

Plastic Changes of Motor Network after Constraint-Induced Movement Therapy

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The effects of short-term constraint-induced movement (CIM) therapy on the activation of the motor network were investigated with functional magnetic resonance imaging (fMRI). Movement of the less-affected arms of five patients was restricted and intensive training of the affected upper limb was performed. Functional MRI was acquired before and after two-weeks of CIM therapy. All patients showed significant improvement of motor function in their paretic limbs after CIM therapy. For three patients, new activation in the contralateral motor/premotor cortices was observed after CIM therapy. Increased activation of the ipsilateral motor cortex and SMA was observed in the other patient. Our results demonstrated that plastic changes of the motor network occurred as a neural basis of the improvement subsequent to CIM therapy following brain injury.

Key Words: Constraint-induced movement therapy, functional MRI, motor network, plasticity

INTRODUCTION

Constraint-induced movement (CIM) therapy was originally introduced as a new treatment of the paretic upper extremities of stroke patients.¹

The principle of CIM therapy is to make use of the more-affected limb for 90% of the patient's waking hours by constraining or reducing the use of the less-affected limb for 2 to 3 weeks. CIM therapy has been designed to resolve the problem of "learned non-use" in brain-injured patients and to encourage large improvement in the use of the paretic upper extremities.¹⁻⁷ It is estimated that at least 50% of the total stroke population would benefit from CIM therapy. Clinical efficacy of CIM therapy has been demonstrated to have documented positive effects on motor outcome, and the therapeutic effects are considered able to be transferred from the clinic to the 'real world', such as the patient's home and society.^{2,8} One explanation for the success of CIM therapy is the possibility of cortical reorganization as a recovery mechanism. Liepert et al. demonstrated that treatment-induced cortical plasticity occurred in stroke patients after CIM therapy using transcranial magnetic stimulation.⁹ Recently, Levy et al. demonstrated changes in the activation of the motor cortex after CIM therapy using fMRI.⁷ However, the brain areas of plastic change were not yet clearly identified. The purpose of this study is to confirm the effect of short-term CIM therapy on the plasticity of the motor network, and to identify the areas of the brain responsible for the clinical improvements from CIM therapy using functional magnetic resonance imaging (fMRI).

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MATERIALS AND METHODS

Subjects

Five patients with brain injury who met the criteria for participation in our study were enrolled (4 stroke, 1 trauma). The mean age was 54.8 ± 9.0 years (range: 43 - 64 years) and the mean modified Edinburgh score of prestroke status was +100. Three patients with right hemiparesis had lesions in the left primary motor cortex; two of them had infarction in the middle cerebral artery (MCA), and one had encephalomalacia after traumatic brain injury. Out of two patients with left hemiparesis, one had infarction in the right MCA and the other in the right internal capsule. All subjects had the ability to extend their parietic wrist 20° and to open at least two of their fingers and their thumbs 10° at the metacarpophalangeal joints. They had no serious balance problem or cognitive deficit, no uncontrolled medical problem, and no severe spasticity or pain. Mean post-onset duration after brain injury was 21.4 ± 10.6 months (range: 9-38 months). All patients gave informed consent to participate in this study.

Movement restriction and intervention

Patients were instructed to wear specially designed constraint garments. The ventral surface of the affected forearm and hand were placed in a custom-made sling that was fastened by a Velcro[®] strap and attached to a wide waist belt. The garment was used to prohibit shoulder flexion and abduction, wrist flexion and finger grasp in order to prevent the patient from manipulating objects. The patient was instructed to wear the constraint garment during the daytime but was allowed to take the garment off under the following conditions, such as toileting, dressing, bathing, and any activity in which safety would be compromised. A ten-minute rest period was also given every hour.

The intervention consisted of intensive upper-limb training for 7 hours per day over 2 weeks. Tasks for the training of the parietic extremity included gross motor activities such as throwing a ball and simulating hockey, fine motor activities using pegs or putty, and general activities related

to daily living (ADL). Patients were encouraged to perform strengthening and range-of-motion exercises for the less affected arm during each rest period to avoid functional deterioration caused by disuse.

Evaluation of motor performance

Motor performance was assessed before and just after the CIM therapy and then reevaluated 2 months after cessation of therapy. The Fugl-Meyer assessment (FMA) scale, the 9-hole peg test (9-HPT), and the Jebsen hand function test (JHFT) were used to assess movement quality, coordination, and motor performance. Activities on the JHFT test and the 9-HPT were timed to a maximum of 5 minutes for each subtest.

FMRI tasks

The two motor tasks used for the fMRI study consisted of a gross motor task (repeatedly making a fist) and a fine motor task (sequentially opposing the thumb to the tips of the other four fingers) performed during fMRI scanning. Subjects were asked to practice the tasks before the imaging session and were instructed to perform at the maximum rate of their ability during functional scanning. An investigator communicated with the subjects through a speaker and earphones, and gave a verbal cue to indicate the time to change between rest and task sessions. The investigator also monitored the presence of mirror movement with the patients' opposite hands during scanning.

Data acquisition and analysis

Imaging was performed on a 1.5T Simens Vision unit. Foam padding was used to secure and limit the participant's head motion within the coil. Twenty slices were acquired using single shot EPI sequences (TR/TE=3840/40 ms, Flip angle 90° , FOV 220 mm, 64×64 matrix, slice thickness 6 mm). In all functional runs, the MR signal was allowed to achieve equilibrium over four scans that were excluded from analysis. Each functional run consisted of 54 images, 4 dummy scans and 50 experimental scans (5 active/control, repeated

5 times). T1-weighted anatomic images were acquired in the transaxial planes parallel to the anterior commissure-posterior commissure (AC-PC) line for use as the anatomic overlay.

fMRI data were analyzed using SPM-99 software (Wellcome Department of Cognitive Neurology, London, UK) running under the MATLAB environment (the Mathwork, Inc., Natick, Ma, USA). All functional images were realigned and coregistered to the anatomic images. The images were then smoothed with an 8 mm isotropic Gaussian kernel. Statistical parametric maps (SPMs) were obtained and voxels were considered significant at a threshold of $p < 0.001$, uncorrected.

RESULTS

Fugl-Meyer assessment

The mean (standard deviation) FMA scores were 55.4 (2.6), 61.6 (1.1), and 61.6 (1.6) at pre-treatment, immediately after 2 weeks of CIM therapy, and 2 months after cessation of therapy, respectively. Significant improvement was found at the post-treatment compared to the pretreatment stage ($p < 0.05$). Long-term effects were also observed at the 2-month follow-up stage after treatment ($p < 0.05$). Prominent changes of FMA scores after intervention were observed in patients

1, 2, and 3 (Fig. 1).

Nine-hole peg test & jebesen hand function test

Hand coordination, defined as the time taken to perform the 9-HPT, was significantly improved in four patients after CIM therapy. Three out of these four maintained their improvement up to 2 months after therapy. All patients showed improvement in the performance of many JHFT subtests. Three patients (patients 1, 4, and 5) showed improvement in all subtests, except one, at the time of post-treatment and continuously maintained their functional improvements at the follow-up point. Two patients (patients 2 and 3) had shown improvement at the post-treatment time but showed deterioration at the follow-up stage (Table 1).

Functional MRI activation analysis

The results of functional imaging data analyses revealed that CIM therapy for patients with brain injury had effect on the motor network in the brain. Three patients showed much more activation in the contralateral motor network after CIM therapy, which had not shown activation at the pretreatment stage (Fig. 2A, B, and C). One (patient 1) showed activation in the ipsilateral primary motor cortex area before CIM therapy, however, robust activation in the contralateral

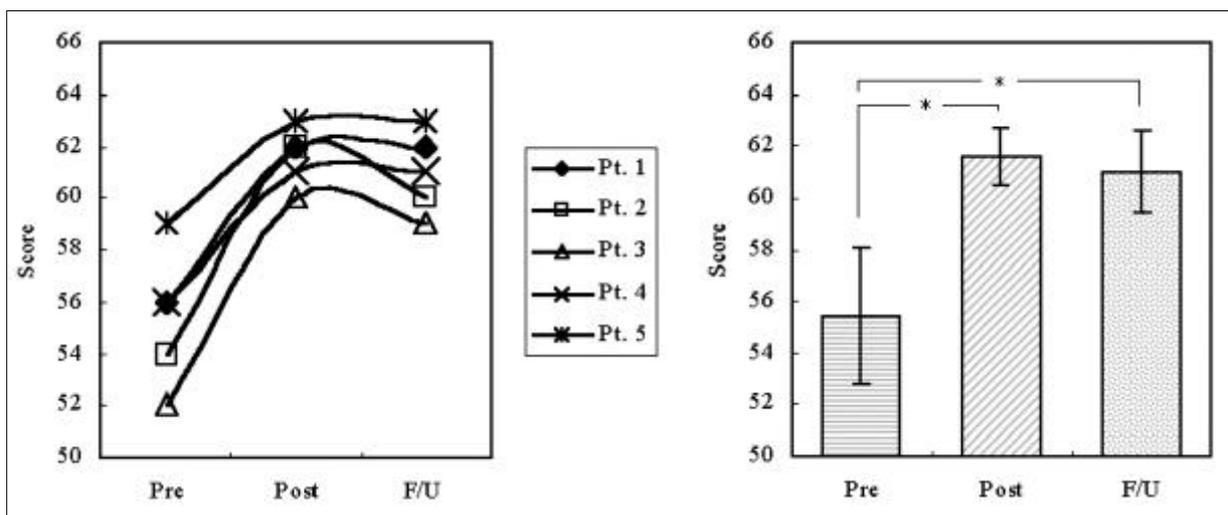


Fig. 1. Individual (A) and mean (B) FMA scores at pre-CIM (Pre), post-CIM (Post), and 2 months after CIM (F/U) intervention. * $p < 0.05$.

Table 1. Performance Time (sec) for the 9-Hole Peg Test and JHFT in Individuals

Test items	Patient 1			Patient 2			Patient 3			Patient 4			Patient 5		
	Pre	Post	F/U												
9-HPT	NT	195	220	NT	219	NT	NT	NT	NT	60	44	48	98	72	78
JHFT															
Writing	NT	195	157	104	102	137	NT	87	137	57	56	62	79	75	74
Cards	NT	49	36	NT	24	45	NT	66	163	27	17	13	15	12	12
SO	102	68	54	NT	61	NT	NT	NT	NT	30	24	22	27	22	23
SF	NT	NT	87	57	27	112	NT	NT	NT	33	35	29	43	27	31
Checker	43	26	23	NT	39	NT	NT	80	NT	15	8	12	23	9	9
LLO	33	26	28	NT	17	30	30	29	37	10	9	9	10	9	9
LHO	34	22	31	NT	16	45	NT	65	37	12	9	9	9	8	7

JHFT stands for Jebsen Hand Function Test; 9-HPT, 9-hole peg test; Pre, Pre-CIM intervention; Post, Post-CIM intervention; F/U, Two months after CIM intervention; NT, Not testable because of patient's disability; SO, Small objects; SF, Simulated feeding; LLO, Lift light objects; LHO, Lift heavy objects.

primary motor cortex was observed after treatment. For patient 2, activation in the ipsilateral primary motor cortex and parietal lobe was observed before CIM therapy, but after therapy, additional activation in the contralateral primary motor cortex and SMA was observed. Patient 3 had shown no significant voxel activation in any part of the motor network before CIM therapy, but showed significant activation in the contralateral premotor area after treatment. In this patient, the contralateral primary motor-sensory area was destroyed because of post-traumatic encephalomalacia. For patient 4, greater activation in the ipsilateral motor cortex and SMA was observed after CIM intervention, compared to the pre-treatment stage (Fig. 2D). For the remaining patient (patient 5) the activation of contralateral motor cortex was decreased and additional activation of SMA was observed after CIM therapy (Fig. 2E).

DISCUSSION

Our patients experienced significant improvement in motor function in their paretic upper extremities after CIM therapy. Results of fMRI taken at the session before the start of CIM therapy identified atypical activation in the motor network, which meant that injury-related cortical plasticity had occurred.³ The ipsilateral

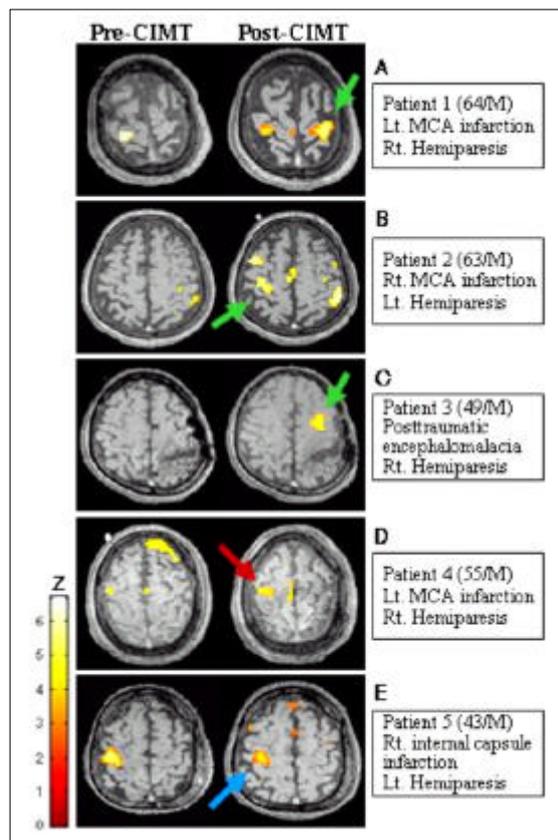


Fig. 2. Areas of activation in fMRI before and after CIM therapy. Activation in the contralateral motor network (motor/premotor/SMA) was shown after two-weeks of treatment (A, B, and C, green arrow). The ipsilateral premotor area and SMA after were more activated than before CIM Therapy (D, red arrow). Decreased activation in primary motor cortex appeared at the post-treatment fMRI (E, blue arrow).

motor cortex was activated in three out of five patients. Parietal cortex activation during motor performance was seen in one of these patients. The fMRI maps taken after CIM therapy showed that the plastic changes of the motor network happened in accordance with the behavioral improvement that resulted from therapeutic intervention.

Recent focal transcranial magnetic stimulation (TMS), neuroelectric source imaging, and magnetic source imaging studies carried out in monkeys and humans by various investigators suggested that cortical reorganization might appear in association with the effects of forced use of affected extremities.¹⁰⁻¹³ Pons et al. found that massive cortical reorganization took place after somatosensory deafferentation of the entire forelimbs in monkeys.¹⁴ Elbert et al. and Yang et al. proved the same findings in humans.^{15,16} The evidence that CIM therapy produces a use-dependent cortical reorganization in humans with CNS injury-related paresis of the upper limb was recently reported in a few studies. Liepert et al. used TMS before and after CIM therapy to map the areas of the brain that control arm movement in 6 patients with chronic hemiparesis. After CIM therapy, they reported changes in the size of the cortical motor area and shifts in the mean center of gravity of motor output maps in the damaged hemisphere.⁹ They suggested that CIM therapy lead to the recruitment of a large number of neurons adjacent to those originally involved in the control of the stroke-affected limb. Kopp et al. applied dipole modeling of steady-state movement-related cortical potentials before and after CIM therapy and again 3 months later. The source locations associated with affected hand movement were unusual at follow-up because activation of the ipsilateral hemisphere was found in the absence of mirror movements of the unaffected hand.¹⁷ This long-term change was considered to be an initial demonstration of large-scale neuroplasticity associated with increased use of the paretic limb after the application of CIM therapy.

Using fMRI, Levy et al. demonstrated neural plasticity induced by CIM therapy in two stroke patients. They reported activations in the perinfarction area and other areas after CIM therapy.⁷

In their study, it was evident that plastic changes of the motor network occurred by short-term therapeutic intervention, however, the exact areas of plastic changes within the motor network were not clearly demonstrated. In our study, three patients (patients 1-3) showed robust activation in the contralateral motor network, two in the primary motor and one in the premotor cortices after CIM therapy. For these three patients, improvement of motor performance measured by FMA was more prominent than the remaining two patients, who showed relatively small changes in the fMRI map after the CIM therapy. In patient 5, who had the best fine motor coordination at the pretreatment stage, activation of the contralateral primary motor cortex was decreased after the CIM therapy, however, the functional improvement lasted without deterioration until follow-up. These findings are partially congruent with the recent study of Johansen-Berg et al. which reported the correlation between the improvement of hand function and the increase in fMRI activity after rehabilitation therapy with restraint of the unaffected limb.¹⁸ It appeared that CIM therapy helped patients to increase the use of their paretic arms through the sustained and repeated practice of functional arm movement, and produced the main effects on the activity of the contralateral cortical areas, which were known to control the movement of the paretic arm.¹⁹ Moreover, recruitment of the ipsilateral areas also played a role for the motor improvement induced by CIM therapy in the selected patients, however, the factors influencing the pattern of reorganization may need to be further clarified.

We could conclude that the short-term CIM therapy produced changes in the functional organization of the motor network after brain injury, but the area and pattern of reorganization were patient dependent. This plasticity of the motor network might be considered as a neural basis for the improvement of the affected arm by CIM therapy. The results of this study confidently support the effectiveness of CIM therapy in a clinical setting by providing a neurophysiological basis for the therapy-induced effects on the neural network. Further studies with long-term follow up and precise evaluation on the pretreatment status, degree of functional change, and type and

location of the lesions may give more insights.

REFERENCES

- Miltner WH, Bauder H, Sommer M, Dettmers C, Taub E. Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke. *Stroke* 1999;30:586-92.
- Taub E, Crago JE, Uswatte G. Constraint-induced movement therapy: A new approach to treatment in physical rehabilitation. *Rehabil Psychol* 1998;43:152-70.
- Blanton S, Wolf SL. An application of upper-extremity constraint-induced movement therapy in a patient with subacute stroke. *Phys Ther* 1999;79:847-53.
- Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK, et al. A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke* 1997;28:2518-27.
- Kunkel A, Kopp B, Muller G, Villringer K, Villringer A, Taub E, et al. Constraint-induced movement therapy for motor recovery in chronic stroke patients. *Arch Phys Med Rehabil* 1999;80:624-8.
- Sabari JS, Kane L, Flanagan SR, Steinberg A. Constraint-induced motor relearning after stroke: a naturalistic case report. *Arch Phys Med Rehabil* 2001;82:524-8.
- Levy CE, Nichols DS, Schmalbrock PM, Keller P, Chakeres DW. Functional MRI evidence of cortical reorganization in upper-limb stroke hemiparesis treated with constraint-induced movement therapy. *Am J Phys Med Rehabil* 2001;80:4-12.
- Taub E, Uswatte G, Pidikiti R. Constraint-Induced Movement Therapy: A new family of techniques with broad application to physical rehabilitation-a clinical review. *J Rehabil Res Dev* 1999;36:238-51.
- Liepert J, Miltner WHR, Bauder H, Sommer M, Dettmers C, Taub E, et al. Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neurosci Lett* 1998;250:5-8.
- Jenkins WM, Merzenich MM, Ochs MT, Allard T, Guic-Robles E. Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation. *J Neurophysiol* 1990;63:82-104.
- Recanzone GH, Jenkins WM, Merzenich MM. Progressive improvement in discriminative abilities in adult owl monkeys performing a tactile frequency discrimination task. *J Neurophysiol* 1992;67:1015-30.
- Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. Increased use of the left hand in string players associated with increased cortical representation of the fingers. *Science* 1995;220:21-3.
- Sterr A, Mueller MM, Elbert T, Rockstroh B, Pantev C, Taub E. Changed perceptions in Braille readers. *Nature* 1998;391:134-5.
- Pons TP, Garraghty AK, Ommaya AK, Kaas JH, Taub E, Mishkin M. Massive cortical reorganization after sensory deafferentation in adult macaques. *Science* 1991;252:1857-60.
- Elbert T, Flor H, Birbaumer N, Knecht S, Hampson S, Larbig W, et al. Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury. *Neuroreport* 1994;5:2593-7.
- Yang TT, Gallen C, Schwartz B, Bloom FE, Ramachandran VS, Cobb S. Sensory maps in the human brain. *Nature* 1994;368:592-3.
- Kopp B, Kunkel A, Muhlneckel W, Villringer K, Taub E, Flor H. Plasticity in the motor system related to therapy-induced improvement of movement after stroke. *Neuroreport* 1999;10:807-10.
- Johansen-Berg H, Dawes H, Guy C, Smith SM, Wade DT, Matthews PM. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain* 2002;125:2731-42.
- Taub E, Uswatte G, Morris DM. Improved motor recovery after stroke and massive cortical reorganization following constrain-induced movement therapy. *Phys Med Rehabil Clin North Am* 2003;14:S77-S91.