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Presented, in part, at the 60th Annual Meeting of the American Academy of Physical Medicine and Rehabilitation, October 1998, Seattle, Washington.

## **Reprints:**

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#### **Disclosures:**

Supported, in part, from the Veterans Affairs Brain Rehabilitation Research Center.

0894-9115/01/8001-0004/0 American Journal of Physical Medicine & Rehabilitation Copyright © 2001 by Lippincott Williams & Wilkins Hemiparesis

# **Research Article**

# Functional MRI Evidence of Cortical Reorganization in Upper-Limb Stroke Hemiplegia Treated with Constraint-Induced Movement Therapy

# ABSTRACT

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.

**Objective:** The purpose of this pilot study was to test constraint-induced movement therapy for chronic upper-limb stroke hemiparesis and to investigate the neural correlates of recovery with functional magnetic resonance imaging (MRI) in two subjects. Both subjects had been discharged from traditional therapy because no further improvement was anticipated.

**Design:** Constraint-induced movement therapy consisted of 6 hr of daily upper-limb training for 2 wk; a restrictive mitt was worn on the nonparetic limb during waking hours. Functional MRI was performed on a 1.5-T MRI with echo-planar imaging; at the same time, the subjects attempted sequential finger-tapping.

**Results:** Compared with baseline, performance time improved an average of 24% immediately after training and also continued to improve up to 33% 3 mo after training. Lift, grip strength, and Motor Activity Log scores likewise improved. Initially, on functional MRI, subject 1 activated scattered regions in the ipsilateral posterior parietal and occipital cortices. Subject 2 showed almost no areas of significant activation. After training, subject 1 showed activity bordering the lesion, bilateral activation in the association motor cortices, and ipsilateral activation in the primary motor cortex. Subject 2 showed activation near the lesion site.

**Conclusion:** Constraint-induced movement therapy produced significant functional improvement and resulted in plasticity as demonstrated by functional MRI.

Key Words: Stroke, Constraint-Induced Movement Therapy, Functional Magnetic Resonance Imaging, Plasticity **S**troke is the third leading cause of death in the western world, trailing only behind heart disease and cancer. More than one-half million new strokes occur in the United States annually. Approximately 60% to 80% of patients with stroke survive. In the United States, about 1.7 million survivors with disabilities incur healthcare costs of more than \$7 billion per year.<sup>1</sup>

Hemiparesis is the most common deficit after stroke, affecting >80% of subjects acutely and >40%chronically.<sup>2</sup> Rehabilitation techniques have been more successful in restoring function in the lower limb than in the upper limb.<sup>3</sup> Unfortunately, upperlimb function is more important for independent living and self-esteem.4, 5 The time course of upper-limb recovery has been placed at 11 wks poststroke. If functional recovery has not occurred by the 11th week, Nakayama and colleagues<sup>6</sup> reported that "further recovery of upper extremity function should not be expected."

A challenge to the accepted dogma that little can be done to restore function in the paretic upper limb in the postacute or chronic state has been offered by Taub et al.,7-9 proponents of constraint-induced movement therapy (CI) to treat upper-limb hemiparesis after stroke. CI has its roots in animal experiments. When the monkeys' forelimbs were deafferented by severing the dorsal roots innervating that limb, the monkeys ceased to use the affected limbs. This nonuse was "unlearned" by restricting the intact limb with a sling.<sup>7</sup> Restriction for 1 to 2 wk resulted in restoration of use of the previously ignored limb. Taub et al.7-9 posited that a component of upper-limb hemiparesis in humans was learned nonuse, which was amenable to reversal by intensive physical therapy that incorporated restriction of the able limb with a sling or a mitt.

In a series of studies involving post-stroke upper-limb hemiparesis, a

total of 27 subjects, 1 to 18 vrs poststroke, were enrolled in a CI protocol.7-9 Five control subjects received sham therapy emphasizing a passive range of motion exercises. These subjects were exhorted to use the paretic limb in as many new activities as possible. Sixteen patients were divided equally into four groups: (1) sling and supervision; (2) sling and shaping; (3) half-glove and shaping; or (4) no restraint with shaping alone. A fifth group of six patients received an intensive course of physical therapy, 6 hr per day for 10 consecutive week-days without any restraining device. All subjects were evaluated using the Wolf Motor Function Test (WMFT), the Arm Motor Activity Test, and the Motor Activity Log (MAL). All of the experimental subjects showed significantly improved performance compared with baseline across measures, and most subjects maintained these gains 2 yrs after training. The control subjects showed only minor improvements in the outcome measures which were lost by the 2-yr follow-up.

Recently, a group including Dr. Taub has successfully applied CI to an additional 15 patients in Germany.<sup>10</sup> Six of these patients were also studied with transcortical magnetic stimulation; they were found to have greater areas of motor excitability and greater amplitudes of motor evoked potentials after therapy.<sup>11</sup>

In the current pilot study, two individuals with upper-limb hemiparesis as a result of stroke were enrolled in a 2-wk CI program to independently verify Taub and Wolf's clinical findings. Functional magnetic resonance imaging (fMRI) was used to detect the anatomic correlates to the improvements in function predicted by the previous CI studies.

## SUBJECTS AND METHODS

*Subjects.* The two subjects were enrolled in a pilot study of CI training with pre- and posttraining fMRI

scans. These subjects met the following criteria: (1) age between 21 and 80 yr, with an upper-limb hemiparesis secondary to the first stroke; (2) the ability to extend their paretic wrist 20° and at least two of their fingers and their thumbs 10° at the metacarpal-phalangeal joints, in accordance with previous CI protocols; and (3) 3-month duration from the onset of the stroke.

The first subject was a 48-yr-old, right-handed gentleman who sustained a right frontoparietal, subarachnoid hemorrhage, the result of a complication from a biopsy of a 2.5  $\times$  2 cm lesion that proved to be an oligodendroglioma. Besides this lesion, a previous magnetic resonance imaging (MRI) showed a lesion <2cm at the frontoparietal junction and an additional lesion <1 cm near the falx. Before the biopsy, this gentleman had experienced gradually advancing upper-limb weakness for 2 mo but no loss of coordination or range of movement.

As a result of the stroke, the patient sustained a severe left hemiparesis, affecting the upper limb more severely than the lower limb. He was admitted to an acute inpatient rehabilitation service where he received traditional physical and occupational therapy at least 2 hrs per day for 17 days. By the time of discharge, he was a functional ambulator. However, his severe upper-limb paresis was resistant to treatment, and he remained weak with Medical Research Council Scale scores of 2/5 in the hand intrinsics, wrist extensors, and flexors. After 4.5 mo, when he enrolled in the study, he had not gained functional use of the left upper limb, despite two 1-hr sessions per week of outpatient occupational therapy for 10 wk. which was discontinued before participation in the study because his upper-limb function had plateaued. The therapy administered was traditionally based amalgam including elements of motor learning and Bobath techniques. The plegic upper limb

was not being incorporated into activities of daily living at the time of admission to the study protocol.

The second subject was a 49-yrold left-handed woman with a history of hyperthyroidism and hypertension who sustained a right brain parietal, intraparenchymal hemorrhage measuring about  $2 \times 2$  cm in the region of the sensorimotor cortex 9 mo before enrolling in the pilot study. She was admitted to an acute inpatient rehabilitation hospital 3 days poststroke. She received traditional physical and occupational therapy at least 2 hr per day for 24 days. Here the subject's gait improved from an inability to walk on rehabilitation day 1 to walking 150 feet with a wide-based quad cane at the time of discharge. Speech also responded to therapy. This subject was then enrolled in a standard outpatient physical and occupational therapy program based on motor learning and neurodevelopmental treatment principles twice a week for 8 wk. She eventually mastered independent ambulation with an ankle-foot-orthosis on the left. Although she gained independence for all activities of daily living, she relied on the "normal" hand. The left hand remained weak and was not incorporated into her daily repertoire.

Both subjects were enrolled in an Institutional Review Board-approved protocol and gave informed consent to participate in our study.

*Training.* CI consisted of 6 hr of intensive upper-limb training 5 days per week for 2 wk, during which period each subject was challenged to perform a series of activities to train the hemiparetic limb. Tasks included bean bag toss at target, reaching, grasping, and carrying selected objects, stacking blocks, moving blocks from one container to another, turning the pages of a magazine, card activities, writing activities, food preparation, ironing, vacuuming, folding paper and laundry, and feeding. Participants were instructed to wear a restrictive mitt on the nonparetic hand during 90% of their waking hours. A behavioral contract was developed with each subject, which defined activities for which the mitt could be removed (e.g., carrying hot beverages, bathroom activities, and dressing) The mitt was also removed four times a day for 5-min intervals. During this time, the participants were instructed to perform a range of motion exercises on the fingers and wrist to avoid limitations caused by disuse. If cramping and numbness of the fingers occurred as the subjects wore the mitt at other times of the day, the mitt was to be removed and the same exercises were to be performed. Participants were instructed to keep a log of the times and the duration of mitt removal. A staff of six volunteers was recruited and trained to administer the CI. This staff consisted of graduate students in physical therapy and practicing physical therapists.

*Functional Imaging.* At baseline and after the 2-wk training period, the subjects were evaluated with fMRI as they attempted to sequentially tap the thumb to the index, middle, ring, and fifth fingers.

Behavioral Testing. The WMFT<sup>8</sup> and the MAL were administered at baseline and at the completion of the training. The MAL was also administered daily before the training session. The WMFT consists of 17 tasks, which include the performance of basic limb movements, grip strength, tolerance to lift a weight from the table to shoulder height in sitting, and simple tasks such as turning a key in a lock, lifting a pencil, paperclip, and pop can, and folding a towel. The MAL<sup>8</sup> is an activity log that focuses on actual upper-limb use in daily living situation and consists of 30 common and important activities of daily living such as feeding, dressing, and grooming. Each activity is scored on a 6-point scale (0-5),

where a score of 0 indicates that the subject did not use the paretic limb for the task at all and a score of 5 indicates that the subject uses the paretic arm as he or she did before the stroke. Both quality of movement (QOM) and functional ability (amount of use or AOU) are measured by the MAL, with subscores measured for each.

One of the authors (DSN) of this article was trained to administer these tests in a CI Laboratory at the University of Alabama at Birmingham supervised by Dr. Taub and his staff.

Functional Magnetic Resonance Imaging. Images were acquired in the clinical 1.5 T MRI unit (Signa, General Electric, Milwaukee, WI) equipped with a high-speed gradient system, using a gradient echo planar imaging method. The fMRI data were acquired with TR/ TE/flip angle of 3000 ms/40 ms/90°, 20 cm field of view,  $64 \times 64$  matrix size, and 5-mm slice thickness. Eight axial sections (slices) were acquired in an interleaved fashion during each TR time interval (i.e., 8 slices/3 sec). This was repeated eight times resulting in an acquisition of 64 images every 24 sec. This protocol is similar to techniques previously described in the literature.

The subjects were placed in the MRI system; they were verbally instructed via the MRI system intercom. The subjects were instructed to attempt to perform sequential fingertapping of the thumb to the index, middle, ring, fifth fingers at a comfortable rate at the same time as the first 64 images (eight slices, eight repetitions) were acquired. Next, the subjects were instructed to rest during the acquisition of the following eight images. This was repeated for an acquisition of a total of 512 images. After all data were collected for the affected hand, the routine was repeated for the nonparetic hand. For the second subject, during the baseline scans, a computer failure occurred and only 384 images were col-

## TABLE 1

Task	Subject 1		Posttest	Subject 2		Posttest
	Pretest	Posttest	$\times 3 \text{ mo}$	Pretest	Posttest	$\times 3 \text{ mo}$
Lift forearm to table	1.20 s	0.86 s	.78 s	2.36 s	1.26 s	.90
Lift forearm to box	1.81 s	1.24 s	1.12	3.65 s	2.98 s	1.67
Extend elbow (side)	1.14 s	0.83 s	0.72	2.58 s	1.30 s	.97
Extend elbow (push 1 lb)	0.80 s	0.54 s	0.59	1.80 s	1.18 s	.63
Hand to table (front)	1.49 s	0.98 s	1.12	2.10 s	1.54 s	1.19
Hand to box (front)	1.50 s	1.00 s	1.07	2.08 s	1.88 s	1.45
Weight to box (lb)	7	12	10	5	5	8
Reach and retrieve 1 lb wt	0.86 s	0.80 s	0.53	1.06 s	0.98 s	1.02
Lift pop can	8.66 s	8.70 s	46.47" <sup>a</sup>	$120.00 \text{ s}^{b}$	12.88 s	10.53
Lift pencil	94.31 s	$101.28 \ s^{c}$	46.47"	13.30 s	$32.48^{\circ}$	$47.95^{\circ}$
Lift paper clip	$120.00 \text{ s}^{b}$	120.00 s <sup>b</sup>	$120^{b}$	9.83 s	$17.19^{c}$	$12.80^{\circ}$
Stack checkers	$120.00 \text{ s}^{b}$	120.00 s <sup>b</sup>	41.1"	$120.00 \text{ s}^{b}$	$120.00 \text{ s}^{b}$	$120^{b}$
Flip cards	43.40 s	41.34 s	28.66"	31.70 s	20.98 s	19.21
Grip strength (kg)	6	9	14	5.7	8	7.7
Turn key in lock	57.01 s	20.27 s	26.1	91.60 s	20.59 s	52.54
Fold towel	21.60 s	8.88 s	10.37	23.51 s	13.84 s	10.66
Lift basket with 3 lb wt	25.60 s	21.55 s	14.18	14.33 s	10.86 s	8.73

<sup>a</sup>Outlier, excluded from calculations.

<sup>b</sup>Subject was unable to complete in the time allotted; task was terminated at 120 sec.

<sup>c</sup>Demonstrates a decrement in performance from pretest to posttest.

s, sec.

lected although the affected hand attempted the task.

Data Analysis. The images were transferred to a SUN SPARC 10 workstation for postprocessing. The workstation was equipped with Interactive Data Language (RSI, Boulder, CO) and the analysis software was developed in this language. Data were analyzed slice by slice. The first image of each set of eight images had to be discarded because it showed irregular contrast acquired before the MRI signal had reached an equilibrium state. Thus, the final data set consisted of four cycles of seven task and seven rest images for a total of 56 images. A 56-point task function was defined as "1" during the task and "0" during rest (i.e., 11111110000000 repeated four times). Next, the correlation coefficient between this task function and each image pixel was computed. (There were 56 images; thus, for each pixel, there is a data array of 56 points.) In this fashion, an image was created in which the color (red, orange, or yellow) represented the correlation coefficient. The color red signified  $r \ge 0.78$ ; the color orange  $r \ge$ 0.75, r < 0.78; yellow  $r \ge 0.70$ , r <0.75. A greater correlation between the task function and the MRI signal (i.e., increased signal during finger tap, decreased signal during rest) resulted in a larger value for r. The voxels with a greater r value were regions for which the blood oxygen level-dependent (BOLD) signal enhancement caused by the change in blood oxygenation occurred in accordance with the task.

Functional MRI has been validated as a method to study cerebral activation during upper-limb motor tasks in normal persons. Simple, selfpaced flexion and extension of the fingers generate signal primarily in the contralateral motorstrip, whereas more complex tasks activate the contralateral and (to a lesser extent) the ipsilateral primary motor cortex, the contralateral supplementary motor area (SMA), bilaterally in the premotor cortex, and the contralateral somatosensory cortex.<sup>12, 13</sup> These findings are in accordance with positron emission tomography (PET) data.<sup>14</sup> Increasing the rate of flexion-extension from 1 to 5 Hz in the right hand of right-handed individuals was found to be related linearly to the percentage of signal change generated in the contralateral primary motor cortex.<sup>15</sup> Test-retest reliability has been established in fMRI specifically in a thumb/finger opposition task.<sup>16</sup>

## RESULTS

*Behavioral Recovery.* Both subjects showed marked improvement on both the WMFT (Table 1) and MAL. Subject 1 improved his performance on 13 of 17 tasks on the WMFT. He was unable to complete two tasks in the 2 min allotted both before and after training, and his performance remained the same on one item and declined on another. The average percentage of improvement (decrease in time to perform the task or increase

# Subject 1A











Subject 2A







 $r \ge 0.70, < 0.75$ 

Figure 1: Finger-tapping pre- and postconstraint-induced movement therapy (CI). Echoplanar functional magnetic resonance imaging axial images of subjects 1 and 2 attempting to finger-tap before and after CI. The superior parietal

 $r \geq 0.75, <\!\!0.78$ 

r ≥ 0.78

in strength) for the tasks completed was 25.5%. Strength improved from a maximum of 7 lbs lifted initially to 12 lbs after 2 wk of training. Grip strength likewise improved from 6 to 9 kg (Table 1).

His scores on the MAL also improved over the 2-wk period. At baseline, his MAL QOM subscore was 1.1, whereas the AOU subscore was 1.2. At 1 wk, these scores reached 1.7 and 1.9, respectively. In the second week of training, the subject experienced the death of a close friend. He admitted to having a problem with compliance with wearing the mitt when unsupervised during this week, and he also was more despondent. His scores dropped to 1.4 and 1.6, respectively, at the end of 2 wk, but this still reflected an overall improvement consistent with the previously reported improvement.

At 3 mo, subject 1 had improved on a total of 15 of 17 tasks in the WMFT. His average improvement was 44% compared with baseline (excluding one outlier). Lift remained above baseline at 10 lbs; grip improved to 12 kg. MAL QOM and AOU improved to 1.7 each.

Subject 2 improved her performance on 13 of 17 items in the WMFT. A decrement in performance (an increase in the time to perform the task) was noted in two tasks. Average improvement on all completed tasks equaled 22.8%. Weight lifted remained at 5 lbs, but grip strength improved from 5.7 to 8 kg (Table 1). On the MAL, her AOU and QOM subscores improved from 0.2 to 1.7 from the pretest to posttest, again consistent with published data. $^{7-11}$ 

At 3 mo, subject 2 had improved on a total of 14 of 17 tasks in the WMFT. Her average improvement was 23% compared with baseline. Lift improved to 8 lb; grip remained above baseline at 7.7 kg. MAL QOM and AOU improved to 2.5 each.

*Functional Brain Maps.* Figure 1 shows the echoplanar fMRI images with an overlay of the BOLD regions of activation for subjects 1 and 2 during the finger-tapping task. The large areas of signal void present in subject 1 are attributed to artifacts caused by residual blood and hemosiderin deposits in the area of the stroke. When the images are viewed with less contrast, more brain tissue is apparent. These regions show infarcted brain tissue and tumor in conventional MRIs for subject 1.

Both subjects had great difficulty performing finger-tapping of the affected limb at the time of the first fMRIs. This condition improved significantly in terms of rate and range of motion by the second fMRIs.

Before CI training, subject 1 displays scattered activation mainly in the hemisphere ipsilateral to the paretic hand and contralateral to the lesion. It is difficult to assign these areas of activation to functional anatomic landmarks. Movement artifact is evident at the posterior skull. Subject 2 shows few areas of significant activation.

After training, subject 1 shows an abundance of activity in the regions bordering the lesion. These regions are not in the classic distribution of the motor strip. There is also extensive activation in the sensorimotor cortex, supplementary motor area, and the premotor area, more so in the unlesioned cortex. Movement artifact is evident to a lesser extent at the skull. Subject 2 after training shows large areas of activation near the lesion site and in the supplementary motor area near the lesion. Some of the activity seen at the posterior lateral rim of the brain in the inferior slices may represent movement artifact.

## DISCUSSION

Behavioral Recovery. These results indicate that our subjects experienced significant improvement of motor function in the paretic limb in response to CI, despite the fact that before enrollment both subjects had been discontinued from traditional therapy programs because they had reached plateaus and were judged to have no more potential to improve. Both subjects were at least 3 mo poststroke, after the period that Nakayama et al.<sup>6</sup> identified as the outer borders for return of hand function after stroke. Subject 1, at 4.5 mo post-stroke, was enrolled in the study earlier than subjects previously reported (6 mo). This suggests that the window of opportunity for improvement with CI may lie earlier in the postacute phase. The improvement noted is of similar magnitude as that of previous reports, supporting the

region corresponding to the motor strip is represented in these slices. Low signal intensity is related to the infarction. Upper left, subject 1 attempting to finger-tap before CI. No activity is seen surrounding the infarction, and very little activity is detected in the right (lesioned) hemisphere. Movement artifact is seen at the posterior occiput. Upper right, subject 1 attempting to finger-tap after 2 wk of CI. Activity is evident in the peri-infarction area (red arrow), and the contralateral sensorimotor cortex in a slightly anterior, superior, and lateral position (green arrow), and in the supplementary motor areas bilaterally (blue arrow). Lower left, subject 2 attempting to finger-tap before CI. Only a few scattered areas of activation are evident. No activity is seen surrounding the infarction. Lower right, subject 2 attempting to finger-tap after 2 weeks of CI. Activity is evident in the peri-infarction area (black arrow), and in posterior regions not normally associated with motor activity (red arrow). Some of this latter activity may represent movement artifact (yellow arrow). The correlation coefficient (r) for each pixel is indicated according to color, as shown in the key at the bottom of the illustration.

effectiveness of CI in the recovery of upper-limb function after stroke. This study was conducted at a site completely independent of Taub and Wolf,7 thereby verifying the benefits of CI.

Changes in Brain Activation as Detected by FMRI. PET and fMRI are attractive methods to investigate brain function because they allow functional imaging of the entire brain with superior temporal and anatomic detail. A review of the existing literature is useful to establish context for the neuroimaging results produced by this study. Four notable studies have used either PET or fMRI to examine individuals who experienced robust recovery of upper-limb function after hemiplegia caused by stroke. This study builds on the reviewed studies by documenting changes in patterns of cerebral activation in response to a specific therapy regimen.

Chollet et al.<sup>17</sup> used PET scanning to study six individuals who had recovered hand function after hemiparesis or hemiplegia secondary to a first, single, middle cerebral artery, ischemic stroke. Five of the six persons had left hemispheric lesions, whereas one subject had a right hemispheric lesion. The side of the lesioned hemisphere was standardized to the left. Regional cerebral blood flow (rCBF) associated with the "normal" hand activity was compared with the recovered hand during a 4-min repetitive sequential thumbto-fingers opposition task. When the "normal" fingers were moved, rCBF increased significantly in the contralateral primary sensorimotor cortex, and in the ipsilateral cerebellar hemisphere. When the recovered fingers were moved, significant rCBF increases were noted in both the contralateral and ipsilateral primary sensorimotor cortex, in both cerebellar hemispheres, the insula, inferior parietal, and premotor cortex. These findings were interpreted as evidence that neuroplasticity had occurred and that ipsilateral motor pathways may play a role in the recovery of motor function after ischemic stroke.

A follow-up study from this same group included two of these patients in a sample of ten patients who had recovered upper-limb function after striatocapsular infarctions.<sup>18</sup> Half of the subjects had a complete recovery, whereas the other half complained of mild clumsiness in performance of the thumb to finger opposition task. The rCBF generated was compared between the "normal" hand, the affected hand, and the rCBFs of normal control subjects completing the same tasks. Activation during the task in the recovered hand was equivalent to that found in normal control subjects in contralateral motor areas and the ipsilateral cerebellum. However, activation was greater in both insulae, the inferior parietal, prefrontal, and anterior cingulate cortices, the ipsilateral premotor cortex and basal ganglia, and the contralateral cerebellum. Cerebral activity accompanying finger tapping of the "normal" hand was also found to differ from that of the control subjects. Patients activated the insula, striatum, and lateral prefrontal, premotor, inferior parietal, cortices in the hemisphere ipsilateral to the recovered hand more than control subjects. The authors postulated that the striatocapsular lesions caused a functional disinhibition of the contralateral premotor cortex and caudate nucleus, implying a functional inhibition of these areas in normal conditions. The bilateral activation of motor pathways, the recruitment of the inferior parietal cortex, and the anterior aspects of the insula after striatocapsular infarction along with motor recovery suggested that the higher-order areas of sensorimotor cortex have a greater potential for plasticity than do the primary areas.

A third investigation from this group studied eight subjects, five of whom had been reported in a previous work.<sup>19</sup> All had complete recovery from striatocapsular infarctions. The patterns of cerebral activation in each individual patient were compared with the pattern found in a representative sample of ten normal subjects. The tasks that they performed were described. A new statistical method allowed the study of each subject individually, whereas the previous articles had studied the patients as a group. Averaging of the data had been necessary to detect the small differences in local brain activation. The new method consisted of generating maps of Z scores and comparing the change of the individuals' rCBF within each image voxel to the mean rCBF change of ten healthy control subjects. Greater activation was seen in variable combinations in the supplementary motor areas, the insula, the frontal operculum, and the parietal cortex. Structures belonging to motor pathways ipsilateral to the recovered limb were activated to a greater extent in the experimental subjects. Four subjects who exhibited mirror movements of the unaffected hand when executing the task in the affected hand showed additional activation of the ipsilateral sensorimotor cortex.

Cramer et al.<sup>20</sup> studied ten individuals with a history of nonhemorrhagic, hemiparetic stroke affecting the upper limb. Each patient had good motor recovery (resolution of synkinesis, improvement in wrist extensor and interossei strength by at least one level on the Medical Research Council Scale, and a final strength in those muscles rated at least 4+/5). The fMRI was performed at rest and during a finger-tapping exercise using echoplanar imaging in a 1.5-T instrument. Brain activation in those patients with strokes was compared with that of nine normal control subjects. In normal subjects, the following regions were activated: the contralateral sensorimotor, the ipsilateral cerebellum, the ipsilateral SMA, and the contralateral SMA.

These same areas were activated when those individuals with strokes performed finger taps with the affected hand. Furthermore, they activated the ipsilateral sensorimotor cortex to a greater degree than that seen in the controls in six of nine patients. Lesser increases were also noted at either SMA, the ipsilateral premotor cortex, and the contralateral cerebellum. Three of five patients who had cortical strokes showed increased activation at the rim of the infarction. The areas of activation noted in this study were similar to those seen in the PET studies of Chollet et al.<sup>17</sup> Weiller et al.<sup>18, 19</sup> Thus far, both the PET and fMRI studies suggest three processes associated with motor recovery: (1) increased activation of the sensorimotor areas; (2) increased activation of the association cortices; and (3) increased activity at the rim of the infarction in cortical strokes.

Figure 1 represents the echoplanar activation maps from the two subjects. Clearer anatomic resolution could have been obtained if the areas of activation obtained during echoplanar imaging had been superimposed on conventional anatomic images. The movement artifact could have been reduced by better stabilization of the head and a more sophisticated data analysis. Despite these weaknesses, fMRI scans reveal markedly increased cerebral activity, including the regions surrounding the infarcted tissue, as seen in those patients who experienced a more spontaneous recovery from stroke hemiparesis. This suggests that CI can reverse stroke hemiparesis in selected individuals, but that it can also accomplish this by using neurologic mechanisms similar to those encountered in individuals who have enjoyed a more rapid and usual recovery.

The findings of subject 1 are particularly interesting. The activation at the rim of the infarction, as well as increased bilateral sensorimotor cortex, matches the descriptions of those with upper-limb hemiparesis as a result of stroke who experienced good recoveries (all received standard "motor rehabilitation therapy"), as described by Cramer's group.<sup>20</sup> Cramer and colleagues<sup>21</sup> also described the location of activation of the cortex ipsilateral to the hand performing the task. They described a site that is superior, lateral, and anterior to that of the site activated in the contralateral cortex. An area similar to this can be seen in subject 1's scan (Fig. 1). Bilateral activation has also been described in those with brain tumors of the sensorimotor cortex.<sup>22</sup> In normal subjects, simple finger-tapping is associated with activation of the contralateral primary cortex, whereas the more demanding tasks are associated with additional activation of the contralateral and (to a lesser extent) the ipsilateral primary motor cortex, the contralateral SMA, bilaterally in the premotor cortex, and in the contralateral somatosensory cortex.<sup>12, 13</sup> The pattern of activation in subject 1, performing the relatively simple fingertapping task, resembles the activation patterns of normal subjects performing complex tasks, suggesting that higher levels of activation are needed to drive his damaged motor system. In contrast to the findings in subject 1, cerebral activation in response to finger-tapping is almost exclusively confined to the damaged hemisphere in subject 2. Although it is tempting to conclude that these differences in activation patterns suggest that each subject is relying on a different strategy to produce motor output, it is also possible that our methods were not sensitive enough to detect ipsilateral activation in subject 2.

The typical person who acquires upper-limb hemiparesis after a stroke is older than our subjects were at presentation, and would have had a nonhemorrhagic event. However, although acute mechanisms of recovery may differ between hemorrhagic and nonhemorrhagic stroke, there is nothing to indicate that the postacute course of a relatively fixed deficit differs significantly. On initial inspection, subject 1, with a stroke as a secondary complication of a brain tumor, does not present with a "pure" stroke. The fact that subject 1 also had a brain tumor makes his progress under CI even more remarkable. This pilot work must be verified by larger trials of patients with strokes of various etiologies before these results can be generalized to patients with all types of stroke.

The success of CI suggests that learned nonuse may underlie seemingly intractable deficits, and that intensive training and practice may release previously undetected function. It would be interesting to explore whether learned nonuse could also play a role in other realms of dysfunction, such as cognitive deficits after stroke or traumatic brain injury. Novel approaches to cognitive or behavioral remediation may be constructed.

This study also suggests potential applications of fMRI in rehabilitation medicine. Functional MRI is believed to be virtually without risk (excluding metal fragments, instrumentation, some implantable devices, and claustrophobia), is anatomically precise, and is repeatable. BOLD fMRI can be implemented on most commercial 1.5-T MRIs.23 Adding echoplanar imaging reduces the acquisition time of an MRI brain slice with good anatomic resolution to <50 msec. Although this adds about 15% to the cost of a scanner, echoplanar imaging is being introduced rapidly in clinical centers because it reduces motion artifact in the thoracic and abdominal region and aids in the acquisition of accurate imaging of agitated patients.<sup>23</sup> Unlike PET scanning, fMRI could evolve to be a routine procedure in any well-equipped medical center. Protocols using fMRI could be instituted wherever medicine is practiced, above a certain level of technical sophistication.

Patient selection for participation in experimental trials of physiotherapy or pharmacotherapy based on fMRI could improve the homogeneity of the tested population, improving the yield of treatment effects. Serial monitoring of such patients with fMRI might help to explain treatment successes and failures. The ability to identify activation patterns and correlate them to functional deficits could allow more accurate prognostication. Therapy programs could be more precisely targeted not only according to gross function but to neuroanatomic activity.

#### REFERENCES

1. Dobkin B: *Neurologic Rehabilitation*. Philadelphia, FA Davis, 1996, pp 157–9

2. Gresham GE, Duncan PW, Stason WB, et al: *Post-Stroke Rehabilitation*. Rockville, MD, US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, 1995

3. Basmajian JV: The winter of our discontent: breaking intolerable time locks for stroke survivors. *Arch Phys Med Rehabil* 1989;70:92–4

4. Granger CV, Hamilton BB, Gresham GE, et al: The stroke rehabilitation outcome study. Part II. Relative merits of the total Barthel Index Score and a four item subscore in predicting patient outcomes. *Arch Phys Med Rehabil* 1989;70:100–3

5. Balliet R, Levy B, Blood K: Upper extremity sensory feedback therapy in chronic cerebrovascular accident patients with impaired expressive aphasia and auditory comprehension. *Arch Phys Med Rehabil* 1986;67:304–10

6. Nakayama H, Jorgenson HS, Raaschou

HO, et al: Recovery of upper extremity function in stroke patients: the Copenhagen stroke study. *Arch Phys Med Rehabil* 1994;75:394–8

7. Taub E, Wolf SL: Constraint induced movement techniques to facilitate upper extremity use in stroke patients. *Top Stroke Rehabil* 1997;3:38–61

8. Taub E, Miller NE, Novack TA, et al: Technique to improve chronic motor deficit after stroke. *Arch Phys Med Rehabil* 1993;74:347–54

9. Taub E, Pidikiti RD, Deluca SC, et al: Effects of motor restriction of an unimpaired upper extremity and training on improving functional tasks and altering brain behaviors, in Toole J, Good D (eds): *Imaging in Neurologic Rehabilitation*. New York, Demos Vermande, 1996, pp 133–54

10. Miltner WHR, Bauder HB, Sommer M, et al: Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke. *Stroke* 1999;30:586–92

11. Liepert J, Miltner, WHR, Bauder H, et al: Motor cortex plasticity during CIMT in stroke patients. *Neurosci Lett* 1998;250: 5–8

12. Rao SM, Binder JR, Bandettini BS, et al: Functional magnetic resonance imaging of complex human movements. *Neurology* 1993;43:2311–8

13. Rao SM, Binder JR, Hammeke TA, et al: Somatotopic mapping of the human primary motor cortex with functional magnetic resonance imaging. Neurology 1995;45:919–24

14. Roland PE, Larson B, Lassen NA, et al: Supplementary motor area and other cortical areas in organization of voluntary

movements in man. *J Neurophysiol* 1980; 43:118–36

15. Rao SM, Harrington DL, Haaland KY, et al: Distributed neural systems under the timing of movements. *J Neurosci* 1997;17:5528–35

16. Yetkin FZ, McAuliffe TL, Cox R, et al: Test-retest precision of functional MR in sensory and motor task activation. *AJNR Am J Neuroradiol* 1996;17:95–8

17. Chollet F, DiPiero V, Wise RJS, et al: The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. *Ann Neurol* 1991;29:63–71

18. Weiller C, Chollet F, Friston KJ, et al: Functional reorganization of the brain in recovery from striatocapsular infarction in man. *Ann Neurol* 1992;31:463-72

19. Weiller C, Ramsay SC, Wise RJS, et al: Individual patterns of functional reorganization in the human cerebral cortex after capsular infarction. *Ann Neurol* 1993;33:181–9

20. Cramer SC, Gereon N, Benson RR, et al: A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke* 1997;28:2518–27

21. Cramer SC, Finklestein SP, Schaechter JD, et al: Activation of distinct motor cortex regions during ipsilateral and contralateral finger movements. *J Neurophysiol* 1999;81:383–7

22. Fellner C, Schlair J, Fellner F, et al: Functional MR imaging of the motor cortex in healthy volunteers and patients with brain tumours: qualitative and quantitative results. *Rontgenpraxis* 1999; 52:3–14

23. Pritchard JW, Cummings JL: The insistant call from functional MRI. *Neurology* 1997;48:797–800