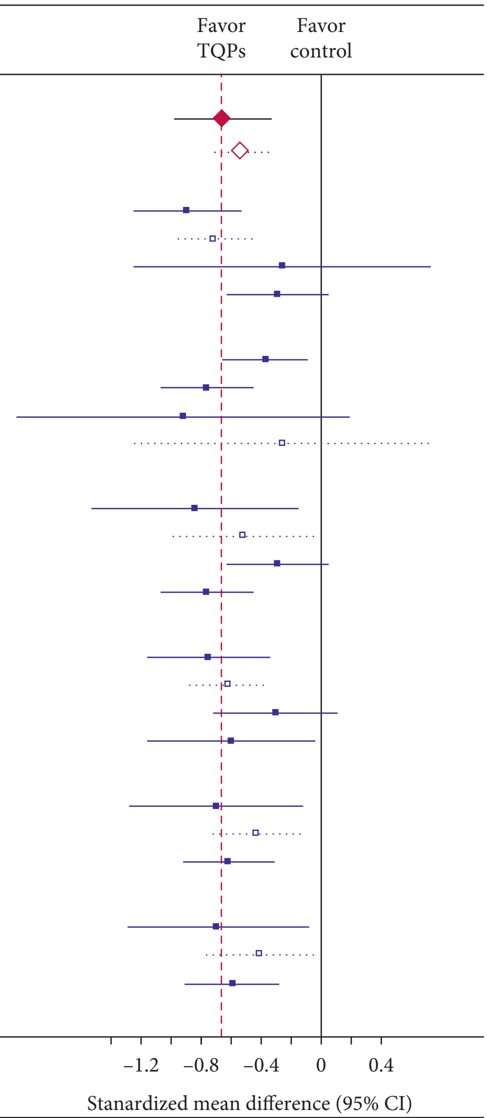

Figure 4: Influence of various study characteristics on the pooled effect and their contributions to heterogeneity. [a]Details of meta-analysis results showing individual study data are presented in Appendix 2.

has been reported that the activity and connectivity of key brain regions related to depression, the autonomic nervous system, and neuroinflammatory sensitization can be modulated by TaiChi and Qigong [18]. Another proposed mechanism suggests that the antidepressant effects of TaiChi and Qigong are associated with improvement in other clinical outcomes such as functional capacity and quality of life [18]. Measures of psychological variables and a multitude of other outcome measures are empirically interrelated, and treatment of each outcome can reciprocally and exponentially improve the other. Additionally, the mutual encouragement and friendly companionship from peers due to the collective activities of TQPs benefit the cognitive control network, adding to the effects related to the TaiChi or Qigong intervention [23].

4.1. Implications for Future Research. Although promising, several knowledge gaps identified in the present review need rational consideration and emphasis in future research. Data from the present review suggests favorable effects of TQPs on depressive symptoms among patients with HF, but this effect is restricted to depressed patients with HFrEF; it is not presented among depressed patients with HFpEF. The negative effects of TQPs on depressive symptoms in HFpEF remain to be determined because there was only one study [32] reviewed in our article regarding TQPs' effects on HFpEF, and it had a small sample size ($n = 16$). These findings accord with a previous meta-analysis assessing exercise training for patients with HF and comorbid depression in which only three trials were available regarding the antidepressive effect of exercise training on HFpEF [40].

There is no denying that insufficient samples partially explain the limited benefits experienced by patients with HFpEF and depression. Therefore, future large-scale multicenter RCTs with a sufficient number of participants are needed to verify TQPs' positive effects among this population. Likewise, the antidepressive effect of TQPs for patients with HF and comorbid major depression is less established. In our review, the available data describe the improvement due to TQPs in minor and moderate depression, and even depression without clear severity in patients with HF, except for major depression. Prior work [12] has emphasized that patients with HF combined with various depression severity have significant differences in the patterns of studies' findings of primary outcomes, such as depression, physical function, and quality of life. This suggests that the findings should be dichotomized according to depression severity to clarify the intervention effects. For this reason, it would be unreasonable to speculate TQPs' benefit on major depression based on its antidepressive effect on minor or moderate depression. Future studies need to enroll patients with HF whose major depression can be diagnosed definitively to evaluate TQPs' antidepressive effect.

In terms of TQPs' antidepressive effect, the present review indicates that it varies depending on the depression instruments used. In this light, it would be informative to consider whether and how to choose suitable depression instruments based on patient population, depression severity, and study setting when evaluating the intervention effects. Thus far, at least two instruments beyond those mentioned in our review have been widely applied to studies to detect and quantify depression in HF, i.e., the 9-item Patient Health Questionnaire (PHQ-9) [41] and the Montgomery and Asberg Depression Rating Scale (MADRS) [42]. However, many studies, including influential trials such as the HF-ACTION [43], the MOOD-HF [42], and the SADAHRT-CHF [44] do not state the usage reasons for a specific instrument. Thus, their results are less convincing. The 21-item Beck Depression Inventory (BDI-II) and the PHQ-9 are the more mature instruments and are recommended in HF combined with depression [43, 45, 46]. In view of a lack of specific guidelines for using depression instruments in HF, hopefully future clinical trials using BDI-II and PHQ-9 will accurately measure depressive symptoms and disorders in patients with HF.

In addition, data indicated that Qigong, or TaiChi combined with Qigong, is less promising than TaiChi alone for depressed patients with HF. This leaves TaiChi as the state-of-the-art mind-body exercise for heart failure and depression in Chinese medicine. Yet definitive answers are missing, and the most effective type of intervention remains to be determined. According to our systematic review, to date there has only been one trial [28] with a small sample reporting changes in depressive symptoms with Qigong practice. This is insufficient to conclude that patients with HF suffering from depression do not respond well to Qigong. Moreover, the reduction in Qigong's comparative disadvantage to TaiChi was achieved indirectly by comparing to control groups. The results of this analysis are similar to another meta-analysis on traditional Chinese exercises (TCEs) for depression accompanying cardiovascular disease [24], which failed to investigate the benefits of specific TCEs to identify the ideal intervention. The situation for TaiChi and Qigong [29] is similar. In this light, there is an unmet need in HF for sufficiently powered trials of TQPs' effect on depression remission. Moreover, a larger-scale RCT on Qigong, an RCT to compare TCEs, and a network meta-analysis comparing TCEs could fill this research gap, thus determining the optimal TCEs to treat depression in HF.

Furthermore, data existing fails to demonstrate differences between the TQPs' effects compared with general exercise on depression in patients with HF. A recent systematic review and network meta-analysis on clinical depression in older adults [47] pointed out that mind-body exercise showed the largest improvement on depressive symptoms, followed by aerobic exercise and resistance exercise, despite a lack of statistically significant differences. Nevertheless, the results only provide limited insight into TQPs for depression in HF. In line with the present review, at this stage, we can only speculate on the relative benefits of TQPs based on two studies. These studies compared the antidepressive effect between TaiChi and aerobic exercise and between Qigong and resistance band training. Therefore, well-designed RCTs are needed to verify the relative benefits of TQPs for depression in HF to general exercise, including aerobic exercise and resistance exercise. This could promote a more solid foundation for treatment recommendations.

However, data from our review have demonstrated how TQPs mitigate depressive symptoms, but the benefits in clinical outcomes such as hospitalization and mortality remain uncertain. Logic would allow one to assume that treating depression may decrease poor outcomes in patients with HF, given that depression can increase the risk of poor outcomes for patients experiencing HF. For example, the HF-ACTION trials [43] showed that exercise benefits patients with HF. Its ancillary study documented that reduced depressive symptoms were associated with improved clinical outcomes. This provided valuable insight into the screening and exercise treatment of depression in patients with HF. Thus, future studies should be designed to determine whether reduced depressive symptoms are associated with improved clinical outcomes, in addition to assessing the effects of TQPs on depressive symptoms.

4.2. Limitations. Several limitations in the present analysis should be noted. First, our analysis of the depression data symptoms was restricted to an SMD, as numerous depression scales were used in the included trials. Therefore, the results should be interpreted with this in mind. Another limitation is the presence of statistical heterogeneity between the trials in this meta-analysis. In order to provide the studies with more uniform weight, we used a random effects model. A sensitivity analysis and subgroup analysis were also performed to investigate the heterogeneity. In our meta-analysis, the beneficial effects [31] were preserved without heterogeneity when the study with the largest effect was removed. Finally, our conclusions were constrained by the quality of the trials reviewed. The main shortcomings were the lack of blinding procedures. However, in exercise interventions, double-blinding is not feasible without deception. In addition, most of the instruments used were self-rated scales where blinding the outcome assessors, i.e., the patients themselves, would have been impossible. These two features could have led to favorable responses among the participants in the intervention group. Therefore, blinding statisticians is essential in this type of trial, but only one included trial provided this information. The absence of randomization concealment and of the intention-to-treat (ITT) analyses is another concern when interpreting the results. Publication bias, although not evaluated, might have been present in the included studies since positive trials are more likely to be published than negative trials. Hence, the effect sizes might have been overestimated. Finally, many studies have neglected critical information in terms of allocation concealment, outcome assessor blinding, adequate follow-up, and ITT analysis. Future RCTs are warranted to improve the methodological quality by adhering to the Consolidated Standards of Reporting Trials statement (CONSORT) [48] or its extensions [49].

5. Conclusion

The evidence presented in this review should encourage physicians to recommend TQPs as clinically effective ways to reduce depressive symptoms in patients with HF. Additional RCTs with rigorous research design, which focus on the above research gaps, are warranted to establish the therapeutic effects of TQPs for depression in HF.

Abbreviations

BDI:	Beck Depression Inventory
CI:	Confidence intervals
EF:	Ejection fraction
HADS:	Hospital Anxiety and Depression Scale
HAM-D:	Hamilton Rating Scale for Depression
HF:	Heart failure
HFpEF:	Heart failure with preserved ejection fraction
HFrEF:	Heart failure with reduced ejection fraction
IQR:	Interquartile ranges
ITT:	Intention-to-treat
LVEF:	Left ventricular ejection fraction
MADRS:	Montgomery and Asberg Depression Rating Scale
NYHA:	New York Heart Association
PHQ-9:	9-item Patient Health Questionnaire
PMOS:	Profile of Mood States
PROs:	Patient-reported outcomes
RCTs:	Randomized controlled trials
RM:	Routine management
SCL-90R:	Symptom Checklist 90-Revised
SDs:	Standard deviations
SMD:	Standardized mean difference
TCEs:	Traditional Chinese exercises
TQPs:	TaiChi and/or Qigong practices.

Data Availability

The extracted data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

This study was part of a PhD thesis supported by the China Scholarships Council (201608440264).

Conflicts of Interest

All authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

WJ and SL contributed equally to this work, conducted the main analysis, and drafted this manuscript. WJ and XC designed the research. GM, ZW, and WL joined in the discussion and offered interesting ideas. CL assisted in the preparation of the research. ZW and WL reviewed the text and guided the structure of the manuscript. All authors took part in the research and wrote, read, and approved the manuscript.

Acknowledgments

This work was supported by the General Research Fund of Traditional Chinese Medicine Science and Technology from the Guangdong Provincial Hospital of Chinese Medicine (YN2018ML02) and the Clinical Research Fund of the Traditional Chinese Medicine Science and Technology (Project 1010) from Guangdong Provincial Hospital of Chinese Medicine (YN10101910).

Supplementary Materials

Appendix 1: search strategy. Appendix 2: subgroup analysis. Appendix 3: risk of bias analysis. Appendix 4: PRISMA 2009 checklist. (*Supplementary Materials*)

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Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2021, Article ID 6633658, 8 pages
https://doi.org/10.1155/2021/6633658

Research Article

Examining the Effects of Brief Mindfulness Training on Athletes' Flow: The Mediating Role of Resilience

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Received 18 December 2020; Revised 19 April 2021; Accepted 13 May 2021; Published 24 May 2021

Academic Editor: Parco M. Siu

Background. Flow is characterized by the strong concentration in competitions, eliminating irrelevant thoughts and emotions, integrating all tasks, and continuing the competition smoothly even in challenging situations. The present study was into whether or not brief mindfulness training can improve athletes' flow and further explore the mediating effect of resilience in the intervention. *Methods*. The 2 (experimental conditions) × 2 (time) mixed design was used in this study. Fifty-seven student-athletes were recruited and randomly assigned into either a brief mindfulness group ($n = 29$) or a control group ($n = 28$). Before and after the intervention, every participant completed a self-report measure including mindfulness, flow, and resilience. *Results*. Participants in the brief mindfulness group showed increased mindfulness, flow, and resilience ($p < 0.001$) after brief mindfulness training; when putting resilience change ($B = 0.30$, 95% CI [0.031, 0.564]) into the equation, the direct (95% CI [3.156, 13.583]) and indirect (95% CI [0.470, 5.048]) effects of mindfulness training were both significant. *Conclusion*. It was concluded that brief mindfulness training could significantly improve athletes' flow and resilience, and resilience partly mediated the effects of brief mindfulness training on flow.

1. Introduction

With the continuous improvement of science, technology, and training level, the differences in techniques and tactics of athletes are gradually reduced. Therefore, the psychological state has been regarded as the key factor for athletes to win in competitions and has continuously attracted the attention of researchers. "The optimal competitive state" theory [1] also pointed out that the optimal psychological state was the basis for athletes to compete on the court. With the aim of improving athletes' psychological state (e.g., flow or well-being) and managing their mental health disorders (e.g., anxiety or depression), mindfulness has been integrated into cognitive behavioural training in the sport context [2]. Compared to traditional cognitive behavioural training (e.g., relaxation training and imagery training), which builds on the rationale of controlling or changing the contents of performers' undesirable psychological events in order to achieve the optimal psychological states [3], mindfulness training is an alternative approach for individuals to experience their psychological events (i.e., perceptual experiences). In a state of mindfulness, individuals apply an accepting and nonjudging approach to act and think rather than trying to change or control those experiences [4]. Therefore, mindfulness training encourages individuals to pay attention to the present, which helps disengage distractions from their ruminative states. In other words, mindfulness training may help individuals avoid ineffective or counterproductive psychological states [5].

Athletes' optimal psychological state that has been most discussed in recent years is "flow." Flow is characterized by strong concentration in competitions, eliminating irrelevant thoughts and emotions, integrating all tasks, and continuing the competition smoothly even in challenging situations [6], which has an important positive effect on the performance of athletes. Therefore, how to increase athletes' flow has become an important topic in the field of sports.

The benefits of mindfulness training on flow have been explained by recent studies [7]. Theoretically, it has been proposed that mindfulness (e.g., brief meditation) can help individuals keep their attention in the present and enhance their body awareness and emotion regulation [8], while the purpose of flow is to develop the consciousness or emotion which is helpful for their optimal performance through devoting themselves to the task [9]. With regard to the empirical evidence on the mechanisms of attention control and emotion, it has been demonstrated that mindfulness training can cause a structural change of grey matter in the brain [8]. As such, mindfulness training might well be useful for increasing flow because of its neurological effects related to psychological effects, such as attention and emotion control [10], which both are the basis of flow.

Although there has been some evidence on the link between mindfulness and athletes' flow [3], the application of brief mindfulness training on flow and its mediating mechanism has not been researched. It was found that when discussing athletes' mindfulness and flow, it was always associated with resilience [11]. Resilience refers to the good adaptation process of human beings in the face of adversity, trauma, or stress, which is an important quality of athletes [12]. The competition in sports is very fierce, so the adversity and stress experience of athletes is quite common. A number of empirical studies have shown that mindfulness training can improve athletes' resilience [13, 14]. The reason is that the concept of mindfulness is acceptance, nonjudgment, and paying attention to the present. Thus, athletes can still focus on the task when facing threats or challenges in their training or competitions and can adapt to changes from the external environment; that is, the level of resilience is improved.

In addition, when the athlete's ability to adapt to threats and challenges is improved, they can get rid of the fear of failure, form a positive evaluation of their own performance, and experience more positive emotions such as self-realization and psychological satisfaction [15]. According to the extended construction theory of positive emotions, the above-mentioned positive emotion experience can enhance athletes' cognitive flexibility and make them more creative in methods exploration of emotion regulation, which are all helpful for enhancing pathway thinking and improving resilience [16]. As flow is characterized by eliminating irrelevant thoughts and emotions, therefore, the increase of flow is more predictable. That is, by mindfully accepting experiences instead of perseverating on them, cognitive resources are freed up to broaden the scope of attention to encompass pleasurable and meaningful events [17] and thereby build motivation toward purposeful engagement with competitions, which is helpful for increasing athletes' flow.

The majority of previous studies had focused on the effects of long-term mindfulness training on flow and resilience [13, 18], and a few intervention studies had explored the relationship between brief mindfulness, flow, and resilience for athletes; thus, the adoption of brief mindfulness training in this study is purposeful and fills a missing research gap. Clearly, there could be potential confounding factors arising from prolonged mindfulness interventions, such as improved attentional control [19], which makes it difficult for singling out mindfulness practice as the cause of improved flow [20]. Here, evidence of whether a brief mindfulness training affects the flow of athletes reveals the effects more directly. Furthermore, some scholars highlighted the potential difficulty in getting athletes to use mindfulness strategies effectively [21]. Long-term mindfulness training, for example, has been known to be easy for participants to drop out, particularly for athletes [22]. Currently, research evidence suggests the effectiveness of brief mindfulness training in eliciting positive outcomes, such as goal motivation and tolerance to negative affect [14]. The effects of such brief interventions led us to consider whether a brief mindfulness training would similarly improve athletes' flow and resilience.

Previous studies have examined the changes in flow and resilience before and after mindfulness training [13, 18]. However, the mediating mechanism by which mindfulness training improves athletes' flow has rarely been explored. In addition, our efforts in testing the effects of brief mindfulness training over a short duration of 30 minutes hopefully contribute to the development of a simple strategy that can be readily applied by athletes without expectation for prolonged sitting meditation. Therefore, the aim of the present study was to examine the effects of brief mindfulness training on athletes' flow and its mediating mechanism. Based on the presented theoretical review we developed the following hypotheses: (1) brief mindfulness training can improve the level of flow among athletes; (2) brief mindfulness training can improve the level of resilience among athletes; (3) resilience plays a mediating role between brief mindfulness training and flow; that is, brief mindfulness training can increase athletes' flow through improving their resilience.

2. Methods

2.1. Participants. Ethics clearance was granted by the research ethics committee of the Beijing Sport University. Bühlmayer reported a medium-to-large effect size of the mindfulness effect for athletes [23]. An a priori power analysis determined that we would need a total sample size of 52 participants to detect this effect size (G∗power; effect size $f = 0.35$, $\alpha = 0.05$, $1-\beta = 0.80$, Corr among rep measures = 0.50).

All participants were recruited from a sport university in China, who were all above level 2 and right-handed, had a normal or corrected-to-normal vision, and did not have any mindfulness training experience. In total, 60 student-athletes (20 females and 40 males) participated voluntarily in this study. Participants were randomly separated into two groups: the brief mindfulness group ($n = 30$) and the control group ($n = 30$) using a random number generator.

Due to time commitment, 29 of 30 athletes in the brief mindfulness group (9 females and 20 males; age average = 19.9, $SD = .7$) and 28 of 30 athletes in the control group (9 females and 19 males; age average = 19.5, $SD = .8$) completed the study. Written informed consent was provided to participants before inclusion and the confidentiality and anonymity of their participation were assured.

2.2. Procedure. A 2 × 2 mixed factorial design was employed, with the group (brief mindfulness group vs. control group) as a between-subject factor, and the time (preintervention vs. postintervention) as a within-subject factor. All participants were tested individually. Before the experiment, each participant completed a brief demographic questionnaire to assess age, sex, and meditation experience. Afterward, each participant completed a self-report measure of mindfulness, flow, and resilience and was then randomly assigned to one of the two groups.

Participants in the brief mindfulness group were seated in an empty classroom and were instructed to listen to a mindfulness training audio recording (30 minutes) and complete the exercises outlined in the audio recording. The brief mindfulness training recording was recorded in advance by a mindfulness instructor who has more than 6 years of mindfulness intervention experience. All participants were intervened based on the Gardner and Moore MAC Protocol [2]. The instructor introduced the MAC approach and provided an explanation of the fundamental concepts of mindfulness. The instructor then led the brief centering exercise, where participants attended to their breath and switched their attention to their surroundings, then back to their body. Participants then were asked to complete the body scan exercise, in which participants attended to their breath then progressively moved their attention from one area of the body to another. The goal is to learn how to flexibly move their attention between internal and external sensations and redirect their attention from internal processes (emotions or thoughts) to an external task [14].

Participants in the control group were instructed to listen to a neutral news audio recording for the same duration (30 min). Following the mindfulness or neutral recording, every participant completed a self-report measure of mindfulness, flow, and resilience.

Finally, the fidelity of the intervention was emphasized through the adherence to the protocol, providing uniform delivery to all the participants, observing participant responsiveness and engagement in the intervention, and careful collaboration between the researchers, athletes, and coaches with the goal of determining the elements of the intervention that were essential for its success [24].

2.3. Measures. Mindfulness was measured using the Chinese version [25] of the Five Facet Mindfulness Questionnaire (FFMQ) [26], assessing five facets of mindfulness: observing, describing, acting with awareness, nonjudging of inner experience, and nonreactivity to inner experience. Participants rated the 39 items (e.g., "I notice the smells and aromas of things") of FFMQ by using a five-point Likert scale (1 = never or very rarely true; 5 = very often or always true). For the total measure, scores can range from 39 to 195, with higher scores representing higher levels of mindfulness. The internal consistency reliability of FFMQ was satisfactory across our assessments ($\alpha = 0.67$ to 0.81).

Flow was measured using the Chinese version [27] of Dispositional Flow Scale 2 (DFS-2) [28], assessing nine facets of flow: challenge skill balance, action awareness, clear goals, unambiguous feedback, concentration on task, sense of control, loss self-consciousness, transformation of time, and autotelic experience. Participants rated the 33 items (e.g., "I feel I am competent enough to meet the high demands of the situation") of DFS-2 by using a five-point Likert scale (1 = never; 5 = always). Their responses were summed to create flow scores. Scores can range from 33 to 165, with higher scores indicating a greater frequency of flow. The internal consistency reliability of DFS was satisfactory across our assessments ($\alpha = 0.74$ to 0.87).

Resilience was measured using the Chinese version [29] of the Resilience Scale (RISC) [30], assessing three facets of resilience: toughness, strength, and optimism. Participants rated the 25 items (e.g., "I can adapt to changes") of RISC by using a 5-point Likert scale (0 = never; 4 = always). Their responses were summed to create resilience scores. Scores can range from 0 to 100, with higher scores indicating greater levels of resilience. The internal consistency reliability of RISC was satisfactory across our assessments ($\alpha = 0.63$ to 0.87).

2.4. Data Analysis. Independent-sample *t*-tests were used to compare the preintervention scores of the brief mindfulness group and control group. Two-way repeated-measures analyses of variance (ANOVA) were conducted to test the effect of time (within-subject independent variable: levels = - preintervention and postintervention) and group (between-subject independent variable: levels = brief mindfulness group and control group) on mindfulness, flow, and resilience, respectively. Post hoc simple effect analysis was used to investigate whether there was any difference between pretest and posttest of each group. The macro program PROCESS of SPSS compiled by Hayes [31] was used to test the mediating effect of resilience between brief mindfulness training and flow. The number of Bootstrap samples was 5000. Under the 95% confidence interval, postintervention score of flow was used as the dependent variable, the group was used as the independent variable, and the score change of resilience (postintervention minus preintervention) was used as the mediating variable. Since the postintervention score of flow was affected by preintervention score, therefore, gender, age, and preintervention score of flow were all controlled as covariates.

3. Results

In preliminary data screening, no missing data were observed. See Table 1 for the means, standard deviations, and preintervention comparison of the study variables of each group.

Repeated-measures ANOVA of mindfulness revealed a significant time by group interaction effect, F (1, 55) = 13.75, $p < 0.001$, $\eta_p^2 = 0.200$, and within-subject difference of mindfulness across time was significant, F (1, 55) = 7.73, $p = 0.007$, $\eta_p^2 = 0.123$. Furthermore, a between-group difference of mindfulness was not significant, F (1, 55) = 0.02, $p = 0.886$, $\eta_p^2 < 0.001$; see Table 2. Further simple effect analysis indicated that the mindfulness level of the brief mindfulness group was

Table 1: Descriptive statistics (M ± SD) of the two groups across preintervention and postintervention and summaries of preintervention independent-sample t-test comparison.

Variables	Brief mindfulness group ($n = 29$)		Control group ($n = 28$)		Comparison of preintervention	
	Preintervention	Postintervention	Preintervention	Postintervention	t	p
Observing	24.83 ± 5.35	27.55 ± 4.85	28.29 ± 5.00	27.75 ± 5.16	−2.51	0.015
Describing	24.07 ± 4.41	25.62 ± 3.82	24.86 ± 4.39	24.11 ± 3.44	−0.68	0.502
Acting with awareness	26.69 ± 4.49	25.17 ± 4.38	24.86 ± 5.67	23.61 ± 5.47	1.35	0.183
Nonjudging	20.03 ± 5.24	19.28 ± 4.23	19.64 ± 4.74	20.07 ± 4.68	0.30	0.768
Nonreactivity	19.66 ± 3.58	23.90 ± 4.50	20.86 ± 3.36	22.07 ± 4.39	−1.32	0.192
Mindfulness	115.28 ± 10.97	121.52 ± 9.87	118.50 ± 9.43	117.61 ± 8.37	−1.19	0.239
Challenge skill balance	12.97 ± 2.53	14.10 ± 2.45	14.64 ± 2.78	14.21 ± 3.15	−2.38	0.021
Action awareness	9.52 ± 2.35	10.31 ± 2.04	10.07 ± 2.29	9.57 ± 2.03	−0.90	0.372
Clear goals	11.59 ± 2.26	11.28 ± 2.40	11.57 ± 2.12	11.04 ± 2.15	0.03	0.980
Unambiguous feedback	15.03 ± 2.47	15.07 ± 2.05	15.11 ± 2.20	14.29 ± 2.34	−0.12	0.907
Concentration on task	12.62 ± 2.43	14.03 ± 2.64	13.64 ± 2.21	13.32 ± 2.58	−1.66	0.102
Sense of control	8.90 ± 1.99	9.59 ± 1.35	10.14 ± 1.60	9.61 ± 1.40	−2.61	0.012
Loss self-consciousness	10.62 ± 3.82	11.31 ± 3.80	11.25 ± 2.88	10.57 ± 3.28	−0.70	0.484
Transformation of time	12.76 ± 3.59	13.62 ± 3.59	14.11 ± 3.38	13.50 ± 2.95	−1.46	0.150
Autotelic experience	13.41 ± 2.83	14.24 ± 2.50	15.21 ± 3.00	14.50 ± 3.35	−2.33	0.024
Flow	107.41 ± 11.98	113.55 ± 12.76	115.75 ± 12.86	110.60 ± 14.74	−2.53	0.014
Toughness	41.79 ± 7.01	47.31 ± 7.36	44.04 ± 6.60	45.57 ± 7.03	−1.25	0.219
Strength	28.90 ± 3.68	31.14 ± 4.05	28.57 ± 4.35	29.21 ± 5.41	0.30	0.762
Optimism	13.38 ± 2.58	14.31 ± 2.44	13.61 ± 2.31	13.79 ± 2.50	−0.35	0.727
Resilience	84.07 ± 11.75	92.76 ± 12.45	86.21 ± 11.95	88.57 ± 13.51	−0.68	0.497

Table 2: Summaries of two-way repeated-measures ANOVA comparison.

Variables	Within-subject						Between-subject		
	Time			Time × group					
	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
Observing	7.65	0.008	0.122	16.966	<0.001	0.236	2.01	0.162	0.035
Describing	0.74	0.395	0.013	6.06	0.017	0.099	0.14	0.708	0.003
Acting with awareness	6.92	0.011	0.112	0.07	0.800	0.001	1.93	0.171	0.034
Nonjudging	0.16	0.691	0.003	2.06	0.157	0.036	0.03	0.865	0.001
Nonreactivity	3.80	<0.001	0.420	12.25	0.001	0.182	0.11	0.747	0.002
Mindfulness	7.73	0.007	0.123	13.75	<0.001	0.200	0.02	0.886	<0.001
Challenge skill balance	2.43	0.125	0.042	11.85	0.001	0.177	1.68	0.200	0.030
Action awareness	0.36	0.550	0.007	7.05	0.010	0.114	0.03	0.861	0.001
Clear goals	3.28	0.076	0.056	0.23	0.632	0.004	0.06	0.816	0.001
Unambiguous feedback	2.00	0.163	0.035	2.36	0.130	0.041	0.44	0.508	0.008
Concentration on task	3.04	0.087	0.052	7.68	0.008	0.123	0.07	0.789	0.001
Sense of control	0.13	0.718	0.002	8.33	0.006	0.132	2.95	0.091	0.051
Loss self-consciousness	<0.001	0.989	<0.001	3.13	0.082	0.054	0.01	0.948	<0.001
Transformation of time	0.27	0.605	0.005	8.99	0.004	0.140	0.51	0.477	0.009
Autotelic experience	0.04	0.848	0.001	6.90	0.011	0.112	2.05	0.158	0.036
Flow	0.18	0.673	0.003	23.17	<0.001	0.296	0.68	0.413	0.012
Toughness	25.08	<0.001	0.313	7.99	0.007	0.127	0.02	0.884	<0.001
Strength	13.47	0.001	0.197	4.14	0.047	0.070	1.04	0.311	0.019
Optimism	5.30	0.025	0.088	2.44	0.124	0.042	0.06	0.807	0.001
Resilience	24.08	<0.001	0.305	7.91	0.007	0.126	0.11	0.743	0.002

Note. η_p^2: partial η^2.

significantly higher in postintervention, as compared to that of preintervention ($p < 0.001$), while the mindfulness level of the control group was a little lower in postintervention, as compared to that of preintervention ($p = 0.518$); see Figure 1.

Repeated-measures ANOVA of flow revealed a significant time by group interaction effect, F (1, 55) = 23.17, $p < 0.001$, $\eta_p^2 = 0.296$, and within-subject difference of flow across time was not significant, F (1, 55) = .18, $p = 0.673$, $\eta_p^2 = 0.003$. Furthermore, a between-group difference of flow was not significant, F (1, 55) = 0.68, $p = 0.413$, $\eta_p^2 = 0.012$; see Table 2. Further simple effect analysis indicated that the flow of brief mindfulness group was significantly higher in

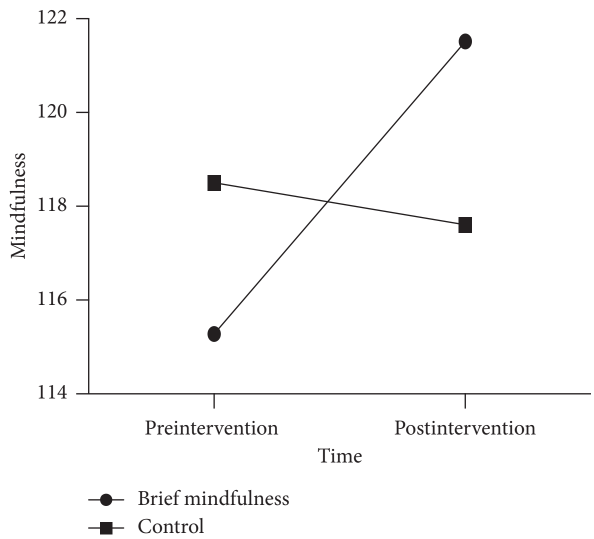

Figure 1: Mindfulness scores of two groups in pre- and postintervention.

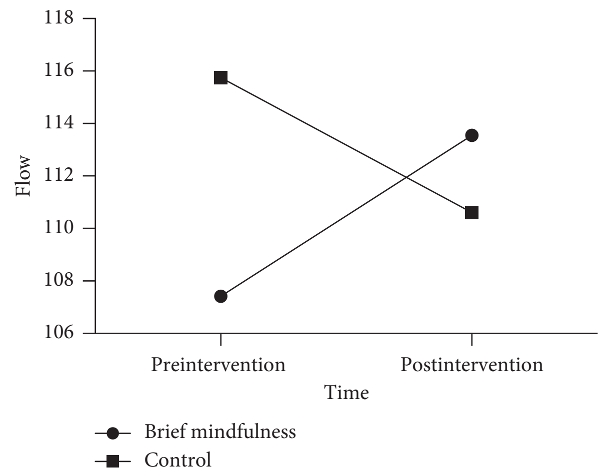

Figure 2: Flow scores of two groups in pre- and postintervention.

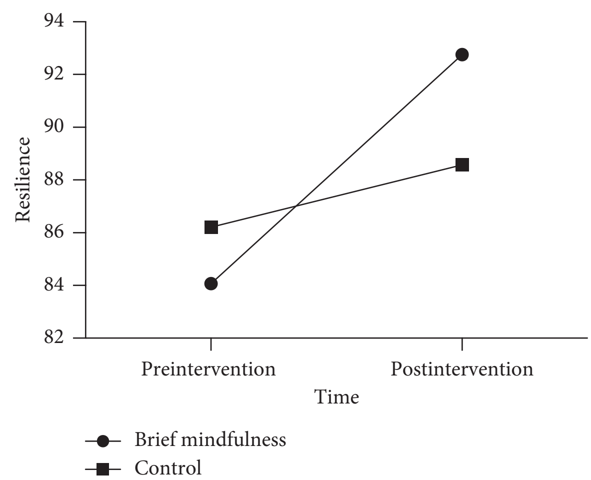

Figure 3: Resilience scores of two groups in pre- and postintervention.

postintervention, as compared to that of preintervention ($p < 0.001$) while the flow of control group was significantly lower in postintervention, as compared to that of preintervention ($p = 0.003$). Hypothesis 1 was verified; see Figure 2.

Repeated-measures ANOVA of resilience revealed a significant time by group interaction effect, F (1, 55) = 7.91, $p = 0.007$, $\eta_p{}^2 = 0.126$, and within-subject difference of resilience across time was significant, F (1, 55) = 24.08, $p < 0.001$, $\eta_p{}^2 = 0.306$. Furthermore, a between-group difference of resilience was not significant, F (1, 55) = 0.11, $p = 0.743$, $\eta_p{}^2 = 0.002$; see Table 2. Further simple effect analysis indicated that the resilience of the brief mindfulness group was significantly higher in postintervention, as compared to that of preintervention ($p < 0.001$) while the resilience of the control group was a little higher in postintervention, as compared to that of preintervention ($p = 0.148$). Hypothesis 2 was verified; see Figure 3.

From Table 3, it can be found that the total effect of the group on postintervention flow was significant ($B = 10.38$, 95% CI [5.302, 15.457]); resilience change had a significant predictive effect on postintervention flow ($B = .30$, 95% CI [0.031, 0.564]). Further analysis found that after the mediating variable entered the equation, the indirect effect Bootstrap 95% CI [0.470, 5.048] did not contain 0; besides, the direct effect bootstrap 95 % CI [3.156, 13.583] did not contain 0. Hypothesis 3 was verified.

4. Discussion

The current study provides preliminary evidence for the effectiveness of brief mindfulness training on mindfulness, flow, and resilience for athletes. Compared with the control group, athletes who completed the brief mindfulness training significantly improved their mindfulness, flow, and resilience at the postintervention test, indicating the positive effects of brief mindfulness training for athletes.

First, we predicted that brief mindfulness training would increase levels of trait mindfulness, as measured by total FFMQ scores, compared with the control group. On the one hand, total FFMQ scores were greater in the brief mindfulness group compared with the control group, which is consistent with our hypothesis and provides additional support for previous studies that used brief mindfulness training [32]. On the other hand, considering that baseline total FFMQ scores did not significantly differ across groups, it is unlikely that these results are simply due to preintervention differences in trait mindfulness across groups. This finding is consistent with previous research [32] and demonstrates the mindfulness benefits associated with brief mindfulness training programs.

Mindfulness has been linked to significant and positive relations with flow in previous correlational and intervention studies [18, 33]. As shown in our study, the brief mindfulness group had consistently reported higher flow than the control group, which is consistent with our hypothesis. The results validated the positive impact of the brief mindfulness intervention on flow, again. Previous studies

Table 3: Summaries of PROCESS mediating effect test.

Dependent variable: postintervention flow	Coefficient/effect	Boot se	95% CI LL	95% CI UL
Independent variables:				
Gender	−4.29	2.42	−9.148	0.568
Age	−0.70	1.56	−3.826	2.428
Preintervention flow	0.85	0.09	0.664	1.029
Δ resilience	0.30	0.13	0.031	0.564
Direct effect	8.37	2.60	3.156	13.583
Indirect effect	2.01	1.09	0.470	5.048
Total effect	10.38	2.53	5.302	15.457

Note. CI = confidence interval; LL = lower limit; UL = upper limit; group 1 = control group, group 2 = brief mindfulness group; Δ = postintervention score minus preintervention score.

showed that the process of mindfulness training emphasizes individuals' perception of inner experience, including emotion, thought, and intention [34], that is, focusing on actions that need to be completed and living in the present, which was the basis of flow.

Our findings are also broadly consistent with the results of the previous research [35]. These latter authors found that athletes who scored highly in mindfulness reported greater scores for some flow dimensions (e.g., sense of control, action awareness, concentration on task) than did athletes with lower mindfulness scores. Our results are understandable given that these dimensions of flow are related to the self-regulation of attention [36]. Thus, with heightened self-regulation of attention, those who are mindful are more likely to concentrate on their tasks and be aware of their action. Likewise, according to Bishop et al. [36] contention, the improvement of the sense of control is also related to self-regulation of attention. However, a noticeable difference is that this study did not find that brief mindfulness training significantly led to increased scores on the flow subscales of "clear goals," "unambiguous feedback," and "loss of self-consciousness." One possible explanation is that the participants were only asked to do a brief centering exercise and body scan exercise in one single-session mindfulness intervention, which was not aiming at improving these three abilities. Further research choosing longer-term interventions and thus greater statistical power will be needed to confirm these findings [18]. It would be premature to conclude that mindfulness does not influence the aspects of flow for which statistically significant effects were not detected in this study.

Moreover, the brief mindfulness group had consistently reported higher resilience than the control group, which is consistent with our hypothesis. The current results showed that brief mindfulness training could help improve athletes' resilience, which meant that brief mindfulness training could improve athletes' receptive ability and avoid being affected by negative events. Previous studies pointed out that the idea of mindfulness originated from Eastern religions and philosophy. It is a concern for nonjudgment of current experience [37], and a "frank awareness", emphasizing nonjudgment and nonevaluation of the actual situation at present. Although athletes are able to pay attention to the actual situation at present, they will not judge right or wrong, whose purposes are not to control or change their own internal state [38]. Another possible explanation is that mindfulness training facilitates active emotion-focused coping (e.g., cognitive reappraisal). Consistent with this active emotion-focused coping account, one previous study indicates that mindfulness training increases resilience for stressful events [39].

Although positive relations between mindfulness and resilience were shown in previous correlational and intervention studies [40, 41], this study did not find that brief mindfulness training significantly led to increased scores on the resilience subscales of "optimism." One testable hypothesis is that optimistic coping efforts may be particularly deliberate and effortful after brief mindfulness meditation training but then become more automatic after longer periods of training [42].

Finally, we revealed the mediating mechanism of a brief mindfulness intervention on flow among athletes, which is consistent with our hypothesis. We found that resilience played a partly mediating role in the process of a brief mindfulness intervention improving flow; that is, a brief mindfulness intervention can not only directly improve flow among athletes but also indirectly improve flow through resilience. This reveals the relationship between mindfulness and flow from the perspective of nonjudgment and nonreaction, which is more consistent with the reality of athletes and the "attention control" theory proposed by Diamond [43]. On the one hand, mindfulness emphasizes the psychological characteristics of not judging the past and not worrying about the future. If athletes can be nonjudgmental and nonreactive, they will pay more attention to current tasks and alleviate negative events, which mean the improvement of resilience and are the basis of flow, or they will be immersed in negative events and experiences. On the other hand, mindfulness is a complex psychological state related to the ability of attention control, which can reduce individuals' response to the surrounding environment, and it also means the improvement of resilience and is the basis of flow. This explains why resilience mediates the influence of the brief mindfulness intervention on flow.

While the results of this study are encouraging, several limitations of the present study must be considered. First, we did not examine the follow-up effect of the brief mindfulness intervention. While anecdotal statements from student-athletes a few weeks past the intervention indicated retention of the mindfulness skills, this study did not conduct a formal assessment of the intervention retention. In addition, the sample consisted entirely of student-athletes; thus, whether the conclusion of this study is applicable to elite athletes needs further verification. Future research should include a follow-up with a larger sample size of elite athletes. Moreover, a brief single-session mindfulness intervention was used; thus, this study did not find that mindfulness training led to increased scores on some subscales of mindfulness, resilience, and flow. A longer period of mindfulness training should be used in the future to establish statistically significant changes in every subscale of mindfulness, resilience, and flow when assessed quantitatively. Another limitation is the exclusive reliance on self-report measures. Although the instruments used here have good psychometric support, self-report measures can be subject to biases. Future research may consider including neuron electrophysiology in outcome measures as supplements of an objective indicator of mental status, for example, EEG and MRI.

In summary, brief single-session mindfulness interventions are increasingly being used to examine the effects of mindfulness in a controlled laboratory setting. However, limited brief mindfulness studies have been conducted on athletes' flow. We investigated the degree to which one of these interventions affected measures of flow, and whether the efficacy of the intervention is mediated by resilience. This study expands the functions of brief mindfulness interventions in the field of sports, enriches the mediating mechanism of a brief mindfulness intervention, and focuses on the effects of a brief mindfulness intervention on flow and resilience, which are closely related to athletes' performance and mental health.

5. Conclusion

The present study provided initial evidence supporting the application of brief mindfulness training in improving mindfulness, flow, and resilience for athletes. Brief mindfulness training not only appeared to be adaptive to athletes' mindfulness but also seemed to improve their flow and resilience. More importantly, resilience played a mediating role in the process of mindfulness intervention improving athletes' flow. The importance of preserving the habit of regular mindfulness practice after the completion of a brief mindfulness intervention is highlighted.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors certify that there are no conflicts of interest with any financial organization regarding the material discussed in the manuscript.

Authors' Contributions

Fengbo LIU contributed to the literature review, experimental design, data collection, and writing of the manuscript; Shuqiang LIU contributed to the draft editing of the manuscript; Nan Zhang contributed to the mindfulness intervention; Zhongqiu Zhang contributed to the research concept. All authors approved the final version of the manuscript for submission.

Acknowledgments

This study was supported by a grant (19dz1200700) from the Shanghai Science and Technology Committee.19dz1200700 The authors thank Beijing Sport University and Shandong Sport University for providing the psychological laboratories. Also, the authors thank Mr. Yu Song for data collection at the initial stage of this study.

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Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2021, Article ID 5549006, 12 pages
https://doi.org/10.1155/2021/5549006

Review Article

The Effect of Tai Chi Chuan on Emotional Health: Potential Mechanisms and Prefrontal Cortex Hypothesis

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Received 5 January 2021; Revised 25 March 2021; Accepted 22 April 2021; Published 3 May 2021

Academic Editor: Jian Kong

Deep involvement in the negative mood over long periods of time likely results in emotional disturbances/disorders and poor mental health. Tai Chi Chuan (TCC) is regarded as a typical mind-body practice combining aerobic exercise and meditation to prevent and treat negative mood. Although there are an increasing number of TCC studies examining anxiety, depression, and mental stress, the mechanisms underlying these negative emotions are not fully understood. This review study examined TCC studies related to emotional health from both clinical patients and healthy individuals. Next, several potential mechanisms from physiological, psychological, and neurological perspectives were evaluated based on direct and indirect research evidence. We reviewed recent functional magnetic resonance imaging studies, which demonstrated changes in brain anatomy and function, mainly in the prefrontal cortex, following TCC practice. Finally, the effects of TCC on emotion/mental health is depicted with a prefrontal cortex hypothesis that proposed "an immune system of the mind" indicating the role of the prefrontal cortex as a flexible hub in regulating an individual's mental health. The prefrontal cortex is likely a key biomarker among the multiple complex neural correlates to help an individual manage negative emotions/mental health. Future research is needed to examine TCC effects on mental health by examining the relationship between the executive control system (mainly prefrontal cortex) and limbic network (including amygdala, insula, and hippocampal gyrus).

1. Introduction

There are an estimated 350 million people of all ages worldwide, suffering from depression [1]. Similarly, anxiety disorders are among the most prevalent mental health conditions, despite differences in cultural beliefs and practices. Mental health conditions, such as depression and anxiety, are highly intertwined with the leading causes of illness and disability (e.g., heart disease and stroke), leading to high family and social burden due to increased healthcare costs. Many clinicians and research scientists support mental health prevention (instead of intervention) for treating disorders [2]. Although there are known effective treatments for mental health disorders, worldwide, fewer than half of those individuals affected (many countries are less than 10%) received any treatments due to a variety of barriers such as high costs, lack of facilities, or challenges associated with diagnosis of the condition [3]. Given the accessibility of physical activity among individuals of all ages, it is promising to develop new, simple, and effective strategies to prevent and manage mental health disorders.

Tai Chi Chuan (TCC) is one of the Chinese traditional exercises which includes the three treasures of Jing, Qi and Shen, according to Taoism philosophy and based on hundreds of years of practice [4]. It emphasizes the key roles of mind and body, the harmony and coordination of these two components, as well as the importance of simultaneous performance of relaxation and concentration. Currently, increasing evidences showed that TCC practice could significantly enhance positive emotions and alleviate depression, anxiety, as well as mental stress [4–6]. Regarding the mechanism underlying the effect of TCC on mental health, researchers have proposed several theoretical hypotheses from the features of TCC practice. Some address the traditional feature of TCC on aerobic activity, linking to increased levels of brain-derived neurotrophic factors implicated in mood disorders [7, 8]. Others suggest that the beneficial effects of TCC might be associated with breath and imagery-related changes in autonomic tone [9]. Recently, one hypothesis is provided to emphasize the role of body postures during TCC practice [4]. It demonstrates that the body shapes and movement patterns trained in TCC may be associated with the improvements in psychological well-being reported in clinical trials. Specifically, the specific static and dynamic postures including balanced muscular tone and steadier gait dynamics might exert influence on mood [10]. These assumptions undoubtedly advance the better understandings of the effects of TCC on emotional health from multiple perspectives. However, it remains largely unknown for the neurophysiological mechanism underlying the effect of TCC practice on emotional-related health outcomes [11–13]. Thus, the aim of this study was (1) to summarize the existing TCC studies reporting both negative and positive emotions impacting mental health and (2) to analyze the potential mechanisms of how TCC works to improve emotional health from physiological, psychological, and neurological perspectives.

Therefore, three English-language databases (PubMed, Web of Science, and EBSCO) and two Chinese-language databases (China National Knowledge Infrastructure and Wanfang) were searched from inception until October 2020. To obtain a maximum of relevant studies, we used three groups of keywords: “anxiety” OR “depression” OR “stress” OR “emotion” OR “affect”; “Tai Chi” OR “taiji.” A total of 400 articles were retrieved based on the searching result. We found that the number of publications is dramatically increasing, especially in the last decade (Figure S1). Finally, we added “functional MRI” OR “MRI” OR “EEG” OR “ERP” OR “fNIRS” to search the brain imaging studies relevant to this topic. Only 6 studies were retrieved including two reviews.

2. The Effect of TCC Practice on Emotional Health

2.1. The Effect of TCC Practice on Depression. Self-report measurements such as Hamilton Depression scale [14], Depression scales [15], and Beck Depression Inventory [16] are widely applied in studies on the effect of TCC on depression. A large sample cross-sectional study using the elderly depression scale and the depression self-report scale showed that the depression odds ratios were significantly reduced after TCC practice ($F\,(1, 27) = 6.61$, $p < 0.05$, partial $\eta^2 = 0.19$) [17]. Another study found that after 8-week TCC intervention, the depression levels of subthreshold depression adolescents decreased significantly ($F = 59.482$, $p < 0.001$) [18]. The same effect was also found in the elderly after 6-month TCC intervention [19]. These studies have consistently found that TCC is effective for depression throughout the lifespan. Besides, TCC interventions investigated ninety-two prenatally depressed pregnant women for 22 weeks. Their depression (CES-D) scores were significantly reduced [20]. The behavioral evidences greatly supported the positive role of TCC on the decreasing depressive level in nonclinical populations. Moreover, TCC could also ameliorate the depressive level in patients with physical diseases or mental disorders. For instance, a 12-week intervention study with random control trial design reported that the scores on the depression scales decreased significantly after 12-week TCC practice among the old adults with depressive disorder [21]. Some studies lasted for at least 2 months and also showed TCC intervention decreased depression score in patients with Parkinson disease [22], cerebrovascular disease [23], as well as multiple sclerosis [17]. Recently, a meta-analysis study of our group examined the effect size of depressive symptom in 1,159 schizophrenic patients, which showed that patients showed moderately significant effects in favor of mind-body exercise intervention to improve depression ($SMD = 0.88$; 95% CI 0.63–1.13; $p < 0.00001$) [24].

2.2. The Effect of TCC Practice on Anxiety. Anxiety frequently brings about some physical symptoms such as shortness of breath, vertigo, palpitation, digestive problems, or other somatic discomforts. Some studies generally combine anxiety scales along with some physiological measurements including sleep, blood pressure, heart rate, electroencephalogram (EEG), electrocardiogram, and other physiological parameters. Most of the evidence supports the positive effect of TCC on reducing anxiety. A 12-week intervention study investigated the change of anxiety among individuals with normal blood pressure having slight anxious symptoms, which showed both state anxiety and trait anxiety decreased as well as other physiological indices including improvements in blood pressure and blood lipids, relative to the control group [25]. TCC interventions were also effective among patients with moderate anxiety symptoms. For example, a group of middle-aged people, scoring higher than 17 points on Hamilton Depression scale, had significantly decreased anxiety after a 10-week TCC intervention [26]. In addition, TCC was found to play a moderating role in reducing anxiety when combined with other interventions [27]. A recent meta-analysis showed that the TCC practice was moderately to largely significant in improving anxiety in nonclinical population [28], which reliably supported that TCC is a worthy complementary nonpharmacological resource towards anxiety.

2.3. The Effect of TCC Practice on Stress. Perceived Stress Scale is a common measurement to evaluate the effect of TCC intervention on stress. In a 15-week interventional study, TCC participants used this scale to examine its beneficial effect, which showed that TCC practitioners had lower stress scores after intervention [29]. Regarding the duration of this effect, an investigation found that the effect of TCC on the stress level lasted for 8 weeks after the intervention [30]. Some studies have used physiological measurements such as salivary cortisol, α-amylase, heart rate, and other indices to evaluate the effects of TCC on stress. A study randomly assigned all participants into four groups as TCC, walking, mindfulness, and reading groups and administrated two types of stress tasks [31]. The mental arithmetic task and the IQ test were used to induce cognitive stress, while negative movie clips were used to induce emotional stress. The results showed that the TCC group had a significantly lower adrenaline level compared with the mindfulness group, through the higher noradrenaline level relative to the reading group. Furthermore, all groups had a decreased salivary cortisol level after the intervention [31]. This study highlighted the importance of the research methodology needed to investigate the effect of TCC on stress. Although varied measurements were adopted in the studies investigating the role of TCC practice on stress, the results of most studies are consistent both in the condition of long-term intervention and a single bout of TCC practice.

2.4. The Effect of TCC Practice on Positive Emotion. It was consistently found that TCC practice could induce positive emotion. A 15-week TCC training could increase the happiness score in the four-dimensional emotional scale among college students. Moreover, those increased scores in happiness, energy, and peacefulness were associated with the increased mindfulness scores [29]. Another study similarly showed 6-month TCC intervention that improved happiness and life satisfaction among the elderly, in which increased scores were associated with the duration of TCC intervention [19]. TCC practice also enhances positive emotion in patients diagnosed with physical diseases. TCC intervention could not only reduce headache scores among tension-type headache patients but also improve happiness feeling, energy, and mental health [32]. Another investigation showed that TCC decreased scores of 39 symptom-related items and increased happiness scores in Parkinson patients [33]. In addition to application into physical disease, TCC was also adopted as a treatment for brain injury, which showed that the scores of sadness, confusion, anger, nervousness, and fear significantly decreased after 3-week TCC training, while happiness and vigor scores dramatically increased [34].

2.5. The Integrative Intervention Combining TCC Practice with Other Interventions. Regarding the effect size, some studies also compared TCC practice with other intervention forms as well as the combination of these interventions. A study focusing on comparing TCC and Pilates showed that both exercises could improve college students' mental health including increased self-efficacy and decreased negative experience after 15-week training, which emphasized that the effect of TCC on positive emotion [35]. An acute intervention study administrated questionnaires to 174 participants randomly being assigned into TCC, yoga, wushu, weightlifting, aerobic dancing, and the musical appreciation group at 5 minutes before, 5 minutes after, and 3 hours after the intervention, which showed that after controlling the baseline level and exercise intensity, the combination of TCC and yoga for 60–75 minutes could significantly induce greater calmness and lowered fatigue and exhaustion [36]. Even an integrative intervention of combining TCC with mindfulness that lasted for only 5 weeks increased middle school students' happiness, calmness and relaxation, sleep quality, and self-consciousness, which suggested TCC could be popularized among adolescents [37]. Recently, TCC practice, as one of the main components of multiple model intervention, increasingly attracts researchers' attention for its beneficial role for alleviating negative emotions and enhancing positive emotions.

3. Potential Mechanisms Underlying the Effect of TCC on Improving Emotional Health

Although most of studies reviewed better emotional health following a TCC intervention, it remains largely unknown the mechanisms through which TCC leads to these effects. One reason is that there is no relevant theoretical framework focused on revealing TCC's effect on emotional health. Another reason may be the difficulty of TCC exercise regimen, which may be viewed as a barrier, hindering the ability to evaluate TCC's function in this regard. Here, three potential mechanisms are proposed (Figure 1).

3.1. Potential Physiological Mechanisms and Relevant Moderators. It has been suggested that the effect of TCC on emotional health may be related to the change of immune levels. A group of elderly patients taking medication for depression (i.e., escitalopram) had decreased levels of inflammatory markers in C-reactive protein after the TCC intervention [38]. TCC practitioners also had a lower level of interleukin (IL-6), which is associated with decreased depression severity [39]. Researchers have also investigated the relationship between the immune level and emotional health during TCC practice among individuals with chronic health conditions. For example, after 12-week TCC intervention, IL-6, IL-8, and the glucose level increased significantly, which were also associated with decreased anxiety and stress levels in breast cancer patients [40]. Some research evidence indicates that immune levels were increased after 12 weeks of TCC training in both healthy people and diabetic patients, which were also significantly correlated with the clinical symptoms [41, 42]. Similar findings in the cell-mediation immune level of varicella zoster virus demonstrated that the effect of TCC on an individual's immune level could equal that of injecting the varicella vaccine. Additionally, this study also observed that the combination of TCC with varicella zoster virus is far more effective than injecting vaccine only (95% CI = 0.003–0.01; $p < 0.001$). The TCC group had better emotional health after intervention

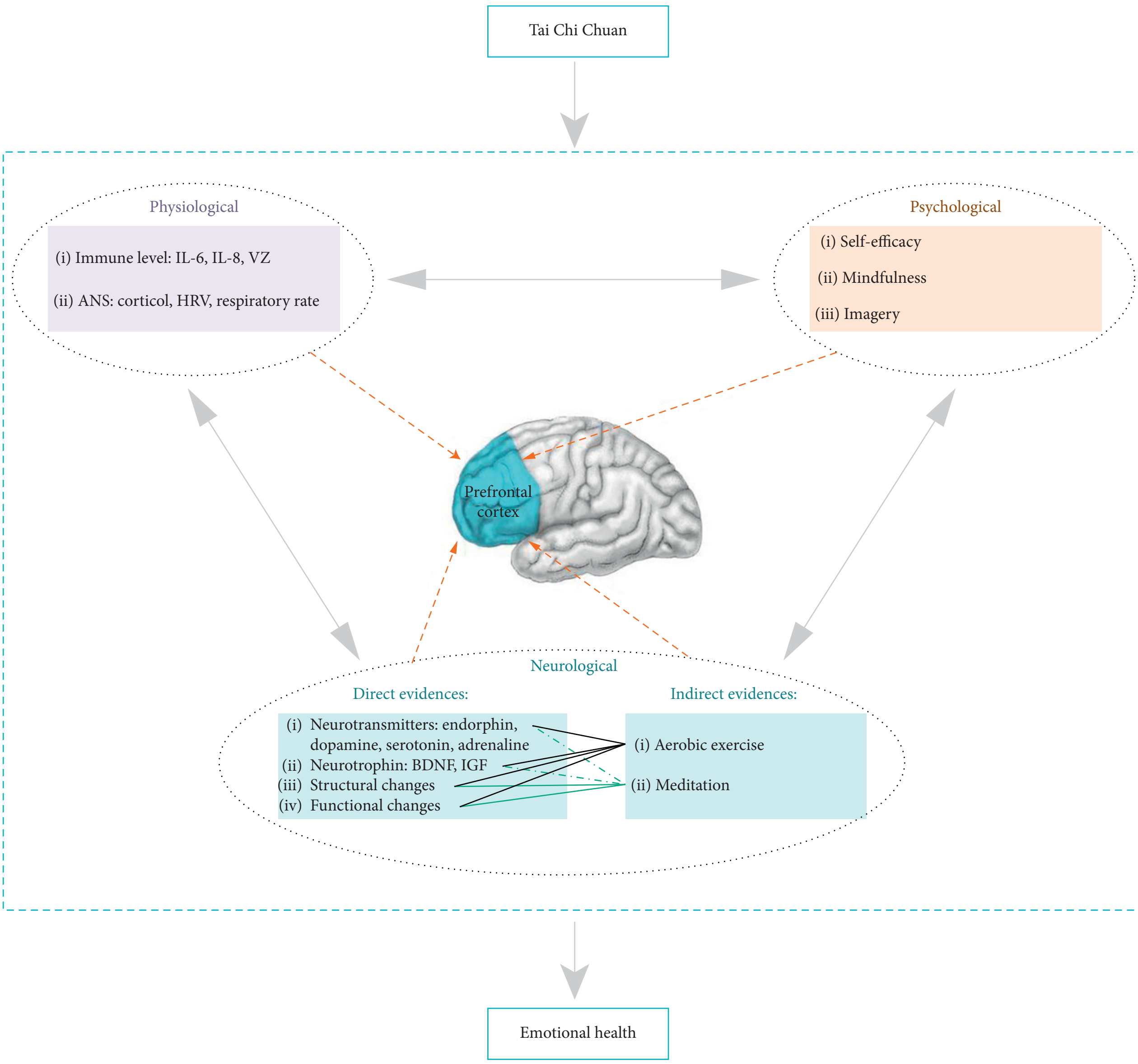

Figure 1: An illustration on multifaceted mechanism of TCC-induced effects on mental health, indicating potential mechanisms from physiological, psychological, and neurological perspectives. The prefrontal cortex hypothesis is proposed based on available direct and indirect research evidence.

compared to baseline, while the control group had worse emotional health [43]. Accordingly, one potential mechanism is that TCC improves immune levels in the body, leading to better mental health.

Furthermore, it has been hypothesized that the effect of TCC on emotional regulation is closely associated with the autonomic nervous system (ANS) [44]. TCC practice leads to decreased heart rate, which is a biomarker of the sympathetic nervous system [45]. Some studies indicate that the increased salivary cortisol level was associated with increased anxiety [46, 47]. Salivary cortisol is a key hormone controlled by hypothalamic-pituitary-adrenal axis. Evidence has shown that salivary cortisol in TCC groups was lower than other moderate intensity exercise groups or controls [30]. Additionally, heart rate variability (HRV), an important parameter to reflect the activity of the ANS was found to be altered after TCC intervention, because the change maintained the balance of the sympathetic and parasympathetic nervous system and make people's mood more relaxed [48]. Importantly, low frequency and high frequency HRV components are generally considered to be related to sympathetic and parasympathetic responses, while low/high frequency ratio is related to the balance between two. It was observed that low frequency, low/high frequency ratio [49], and total frequency [50] of HRV were greater among TCC practitioners relative to controls at rest [9].

It is well known that irregular respiration is a common symptom among patients with anxiety and panic disorders [51, 52]. The change of the respiratory pattern can be observed when individuals experience a change in emotions such as anger, fear, happiness, and sadness [53]. Respiratory rate was observed to be positively correlated with scores of state anxiety ($r = 0.756$, $p < 0.05$) [54]. A recent study indicated that the sympathetic nervous system during the resting state differed from that of abdominal breathing among experienced TCC practitioners with 21 years of training experience. Specifically, during abdominal breathing, the low frequency, total power frequency, and normalized low frequency components as well as the low-frequency/high-frequency ratio were significantly higher, whereas the normalized high frequency was significantly lower in the TCC practitioners relative to controls during the abdominal breathing state. However, there was no significant difference for these components during the resting breathing state, which provided additional direct physiological evidence for the role of TCC practice in stress reduction [9]. Hence, it is likely that TCC regulates the sympathetic nervous system via abdominal breathing to improve mental health [55, 56].

3.2. Potential Psychological Mechanisms and Moderators. Psychological factors are also important variables that influence emotional health during TCC practice. Previous research reported that TCC improved emotional health by improving self-efficacy [57]. Social support was another crucial factor during TCC practice, which enhanced the effect of TCC on mental health [58]. Moreover, mindfulness and imagery are possibly variables that aid in moderating mental health during TCC [59]. TCC is termed as "moving meditation" as it requires quieting the mind while concentrating on slow and gentle movements [59]. An increasing number of research evidence indicates that mindfulness could enhance immune function and improve mood/mental health [60–62] and decrease depression [63]. Hence, the mindfulness component during TCC practice likely contributes to changes in emotional health, as the individual is instructed to quiet the mind and let go of negative emotions [64]. Another unique feature of TCC is imagery. Imagery utilizes multiple pathways including sensation, emotion, and interception to process mental state. It has been consistently observed that imagery decreases depression and enhances positive emotion and life quality [65]. Guided imagery is a general technique to treat mental diseases, such as posttraumatic stress disorder, or social phobia [66, 67]. TCC practice contains various movements following the principle of "the mind guides qi, and the qi operates body" [68]. For instance, "cloud hands," "white crane spreads its wings," and "parting the wild horse's mane" are performed while visualizing the movements and leading to less depression [59].

3.3. Potential Neurological Mechanisms. There is no direct neurological research evidence to reveal the brain mechanism underlying the TCC on improving emotional health at present. However, researchers provide several potential hypotheses of TCC-induced emotional processing from different perspectives. One emphasizes that TCC could modulate the activity and connectivity of key brain regions or networks involved in emotional disorders such as anxiety and depression [6]. The cognitive control network and default mode network might be altered after practicing TCC for their involvement in attention regulation, self-referential processing, affective cognition, and emotion regulation, in which impairments are typical symptoms of depression [69]. These findings indicate that the central nervous system may play an important role in the modulation effect of TCC. Another valuable hypothesis suggests that the automatic nervous system may also be involved in the modulation effects of TCC on emotional disorders (depression) since accumulating evidences showed TCC practice could optimize the activity of heart rate variability [6, 70].

Although these hypotheses provide insightful viewpoints for future investigation, very few direct evidences to support their role of altering emotional processing or regulation are induced by TCC practice. Therefore, given the complexity of TCC practice involved both in body postures and mind guidance, it is plausible to seek some indirect evidences from the components of TCC such as aerobic exercise and meditation. The average oxygen consumption volume of TCC practice is 55% of maximum oxygen uptake (VO_2 max) with heart rate at 58% of the optimal heart rate zone [71], so it is regarded as a typical moderate intensity aerobic exercise. In addition, TCC contains meditative components [72, 73], which are an integral part of this mind-body exercise [74], instead the effects of aerobic exercise and meditation training on emotion/mental health provide the underpinning for investigating the effect of TCC on mental health.

3.3.1. Exercise Modulates Brain Function. Most relevant studies have explored the neural correlates underlying the effect of exercise on emotional health by using experimental paradigm-acute exercise. For instance, Pertruzzello and Tate Petruzzello and Tate utilized EEG to investigate the effect of different kinds of exercise intensity on emotions on baseline, 5 minutes, 10 minutes, 20 minutes, and 30 minutes after the intervention. They observed that EEG activity in prefrontal cortex at 5 minutes after intervention contributed to a 23% change in state anxiety, while EEG activity at 25 minutes after intervention resulted in a 22% improvement in overall mental health [75]. Another study used EEG and near-infrared spectroscopy (NIRS) to explore if mood could be changed from 15 minutes of acute exercise (bicycle ergometer). The results found that the blood oxygen level in the ventral prefrontal cortex increased during exercise along with increases in the α-wave, while the scores of negative mood decreased and the scores of vigor increased [76]. However, a recent electromagnetic tomography study observed that exercise with maximum intensity significantly worsened negative mood and that α- and β-activity decreased in the parahippocampus [77].

3.3.2. Exercise Alters Brain Neurotransmitters. It is commonly accepted that endorphins are a key neurotransmitter to regulate emotions during exercise at the molecular level [78]. This hypothesis suggests that the increased positive mood and well-being contribute to releasing endogenous opioids such as beta-endorphins [79]. Endorphin spreads across the central nervous system, which regulates the neuroendocrine system and ANS [80]. It is thought that the opioid peptide is related to positive emotional coping when in a stressful environment [81], while the monoamine hypothesis [82] suggests that exercise prompts releasing neurotransmitters such as dopamine, serotonin, and adrenaline in the brain, which is associated with decreased anxiety and the depression level [83].

3.3.3. Exercise Changes of the Brain-Derived Neurotrophic Factor Level. At the molecular level, the brain-derived neurotrophic factor (BDNF) is another common protein to be associated with decreased depression. Evidence from animal models shows that stress-induced depression changed the BDNF level via cell signal detection [84]. In an electroconvulsive therapy (ECT) study in treating depression, the BDNF level was increased in the hippocampus [85]. Besides, BDNF, Val66Met, and Val/Met were found to be associated with mental disorders in adolescents [84]. Taking together, a lot of animal and human studies have reported that aerobic exercise improves BDNF levels in the brain, increases regeneration in the parahippocampal gyrus [86], and leads to antiaging of the hippocampus [87]. Therefore, TCC likely regulates neuroendocrine cells in key regions relevant to mental health/emotion processing in the brain such as the amygdala, hippocampus, and prefrontal cortex.

3.3.4. Meditation Reshapes Brain Structure and Modulates Brain Function. Neuroimaging studies indicated that long-term meditation increases the cortical thickness in prefrontal and temporal cortex and decreases cortical thickness in the parietal and occipital cortex, as well as altered white matter. These neural processes supported for better sustained attention and emotion [88]. From the perspective of brain structure, it provides the basis for TCC to have a positive impact on human cognitive function. A mindfulness study among generalized anxiety disorder patients reported that activation in prefrontal cortex increased significantly in the mindfulness group compared to the control group. Also, they found that functional connectivity increased between the amygdala and prefrontal cortex. Moreover, it also showed that these changes in brain activation were correlated positively with participants depression scores [89]. Similarly, a study used functional magnetic resonance imaging to examine the mindfulness-induced emotional effect among the patients with bipolar disorder, which found that an 8-week mindfulness intervention enhanced the ability to regulate emotions and increased the blood oxygen level dependent (BOLD) score in the medial prefrontal cortex and posterior parietal cortex [90].

Notably, it was observed that the increased cortical thickness found in TCC experts overlapped with that of mediation experts [91]. Intriguingly, the altered brain anatomical structures in TCC experts were also similar to the findings on aerobic exercise [91, 92]. Although the relationships among TCC, aerobic exercise, and meditation remain unknown, we surmise that these practices likely share some common neural correlates, though this needs to be investigated in the future.

4. The Role of Prefrontal Cortex: A Hypothesis

Ample research evidence demonstrates that the prefrontal cortex plays a crucial role in the effect of mind/body training on emotions/mental health, providing support for our hypothesis. Based on the following evidence, it is reasonable to hypothesize that the prefrontal cortex, as a core component of the human brain network, implements its function on mediating emotions via multiple neuroimmunological and neuropsychological pathways.

4.1. Direct Research Evidence. Recently, we directly examined the association between brain plasticity and TCC practice, using the newly developed regional homogeneity (ReHo) method of resting-state functional magnetic resonance imaging (R-fMRI) to examine the differences in intrinsic functional architecture between TCC experts and controls. Our results showed that regional homogeneity in some brain regions relevant to low-level sensory motor function was significantly higher among experts and that homogeneity in other regions relevant to high-level cognitive functioning was significantly lower relative to controls. Intriguingly, optimized local functional organization predicted performance gains on the attention network task among TCC practitioners. Another study investigated whether TCC practice could induce cortical structural change [91]. The results indicated that the cortical thickness in several key brain regions (such as the prefrontal cortex) of TCC practitioners differed significantly from that of the controls. These differences were similar to the reported change in brain structure induced by aerobic fitness and meditation. We hypothesized that TCC might share some common neural correlates associated with meditation and aerobic exercise. Using resting fMRI, we characterized dynamic fluctuations of large-scale intrinsic connectivity networks associated with mind-body practice and examined the difference between healthy controls and TCC practitioners. Compared with the control group, the TCC group had significantly decreased fractional amplitude of low frequency fluctuations (fALFF) in the bilateral frontoparietal network, default mode network, and dorsal prefrontal-angular gyri network. Furthermore, we detected significant associations between mind-body practice experience and fALFF in the default mode network as well as the association between cognitive control performance and fALFF in the frontoparietal network [69]. This study provided initial evidence of the large-scale functional connectivity of brain networks associated with mind-body practice, shedding light into neural network changes accompanying intensive mind-body training, and highlighted the function of the frontoparietal network in the context of the “immune system” of mental health, which was recently developed on the basis of the flexible hub theory. In a different 10-month longitudinal study, we found that TCC training decreased the negative mood, which was correlated with functional connectivity between the prefrontal cortex and key regions relevant to emotion, as well as the grey matter in the prefrontal cortex [9].

4.2. Indirect Research Evidence. First, current neuroimaging research evidence supports the critical role of prefrontal cortex among individuals participating in aerobic exercise and meditation training. It is reasonable to infer that the aerobic exercise and meditation components of TCC practice play an important role in emotions/mental health processed by the prefrontal cortex. For instance, mindfulness regulates attention via the lateral prefrontal cortex, which affects the typical neural pathways relevant to the negative mood [93]. Importantly, previous brain imaging studies revealed that exercise regulates negative emotions by increasing the activity of the prefrontal cortex. For example, EEG studies observed that acute aerobic exercise reduced nervousness and anxiety, while simultaneously increasing alpha-1 activity in the right prefrontal cortex, with decreased alpha-2 activity in the anterior cingulate cortex [94]. In another study, NIRS was used to examine the effect of acute exercise on emotions. These results indicate that 15 minutes of aerobic exercise can significantly decrease negative emotions, which was associated with greater activation in the ventral prefrontal cortex. [76] Additionally, an fMRI study also observed that 30 minutes of acute exercise improved negative emotion and decreased activation in reward-related cortex [95]. In a different study, both aerobic exercise and meditation resulted in lasting benefits for 8 weeks after the interventions, with decreased negative emotions and increased activation in the ventral prefrontal cortex [96]. This research evidence suggests that aerobic exercise and meditation/mindfulness components during TCC practice likely reduce negative emotions by reshaping anatomical structures and modulating functional activity in the prefrontal cortex.

Second, some research evidence at the molecular level was conducted to address the role of the prefrontal cortex in the regulation of emotions. A growing number of studies have demonstrated that the prefrontal cortex is involved in an emotion-related immunomodulation process within multiple cell molecular levels. For example, in the human brain, human herpesvirus 6 (HHV-6) and the varicella-zoster virus have been identified [97]. In a random control trial, TCC led to the increased cells-mediated immune level, which was also associated with improved mood/mental health [39, 43]. Although there is no direct evidence to reveal the relationship between TCC practice, immune level and brain activity, we speculate that it is likely that TCC could regulate negative emotions via changing the number of immune antibodies in the prefrontal cortex. Additionally, Kuper and his colleagues observed that decreased grey matter in HIV patients were positively correlated with disease course [98]. Furthermore, the decreased grey matter in the occipital cortex was correlated with numbers of lower CD4 (a type of immunosuppressive T lymphocytes) [98]. These results suggest that TCC could increase CD4 levels, which indirectly supports the potential effect of TCC practice on emotion-related immune cells. TCC practice may possibly influence immune response via the prefrontal cortex or some other brain structures connecting with the prefrontal cortex, leading to changes in emotions/mental health.

Third, transmitters related to emotion in the prefrontal cortex likely contribute to the effect of TCC on emotions. Medial prefrontal cortex (mPFC) plays an important role in the HPA axis [99]. For example, increased dopamine in the HPA axis was associated with increased dopamine receptors in the mPFC among pregnant rats exposed to alcohol [97]. Such evidence further supports the role of the prefrontal cortex as a bridge between the central nervous system and the autonomic nervous system along the stress-related neural pathway. The most direct evidence from molecular mechanisms related to negative emotion indicated that opioid-mediated placebo effects greatly reduced pain and negative emotion, which generally regarded as a function of dorsal lateral prefrontal cortex (DLPFC) [100]. Similarly, another study found that when the prelimbic area in the prefrontal cortex (responsible for defensive behavior) was injected with cannabidiol (CBD), rats were performed in the opposite behavior. This CBD effect was described as being mediated by serotonin receptors [101]. Clinical research evidence indicates that continuously decreasing activity in the prefrontal cortex was linked to decreased dopamine levels in patients with schizophrenia. This suggests that there is an association between mental health disorders and altered transmitters in the prefrontal cortex [102].

Based on prior research, we hypothesize that the prefrontal cortex is likely a biomarker responsible for the neural mechanisms mediating the effects on emotions/mental health, especially negative emotions (Figure 2).

4.3. Limitations. First, there are no standards or consistent principles regarding TCC exercises regimen such as intensity, frequency, and duration [103, 104], which undoubtedly leads to challenges when attempting to make direct comparisons among results of previous studies. The American College of Sports Medicine (ACSM) defined moderate intensity as 60–75% or 50–74% VO_2 max. Both the Centers for Disease Control and Prevention in the United States and ACSM suggest that 30 minutes of moderate intensity exercise 5 times each week is effective for improving mental health. To date, no TCC study has focused on different dose-effects on regulating emotional health. Second, most of the prior TCC studies examined the TCC's effect on various negative emotions in a single study. Thus, it is unknown if a specific emotion was influenced more by TCC practice. In view of these issues, we were unable to determine the effect size on each emotion and could not provide scientific evidence to guide clinical treatments/practice. Another problem is that multiple interventions were used simultaneously to examine the effect of TCC on positive emotions. Notably, the placebo effect should be considered in some studies that failed to employ a true control group. Third, it is important to pay attention to the duration of the TCC's effect after intervention in longitudinal studies, when

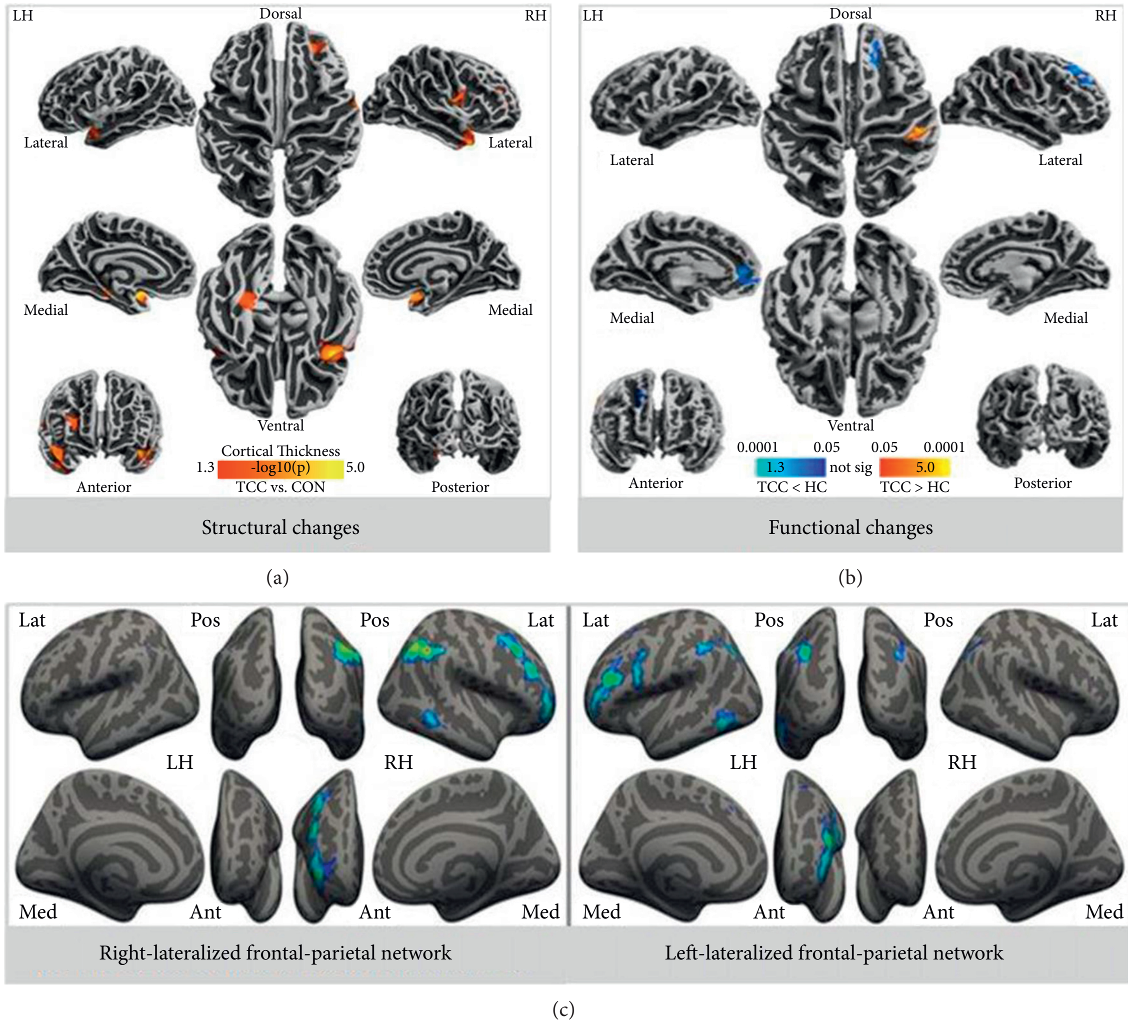

Figure 2: An illustration of direct research evidence from brain imaging of the prefrontal cortex. (a) Structural changes: thicker cortical regions in the TCC group; (b) functional changes: functional homogeneity measured by 2dReHo in the TCC group compared to the control group (blue colors indicate decreases in 2dReHo, while red colors indicate increases in 2dReHo; (c) intrinsic connectivity network based on 12 brain networks, the left panel indicates the right-lateralized frontal-parietal network, while the right panel indicates the left-lateralized frontal-parietal network.

examining changes in emotional health. This information could provide meaningful data to support treatments for mental health disorders. Fourth, study samples contained different demographic characteristics including age, health status, diseases types, and personalities, which may have influenced the results obtained. It is important to note that there are significant individual differences in emotional regulation, which may have limited the popularity of TCC practice. Moreover, cognitive style might be another important variable to investigate alongside mental health, as this undoubtedly plays a key role during TCC practice. Finally, there are many TCC styles such as Chen, Yang, Sun, Wu, and other family styles. While the various TCC styles follow the same principles (e.g., movements come from center), differences among these styles still exist such as the speed of motions, the order of poses, the size of the movements, hand orientation, as well as the way in which the movements are performed. However, some studies failed to provide details on TCC style used and its movement characteristics, which might be challenging when exploring its effect on emotional health in order to make recommendations for clinical practice/treatments.

5. Conclusion

TCC is a traditional physical exercise with multiple components and has played an important role in alternative, complementary, and integrative medicine for several decades both in the east and west. Although a substantial body of literature has documented the physical health benefits of TCC, researchers are far from understanding its potential mechanisms. Many questions regarding the general effects of TCC on the brain, at the molecular level, and on genetic transcription cascades remained unresolved. Based on some direct and indirect research evidence, several potential mechanisms from physiological, psychological, and neurological perspectives have been put forward in this review study. Importantly, studies with fMRI demonstrated the relevant change of brain anatomy and function mainly on the prefrontal cortex following TCC practice. Notably, a significant activity pattern in the prefrontal cortex among TCC experts was found. Therefore, the effects of TCC on emotional health is likely due to the prefrontal cortex hypothesis, the "immune system of the mind" indicating the role of the prefrontal cortex as a flexible hub in regulating an individual's emotional health. TCC practice may also initiate brain feedback tools including meditation, deep breathing, and exercise to improve mental health. Thus, the prefrontal cortex is likely a key biomarker among the multiple complex neural correlates to aid with emotional conflicts and negative experiences during daily life.

Future studies are needed to confirm these preliminary observations by adopting rigorous methodologies and by further combining multiple measurements, including physical and psychological measurements, along with basic research. It is especially important to adopt brain imaging techniques to investigate the association between the body, mind, and brain within a TCC theoretical framework to investigate mental health/emotional issues. A promising area of research to pursue is the effect of TCC on emotions/mental health from a brain network perspective, especially exploring the anatomical and functional connections between the executive control system (mainly prefrontal cortex) and limbic network (including amygdala, insula, and hippocampal gyrus).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (31671163), open project from CAS Key Laboratory of Behavioral Science, Institute of Psychology, and open project from CAS Key Laboratory of Mental Health, Institute of Psychology.

Supplementary Materials

Figure S1. Topic-related annual number of studies. Table S1. Study on the brain mechanism of Tai Chi regulating emotion. (*Supplementary Materials*)

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