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# Constraint-induced movement therapy promotes brain functional reorganization in stroke patients with hemiplegia

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## Abstract

Stroke patients with hemiplegia exhibit flexor spasms in the upper limb and extensor spasms in the lower limb, and their movement patterns vary greatly. Constraint-induced movement therapy is an upper limb rehabilitation technique used in stroke patients with hemiplegia; however, studies of lower extremity rehabilitation are scarce. In this study, stroke patients with lower limb hemiplegia underwent conventional Bobath therapy for 4 weeks as baseline treatment, followed by constraint-induced movement therapy for an additional 4 weeks. The 10-m maximum walking speed and Berg balance scale scores significantly improved following treatment, and lower extremity motor function also improved. The results of functional MRI showed that constraint-induced movement therapy alleviates the reduction in cerebral functional activation in patients, which indicates activation of functional brain regions and a significant increase in cerebral blood perfusion. These results demonstrate that constraint-induced movement therapy promotes brain functional reorganization in stroke patients with lower limb hemiplegia.

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## Key Words

stroke; constraint-induced movement therapy; functional MRI; lower extremity; maximum walking speed; Berg balance scale; central nervous injury; neuroimaging; regeneration; neural regeneration

## Research Highlights

- (1) The maximum walking speed and Berg balance scale scores were assessed to evaluate the influence of constraint-induced movement therapy on the walking speed and balance function of stroke patients.
- (2) Functional MRI examination demonstrated new activation in the lower limb dominant area on the affected side and functional reorganization of the cerebral cortex on the healthy side.
- (3) We speculate that constraint-induced movement therapy promotes functional reorganization following brain injury.

## INTRODUCTION

Existing functional imaging studies, such as positron emission tomography and single photon emission computed tomography, are mainly applied to the upper extremities. Functional MRI studies have revealed that the number of newly activated foci in the motor cortex or premotor cortex on the contralateral side (affected side) and the number of activated foci in the motor cortex and supplementary motor area on the ipsilateral side (unaffected side) are significantly increased<sup>[1-9]</sup>. Constraint-induced movement therapy is a new technique for upper limb rehabilitation in hemiplegic patients<sup>[3-4]</sup>. There is limited information from functional MRI studies on the mechanism of cerebral cortical recovery associated with lower extremity motor functional improvement<sup>[10]</sup>. It has been reported that rehabilitation treatment is more effective for the recovery of lower limb function than for upper limb function<sup>[11]</sup>.

Hemiplegic patients exhibit flexor spasms in the upper limb and extensor spasms in the lower limb; thus, these movement patterns differ. The upper limb is chiefly used for grasping and protrusive movements, while the lower limb is primarily used for standing and walking; thus, the mechanism of cerebral cortical recovery associated with the upper limb cannot completely underlie recovery of lower limb function<sup>[12]</sup>. At present, the effect of constraint-induced movement therapy in stroke patients with hemiplegia is unclear, especially for lower limb function. This study aimed to examine cerebral cortical changes in hemiplegic patients before and after constraint-induced movement therapy using functional MRI.

## RESULTS

### Quantitative analysis of subjects

Five stroke patients were involved in this study, and all of them were entered into the final analysis without any dropout or loss.

### Baseline data of subjects

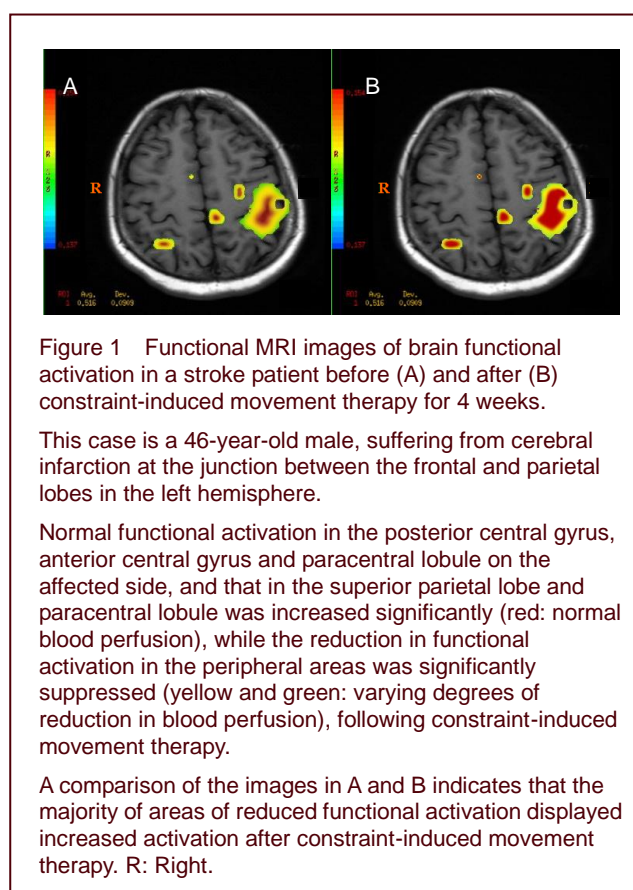
Five stroke patients, aged 34–75 years, with a mean of  $54.3 \pm 11.8$  years, consisted of four men and one woman. The disease course ranged between 2–6 months, with a mean of  $4.2 \pm 1.6$  months. There were three cases of cerebral infarction and two cases of cerebral hemorrhage.

### Distribution of brain functional activation zones in stroke patients

All five patients were subjected to functional MRI

examination before and after constraint-induced movement therapy. Regions of functional activation were located in the postcentral gyrus and precentral gyrus, paracentral lobule and contralateral superior parietal gyrus in the left hemisphere of two patients; in the postcentral gyrus and precentral gyrus, as well as the ipsilateral paracentral lobule in the left hemisphere of one patient; in the postcentral gyrus and precentral gyrus, as well as the ipsilateral paracentral lobule in the right hemisphere of one patient; and in the postcentral gyrus and precentral gyrus in the right hemisphere of one patient.

After constraint-induced movement therapy, the areas of functional activation were enlarged to varying degrees, and the reduction in activation of regions was alleviated (Figure 1), compared with before treatment.



### Complications during constraint-induced movement therapy

One male with hypertension displayed transient dizziness during the first and fifth treadmill exercises, and resumed training after a 2-day period of oral administration of antihypertensive drugs. One female with knee osteoarthritis complained of pain at 5 weeks, which was relieved by intra-articular injection of 20 mg Triamcinolone Acetonide. The other patients completed the treatment regimen as scheduled.

After neurodevelopmental treatment, mainly lower extremity physical therapy during the baseline period, the maximum walking speed and Berg balance scale scores were unchanged in five patients ( $P > 0.05$ ). After 4 weeks of constraint-induced movement therapy, the maximum walking speed and Berg balance scale scores were significantly increased when compared with those before treatment ( $P < 0.01$ ; Table 1).

Table 1 Effect of constraint-induced movement therapy on lower extremity motor function in hemiplegic patients after stroke

Item	Baseline	Before treatment	After treatment
MWS (m/min)	25.8±12.5	27.6±10.5	57.1±6.9 <sup>a</sup>
BBS (scores)	31.6±5.7	33.8±4.9	45.4±9.5 <sup>a</sup>

<sup>a</sup> $P < 0.01$ , vs. before treatment. Data were expressed as mean ± SD,  $n = 5$ , paired  $t$ -test. MWS: Maximum walking speed; BBS: Berg balance scale.

## DISCUSSION

Constraint-induced movement therapy is an increasingly popular rehabilitation technique based on the principle of learned non-use<sup>[13]</sup>, and mainly involves training the affected limbs while restricting the healthy ones. A recent study showed that constraint-induced movement therapy has a training effect on the upper limbs similar to that achieved with bilateral training<sup>[14]</sup>, which suggests that the intensity of exercise is the most critical factor in constraint-induced movement therapy. Kwakkel *et al*<sup>[15]</sup> performed a meta-analysis and found that weekly training of more than 16 hours within 6 months after stroke significantly improved activities of daily living. Even several months or years after stroke, rehabilitation treatment is still effective in improving motor function and activities of daily living<sup>[16]</sup>. However, rehabilitation has greatest efficacy within 6 months of stroke<sup>[17]</sup>. In this study, the 10-m maximum walking speed and Berg balance scale scores demonstrated that constraint-induced movement therapy can apparently increase walking speed and promote functional recovery of balance in stroke patients. The functional MRI observations revealed new activation in the lower limb functional innervation area and functional reorganization in the contralateral cortex. Presumably, this is due to the ability of constraint-induced movement therapy to promote functional reorganization following brain injury. Three examinations of functional MRI and TMS-induced pyramidal tract reaction test were applied to determine the motor function of the upper limb in stroke patients. The results demonstrated that activation patterns in the cerebral cortex did not

contribute to the recovery of motor function in the affected limb, nor were they associated with pyramidal tract Wallerian degeneration<sup>[18-19]</sup>. However, the degree of functional recovery of the affected limbs appears to be associated with Wallerian degeneration.

In the study of Price *et al*<sup>[20]</sup>, the white matter tract anomalies displayed by conventional MRI and diffusion tensor imaging were compared using the FA value, and results showed that diffusion tensor imaging can provide more comprehensive information about white matter tract damage, consistent with the results of Schonberg *et al*<sup>[21]</sup>. We hypothesize that the correlation between the functional recovery of the affected hands and brain activation patterns is determined by the number of intact nerve fibers in the impaired corticospinal tract; if the number of remaining nerve fibers is insufficient, no activation pattern can promote the functional recovery of the affected hands. Further research is required to clarify the neural basis of recovery mediated by constraint-induced movement therapy. Constraint-induced movement therapy needs no drug application, and is safe, with no risk of adverse reaction<sup>[22]</sup>. The shortcomings of this study include small sample size and lack of long-term follow-up. Lin and Sutcliffe<sup>[23-24]</sup> obtained satisfactory therapeutic effects in a randomized controlled study. However, while functional MRI can reveal cerebral cortical activation patterns and allow clinicians to follow the recovery of motor cortical function, it cannot display the trajectory or structure of subcortical white matter fiber tracts. In contrast, diffusion tensor imaging allows imaging of white matter tracts. Thus, functional MRI and diffusion tensor imaging suitably complement each other<sup>[25-28]</sup>, thereby providing a more reliable assessment of the recovery of motor function after stroke<sup>[29-30]</sup>. The combination of these two imaging techniques promises to advance basic and clinical research, and encourage an increasing number of detailed studies.

In summary, constraint-induced movement therapy of the lower extremity can promote the recovery of motor function after stroke and alter brain neuronal plasticity; this conclusion still needs to be confirmed by large-sample clinical studies. Further research is necessary to clarify the mechanisms underlying the reorganization of motor function to permit the selection of effective treatment strategies.

## SUBJECTS AND METHODS

### Design

A self-controlled experiment.

### **Time and setting**

Experiments were performed from March 2008 to July 2009 in the Department of Rehabilitation Medicine, Affiliated Hospital of Chengde Medical College, China.

### **Subjects**

Five patients with lower limb hemiplegia after stroke were selected from the Department of Rehabilitation Medicine, Affiliated Hospital of Chengde Medical College, China between March 2008 and July 2009.

### **Inclusion criteria**

(1) All cases were diagnosed in accordance with the standards revised in the Fourth National Cerebrovascular Disease Conference, and verified by skull CT or MRI as lower limb hemiplegia after cerebral stroke. (2) Cases aged 60–80 years were included. (3) The duration of disease was less than or equal to 6 months. (4) Cases exhibited clear awareness, with no aphasia, and action instruction was acceptable. (5) Blood pressure and heart rate within the normal range. (6) The hemiplegic lower extremity was graded  $\geq$  II stage by the Brunnstrom classification system<sup>[31]</sup>. (7) The muscle strength of lower limb iliopsoas and quadriceps femoris was  $\geq$  III grade<sup>[32]</sup>. (8) The standing balance and sitting balance were  $\geq$  II grade<sup>[33-34]</sup>. (9) The ability to stand with the assistance of one person and the ability for assisted walking for a distance of 10 m, at a speed of  $<$  36 m/min (half less than normal walking speed).

### **Exclusion criteria**

Patients with severe lower limb bone or joint disease were excluded, as well as those with dementia or severe cognitive impairment.

The clinical experiment complied with the “*Declaration of Helsinki*”. Before the experiment, all subjects and their relatives were informed of the experimental scheme and risk, and they agreed to sign informed consent.

### **Methods**

#### **Baseline treatment**

Baseline treatment included lower extremity loading exercise using the Bobath technique<sup>[35]</sup>, hip adduction and abduction, both lower limbs supporting hip extension, affected limb alone supporting hip extension, gravity center transfer to the paretic side and return to the normal side at the sitting position, anterior-posterior and lateral sitting balance, upper limb loading, and extending and stability training on the affected side. The above treatment was performed twice per day, 2 hours each, 5 times per week, for a total of 4 weeks. Following

Bobath treatment, the patients were forced to exercise for an additional 2 weeks. To avoid the overlapping effect of constraint-induced movement therapy and Bobath treatment, constraint-induced movement therapy was performed when the maximum walking speed and Berg balance scale scores were reduced.

#### **Constraint-induced movement therapy**

Patients were trained on the 3108 Performance Series treadmill (electric; Taiwan, China) for treadmill exercise; the speed was initially slow and was gradually increased. It is a mandatory ambulation training for patients, with the aim to enhance the walking speed and improve the gait pattern. Treadmill exercise training was given six times, each 5 minutes, totaling 30 minutes, twice per day. In addition, constraint-induced movement therapy also included quadriceps femoris training for 1 hour, rehabilitation treadmill for 50 minutes, upstairs and downstairs training for 30 minutes, balance training for 30 minutes, single leg loading for 30 minutes, and lower limb compulsory training for 4 hours per day, five times per week, for 4 weeks.

#### **Evaluation of rehabilitation**

The motor function of the lower limbs was assessed before and after treatment by a therapist who was blinded to the experiment. 10-m maximum walking speed was used to evaluate the walking speed of stroke patients with hemiplegia<sup>[36]</sup>. In brief, the ground was marked with color rubber at the start point, at 3.0 m, at 13.0 m, and at the end point. The time the patients took to walk from 3.0 m to 13.0 m was recorded using a stopwatch, accurate to 0.1 second. The patients were tested three times with a rest interval, and the fastest walking speed of three measurements was taken as the maximum walking speed. Data were expressed as m/min. Berg balance scale was used to evaluate the balance ability of patients<sup>[37]</sup>. There were a total of 14 movements; from sitting to standing, continued standing without support, standing without support, from standing to sitting, transferring, standing without support and with eyes closed, feet and standing without support, standing and extending upper limb, standing and fetching from the ground, standing and turning back, standing and turning 360°, alternating feet on the bench with continued support, continuous standing on one foot, and standing on a leg. In the Berg test, each action was classified into five grades, ranging from 0–4. The maximum score was 56 points and the lowest score was 0 point; a lower score indicated a more severe balance impairment.

#### **Functional MRI**

Dynamic changes in blood perfusion in brain functional

areas were detected using blood oxygen level-dependent contrast technique, which assesses local neuronal functional recovery. 1.5T superconducting magnetic resonance instrument (Toshiba, Tokyo, Japan) was used for oxygen level-dependent functional MRI sequence scanning; in Single shot SEPI sequences, TR = 2 000 ms, TE = 20 ms, slice thickness = 5 mm, space = 0 mm, matrix = 128 × 128, NEX = 1; the scanning was performed from 7 cm above the canthomeatal line to the calvaria. Patients were forced to maintain immobility and performed advance training. The head and waist were fixed using a strap. Image preprocessing was performed used a head correction technique. Patients in the supine position, with the head fixed, were kept motionless and scanned for 30 seconds, and then the patients were forced to consecutively raise and strengthen their leg, and simultaneous scanning was conducted for an additional 30 seconds. 30-second systemic motionless scanning was performed; 30 seconds of raising and strengthening of the affected legs was repeated six times for successive scanning. Data were analyzed and processed into functional MRI images. In the functional MRI images, red color represented normal blood perfusion, indicating normal functional activation, while yellow and green colors represented different levels of decreased blood perfusion, indicating abnormal functional activation. Scanning was performed before and after the 4-week period of constraint-induced movement therapy.

### Statistical analysis

Measurement data were expressed as mean ± SD and were processed using SPSS version 13.0 (SPSS, Chicago, IL, USA). Measurement data were compared using the paired *t*-test. A value of *P* < 0.05 indicated a significant difference.

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**Author contributions:** Wenqing Wang had full access to study concept and design, provided technical information, wrote the manuscript, and validated the study. Aihui Wang was responsible for CT projection, data acquisition and integration. Limin Yu analyzed the cerebral cortical innervation area. Xuesong Han participated in functional MRI image processing and supervised the manuscript. Hongwei Zhang performed statistical processing. Guiyun Jiang and Zhiqiang Zhou, rehabilitation therapists, conducted routine rehabilitation training and constraint-induced movement therapy. Changshui Weng was involved in validation and data analysis.

**Conflicts of interest:** None declared.

**Ethical approval:** The experiment was approved by the Ethics Committee of Affiliated Hospital of Chengde Medical College in China.

**Author statements:** The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application disputations.

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