Authors:

Keh-Chung Lin, ScD, OTR
Hsin-Ying Chung, MS
Ching-Yi Wu, ScD, OTR
Ho-Ling Liu, PhD
Yu-Wei Hsieh, MS
I-Hsuan Chen, MS
Chia-Ling Chen, MD, PhD
Li-Ling Chuang, PhD, PT
Jung-Sen Liu, MD, PhD
Yau-Yau Wai, MD

Affiliations:

From the School of Occupational Therapy (KCL, YWH, LLC), College of Medicine, National Taiwan University, Taipei, Taiwan; Division of Occupational Therapy (KCL), Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Taipei, Taiwan; Department of Physical Medicine and Rehabilitation (HYC), Chung-Ho Memorial Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; Department of Occupational Therapy and Graduate Institute of Clinical Behavioral Science (CYW), Chang Gung University, Taoyuan, Taiwan; MRI Center (HLL and YYW), Chang Gung Memorial Hospital and Department of Medical Imaging and Radiological Sciences, Chang Gung University, Taoyuan, Taiwan; Department of Rehabilitation (CLC), Chang Gung Memorial and Children's Hospital, Taoyuan, Taiwan; Department of Physical Medicine and Rehabilitation (IHC), Song Shan Armed Forces General Hospital, Taipei, Taiwan; Departments of Surgery and Medical Education (JSL), Cathay General Hospital and Fu-Jen Catholic University, Taipei, Taiwan.

Correspondence:

All correspondence and requests for reprints should be addressed to Ching-Yi Wu, ScD, OTR, Department of Occupational Therapy, Chang Gung University, 259 Wen-Hwa 1st. Rd., Kwei-Shan, Taoyuan, Taiwan.

0894-9115/10/8903-0177/0
American Journal of Physical Medicine & Rehabilitation

DOI: 10.1097/PHM.0b013e3181cf1c78

ORIGINAL RESEARCH ARTICLE

Constraint-Induced Therapy Versus Control Intervention in Patients with Stroke

A Functional Magnetic Resonance Imaging Study

ABSTRACT

Lin K-C, Chung H-Y, Wu C-Y, Liu H-L, Hsieh Y-W, Chen I-H, Chen C-L, Chuang L-L, Liu J-S, Wai Y-Y: Constraint-induced therapy versus control intervention in patients with stroke: a functional magnetic resonance imaging study. Am J Phys Med Rehabil 2010;89:177–185.

Objective: This study compared the effects of a distributed form of constraint-induced therapy with control intervention in motor recovery and brain reorganization after stroke.

Design: A two-group randomized controlled trial with pretreatment and posttreatment measures was conducted. Thirteen patients with stroke were randomly assigned to the distributed form of constraint-induced therapy ($n = 5$) or the control intervention group ($n = 8$). Outcome measures included the Fugl-Meyer Assessment, the Motor Activity Log, and functional magnetic resonance imaging examination. The number of activation voxels and laterality index were determined from the functional magnetic resonance imaging data for the study of brain reorganization.

Results: The distributed form of constraint-induced therapy group exhibited significantly greater improvements in the Fugl-Meyer Assessment and Motor Activity Log than the control intervention group. The functional magnetic resonance imaging data showed that distributed form of constraint-induced therapy significantly increased activation in the contralesional hemisphere during movement of the affected and unaffected hand. The control intervention group showed a decrease in primary sensorimotor cortex activation of the ipsilesional hemisphere during movement of the affected hand.

Conclusions: The preliminary findings indicate that brain adaptation may be modulated by specific rehabilitation practices, although generalization of the functional magnetic resonance imaging findings is limited by sample size. Further research is needed to identify the specific neural correlates of the behavioral gains achieved after rehabilitation therapies.

Key Words: Cerebrovascular Disease, Rehabilitation, Upper Limb, Functional Brain Imaging, Plasticity

Disclosures:

This research was partially supported by the National Science Council (NSC 95-2314-B-002-225-MY2, NSC 96-2628-B-002-033-MY2, NSC 96-2320-B-182-029, NSC 97-2314-B-182-004-MY3, NSC 97-2314-B-002-008-MY3, and NSC 98-2811-B-002-015), the National Health Research Institutes (NHRI-EX98-9742PI) and National Taiwan University College of Medicine Research Funds in Taiwan. Financial disclosure statements have been obtained, and no conflicts of interest have been reported by the authors or by any individuals in control of the content of this article.

After stroke, approximately 30%–60% of the survivors report persistent impairment of the upper limbs (UL) and are unable to use the affected arm in normal daily activities.[1] They predominantly use their unaffected UL to perform tasks. This behavior may result in a phenomenon of "learned nonuse," one mechanism that has been proposed to explain a portion of reduced UL use after stroke and which impedes the recovery of movement and function of the affected limb.[2] Constraint-induced therapy (CIT)[3] and its variants, including distributed CIT (dCIT),[4] have been advocated as means to facilitate motor recovery for patients with stroke. The specific techniques of CIT involve restraining the use of the unaffected limb and the performance of intense training of the affected limb through the use of shaping movements.[5]

Several randomized controlled trials have demonstrated the effects of CIT and dCIT on improving motor ability and functional use of the affected UL in patients with stroke.[4,6] However, most of the CIT studies have relied on clinical evaluations to examine the treatment effects, including the Fugl-Meyer Assessment (FMA),[4] Motor Activity Log (MAL),[1] and Wolf Motor Function test.[6] Although these instruments measure the level of motor impairment or functional ability and provide relevant clinical information, they do not offer information on neuroplastic changes in the brain.

Fundamental to advances in stroke rehabilitation is an understanding of how the brain is able to reorganize in response to rehabilitation interventions.[7] Functional magnetic resonance imaging (fMRI) is one neuroimaging technique that makes it possible to study the function of the human brain in vivo and guide clinical research of neurorehabilitation.[8,9] Richards et al.[10] systematically reviewed movement-dependent stroke recovery to summarize the neural plasticity evidence from transcranial magnetic stimulation and fMRI studies. They indicated that neural plastic changes in the motor cortex of the ipsilesional hemisphere accompany functional paretic UL motor gains after rehabilitation interventions in patients with chronic stroke.[10] Functional MRI studies of plastic changes after stroke intervention are needed to elucidate treatment-related neuroplasticity.[11]

To date, only a few small studies[12–15] have used fMRI analysis to study brain reorganization after CIT in patients with stroke, and none of them has included a control group for comparison. Levy et al.[13] first reported fMRI techniques to examine the effects of CIT in 2 patients with chronic stroke. Gains in motor function of the affected hand were accompanied by increased activation in the perilesional areas and bilateral association motor cortices. Schaechter et al.[14] evaluated fMRI changes in 4 patients with chronic stroke after CIT. The activation pattern showed a trend toward a reduced laterality index (LI) and a shift in activation toward the contralesional hemisphere. Kim et al.[12] discovered a new activation in the affected primary motor cortex (M1), premotor cortex (PMC), and supplementary motor area (SMA) for 3 patients after CIT, whereas increased activation in the unaffected SMA was observed for the other patient. In the study by Szaflarski et al.[15] of 4 patients who responded to CIT administered on a distributed schedule, cortical reorganization was positively related to the degree of increase in the use and capability of the affected arm, but the hemispheric fMRI changes were inconsistent.

The results of these fMRI studies varied in patterns of cortical reorganization after CIT. Only a few individual patients were tested in these studies partly because of the complicated and expensive measurement technique. Furthermore, the operation of nonspecific effects on cortical reorganization cannot be ruled out because these studies did not recruit individuals for control intervention (CI) to make a comparison. To overcome this limitation, this study recruited a dose-matched control group that received CI after stroke for comparison with a dCIT group. To examine the benefits of treatment interventions, we used the FMA to reflect the improvement of motor impairment and the MAL to evaluate functional use of the affected arm in life situations. Specifically, we addressed the following two questions:

1. Do patients receiving 3-wk dCIT exhibit better motor and daily functions compared with the CI group?
2. Does dCIT give rise to neuroplastic change in the motor areas that is both specific and different from the patterns of reorganization after CI?

METHODS

Participants

We recruited 13 patients with stroke from two medical centers. Study participants met the follow-

ing inclusion criteria: (1) at least 3 mos after a single stroke that caused unilateral hemiplegia or hemiparesis, (2) sufficient cognitive ability defined as a Mini-Mental State Examination score ≥24, (3) premorbid right-hand dominance evaluated by the Edinburgh Handedness Inventory, (4) the ability to extend actively at least 20° at the wrist and 10° at the metacarpophalangeal and interphalangeal joints on the last four fingers of the affected hand, (5) no seizures in the most recent 6 mos, (6) no metal implant or fixed partial denture, (7) no claustrophobia, and (8) able to perform the repetitive finger flexion-extension motor task. Side of stroke lesion was not a criterion for admission to the study. All participants signed the informed consent forms approved by the Institutional Review Board to receive clinical measures and fMRI. Figure 1 details patient recruitment and assignment.

Interventions

Participants were randomized to the dCIT or the CI group. Treatment in the dCIT group was administered intensively 2 hrs per day, 5 days per week, for three consecutive weeks. The dCIT treatment involved intensive training of the affected UL based on a task-oriented approach that emphasized repetitive practice of functional activities and behavioral shaping. Functional tasks included reaching forward or upward to move a cup, picking up coins, using a utensil to eat food, combing hair, writing, and other functional movements similar to those of daily activities. The shaping procedure involved individualized task selection, graduated task difficulty, verbal feedback, prompting, physically assisting with movements, and modeling. To discourage the use of the less affected hand outside therapy sessions, participants wore a restrictive mitten for a target of 6 hrs per day during the treatment period.

The CI group received traditional rehabilitation matched to the dCIT in duration and intensity. During each 2-hr therapy session, patients were engaged in neurodevelopmental treatments focusing on balance training, stretch of the affected limb, weight bearing with the affected limb, and fine-motor tasks in addition to practice of activities of daily living with the unaffected side.

For both groups, the study treatment occurred during the regularly scheduled occupational therapy session, and all other routine interdisciplinary stroke rehabilitation proceeded as usual. The interventions provided at the participating sites were supervised by two separate certified occupational therapists who were trained in the administration of the intervention protocols and were assessed by the senior authors. A written competency test was administered before the therapists treated and assessed the study participants.

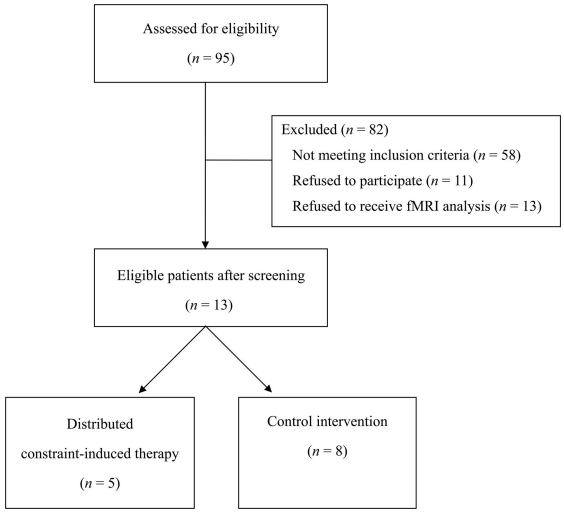

FIGURE 1 *Flowchart shows participant recruitment and group assignment. fMRI, functional magnetic resonance imaging.*

Clinical Measures

The UL subscale of the FMA[16] was used to evaluate motor impairment recovery. The 33 UL items measure movement and reflexes of the shoulder/elbow/forearm, wrist, and hand, and coordination and speed. They are scored on a 3-point ordinal scale (0, cannot perform; 1, performs partially; and 2, performs fully). The reliability and construct validity of the FMA are well established.[17]

The MAL[18] is a semistructured instrument based on self-report. It consists of 30 common and important activities of daily living that are scored from 0 (never use the more affected arm for this activity) to 5 (always use the more affected arm for this activity) on the amount of use subscale and from 0 (unable to use the more affected arm for this activity) to 5 (able to use the more affected arm for this activity) on the quality of movement subscale. The MAL has good interrater reliability and cross-sectional construct validity, and the results are relatively stable in patients with chronic stroke.[18,19]

Functional MRI Measures

This study used the fMRI acquisition parameters that have been previously described.[20] The fMRI sessions occurred before and after intervention. Imaging was performed on a 1.5-T Magnetom Vision MRI scanner (Siemens, Erlangen, Germany). Blood oxygenation level-dependent functional images were collected using a T2*-weighted gradient-echo, echo planar imaging sequence (repetition time, 3 secs; echo time, 60 msecs; field of view, 192 × 192 mm^2; 24 slices; slice thickness, 5 mm). Structural images were collected using T1-

weighted gradient-echo, echo planar imaging (repetition time, 528 msecs; echo time, 12 msecs; field of view, 256 × 256 mm^2). Slices were oriented horizontally, and they covered the cerebral hemispheres and variable portions of the superior part of the cerebellum as determined by variations in brain size.

Approximately a week before the examination, researchers introduced the basic information on the fMRI and motor task to the participants. All participants initially practiced the motor task outside the scanner to be familiar with the task. During scanning sessions, participants lay on the scanning bed. The head coil and a customized low-thermal-plastic splint mask were used to minimize head motion. To avoid mirror movements or associated movements during the motor task, a wooden apparatus and straps were used to stabilize the ULs at the shoulders in the neutral position, with the elbows extended and the forearms and wrists in the neutral position. The nonperforming hand was also constrained with the fingers extended.

The motor task entailed flexion and extension of four fingers at ⅔ Hz. A boxcar function was used during functional imaging, with six 21-sec rest epochs and six 21-sec movement epochs. The patients performed 14 repetitions of finger flexion and extension movement in each 21-sec movement epoch. Each hand of the participants performed the motor task unilaterally, with the order decided randomly. Two research investigators stood beside the scanning bed. One investigator visually inspected the execution of the task and noted possible unintended movements, including mirror movements, cough, or any other relevant situation. The other researcher generated each functional run by tapping the participant's less affected leg.

The fMRI data were analyzed by following techniques reported in previous studies.[20,21] Imaging processing and analysis were performed on the Sun Blade 1000 workstation. Statistical activation maps were generated voxel by voxel using the *t* test, contrasting the images acquired during the rest epochs with those acquired during the movement epochs. To minimize the transient effects of hemodynamic responses, images from the first 9 secs of each epoch were discarded from further data processing. The averaged activation maps of each group with a *t*-value threshold of 3.6 and a cluster threshold of 250 mm^3 ($P < 0.05$, corrected) were calculated by using the AlphaSim program and then overlaid on the corresponding T1 images. All images were normalized to the anatomic images.

Quantification of activation in sensory and motor cortical areas was conducted by a region-of-interest (ROI) analysis. For each participant, the structural images were used to outline three bilateral ROIs on the basis of anatomic landmarks: primary sensorimotor cortex (SMC), PMC, and SMA. The SMC encompassed the posterior half of the precentral gyrus and extended posteriorly to postcentral sulcus. The PMC was taken as the anterior half of the precentral gyrus and extended just rostral of the precentral sulcus. The SMA was taken as the medial cortex superior to the cingulate gyrus, anterior to the mid-precentral gyrus, and extending just rostral of the vertical anterior commissure line. The ROIs of each participant were drawn onto the background T2*-weighted image without any knowledge of the activation patterns and were then overlaid onto the statistical activation map with the T2* background.

The number of activated voxels was counted for each region and used to calculate a LI to indicate the hemispheric dominance.[22] The rationale for using the LI as an outcome measure is to facilitate the description of the hemispheric dominance from functional activation patterns. The LI[23] was defined as $([C - I]/[C + I])$, where C and I represent the number of activated voxels in the ROIs contralateral and ipsilateral to the moving hand, respectively. LI values ranged from +1, indicating that all sensory and motor cortical activation occurred in the hemisphere contralateral to the moving hand, to −1, indicating that all sensory and motor cortical activation occurred in the hemisphere ipsilateral to the moving hand.

Statistical Analysis

For performance improvement on the FMA and MAL, the effectiveness index (EI)[24] was calculated as follows:

$$\text{EI} = (\text{posttest score} - \text{pretest score})/(\text{maximum score} - \text{pretest score})$$

The effectiveness index was used to index the treatment effect taking the baseline level into account. The *t* test was used to test the differences between the two groups, and the effect size *r* was calculated to index the magnitude of the differences. A large effect is presented by an effect size *r* of at least 0.50, a moderate effect by 0.30, and a small effect by 0.10.

For the fMRI data, the Wilcoxon's signed-rank test was used to test the changes of the number of voxels and the LI from the pretest to the posttest for each group. The correlation between improvements on clinical measures and changes in brain activation was studied using the Pearson correlation coefficient. Level of statistical significance was set at 0.05.

RESULTS

Table 1 summarizes the demographic characteristics of the 13 participants (11 men), who were

Table 1 Demographic characteristics of the participants ($n = 13$)

Variable	dCIT Group ($n = 5$)	CI Group ($n = 8$)
Age, mean (SD), yrs	46.4 (26.0)	51.6 (12.4)
Gender, *n*		
Male	3	8
Female	2	0
Side of lesion, *n*		
Right	1	5
Left	4	3
Time after onset, mean (SD), mos	21.5 (12.3)	16.3 (18.3)

dCIT, distributed constraint-induced therapy; CI, control intervention; SD, standard deviation.

a mean age of 49.6 yrs. The average time after onset of a first-ever stroke was 18.3 mos. The dCIT ($n = 5$) and the CI ($n = 8$) groups did not differ significantly in age, gender, time after stroke onset, and side of brain lesion ($P > 0.05$).

Functional Outcomes

The clinical measures of the participants are presented in Table 2. After treatment, the dCIT group showed a significantly greater increase in the effectiveness index than the CI group on the FMA [$t(11) = 1.96$, $P = 0.04$, effect size $r = 0.53$] and the MAL [amount of use: $t(11) = 2.22$, $P = 0.02$, effect size $r = 0.56$; quality of movement: $t(11) = 2.28$, $P = 0.02$, effect size $r = 0.57$].

Functional MRI

The examples of the cortical activation patterns of two dCIT patients (P1 and P2) and two CI patients (P6, and P7) before and after intervention are shown on Figure 2. Table 3 reports the number of activation voxels in each ROI during motor task performance before and after treatment for each study group. Further analyses revealed that several activation changes occurred in the dCIT group after the intervention. During affected hand movement, the dCIT group showed significantly increased PMC activation of the ipsilateral (contralesional) hemisphere ($Z = 2.03$, $P = 0.042$, and $r = 0.64$) and ipsilateral (contralesional) total activation ($Z = 2.02$ and $P = 0.043$). A less impressive increase was noted in total activation of the contralateral (ipsilesional) hemisphere (pretest, 164.80; posttest, 182.80). During movement of the unaffected hand, contralateral (contralesional) SMC activation significantly increased ($Z = 2.02$, $P = 0.043$, $r = 0.63$). In contrast, the decrease in contralateral (ipsilesional) SMC activation for CI patients approached significance ($Z = 1.82$, $P = 0.069$, and $r = 0.45$) during movement of the affected hand (Table 3 and Fig. 2).

Table 4 summarizes the LI of brain activation in each group. Most LIs were positive for either the affected or the unaffected hand, indicating that the hand movement was controlled predominantly by the contralateral hemisphere. However, patients had less total LI when the affected hand was used than when the unaffected hand was used, which indicated that the performance of the affected hand may rely more on the ipsilateral (contralesional) hemisphere. In the dCIT group, the LI of SMA and the total LI significantly decreased during movement of the more affected hand ($Z = 2.02$, $P = 0.043$, $r = 0.63$), which was associated with an increase in ipsilateral (unaffected) hemisphere activation (Tables 3 and 4). In the CI group, none of the LIs significantly changed from pretreatment to posttreatment (Table 4).

Table 2 Clinical measures of the participants ($n = 13$) before and after treatment

	dCIT Group ($n = 5$)			CI Group ($n = 8$)				
	Score			Score				
Instruments	Pre Treatment	Post Treatment	EI	Pre Treatment	Post Treatment	EI	*P* (One-Tailed)	Effect Size *r*
FMA-UL, mean (SD)	55.6 (6.5)	61.2 (3.9)	0.6 (0.2)	49.4 (11.0)	52.9 (11.3)	0.3 (0.2)	0.04*	0.53
MAL-AOU, mean (SD)	1.9 (2.0)	3.4 (1.3)	0.5 (0.2)	1.5 (1.3)	2.1 (1.7)	0.2 (0.3)	0.02*	0.56
MAL-QOM, mean (SD)	1.9 (1.8)	3.6 (1.3)	0.6 (0.3)	1.8 (1.3)	2.3 (1.7)	0.2 (0.3)	0.02*	0.57

dCIT, distributed constraint-induced therapy; CI, control intervention; EI, effectiveness index; FMA-UL, upper limb subset of the Fugl-Meyer Assessment; MAL, Motor Activity Log; AOU, amount of use; QOM, quality of movement; SD, standard deviation.

*$P < 0.05$.

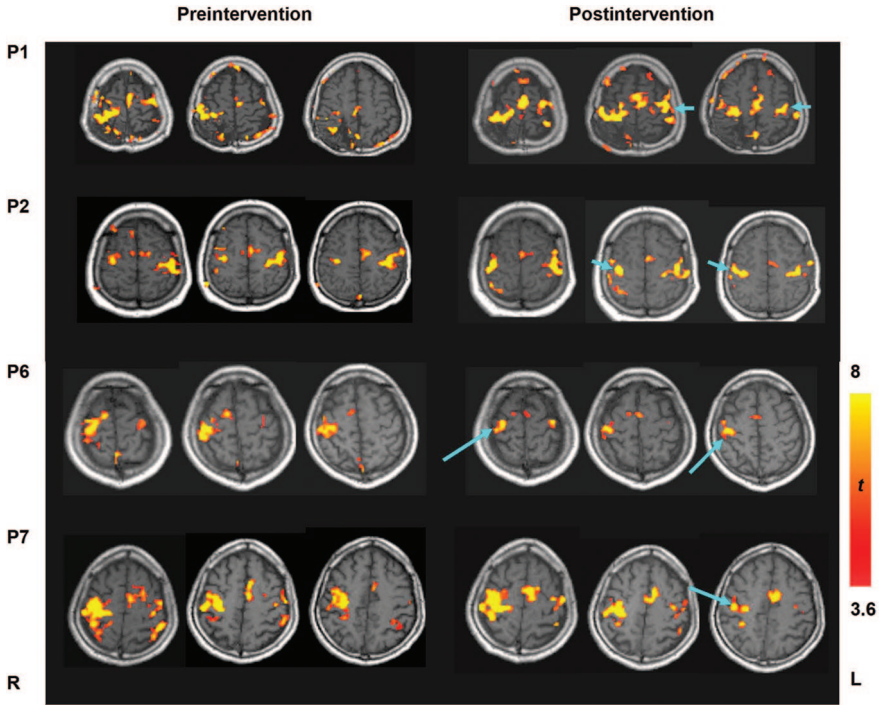

FIGURE 2 *Examples of brain activation patterns before and after intervention in two of the distributed constraint-induced therapy (dCIT) patients and two of the control intervention (CI) patients. Significantly activated areas are displayed in color and overlaid onto the corresponding echo-planar images. In the dCIT group, patient 1 (P1, right parietal-occipital hemorrhage) and patient 2 (P2, left frontal-parietal junction and posterior temporal intracranial hemorrhage) exhibited an increase in activation of bilateral hemispheres, particularly in the unaffected hemisphere (*short arrows*) after treatment. In the CI group, patient 6 (P6, right putaminal hemorrhage) and patient 7 (P7, right thalamic hemorrhage with intraventricular hemorrhage) exhibited a decrease in the sensorimotor cortex activation of the affected hemisphere (*long arrows*) during the more affected hand performance.*

An examination of the relationships between functional gains on the clinical measures and the changes in brain activation revealed no significant correlation ($P > 0.05$).

DISCUSSION

To our knowledge, this is the first fMRI study of CIT to use a control group for comparison. The findings indicated that, compared with the CI group, the dCIT group exhibited significantly greater improvements in motor and functional use of the affected arm, consistent with previous CIT and dCIT studies.[1,4,6] The fMRI study revealed patterns of plastic change specific to rehabilitation therapies. The dCIT groups exhibited increased activation in the bilateral hemispheres immediately after intervention, especially in the contralesional hemisphere during movement of the affected and the unaffected hand. The CI group exhibited a decrease in the SMC activation of the ipsilesional hemisphere during performance of the affected hand that approached significance.

The different patterns of plastic change after the two rehabilitative therapies support the concept of activity-dependent plasticity, one of the suggested mechanisms underlying recovery after stroke. Plastic reorganization may be favorably modified by behavioral experience and specific rehabilitation. The process of reorganization includes neuroanatomic, neurophysiologic, and functional changes adjacent and remote to the infarct regions as well as rerouting of intracortical pathways to novel territories.[25]

The evolution of fMRI activation in the motor networks was characterized by increased activation in the bilateral hemispheres in our dCIT participants. This activation change in the bilateral hemispheres is consistent with the findings of Gauthier et al.[26] They reported profuse increases in activation of sensory and motor area gray matter in the bilateral hemispheres. Our finding of change in the LI is in agreement with the work of Schaechter et al.[14] Both studies observed a reduced LI from pretreatment to posttreatment during movement of the affected hand and indicated that cortical activation may shift toward the contralesional hemisphere during the affected hand movement after CIT.

A possible neural mechanism exists that may explain the shift toward ipsilateral activation (con-

Table 3 Number of activation voxels in each region of interest before and after treatment in each group

	dCIT Group (n = 5)				CI Group (n = 8)			
	Affected Hand		Unaffected Hand		Affected Hand		Unaffected Hand	
ROI	Pre Treatment	Post Treatment	Pre Treatment	Post Treatment	Pre Treatment	Post Treatment	Pre Treatment	Post Treatment
Contralateral								
SMC	97.40 (49.9)	120.60 (57.7)	159.99 (41.8)	210.19 (41.0)*	109.31 (82.3)	65.87 (51.9)†	109.49 (101.6)	92.12 (42.7)
PMC	43.60 (68.5)	32.80 (6.1)	58.20 (37.2)	48.00 (31.5)	21.00 (17.9)	16.50 (11.4)	34.12 (18.3)	20.75 (21.2)
SMA	23.80 (14.7)	29.40 (21.9)	26.00 (27.6)	34.60 (31.3)	6.25 (2.8)	32.00 (42.6)	15.12 (8.2)	19.75 (19.6)
Total	164.80 (71.5)	182.80 (75.5)	244.19 (79.3)	292.79 (86.2)	136.62 (96.4)	114.37 (73.6)	158.74 (110.8)	132.62 (68.9)
Ipsilateral								
SMC	24.80 (31.9)	46.20 (41.8)	5.80 (10.9)	8.80 (10.5)	28.50 (24.4)	36.75 (45.6)	6.75 (9.9)	12.50 (15.3)
PMC	10.20 (13.6)	27.40 (14.9)*	11.20 (11.0)	13.40 (14.3)	13.87 (8.2)	23.50 (22.1)	8.50 (9.6)	8.25 (7.9)
SMA	14.80 (11.8)	29.80 (34.1)	18.60 (16.5)	10.20 (9.5)	14.75 (10.7)	16.12 (18.8)	9.00 (7.0)	8.50 (9.5)
Total	49.80 (45.0)	103.40 (65.6)*	35.60 (25.0)	32.40 (22.9)	57.12 (36.1)	76.37 (62.1)	24.25 (19.6)	29.25 (30.5)

Values are mean and SD (in parentheses). The "total" activations indicate the sum of the voxel counts of the three ROIs (i.e., SMC, PMC, and SMA).

dCIT, distributed constraint-induced therapy; CI, control intervention; SMC, sensorimotor cortex; PMC, premotor cortex; ROI, region of interest; SMA, supplementary motor area; contralateral, hemisphere contralateral to the performing hand; ipsilateral, hemisphere ipsilateral to the performing hand.

*$P < 0.05$.

†$P < 0.07$.

tralesional hemisphere). A study has reported increased activation of the ipsilateral motor cortices in healthy adults when they performed challenging and difficult motor tasks.[27] Participants in the dCIT group were required to use their affected arm to practice on tasks that were challenging and graded in the level of difficulty. Intensive practice on motor tasks potentiated functional use of the affected arm that may have led to increased activation of the contralesional motor cortices after CIT.

A further factor that may contribute to recovery of function after stroke pertains to interhemispheric interaction.[28] The contralateral hemisphere inhibits the ipsilateral corticospinal tract to prevent disturbance of the nonperforming hand. After brain injury, inhibition of the contralesional hemisphere by the ipsilesional hemisphere may be diminished. This disinhibition arising from a unilateral brain insult may facilitate the ipsilateral motor pathway and contribute to motor recovery in patients with stroke. Nelles[29] pointed out that after an ischemic lesion, the contralesional hemisphere may adapt vicariously to substitute for the desired movement strategy until the ipsilesional hemisphere achieves normalization to some degree. CIT may accelerate this adaptive process. The increased activation in the contralesional hemisphere and the decreased total LI in our study may have resulted from this adaptive substitution of the desired movement strategy.

The control group of this study displayed a decrease in activation of the ipsilesional hemisphere and a slight increase in activation of the contralesional hemisphere during movement of

Table 4 Laterality index of brain activation before and after treatment in each group

	dCIT Group (n = 5)				CI Group (n = 8)			
	Affected Hand		Unaffected Hand		Affected Hand		Unaffected Hand	
ROI	Pre Treatment	Post Treatment	Pre Treatment	Post Treatment	Pre Treatment	Post Treatment	Pre Treatment	Post Treatment
SMC	0.70 (0.3)	0.55 (0.3)	0.93 (0.1)	0.93 (0.1)	0.51 (0.6)	0.28 (0.6)	0.92 (0.1)	0.82 (0.2)
PMC	0.59 (0.6)	0.13 (0.3)	0.74 (0.2)	0.71 (0.3)	−0.03 (0.6)	0.04 (0.5)	0.55 (0.4)	0.50 (0.3)
SMA	0.37 (0.4)	0.08 (0.2)*	0.19 (0.6)	0.57 (0.4)	−0.11 (0.7)	0.21 (0.4)	0.31 (0.2)	0.39 (0.3)
Total	0.57 (0.2)	0.33 (0.2)*	0.77 (0.1)	0.82 (0.1)	0.26 (0.5)	0.29 (0.3)	0.71 (0.2)	0.70 (0.1)

Values are the mean and SD (in parentheses).

*$P < 0.05$.

dCIT, distributed constraint-induced therapy; CI, control intervention; SMC, sensorimotor cortex; PMC, premotor cortex; ROI, region of interest; SMA, supplementary motor area.

the affected hand. One study indicated that the decreased motor representation might be a result of the nonuse of the affected limb.[30] In addition, the increase in activation of the contralesional hemisphere might be due to compensatory strategies given in the CI.

The correlation between brain activation changes and motor recovery varies across different studies. This study did not find any significant relationship between improvements of motor function and daily activity and changes in cortical activation, which may be partly due to the small sample size. Dong et al.[23] reported that improvement of hand motor function was correlated with the change of activation in the contralesional PMC. Further research on neuroplastic change during and after motor rehabilitation is needed to examine more precisely the evolution of rehabilitation-mediated recovery and thus aid in the development of optimal neurorehabilitation strategies.

Although these findings are encouraging, certain limitations of this study warrant consideration, and further research is needed. First, the heterogeneity of the study participants (e.g., gender and type of stroke) and the limited sample size of each group should be taken into account. Further research may replicate this study based on a larger sample to establish the robustness of the neuroplastic changes that were observed.

Second, the choice of CI as a contrasting control group posed a potential limitation. This CI may not be representative of current rehabilitation for high-level patients (e.g., goal-directed therapy). Results of this research should therefore not be generalized beyond the scope of the study.

Third, further study may use the fMRI-compatible electromyography system to detect the muscle activation involved in mirror movements. Furthermore, to elucidate the mechanisms associated with spontaneous or treatment-facilitated recovery, further research may recruit an additional control group of patients with stroke who are not undergoing rehabilitation intervention during the study period. In addition, neurorehabilitation trials should compare different training regimens, such as bilateral practice or robot-assisted therapy, using functional neuroimaging methods to identify changes in cortical activity and the neural correlates of behavioral gains specific to different training modalities for patients with moderate motor impairments after stroke.

CONCLUSION

The preliminary findings suggest that the functional improvements produced by dCIT were accompanied by brain plastic reorganization, especially in the contralesional hemisphere, possibly through an ipsilateral motor pathway. Different activation patterns between the dCIT and CI groups indicate that brain adaptation may be modulated by specific rehabilitation approaches. The study also supports the inclusion of functional neuroimaging methods for the study of treatment-mediated recovery during and after stroke rehabilitation. Further research based on a larger sample size is needed to verify the study findings.

REFERENCES

1. van der Lee JH, Wagenaar RC, Lankhorst GJ, et al: Forced use of the upper extremity in chronic stroke patients: Results from a single-blind randomized clinical trial. *Stroke* 1999;30:2369–75
2. Grotta JC, Noser EA, Ro T, et al: Constraint-induced movement therapy. *Stroke* 2004;35:2699–701
3. Taub E, Miller NE, Novack TA, et al: Technique to improve chronic motor deficit after stroke. *Arch Phys Med Rehabil* 1993;74:347–54
4. Lin KC, Wu CY, Liu JS, et al: Constraint-induced therapy versus dose-matched control intervention to improve motor ability, basic/extended daily functions, and quality of life in stroke. *Neurorehabil Neural Repair* 2009;23:160–5
5. Sunderland A, Tuke A: Neuroplasticity, learning and recovery after stroke: A critical evaluation of constraint-induced therapy. *Neuropsychol Rehabil* 2005;15:81–96
6. Wolf SL, Winstein CJ, Miller JP, et al: Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: The EXCITE randomized clinical trial. *JAMA* 2006;296: 2095–104
7. Good DC: Stroke: Promising neurorehabilitation interventions and steps toward testing them. *Am J Phys Med Rehabil* 2003;82:S50–7
8. Boyd LA, Vidoni ED, Daly JJ: Answering the call: The influence of neuroimaging and electrophysiological evidence on rehabilitation. *Phys Ther* 2007;87:684–703
9. Yozbatiran N, Cramer SC: Imaging motor recovery after stroke. *NeuroRx* 2006;3:482–8
10. Richards LG, Stewart KC, Woodbury ML, et al: Movement-dependent stroke recovery: A systematic review and meta-analysis of TMS and fMRI evidence. *Neuropsychologia* 2008;46:3–11
11. Schaechter JD: Motor rehabilitation and brain plasticity after hemiparetic stroke. *Prog Neurobiol* 2004; 73:61–72
12. Kim YH, Park JW, Ko MH, et al: Plastic changes of motor network after constraint-induced movement therapy. *Yonsei Med J* 2004;45:241–6
13. Levy CE, Nichols DS, Schmalbrock PM, et al: Functional MRI evidence of cortical reorganization in upper-limb stroke hemiplegia treated with constraint-induced movement therapy. *Am J Phys Med Rehabil* 2001;80:4–12
14. Schaechter JD, Kraft E, Hilliard TS, et al: Motor recovery and cortical reorganization after con-

straint-induced movement therapy in stroke patients: A preliminary study. *Neurorehabil Neural Repair* 2002;16:326–38

15. Szaflarski JP, Page SJ, Kissela BM, et al: Cortical reorganization following modified constraint-induced movement therapy: A study of 4 patients with chronic stroke. *Arch Phys Med Rehabil* 2006;87: 1052–8
16. Fugl-Meyer AR, Jaasko L, Leyman I, et al: The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scand J Rehabil Med* 1975;7:13–31
17. Platz T, Pinkowski C, van Wijck F, et al: Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer test, Action Research Arm Test and Box and Block Test: A multicentre study. *Clin Rehabil* 2005;19:404–11
18. Uswatte G, Taub E, Morris D, et al: The Motor Activity Log-28: Assessing daily use of the hemiparetic arm after stroke. *Neurology* 2006;67:1189–94
19. van der Lee JH, Beckerman H, Knol DL, et al: Clinimetric properties of the motor activity log for the assessment of arm use in hemiparetic patients. *Stroke* 2004;35:1410–4
20. Dobkin BH, Firestine A, West M, et al: Ankle dorsiflexion as an fMRI paradigm to assay motor control for walking during rehabilitation. *Neuroimage* 2004; 23:370–81
21. Smith SM, Jenkinson M, Woolrich MW, et al: Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004; 23(Suppl 1):S208–19
22. Seghier ML: Laterality index in functional MRI: Methodological issues. *Magn Reson Imaging* 2008; 26:594–601
23. Dong Y, Dobkin BH, Cen SY, et al: Motor cortex activation during treatment may predict therapeutic gains in paretic hand function after stroke. *Stroke* 2006;37:1552–5
24. Kugler C, Altenhoner T, Lochner P, et al: Does age influence early recovery from ischemic stroke? A study from the Hessian Stroke Data Bank. *J Neurol* 2003;250:676–81
25. Nudo RJ: Postinfarct cortical plasticity and behavioral recovery. *Stroke* 2007;38:840–5
26. Gauthier LV, Taub E, Perkins C, et al: Remodeling the brain: Plastic structural brain changes produced by different motor therapies after stroke. *Stroke* 2008;39:1520–5
27. Kim SG, Ashe J, Hendrich K, et al: Functional magnetic resonance imaging of motor cortex: Hemispheric asymmetry and handedness. *Science* 1993; 261:615–7
28. Kobayashi M, Hutchinson S, Schlaug G, et al: Ipsilateral motor cortex activation on functional magnetic resonance imaging during unilateral hand movements is related to interhemispheric interactions. *Neuroimage* 2003;20:2259–70
29. Nelles G: Cortical reorganization—Effects of intensive therapy. *Restor Neurol Neurosci* 2004;22: 239–44
30. Liepert J, Miltner WH, Bauder H, et al: Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neurosci Lett* 1998;250: 5–8