

# Efficacy of Continuous Theta Burst Stimulation on Brain Clearance Recovery in Post-stroke Cognitive Impairment

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## Research

**Keywords:** continuous theta burst stimulation, glymphatic system, diffusion tensor imaging, post-stroke, cognitive impairment

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# Abstract

**Background:** Cognitive impairment is a frequent and often debilitating consequence of stroke. This single-blinded randomized controlled trial examined the therapeutic benefits of continuous theta burst stimulation (cTBS) for patients with post-stroke cognitive impairment (PSCI).

**Methods:** Twenty patients with PSCI were randomly and equally allocated to cTBS and sham cTBS groups. Groups received the indicated treatments five consecutive days per week for 2 weeks (10 sessions) plus 10 sessions of computer-assisted cognitive training. The primary outcomes were changes in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) score and analysis along the perivascular space (ALPS) index.

**Results:** The post-intervention change in ADAS-cog score from baseline was significantly greater in the cTBS group than the sham cTBS group ( $-7.7 \pm 3.8$  vs.  $-3.7 \pm 1.5$ ,  $t = -3.096$ ,  $P = 0.006$ ). Change in ALPS index from baseline was also greater in the cTBS group ( $0.182 \pm 0.097$  vs.  $0.093 \pm 0.080$ ,  $t = 2.236$ ,  $P = 0.038$ ).

**Conclusion:** Continuous theta burst stimulation can improve cognitive outcome and enhance ALPS. Enhanced waste clearance via the glymphatic system induced by cTBS may contribute to improved cognitive function following stroke.

Clinical Trial Registration URL: <http://www.chictr.org.cn>. ChiCTR1800017997. Registered August 25, 2018, retrospectively registered.

## Background

Stroke induces substantial cognitive decline in many survivors<sup>[1]</sup>, and it is estimated that 70–90% of stroke patients incur at least some degree of post-stroke cognitive impairment<sup>[2]</sup>. Moreover, up to 50% of stroke patients demonstrate impairments in multiple cognitive domains<sup>[2]</sup>. This post-stroke cognitive impairment (PSCI) is also associated with progressive dementia, with up to 41% of patients meeting criteria for clinical dementia within the first year post-stroke<sup>[3]</sup>. Although there is no standard definition, PSCI typically refers to any cognitive deficit after a cerebrovascular event and can range from mild cognitive impairment to severe vascular dementia. Cognitive abilities determine functional performance<sup>[4, 5]</sup>, so PSCI is a major cause of functional disability in activities of daily living (ADLs), impaired quality of life, post-stroke depression (PSD), progression to dementia, and reduced long-term survival<sup>[6]</sup>.

The treatment of cognitive impairment and prevention of further decline are essential aspects of stroke rehabilitation. A variety of interventions have been assessed, but there is only limited evidence to suggest beneficial effects of physical activity, cognitive training, and risk factor reduction; thus, more research is needed<sup>[7, 8]</sup>. Indeed, improvement of cognition after stroke has been identified as a research priority by stroke survivors, caregivers, and health professionals<sup>[9]</sup>.

Noninvasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are promising tools to enhance post-stroke recovery because they have the potential to induce long-term increases or decreases in regional cortical excitability<sup>[10]</sup>. In fact, the efficacy of NIBS is well documented for motor recovery<sup>[11, 12]</sup> and language recovery<sup>[13]</sup>, highlighting the potential efficacy of NIBS for rehabilitation. However, further refinement of stimulation protocols is required for enhanced reliability and therapeutic efficacy. For instance, the potential of NIBS for post-stroke recovery of cognitive impairments outside the domain of language is still unclear, as are the methodological variables related to treatment efficacy. Kim<sup>[14]</sup> reported that 1 Hz repetitive transcranial magnetic stimulation (rTMS) over the contralesional posterior parietal cortex (PPC) resulted in a greater improvement of line bisection and letter cancellation tasks among stroke patients with visuospatial neglect. Similarly, Yang<sup>[15]</sup> found that continuous theta burst stimulation (cTBS) over the contralesional PPC improved symptoms of neglect, while Cao et al. reported that iTBS over the contralesional dorsolateral prefrontal cortex (DLPFC) also had significant efficacy in neglect patients<sup>[16]</sup>. Furthermore, 1 Hz rTMS over the right DLPFC resulted in a significant improvement of everyday memory function among PSCI patients<sup>[17]</sup>, and benefits of TMS on executive function and other cognitive domains have been reported<sup>[18]</sup>. Although stimulation protocols and treatment regimens have varied substantially across these studies, most used a figure-8 coil and TMS to modulate cortical excitability in specific brain regions. In addition to changing cortical excitability, our previous animal studies demonstrated that cTBS also enhances metabolite clearance via glymphatic pathways. Therefore, we speculated that enhanced brain glymphatic pathway function by cTBS treatment would accelerate the clearance of metabolic waste and improve cognitive function in patients with PSCI.

The objective of this study was to evaluate the effects of a 2-week daily cTBS regimen combined with computer-assisted cognitive training on global cognitive function, glymphatic pathway clearance efficiency, specific cognitive domains, ADL, and quality of life in patients with PSCI. We speculated that cTBS would enhance the clearance efficiency of glymphatic pathways and improve cognitive function compared to sham cTBS.

## Methods

### Participants

Participants were recruited from the First Affiliated Hospital of Sun Yat-sen University and the First People's Hospital of Guangzhou. Inclusion criteria were first stroke within the previous 12 months as confirmed by computed tomography (CT) scan or magnetic resonance imaging (MRI), evidence of stroke-related cognitive impairment as documented by neuropsychological evaluation, aged 40–80 years, primary school (grade 6) education or above, Mini-Mental State Examination (MMSE) score  $\geq 15$ , Montreal Cognitive Assessment (MoCA) score less than 26, Hamilton Depression Rating Scale (HAMD) score  $< 17$ , not on drugs for cognitive improvement, and having a stable and reliable caregiver. Exclusion criteria were as follows: bilateral or subtentorial lesions; history of nervous system diseases such as

stroke, brain tumor, and brain trauma; other causes of cognitive decline such as Alzheimer's disease, Parkinson's disease, frontotemporal dementia, dementia with Lewy bodies, VitB12 deficiency, or hypothyroidism; severe alcoholism and drug abuse; currently taking medications that may negatively affect cognitive functions such as anticholinergics, antipsychotics, and anticonvulsants; contraindications to MRI; contraindications to TMS treatment; psychiatric disorders such as schizophrenia, bipolar disorder, major depression and delirium; vision or hearing problems that could impede performance on cognitive tests; language deficits or aphasia. A researcher with a background in rehabilitation was responsible for screening and enrolling the participants.

## Ethical considerations

The study protocol was reviewed and approved by the Ethics Committee for Clinical Research and Animal Trials of the First Affiliated Hospital of Sun Yat-sen University ([2018]111). The potential risks and benefits of participation in this study were explained to each participant in advance, and all participants provided signed informed consent before participation. The study is registered at <http://www.chictr.org.cn> (ChiCTR1800017997).

## Study Design

This was a single-blinded randomized controlled trial. After baseline evaluation, participants were randomized equally to the cTBS group or sham cTBS group. Group allocation was concealed in sealed sequentially numbered envelopes that were not opened until completion of baseline assessments. All randomization procedures were performed by an off-site researcher who was not involved in other aspects of the study. All assessments were performed by two researchers blinded to group allocation.

## Intervention

Patients in the cTBS group received cTBS treatment and computer-assisted cognitive training for 2 weeks. Continuous theta-burst stimulation was applied using a Yiruide CCY-IA magnetic stimulator (Wuhan Yiruide Medical Equipment New Technology Co., Ltd., Wuhan, China) with a circular coil (Y125, 125 mm outer diameter). The cTBS protocol comprised 600 pulses delivered in 200 equally spaced bursts over 40 s (5 Hz), with each burst consisting of three pulses at 50 Hz<sup>[19]</sup>. The cTBS was applied over Cz according to the international 10–20 EEG System. The coil was held tangentially to the scalp, with the handle pointing in the posterior direction. Power was set to 80% of each patient's active motor threshold. Participants received one treatment session per day, 5 days per week, for a total of 10 treatment sessions. Computer-assisted cognitive training was delivered using a computerized, multidomain, adaptive training program (Nanjing Wise Spirit Education Technology Co., Ltd., Nanjing, China). The training domains included processing speed, attention, perception, long-term memory, working memory, calculation, executive control, reasoning, and problem solving<sup>[20]</sup>. Participants completed 30 min of training per day, 5 days a week for 2 weeks. Patients in the sham cTBS group received the same protocol, except that the coil was held perpendicular to the scalp.

## Measurements

Demographic information was obtained during a baseline interview. The outcome metrics detailed below were obtained before and after the intervention by researchers blinded to treatment group. The primary outcomes of this study were changes in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) score and analysis along the perivascular space (ALPS) index<sup>[21]</sup>. Safety was evaluated by recording adverse events and laboratory parameters.

## **ADAS-cog**

The ADAS-cog score change from baseline was chosen as the primary endpoint of the trial<sup>[22]</sup>. The ADAS-cog has been widely used to measure cognitive changes in clinical trials of patients with Alzheimer's disease<sup>[23]</sup> and vascular cognitive impairment<sup>[24]</sup>. The ADAS-cog measures cognitive performance by combining ratings on 12 items addressing short-term memory, language, ability to orientate (reflects memory), construction/planning of simple designs, and performance. Although the ADAS-cog scale has not been validated in stroke, we considered it to be the most appropriate tool to assess cognition in stroke.

*ALPS index:* All images were acquired using a 3.0 T clinical scanner (Magnetom Verio, Siemens AG, Erlangen, Germany). T1-weighted images were acquired with the following parameters: 176 axial slices, slice thickness/gap = 1.0/0.5 mm, TR = 2530 ms, TE = 3.39 ms, inversion time (TI) = 900 ms, flip angle = 7°, FOV = 256 × 256 mm<sup>2</sup>. Diffusion tensor imaging (DTI) data were acquired with the following parameters: 45 axial slices, slice thickness/gap = 3.0/0 mm, TR = 8300 ms, TE = 86 ms, 64 diffusion directions with b = 1000 s/mm<sup>2</sup>, acquisition matrix = 128 × 128, FOV = 230 × 230 mm<sup>2</sup>.

The DTI data were preprocessed using PANDA software, a pipeline tool for analyzing brain diffusion images (<http://www.nitrc.org/projects/panda/>)<sup>[25]</sup>. A color-coded fractional anisotropy (FA) map and diffusivity map were also acquired by the software. Then, we split the diffusivity map and acquired diffusivity into separate x-axis, y-axis, and z-axis datasets. On the color-coded FA map of the plane at the level of the lateral ventricle body, we placed 5-mm diameter spherical regions of interest (ROIs) in the area of left hemisphere projection fibers and association fibers, and then calculated mean x-axis diffusivity values, abbreviated  $D_{x,p}$  and  $D_{x,a}$ . We also calculated the mean y-axis diffusivity in the ROI of projection fibers and the mean z-axis diffusivity in the ROI of association fibers, abbreviated as  $D_{y,p}$  and  $D_{z,a}$ . To evaluate the activity of the glymphatic system and the analysis along the perivascular space (ALPS), we calculated a ALPS index using the following formula:

$$\text{ALPS index} = \text{mean} (D_{x,p}, D_{x,a}) / \text{mean} (D_{y,p}, D_{z,a})$$

*Secondary Outcomes:* Secondary endpoints were as follows: global cognition as assessed by the Montreal Cognitive Assessment (MoCA); executive function as assessed by the Digit Span Test (DST), Stroop Test, and Trail Marking Test (TMT); memory function as assessed by the Auditory Verbal Learning Test-Huashan Version (AVLT-H); speech function as assessed by the Verbal Category Fluency Test (VCFT); visuospatial function as assessed by the Clock Drawing Test (CDT); activities of daily living

(ADL) as assessed by the Modified Barthel Index (MBI); quality of life as assessed by the Stroke-Specific Quality of Life Scale (SS-QoL).

## Data analysis

According to pilot experiments, an estimated sample size of 18 PSCI patients (nine per group) would be required for detecting a significant group difference in ADAS-cog score change with 80% power at a two-sided  $\alpha = 0.05$  by independent samples t-test assuming a mean ( $\pm$  standard deviation) score change of  $8.0 \pm 3.0$  in the cTBS group,  $4.0 \pm 2.0$  in the sham cTBS group, and an estimated drop-out rate of 10%. Therefore, we recruited candidates until 20 participants were identified meeting all inclusion criteria, with no reasons for exclusion, and agreeing to participate.

Data entry was performed independently by two researchers to ensure accuracy. Measurement data are expressed as mean  $\pm$  standard deviation. SPSS version 24.0 (IBM, Armonk, NY) was used to conduct all data analyses. A  $P \leq 0.05$  (two-tailed) was considered statistically significant for all tests.

*Comparison of baseline values.* Baseline measurement data such as age, years of education, and course of disease were compared by independent samples t-test if normally distributed or by the non-parametric rank sum test if not normally distributed according to X. Baseline count data, such as sex, stroke type, and hemiplegia side were compared by Fisher's exact test.

*Outcomes analysis.* Group differences in outcomes were compared by independent sample t test or non-parametric rank sum test as indicated.

## Results

Patients were recruited from May 2018 to March 2019. Twenty out of 285 PSCI patients screened met eligibility criteria and were randomly allocated to the cTBS or sham group (Figure 1).

### *Demographics and baseline assessments*

Participant characteristics are summarized in Table 1. There were no significant between-group differences in demographic and outcome variables at baseline ( $P > 0.05$ ).

### *Compliance and adverse events*

All participants completed the treatments and measurements. No adverse events were reported during the treatment period.

### *Effect of cTBS on global cognition*

Figure 2 illustrates the effects of cTBS and sham cTBS on ADAS-cog score. At baseline, ADAS-cog score did not differ significantly between cTBS and sham cTBS groups ( $23.9 \pm 10.3$  vs.  $29.1 \pm 11.3$ ,  $t = -1.077$ ,  $P$

= 0.296), but the change from baseline following intervention was greater in the cTBS group than the sham cTBS group ( $-7.7 \pm 3.8$  vs.  $-3.7 \pm 1.5$ ,  $t = -3.096$ ,  $P = 0.006$ ).

### *Effect of cTBS on the glymphatic system*

We used the ALPS index to evaluate glymphatic system function (Figure 3). At baseline, ALPS index was similar between cTBS and sham cTBS groups ( $1.166 \pm 0.145$  vs.  $1.166 \pm 0.125$ ,  $t = 0.015$ ,  $P = 0.988$ ), while the change from baseline after the intervention was significantly greater in the cTBS group compared to the sham cTBS group ( $0.182 \pm 0.097$  vs.  $0.093 \pm 0.080$ ,  $t = 2.236$ ,  $P = 0.038$ ).

### *Effects of cTBS on other outcomes*

There were no significant differences in MoCA, DST, Stroop Test, TMT, AVLT-H, VCFT, CDT, MBI, and SS-QoL between groups ( $P > 0.05$ ) (Table 2)

## **Discussion**

A brief (2-week, 10-session) cTBS regimen enhanced clearance efficiency along the perivascular space and improved cognitive outcomes in PSCI patients compared to sham cTBS. This is the first demonstration that cTBS can promote metabolite clearance by the glymphatic system in order to improve cognitive function in PSCI.

Post-stroke cognitive impairment arises from multiple pathogenic processes. Cerebrovascular events can directly damage neurons in brain regions critical for higher cognition, such as the frontal, temporal, and parietal lobes, through mutually reinforcing episodes of metabolic failure, excitotoxicity, oxidative stress, osmotic stress, and inflammation. In addition, subcortical infarction or small vessel disease can damage nerve fiber pathways and disrupt functional connectivity among neural networks<sup>[26]</sup>. Post-stroke cognitive impairment patients with previously normal cognition and lacking comorbid neurological diseases may show full or partial recovery without further deterioration of cognitive status<sup>[27]</sup>. However, in PSCI patients with preexisting pathological changes, such as clinically significant A $\beta$  deposition, the cerebrovascular event may damage the cognitive reserve that normally serves to compensate for progressive degenerative changes, limiting recovery and resulting in irreversible cognitive deficits<sup>[26, 28, 29]</sup>. Further, there is a strong relationship among abnormal A $\beta$  deposition, cerebral hypoperfusion, and impaired glymphatic pathways<sup>[30]</sup>. Koistinaho et al found that patients<sup>[30]</sup> with PSCI exhibited lower perfusion in the hemisphere with greater A $\beta$ , suggesting that persistent hypoperfusion accelerates A $\beta$  deposition<sup>[31]</sup>. Further, the clearance efficiency of glymphatic pathways was significantly reduced by vessel ligation or occlusion<sup>[32, 33]</sup>. Therefore, hypoperfusion may impair removal of metabolic waste by glymphatic pathways, resulting in enhanced A $\beta$  deposition. A clinical PET study using the A $\beta$  imaging agent <sup>11</sup>C-PIB also found increased A $\beta$  deposition in patients with PSCI compared to age-matched control stroke patients, as well as a significant negative correlation between the level of cognitive dysfunction and A $\beta$  deposition<sup>[34]</sup>. Therefore, hypoperfusion appears to impair cognitive function by exacerbating A $\beta$ -related

neurodegeneration Moreover, when the changes secondary to strokes, such as hypoperfusion, interact with the previously existing abnormal deposition of A $\beta$ , it not only hinders the recovery of cognitive function, but also accelerates the decline of cognitive function<sup>[27]</sup>. In summary, we speculate that reduced clearance of metabolic waste due to impaired glymphatic pathways is a major contributor to the development of PSCI and an impediment to the recovery of cognitive function. Alternatively, previous animal studies by our research team have confirmed that cTBS can improve the clearance efficiency of glymphatic pathways in mice<sup>[35]</sup>. Therefore, we speculate that cTBS may improve cognitive function in PSCI patients by enhancing glymphatic clearance.

The outcomes of TMS for PSCI have been inconsistent across studies, possibly due to differences in stimulus protocols, outcome measures, and patient heterogeneity. This is the first study in which cTBS was delivered by a circular coil at the apex of the skull (Cz) to influence widely distributed glymphatic pathways. This cTBS delivery method has many advantages, including brief stimulation time (only 40 seconds), which may enhance treatment acceptance, and easy positioning of the coil for greater reproducibility. In addition, TBS uses lower stimulation intensity than traditional rTMS and so is less likely to induce epilepsy or other adverse events. Therefore, we believe that this TMS stimulation protocol can be applied safely and effectively in clinical practice for treatment of PSCI.

The primary outcomes of this study were ADAS-cog score and ALPS index. The change in ADAS-cog score from baseline was significantly larger in the cTBS group than the sham cTBS group, indicating that cTBS can improve global cognitive function in patients with PSCI. In addition, cTBS increased the ALPS index from baseline, indicating improved clearance of metabolites via glymphatic pathways, consistent with our previous animal studies<sup>[35]</sup>. A clinical trial by our research team found that global cognitive function was positively correlated with the clearance efficiency of glymphatic pathways (in press). Among the main targets of glymphatic clearance is A $\beta$ , and cognitive function in PSCI patients is negatively correlated with A $\beta$  deposition<sup>[34]</sup>. Therefore, we speculate that cTBS may improve the cognitive function of PSCI patients by accelerated the clearance of metabolic waste, such as A $\beta$  via the glymphatic system.

In contrast to global cognition and glymphatic function, there were no significant differences in secondary outcomes between cTBS and sham groups. However, it is possible that the intervention was too brief (2 weeks) to induce measurable improvements in specific cognitive domains, ADL, and quality of life. Conversely, the sample size may be insufficient to detect more modest changes in these outcomes. Longer, larger-scale studies are warranted to comprehensively assess the benefits of this cTBS paradigm on the functional recovery of stroke patients.

## Conclusions

Continuous theta burst stimulation can improve cognitive outcome and enhance ALPS. Enhanced waste clearance via the glymphatic system induced by cTBS may contribute to improved cognitive function following stroke.



# Declarations

**Author Contribution** GX, YH, YJ, CW, TL and WL contributed to the conception and design of the study and interpretation of the data. YH, YJ, CW and WL performed the research. YH, QD and YJ conducted the statistical analyses. ZP and CW provided additional statistical expertise related to the analysis. YH, QD and GX drafted the manuscript. YL and GX were the principal investigator of the study and were responsible for the study conception and interpretation of data. YL and GX had final responsibility for the decision to submit for publication. All authors provided final approval for the version of the manuscript submitted for publication and agreed to be accountable for the work.

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## Availability of data and materials

The datasets generated during the present study are available from the corresponding author upon request.

**Ethics Approval and Consent to Participate** This study was conducted at the First Affiliated Hospital of Sun Yat-sen University and Guangzhou First People's Hospital, and the study protocol was reviewed and approved by the Ethics Committee for Clinical Research and Animal Trials of the First Affiliated Hospital of Sun Yat-sen University (Approval Number: [2018]111). This study was performed in line with the principles of the Declaration of Helsinki. The potential risks and benefits of participation in this study were explained to each participant in advance. All participants provided signed informed consent before participation.

**Consent for Publication** Not applicable

**Conflict of Interest** There is no conflict of interest

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## Tables

**Table 1.** Participant characteristics at baseline

	cTBS (n=10)	sham cTBS (n=10)
Basic demographics		
Age, y	70.3±10.0	72.8±6.6
Sex, female (n)	6	5
Education (years)	10.6±3.4	10.2±2.5
Stroke characteristics		
Time since onset (mo)	4.2±3.4	4.3±3.1
Type (ischemic/hemorrhagic; n)	7/3	8/2
Hemiparetic side (left/right; n)	6/4	5/5
MMSE (0-30)	20.1±4.4	19.3±4.4
Medical history		
Diabetes mellitus (n)	5	5
Hypertension (n)	9	9
Myocardial ischemia (n)	0	0
Cerebral arteriosclerosis (n)	6	5
Coronary artery disease (n)	1	2

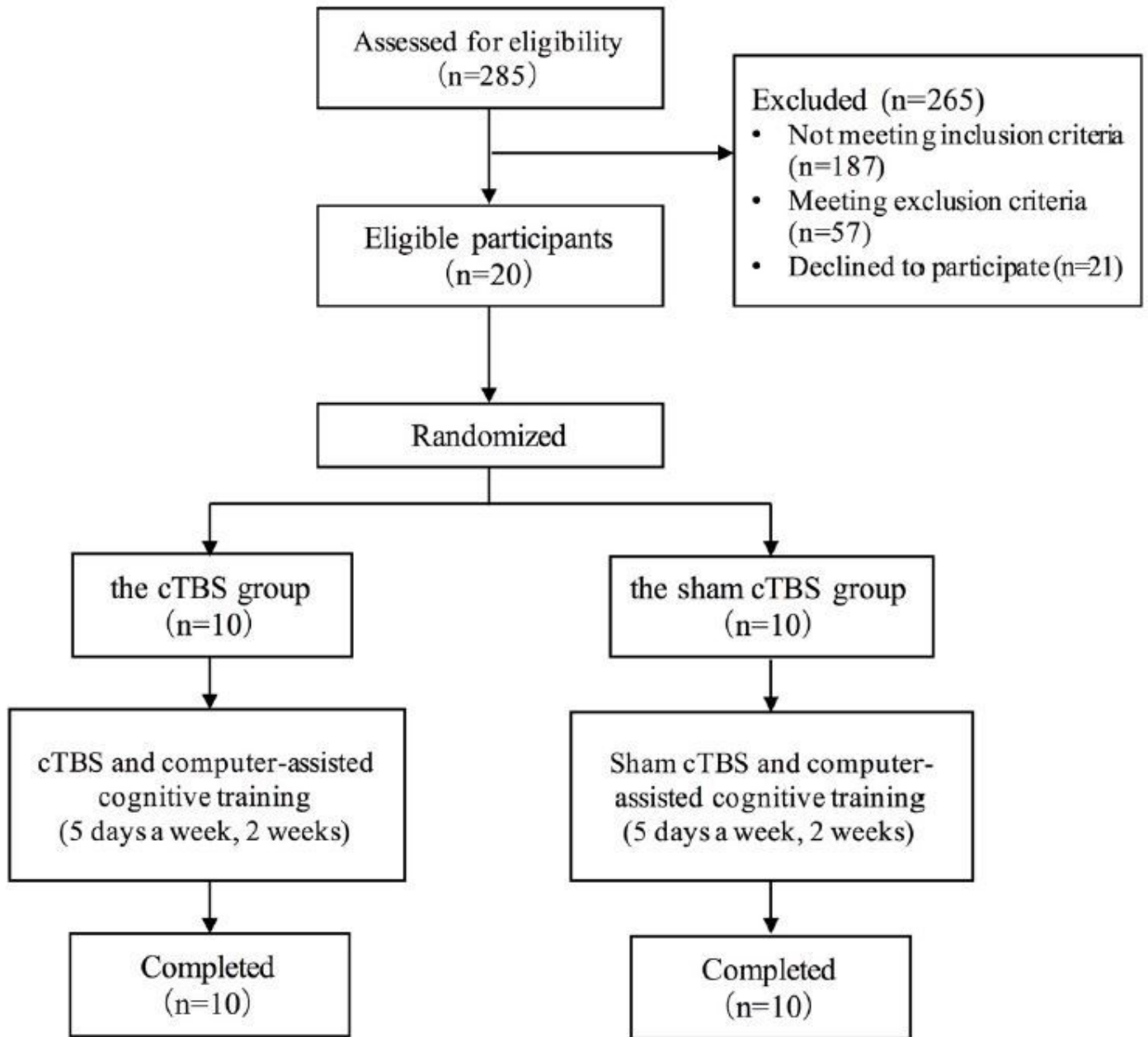
MMSE: Mini-Mental State Examination

**Table 2.** Secondary outcomes

	cTBS	sham cTBS	<i>t/Z</i>	<i>P</i>
MoCA	18.00±4.85	15.60±6.02	1.024	0.306
DST forward	7.20±1.69	6.20±0.92	1.646	0.117
DST backward	3.30±0.95	2.80±0.63	1.268	0.205
Stroop Test -time	111.20±26.86	125.10±26.78	-1.159	0.262
Stroop Test -error	9.00±3.30	9.90±4.70	-0.496	0.626
TMT-A	97.90±28.19	109.00±26.24	-0.911	0.374
TMT-B	254.00±68.06	261.20±58.54	-0.254	0.803
AVLT-1	3.50±1.65	2.40±1.43	1.611	0.107
AVLT-2	4.70±1.64	3.40±1.51	1.849	0.081
AVLT-3	4.90±2.02	4.30±1.83	0.740	0.459
AVLT-4	3.70±1.57	2.60±1.71	1.598	0.110
AVLT-5	1.70±1.06	1.40±1.08	0.653	0.514
AVLT-recognition	10.60±1.58	9.50±1.96	1.383	0.184
VCFT	8.10±2.77	8.50±2.22	-0.191	0.848
CDT	7.00±3.27	6.90±3.73	0.235	0.814
MBI	54.80±20.19	53.60±14.81	0.152	0.881
SS-QoL	148.40±21.99	142.80±17.74	0.627	0.539

MoCA: Montreal Cognitive Assessment; DST: Digit Span Test; TMT: Trail Marking Test; AVLT: Auditory Verbal Learning Test-Huashan Version; VCFT: Auditory Verbal Learning Test; CDT: Clock Drawing Test; MBI: Modified Barthel Index; SS-QoL: Stroke-Specific Quality of Life Scale;

## Figures



**Figure 1**

Enrollment and Outcomes.

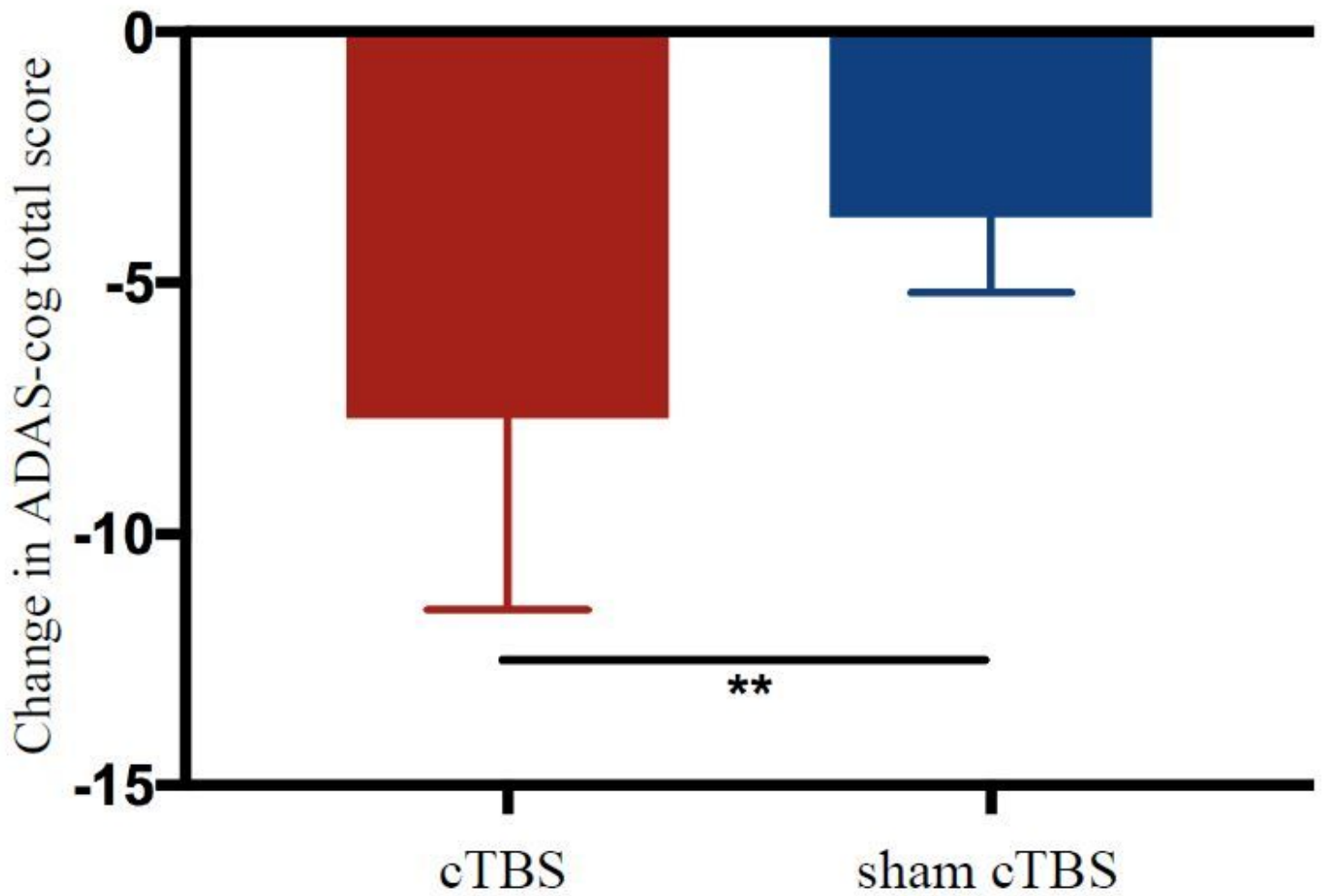


Figure 2

ADAS-cog scores: mean differences from baseline. Differences between the cTBS and sham groups were significant at day 14 ( $P = 0.006$ ).



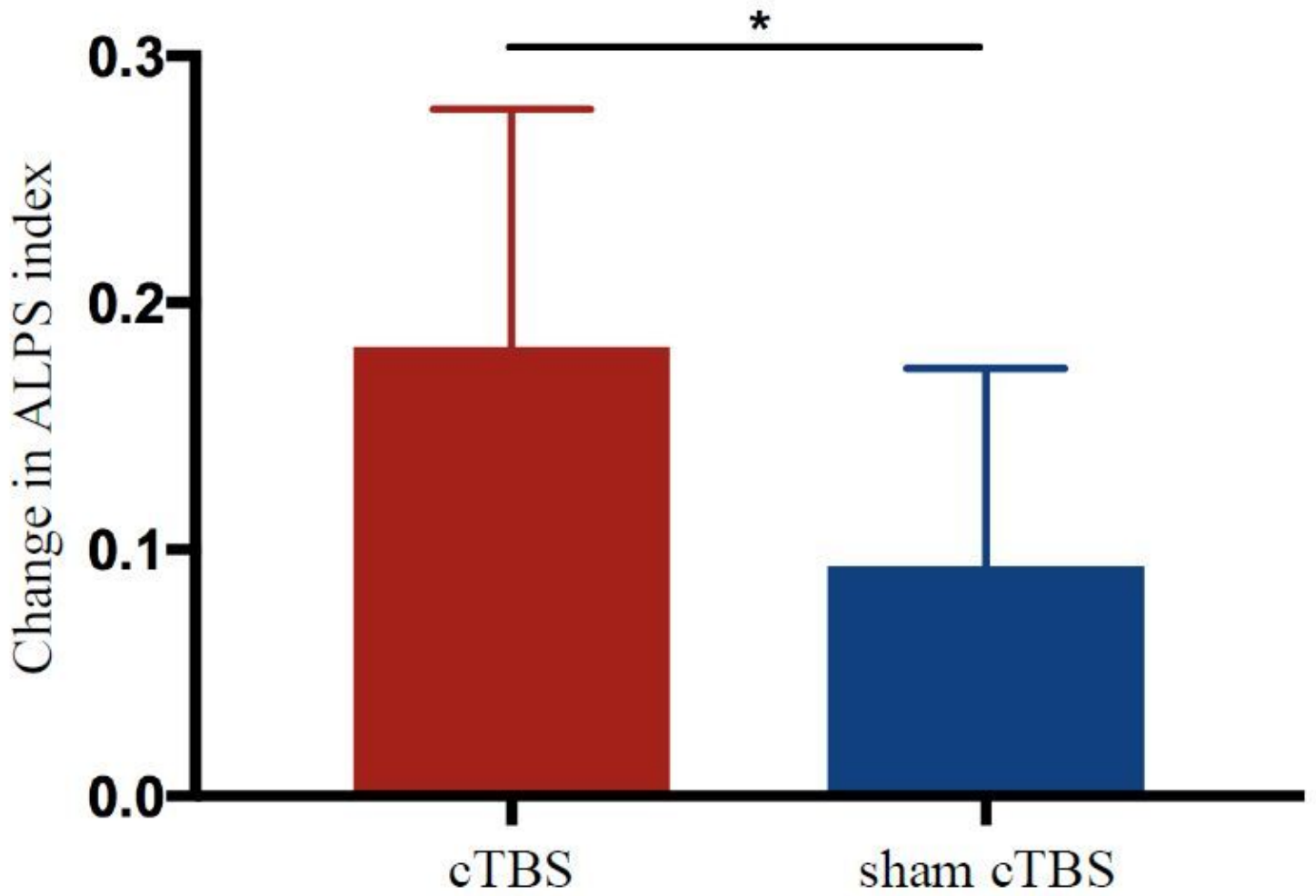


Figure 3

ALPS index scores: mean differences from baseline. Differences between the cTBS and sham groups were significant at day 14 ( $P = 0.038$ ).