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Article *in* Journal of the American Medical Directors Association · August 2016

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Original Study

Clinical Efficacy of Acupuncture Treatment in Combination With RehaCom Cognitive Training for Improving Cognitive Function in Stroke: A 2 × 2 Factorial Design Randomized Controlled Trial

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Keywords:
Acupuncture
RehaCom training
stroke
cognitive dysfunction

A B S T R A C T

Objective: The aim of this study was to identify the clinical efficacy of acupuncture in combination with RehaCom cognitive training in poststroke patients with cognitive dysfunction.

Methods/Design: This study was a 2 × 2 factorial design randomized controlled trial comparing acupuncture, computer-assisted cognitive rehabilitation, and the usual treatment by per-protocol analysis. The trial was completed by 204 stroke patients, including 49 patients in a control group, 52 patients in an acupuncture treatment group, 51 patients in a RehaCom training group, and 52 patients in an acupuncture combined with RehaCom group. All of the patients accepted basic treatment and health education. The interventions continued for 12 weeks (30 minutes per day, 5 days per week). The relative cognitive and functional outcomes were measured at baseline and 12 weeks (at the end of intervention) using the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Functional Independence Measure (FIM) scales.

Results: After 12 weeks of treatment, the functional statuses of the patients in each of the 4 groups showed varying degrees of improvement. Multiple comparisons of the changes in the MMSE, MoCA, and FIM scores indicated that acupuncture combined with RehaCom cognitive training (ACR) had enhanced therapeutic effects on the functional statuses of the stroke patients ($P < .05$). In addition, ACR had similar therapeutic effects on the functional statuses of the stroke patients according to each of the assessment scales applied ($P \triangle_{\text{change value}}$ MMSE = 0.399, $P \triangle$ MoCA = 0.794, $P \triangle$ FIM = 0.862). The interaction effect values between acupuncture and RehaCom training (acceptance or nonacceptance) were as follows: $\triangle$ MMSE: F = 6.251, $P = .013$; $\triangle$ MoCA: F = 4.991, $P = .027$; and $\triangle$ FIM: F = 6.317, $P = .013$. Further, the main effect values for acupuncture and RehaCom training were both significant ($P < .05$).

Conclusions: There is an interaction effect in the treatment of stroke patients using ACR. The use of acupuncture in combination with RehaCom training has better therapeutic effects on the functional statuses of poststroke patients than the use of either treatment alone, demonstrating the clinical significance of this combination therapy.

Stroke, or cerebrovascular accident, is one of the most common causes of death and disability among the elderly worldwide.[1] The term vascular cognitive impairment includes various degrees of cognitive impairment, ranging from mild cognitive impairment to dementia, which are attributable to a variety of cerebral vascular diseases.[2] Cognitive impairment is a common complication occurring after stroke, and it accounts for the progression of 25% of stroke patients to dementia at 3 months after onset, whereas 50%–75% of patients exhibit differing degrees of cognitive impairment.[3] Poststroke cognitive impairment severely limits limb function rehabilitation, resulting

This study was sponsored by the International S&T Cooperation Program of China (ISTCP Program; No. 2011DFG33240), the Ministry of Science and Technology of the People's Republic of China, the Science and technology platform construction project of Fujian science and Technology Department (Grant No. 2015Y2001), the Fujian Key Laboratory of Rehabilitation Technology and the Fujian Provincial Rehabilitation Industrial Institution.

The authors declare no conflicts of interest.

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http://dx.doi.org/10.1016/j.jamda.2016.07.021

in various problems with performing daily activities and decreased participation in social activities. Collectively, these issues result in the decreased quality of life of patients and serious economic losses, along with a sharp increase in medical expenses for family members.[4]

Cognitive rehabilitation (CR) refers to a comprehensive cognitive improvement program[5] that applies a series of systematic and targeted therapeutic measures to treat cognitive dysfunction caused by various acquired brain injuries, including disorientation, sensory disorders, attention disorders, executive function disorders, and memory disorders.[6] It is important that stroke patients with cognitive dysfunction improve their abilities to perform daily activities and, consequently, to enhance their quality of life.

Currently, there is a lack of effective CR programs for improving the cognition and function of patients with vascular cognitive impairment.[2] Although several large and well-designed trials examining cholinesterase inhibitors and N-methyl D-aspartate receptor antagonists have been conducted, these studies have failed to consistently demonstrate the efficacies of the functional measures.[7–10]

Other therapies, such as traditional cognitive retraining, music therapy, and computer-assisted cognitive rehabilitation (CACR), improve cognitive function to some extent.[4,11,12] However, there is currently insufficient evidence to develop a CR program for clinical promotion, and current poststroke treatments for patients with cognitive dysfunction have not produced sufficient improvements.

As cognitive impairment after stroke is complex and increases the difficulty of rehabilitation, a therapeutic approach that addresses cognitive impairment is vital for rehabilitation training. Furthermore, the use of an integrated treatment method is essential for CR.[13]

Acupuncture is central to traditional Chinese medicine (TCM) and is widely used to treat clinical disorders, including stroke-related deficits.[14,15] It has been demonstrated that acupuncture improves the clinical symptoms and cognitive behavioral abilities of poststroke patients with cognitive dysfunction.[16,17]

CACR has been widely used since its introduction in 1986[18] and has dramatically improved with neuroscientific and technological developments. RehaCom (Hasomed Inc, Magdeburg, Germany, http://www.hasomed.de) is a software package that has been translated into different languages (including Chinese) and has been extensively used in the CR of stroke-related deficits. This software includes 5 different therapeutic programs that seek to restore attention, memory, executive functions, and the visual field. Each program has 1 to 4 different tasks from which participants choose during each therapy session. As RehaCom provides a battery of standardized tasks with immediate feedback, it is useful for conducting patient follow-up examinations and for performing clinical studies.[4,19]

In summary, acupuncture is a specialized treatment method in China and has notable regional characteristics. The use of acupuncture for the treatment of cognitive dysfunction associated with stroke is in alignment with China's healthcare development priorities. RehaCom has recently become an increasingly popular treatment method in China and is widely used in the clinic.

Thus, we combined Chinese traditional acupuncture with Western RehaCom, which we believed was beneficial for establishing a CR program that retains Chinese characteristics and is suitable for implementation in China. The main purpose of this study was to determine the clinical efficacy of acupuncture in combination with RehaCom training for the treatment of cognitive dysfunction after stroke and to provide a theoretical basis for promoting the use of this program in the clinic.

Methods

This was a randomized controlled trial with a 2×2 factorial design that systematically evaluated the clinical effectiveness of a CR program (acupuncture combined with RehaCom cognitive training) for the treatment of cognitive dysfunction after stroke.

Between August 2013 and November 2015, 240 poststroke patients with cognitive dysfunction were recruited for this study after providing written informed consent. All of the patients were being treated at the Fujian University of Traditional Chinese Medicine Rehabilitation Hospital and were randomly divided into 4 groups: a control group (CG), acupuncture treatment group (ATG), RehaCom treatment group (RTG), and acupuncture combined with RehaCom group (ACRG). This study had a 2×2 factorial design and was defined by the acceptance or nonacceptance of each intervention (acupuncture and RehaCom training). The interventions lasted for 12 weeks (30 minutes per day, 5 days per week).

The relative cognitive and functional outcomes were measured at baseline and 12 weeks (at the end of the intervention). The detailed design of this study has been reported previously,[20] and the enrollment process of the study participants is shown in Figure 1.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Fujian University of Traditional Chinese Medicine, Fujian, China (2013KY-004-02). All of the patients who participated in this study or their families were fully informed about the trial and provided written informed consent before participation.

Participation and Recruitment

We recruited poststroke patients with cognitive dysfunction from the Fujian University of Traditional Chinese Medicine Rehabilitation Hospital. To ensure recruitment of a sufficient number of stroke patients within the prescribed time limit, the patients and their families were informed of the purpose and significance of the research by publishing relevant ads on the rehabilitation hospital's official website and by distributing flyers in the Fuzhou City Hospital. Patients who were interested and met the following criteria were invited to participate in this study.

There were 4 inclusion criteria as follows: (1) clinical diagnosis of first stroke incident within the preceding 6 months, in accordance with the diagnostic criteria for All Kinds of Cerebral Vascular Diseases[21]; (2) 18–75 years of age; (3) MMSE score within a specific range according to the level of education [ie, MMSE score $\leq$17 for the illiterate group, score $\leq$20 for the primary school (education years $\leq$6) group, and $\leq$24 for the middle school or higher (education years $>$6) group]; and (4) conscious and in stable physical condition.

Patients were excluded if they (1) had an existing mental disorder before stroke onset; (2) had severe hearing or vision problems affecting completion of RehaCom training and assessment; (3) were pregnant and lactating; (4) had a bleeding disease; (5) had a serious disease, such as heart, liver, or kidney failure; or (6) had participated in other clinical trials.

Clinical Intervention

CG

The patients in the CG received only traditional rehabilitation therapy, including basic treatment and health education. They received necessary basic treatment according to the Chinese prevention and treatment guidelines of cerebrovascular disease.[22] Occupational therapy and physical therapy were provided for 30 minutes per day for 5 days per week, with a total of 60 sessions over 3 months. The doctors administered the appropriate treatment, such as another medical treatment, physiotherapy, or occupational therapy, according to the patient's needs. However, to rule out possible confounding factors, none

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram showing the flow of participants through the trial and reasons for dropout.

of the patients in this study took another concomitant medication, such as cholinesterase inhibitors, N-methyl D-aspartate receptor antagonists, etc that could have affected cognitive function. In addition, the patients received health education to intervene with existing unhealthy life-styles and to establish a correct concept of stroke rehabilitation.

ATG

The patients in the ATG were treated with acupuncture on the basis of conventional therapy, similar to those in the CG. They received acupuncture at 2 acupuncture points [Baihui (DU20)] and [Shenting (DU24)] (Table 1), both of which belong to the Du Meridian. All of the

Table 1
Acupuncture Points Selected in This Trial

Acupuncture Point	Location
Shenting|GV24|DU24	On the head, 0.5 B-cun superior to the anterior hairline, on the anterior median line. When the anterior hairline is unclear or changed, GV24 is located 3.5 B-cun superior to the midpoint between the medial ends of the eyebrows.
Baihui|GV20|DU20	On the head, 5 B-cun superior to the anterior hairline, on the anterior median line. GV20 is located in the depression 1 B-cun anterior to the midpoint of the line from the anterior to the posterior hairline. When the ears are folded, GV20 is located at the midpoint of the connecting line between the auricular apices.

From: WHO Standard Acupuncture Point Locations in the Western Pacific Region.

acupuncture treatments were performed by a professional acupuncture therapist.

The patients were administered acupuncture while seated or in the supine position. The targeted acupoints were routinely disinfected with alcohol. Then, the acupuncturist immobilized the area for stimulation with his/her left hand and inserted the acupuncture needles under the scalp using his/her right hand.

The angle of insertion was 10°∼20° (between the needle and scalp), and the needle depth was approximately 0.3–0.5 B-cun. Only sterile, φ 0.35 × 40 mm, stainless, single-use needles (Hwato, Suzhou, China) without guide tubes were used. After insertion, the therapist twirled the needle body rapidly in an alternating clockwise and counterclockwise manner, at approximately 180∼300 per minute, to achieve the sensation known as Deqi.

The needle was kept in this position for 30 minutes. The twisting operation was repeated every 10 minutes (for a total of 4 times). A sterilized, dry cotton ball was gently pressed against the point to prevent bleeding when each needle was withdrawn. The entire course of treatment continued for 30 minutes per day, 5 days per week, for a total of 60 sessions over 3 months.

RTG

The stroke patients in the RTG received CACR training using RehaCom software (RehaCom, Hasomed Inc., Germany, http://www.hasomed.de) translated into Chinese. They also received conventional therapy, similar to the patients in the CG.

RehaCom software includes 5 different treatment programs, designed to restore attention, memory, and executive function and to improve the visual field.

Each program has 3 to 5 levels of varying difficulty. The physiotherapists chose different training programs and difficulty levels according to the specific circumstances of each patient. During training, the physiotherapists provided appropriate guidance or a reminder based on the actual activity of the patient and increased the training difficulty according to patient feedback.

We tried to ensure that RehaCom cognitive training was administered by the same physiotherapist for each patient.

The patients in the RTG trained under the supervision of physiotherapists for 30 minutes per day, 5 days per week, for a total of 60 sessions over 3 months.

ACRG

The patients in the ACRG received conventional and acupuncture treatments, as well as RehaCom training. The cognitive training and acupuncture therapy were performed at the same time; thus, RehaCom training was performed at the same time that the needles were inserted. The specific requirements and operations of the acupuncture therapy and RehaCom cognitive training were similar to those of the other 3 groups. The entire course of treatment was also 30 minutes per day, 5 days per week, for a total of 60 sessions over 3 months. Therefore, the intervention time of the ACRG was similar to those of the ATG and RTG.

Outcome Assessment

The patients' demographic data were obtained when they were determined eligible for study enrollment. Neuropsychological scales were used to evaluate the cognitive function of the poststroke patients, including the MMSE, MoCA, and FIM, at baseline and again at 12 weeks. We tried to ensure that the same therapist completed each patient's cognitive assessment and that he/she did not participate in patient treatment.

In this study, we used the MoCA (designed to assess mild cognitive impairment[23]) and the MMSE (designed to detect moderate to severe cognitive impairment[24]) to assess cognitive deficits, and we used the FIM to evaluate the functional statuses of the patients throughout the rehabilitation process.

The MMSE, the most commonly used cognitive screening scale in the clinic for stroke patients, is a brief 30-point questionnaire that evaluates patients' spatial and temporal orientation, short-term memory, attention and calculation abilities, and language, thinking, and action planning capacities.

The MoCA, which was developed by Nasreddine, is a clinician friendly, validated, brief instrument with high sensitivity and specificity for the detection of mild cognitive impairment.[25] It has been translated into Chinese and has been used nationwide for the evaluation of cognitive function in China[26] since its introduction in China in 2006.

The FIM is a common functional status assessment instrument with high internal consistency and adequate discriminative capabilities for rehabilitation patients.[27] It contains 18 items (13 are designed for assessing motor function, and 5 are designed for assessing cognitive function) and allows for the collection of rehabilitation data in a consistent manner to evaluate patient functional status.[28,29]

Details concerning the outcome assessments are described in the published protocol.[20]

Safety Evaluation

The adverse events that occurred in this study were recorded on a case report form/table after evaluating their relationships with the study intervention. Fortunately, no serious adverse events occurred in this study.

Statistical Analyses

All statistical analyses were performed using SPSS v 18.0 (Chicago, IL) unless otherwise specified. All of the neuropsychological assessment data were expressed as the mean ± standard deviation.

The baseline characteristics of the participants in the 4 arms were compared using χ^2 tests and Fisher exact test for categorical variables and analysis of variance for continuous variables. Intragroup comparisons (changes in the MMSE, MoCA, and FIM scores before and after treatment) were performed using the paired *t*-test. The statistical significance of the observed differences between the groups was assessed using 2 × 2 factorial analysis of variance to test the main effect and interaction effects of the 2 interventions (acupuncture and RehaCom training). Statistical significance was set at $P < .05$. All of the reported *P* values were 2-sided and were not adjusted for multiple comparisons.

Results

Baseline Characteristics

Overall, data for 204 poststroke patients with cognitive dysfunction were used in final analysis; these patients were divided into the CG (n = 49), ATG (n = 52), RTG (n = 51), and ACRG (n = 52). During the entire 12-week intervention period, 36 patients withdrew from the study for a variety of reasons. There were no significant differences in the dropout rates ($\chi^2 = 0.784$, $P = .853$) or in the other demographic characteristics among the 4 groups (Table 2 and Figure 1). The baseline demographic characteristics of the 204 poststroke patients in the 4 groups who completed the entire intervention, including sex, age, years of education, type of stroke, lesion site, and handedness, as well as the MMSE, MoCA, and FIM scores, are presented in Table 3. As shown in this table, no significant differences in the baseline demographic characteristics were detected among the 4 groups ($P < .05$; Table 3).

Effects of Acupuncture Treatment and RehaCom Training on the Functional Statuses of Poststroke Patients

Table 4 depicts the changes in functional performance for the 4 groups from baseline to the end of the 12-week intervention period. As shown in Table 4, after 12 weeks of treatment, the functional statuses of the patients in the 4 groups showed varying degrees of significant improvement.

Multiple comparisons using the least significant difference test showed that acupuncture treatment in combination with RehaCom training had better therapeutic effects on the functional statuses of the stroke patients. In addition, acupuncture treatment and RehaCom cognitive training used alone had similar therapeutic effects on the patients' functional statuses (including the MMSE, MoCA, and FIM scores), with P values of .399, .794, and .862, respectively (Table 5).

Main Effect and Interaction Effects of Acupuncture and RehaCom Training on Functional Outcomes of Ischemic Poststroke Patients

Assessment of the between-subject effects revealed a significant interaction effect between acupuncture and RehaCom training (acceptance and nonacceptance) on the MMSE, MoCA, and FIM scores (MMSE: F = 6.251, $P = .013$; MoCA: F = 4.991, $P = .027$; and FIM: F = 6.317, $P = .013$). The main effects for acupuncture and RehaCom training were both significant (Table 6 and Figure 2).

Discussion

Stroke patients often suffer from multiple neurologic disorders, including cognitive impairment, visual problems, and movement dysfunction. Poststroke cognitive impairment is a common clinical symptom and is associated with increased mortality and a decreased quality of life.[30–32]

Because of the complexity of cognitive impairment after stroke, clinically effective treatments for poststroke rehabilitation remain insufficient and lack reliable large-sample studies to support the treatment efficacies. In this study, we have proposed an integrated CR program combining acupuncture and RehaCom cognitive training, which we believe is in alignment with China's healthcare development priorities, and we have confirm the treatment efficacy using a large sample of clinical studies.

After 3 months of treatment, we found that the patients with cognitive dysfunction (including the CG, ATG, RTG, and ACRG patients) exhibited varying degrees of improvement. Indeed, synergistic effects of acupuncture and RehaCom cognitive training on cognitive impairment after stroke were observed. The combination of the 2 treatments resulted in further improvement of the cognitive function of the stroke patients.

Effect of Basic Therapy on Poststroke Patients

After 3 months of traditional rehabilitation therapy, we observed significant cognitive functional improvement in the CG patients (changes in the MMSE, MoCA, and FIM scores before vs after treatment). These findings suggest that although the CG stroke patients did not receive CR therapy, their overall cognitive function improved to some extent.

In this experiment, we did not strictly limit the clinical medication use of the patients who were receiving conventional medical treatment. The stroke patients who participated in this trial might have been using a number of medications, including drugs that affect neurotransmitters, antioxidants, anti-inflammatory medications, hormone replacement therapy, and neuromodulating drugs. Some of these agents have been shown to have impacts on the cognitive function of patients and to prevent or slow cognitive decline.[33–35]

Furthermore, the improvement of the CG patients might also be partly due to the recovery of motor function in these patients during traditional rehabilitation treatment.

In the past, motor performance and cognition were generally studied in isolation; however, in recent years, there has been increasing evidence that cognitive abilities influence and are influenced by emotional and behavioral challenges, as well as regular

Table 2
Dropout Demographic Characteristics for the 4 Groups

Parameters	CG	ATG	RTG	ACRG	*P* Value
Dropout rate	11/60	8/60	9/60	8/60	.903*
Type of stroke (I/H)	7/4	6/2	7/2	5/3	.891† (1)
Lesion site (L/R/B)	6/4/1	6/2/0	5/4/0	5/2/1	.931† (2)
Handedness (L/R)	2/9	0/8	0/9	1/7	.530† (3)
Sex (male/female)	8/3	5/3	5/4	6/2	.866† (4)
Age (years)	56.18 ± 11.86	57.75 ± 13.74	59.56 ± 10.10	57.88 ± 9.45	.932‡ (1)
Education (years)	9.09 ± 3.51	9.63 ± 3.50	9.22 ± 5.58	9.13 ± 4.02	.993‡ (2)
Duration of disease (days)	40.27 ± 19.17	42.75 ± 20.14	40.56 ± 18.88	41.75 ± 20.56	.993‡ (3)
Baseline MMSE	16.82 ± 4.62	17.38 ± 4.84	17.56 ± 4.25	17.25 ± 4.13	.985‡ (4)
Baseline MoCA	14.36 ± 4.13	15.13 ± 4.09	14.89 ± 4.70	14.63 ± 4.34	.983‡ (5)
Baseline FIM	59.36 ± 9.46	60.38 ± 9.65	60.44 ± 8.82	59.75 ± 8.88	.993‡ (6)

B, bilateral; H, hemorrhagic stroke; I, ischemic stroke; L, left; R, right.
The data are presented as the mean ± standard deviation (SD).
*The P value was obtained by Pearson χ^2 test: $\chi^2 = 0.572$.
†The P value was obtained by Fisher exact test: χ^2 (1) = 0.914; χ^2 (2) = 3.138; χ^2 (3) = 2.605; and χ^2 (4) = 1.124.
‡The P value was obtained by 1-way analysis if variance (ANOVA): F1 = 0.145; F2 = 0.029; F3 = 0.030; F4 = 0.050; F5 = 0.054; and F6 = 0.030.

Table 3
Baseline Demographic Characteristics for the 4 Groups

Parameters	CG	ATG	RTG	ACRG	*P* Value
Handedness (L/R)	3/46	2/50	4/47	3/49	.849*
Type of stroke (I/H)	31/18	37/15	31/20	35/17	.701† (1)
Lesion site (L/R/B)	25/18/6	24/20/8	27/18/6	26/17/9	.974† (2)
Sex (male/female)	24/25	25/27	25/26	23/29	.956† (3)
Age (years)	60.53 ± 9.19	61.58 ± 9.71	62.37 ± 7.89	62.33 ± 7.72	.687‡ (1)
Education (years)	8.80 ± 4.49	8.94 ± 4.60	8.35 ± 4.63	9.08 ± 4.37	.863‡ (2)
Duration of disease (days)	42.76 ± 16.00	41.12 ± 21.71	44.22 ± 17.00	41.13 ± 18.80	.803‡ (3)
Baseline MMSE	18.29 ± 4.24	18.04 ± 4.98	18.22 ± 4.12	18.31 ± 4.45	.990‡ (4)
Baseline MoCA	15.37 ± 5.94	15.13 ± 6.93	15.25 ± 5.38	15.02 ± 5.98	.993‡ (5)
Baseline FIM	60.67 ± 5.82	60.77 ± 6.03	60.84 ± 5.87	60.92 ± 5.34	.997‡ (6)

B, bilateral; H, hemorrhagic stroke; I, ischemic stroke; L, left; R, right.
The data are presented as the mean ± standard deviation (SD).
*The *P* value was obtained by Fisher exact test: $\chi^2 = 0.874$.
†The *P* value was obtained by Pearson χ^2 test: $\chi^2(1) = 1.421$; $\chi^2(2) = 1.260$; and $\chi^2(3) = 0.320$.
‡The *P* value was obtained by one-way analysis of variance (ANOVA): F1 = 0.494; F2 = 0.248; F3 = 0.331; F4 = 0.039; F5 = 0.031; and F6 = 0.017.

physical activity and exercise.[36–38] The brain has a remarkable capacity for modifying its structure and function according to the environment and experience. Previous studies have provided definitive evidence indicating that exercise training increases the hippocampal volume and positively influences memory performance.[39,40]

New evidence indicates that exercise exerts its effects on cognition by affecting molecular events related to the management of energy metabolism and synaptic plasticity. Brain-derived neurotrophic factor is an important facilitator of the molecular machinery that is stimulated by exercise and acts at the interface of metabolism and plasticity.[41] Thus, in our study, the control patients did not receive targeted cognitive training therapy, and their improvements in overall cognitive function might have been due to conventional medical treatment and daily exercise, such as physical therapy, occupational therapy, and/or aerobic exercise.

Analysis of the Efficacy of Acupuncture Treatment

Acupuncture, which can be traced back more than 2000 years in China, is a core component of TCM that has been widely used for the treatment of clinical disorders, including stroke-related deficits. Currently, it is still a useful and popular medical modality for the treatment of various health disorders, as reported by the National Institutes of Health consensus panel.[42]

Today, there are numerous experimental studies discussing the effects of acupuncture on the impairment of cognitive function, and these studies have proposed potential mechanisms underlying the treatment of cognitive dysfunction after stroke.[43–46]

In the TCM theoretical system of acupuncture, the Du Meridian (the government vessel) is one of the meridians of the brain and is closely related to cognitive brain function. Baihui (DU 20) and Shenting (DU24), which were used in this study, both belong to the Du Meridian and were widely used in the treatment of mental and emotional illnesses by ancient Chinese doctors.

Baihui (DU 20) is located at the highest point of the head, where all of the yang meridians meet. Acupuncture of Baihui (GV20) can clear the mind, lift the spirits, tonify yang, strengthen the ascending function of the spleen, eliminate interior wind, and promote resuscitation.[47] Thus, Baihui (GV20) is specifically used to treat neurologic and psychiatric diseases, such as stroke, headache, dizziness, and anxiety.[48] Shenting (DU24) is located on the anterior median line of the head, and it is also an important point of Du. Acupuncture of Shenting (DU24) has a similar therapeutic effect in the treatment of mental diseases, and acupuncture at these 2 locations are often combined for clinical use.

In modern times, various studies using animal models of ischemic stroke have revealed that Baihui (GV20)-based scalp acupuncture has neuroprotective effects on multiple aspects of pathophysiology. Furthermore, to determine whether acupuncture at the Du Meridian [especially Baihui (DU 20) and Shenting (DU24)] improves cognitive function in stroke patients, our research team has also conducted a number of animal experiments in a previous study.

In these animal experiments, we examined different pathways to confirm that acupuncture at the Baihui (DU20) and Shenting (DU24) acupoints can ameliorate anatomic deterioration and learning and memory deficits in the treatment of rats with cerebral ischemia/reperfusion (I/R) injury.

Table 4
Functional Outcomes (Baseline vs Post-treatment) for the 4 Groups

Groups	Scale	Baseline*	Post-treatment	△ Change	*Z*†	*P* Value†
CG (n = 49)	MMSE	18.29 ± 4.24	19.88 ± 4.13	1.59 ± 1.02	−5.687	.000
	MoCA	15.37 ± 5.94	16.69 ± 5.66	1.33 ± 1.20	−5.193	.000
	FIM	60.67 ± 5.82	78.49 ± 5.83	17.82 ± 2.41	−6.126	.000
ATG (n = 52)	MMSE	18.04 ± 4.98	21.10 ± 4.83	3.06 ± 1.46	−6.220	.000
	MoCA	15.13 ± 6.93	17.96 ± 6.74	2.83 ± 1.13	−6.348	.000
	FIM	60.77 ± 6.03	80.73 ± 5.88	19.96 ± 3.22	−6.299	.000
RTG (n = 51)	MMSE	18.22 ± 4.12	21.06 ± 3.78	2.84 ± 1.55	−6.267	.000
	MoCA	15.25 ± 5.38	18.02 ± 4.97	2.76 ± 1.45	−6.002	.000
	FIM	60.84 ± 5.87	80.71 ± 5.39	19.86 ± 3.14	−6.256	.000
ACRG (n = 52)	MMSE	18.31 ± 4.45	23.52 ± 3.83	5.21 ± 1.02	−6.356	.000
	MoCA	15.02 ± 5.98	20.04 ± 5.68	5.02 ± 1.00	−6.350	.000
	FIM	60.92 ± 5.34	84.96 ± 4.93	24.04 ± 2.67	−6.301	.000

The data are presented as the mean ± SD.
△ Change in value before vs after treatment.
*The *P* value was obtained by 1-way analysis of variance (ANOVA): $P > .05$; F(MMSE) = 0.039; F(MoCA) = 0.031; and F(FIM) = 0.017.
†The *P* value was obtained by the paired *t*-test.

Table 5
Multiple Comparisons of ΔMMSE, ΔMoCA, and ΔFIM Scores for the 4 Groups

Groups	△ MMSE *P* Value	△ MoCA *P* Value	△ FIM *P* Value
ATG vs CG	.000	.000	.000
RTG vs CG	.000	.000	.002
ACRG vs CG	.000	.000	.000
ATG vs ACRG	.000	.000	.000
RTG vs ACRG	.000	.000	.000
ATG vs RTG	.399	.794	.862

Multiple comparisons were performed using the least significant difference (LSD) test.

The treatment effects include (1) attenuating brain edema and blood-brain barrier (BBB) disruption caused by cerebral ischemia and inhibiting matrix metalloproteinase (MMP)-9/MMP-2 expression and activity[49,50]; (2) increasing cerebral perfusion in the cerebral cortex, acetylcholine release and muscarinic acetylcholine receptors muscarinic 3 (mAChR M3) expression in the cerebral cortex[51]; (3) increasing the expression of cell division cycle 42, Ras-related C3 botulinum toxin substrate 1 and F-actin proteins and inhibiting the expression of Ras homologous member A[52]; and (4) enhancing cell proliferation and increasing neuroblast plasticity by phosphorylated cyclic adenosine monophosphate (cAMP) response element-binding protein and brain-derived neurotrophic factor activation in the dentate gyrus.[53,54]

In this study, we found that after acupuncture therapy, the cognitive function of all poststroke patients (including the MMSE, MoCA, and FIM scores) improved to varying degrees.

In addition, we demonstrated that acupuncture at the Du Meridian [Baihui (DU 20) and Shenting (DU24) acupoints] improves the cognitive function of poststroke patients to a certain extent, in agreement with previous studies.[50,52,54]

However, further analysis revealed that although acupuncture had a clinical curative effect, it was relatively limited compared with that observed in the ACRG (Table 5).

Therefore, we can also conclude that the use of simple acupuncture treatment in stroke patients with cognitive dysfunction is not sufficient and that it must be used in combination with other treatments.

Analysis of the Effect of Computer-Aided Cognitive Training

From the beginning of rehabilitation, CR training has been one of the most important means by which patients with cognitive impairment after stroke recuperate and recover.

Cognitive training refers to a series of procedures that typically include guided practice on a set of standardized tasks designed to reflect particular cognitive functions, such as memory, attention, and executive ability. The training task is presented in various forms, such as paper-and-pencil and computerized forms, and it might involve analogs of activities of daily living.[55]

Table 6
Assessment of Between-Participant Effects

Dependent Variables	Source of Variation	SS	df	Mean Square	F	*P*
△ MMSE	Acupuncture	187.334	1	187.334	112.824	.000
	RehaCom	147.750	1	147.750	88.984	.000
	Acup * Reha	10.380	1	10.380	6.251	.013
△ MoCA	Acupuncture	179.662	1	179.662	123.745	.000
	RehaCom	167.951	1	167.951	115.679	.000
	Acup * Reha	7.247	1	7.247	4.991	.027
△ FIM	Acupuncture	509.116	1	509.116	61.220	.000
	RehaCom	477.784	1	477.784	57.452	.000
	Acup * Reha	52.537	1	52.537	6.317	.013

Acup, acupuncture treatment; Reha, RehaCom training; SS, type III sum of squares.

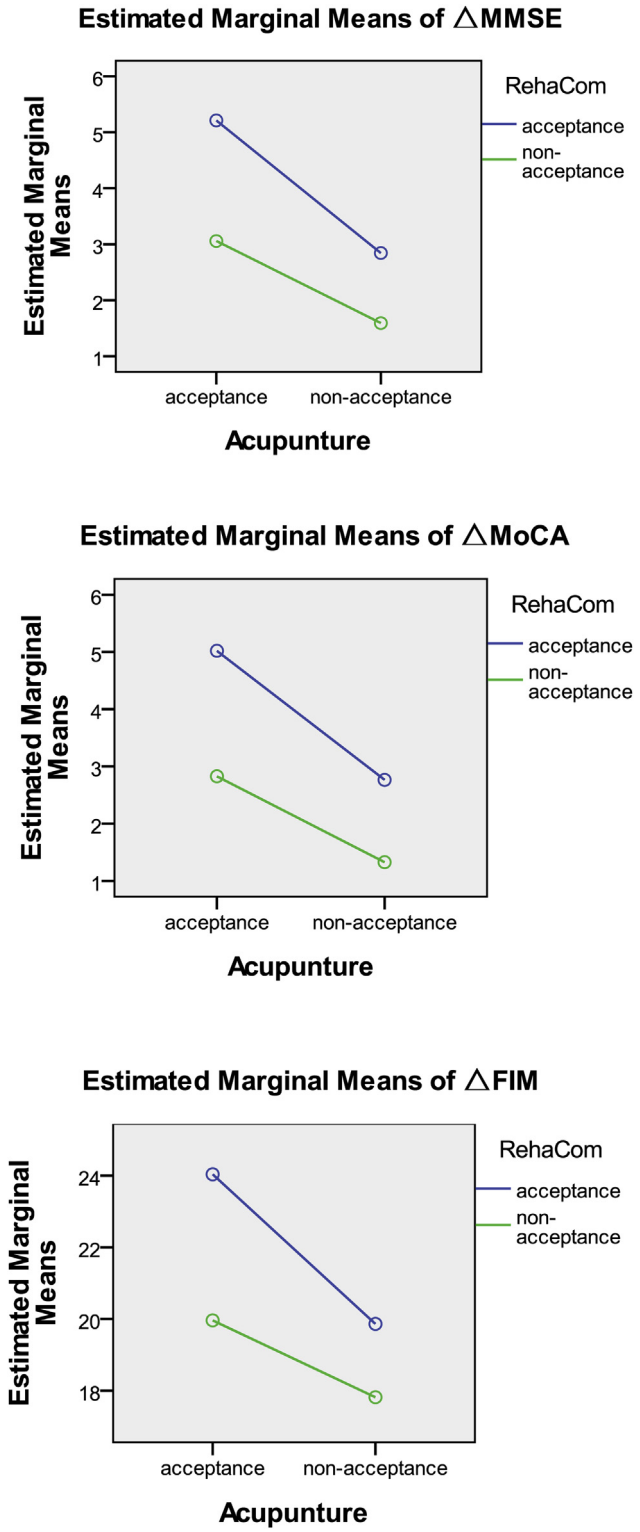

Fig. 2. Estimated marginal means of ΔMMSE, ΔMoCA, and ΔFIM.

With the growing popularization of computer technology, CACR has recently been highlighted as a CR method. In addition, the clinical use of CACR to treat neurologic patients has increased because the level of difficulty can be adjusted to suit an individual's cognitive level, thereby reducing the treatment time for patients and doctors and decreasing costs.

Several studies have shown that brain functional and structural network connectivity can be altered through cognitive interventions. Cognitive training can modulate the activation of brain region structures that are directly related to the training tasks, along with improving the behavioral performance of the tasks.

Although cognitive training goals include improvements in behavioral performance and accompanying modifications in brain activation, neuro-feedback also occurs by the direct targeting of improvements in brain activation and a consequent increase in cognitive performance.[56] In addition, graph theoretical network metrics have demonstrated the reorganization of topological architecture in the brain functional network over multiple temporal scales (ie, minutes, days, and weeks).[57]

In this study, we used the Chinese version of RehaCom to improve poststroke patient cognition. As shown in Table 4, we found that after 12 weeks of intervention therapy, the stroke patients in the RTG showed a significant improvement compared with the baseline.

Further multiple comparisons demonstrated that the use of RehaCom training alone in the treatment of poststroke patients with cognitive dysfunction had a significantly lower therapeutic effect than that observed in the ACRG.

Thus, we draw a similar conclusion that RehaCom training has therapeutic effects on patients with cognitive dysfunction to a certain extent; however, it must be combined with other treatment methods to achieve the best rehabilitation results.

Comparison of Therapeutic Effects Between Acupuncture and CACR

Based on previous literature and the above analysis, we found that the use of either acupuncture therapy or RehaCom training alone improved the cognitive function of the stroke patients to a limited degree.

Thus, these treatments cannot meet the needs of the majority of stroke patients with an expectation of maximal recovery. As previously stated, the results of this study have confirmed that the combination of acupuncture and RehaCom training has synergistic effects that improve the cognitive function of stroke patients (Tables 5 and 6). This combination of treatments resulted in significantly greater improvement in cognitive function than either treatment alone in the stroke patients with cognitive dysfunction.

Theoretically, acupuncture focuses on global cognitive function from the holistic concept of TCM, whereas RehaCom cognitive training targets impaired cognitive function specifically and must be performed from the perspective of symptomatic treatment.

As discussed earlier, CR training can alter brain functional and structural network connectivity over many temporal scales, and acupuncture improves the reversibility of the body by directly activating various brain pathways. In this way, there is a natural complementarity between acupuncture therapy and RehaCom cognitive training.

Throughout human history, acupuncture has been accepted by Chinese patients as a relatively simple, cheap, and safe treatment for the management of various cognitive disorders and psychosomatic diseases, such as stress, ischemia, and dementia.[58] The organic combination of acupuncture therapy and RehaCom cognitive training had synergistic effects on cognitive function rehabilitation. This new therapeutic strategy will help to improve the rehabilitation of the majority of Chinese stroke patients with cognitive impairment. Moreover, this strategy is in agreement with China's current medical development model, which not only makes use of advances in Western medicine but also fully integrates the characteristics and advantages of TCM.

Strengths and Limitations

Although cognitive dysfunction rehabilitation after ischemic stroke is influenced by many variables, we aimed to examine a large sample size and strictly follow procedures to complete patient treatment. In addition, we attempted to persuade patients to complete the experiment in its entirety, despite the treatment length and medical expenses. Unfortunately, we inevitably lost some patients because of economic status, change in condition, personal factors, or the length of the intervention period.

In the published protocol, the initial assessment included the MMSE, MoCA, and FIM and was expected to be performed on all of the groups before and after randomization (at 0, 4, 8, and 12 weeks). Because too many participants were unwilling to undergo assessment during treatment, we were unable to obtain complete data (4 and 8 weeks). Although some of the missing data is due to the withdrawal of patients, the data are still scientifically meaningful.

In addition, the study lacks long-term follow-up and evaluation. Although 12 weeks of cognitive intervention is sufficiently long to assess the short-term efficacy of a rehabilitation modality, we could not assess long-term efficacy. The design of future studies should be more comprehensive to avoid the above problems.

Despite these limitations, several conclusions can be drawn from the results of our study. First, acupuncture treatment alone (ie, separate from RehaCom cognitive training) and acupuncture treatment in combination with RehaCom cognitive training improve the cognitive function of stroke patients with cognitive dysfunction to varying degrees. Second, acupuncture treatment in combination with cognitive training has positive synergistic effects that significantly improve cognitive function compared with each treatment used alone in stroke patients with cognitive dysfunction.

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