Neurocase (2006) **12**, 50–60

ISSN: 1355-4795 print
DOI: 10.1080/13554790500493415

Psychology Press
Taylor & Francis Group

Functional Reorganization and Recovery After Constraint-Induced Movement Therapy in Subacute Stroke: Case Reports

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Preliminary assessments of the feasibility, safety, and effects on neuronal reorganization measured with transcranial magnetic stimulation (TMS) from Constraint-Induced Movement Therapy (CIMT) of the upper extremity were made in eight cases of subacute stroke. Within fourteen days of their stroke, patients were randomly assigned to two weeks of CIMT or traditional therapy. Baseline motor performance and cortical/subcortical representation for movement with TMS were assessed before treatment. Post-treatment assessments were made at the end of treatment and at three months after the stroke. The TMS mapping showed a larger motor representation in the lesioned hemisphere of the CIMT patients as compared to the controls at the three-month follow-up assessment. The enlarged motor representation in the lesioned hemisphere for hand movement correlated with improved motor function of the affected hand, suggesting a link between movement representation size as measured with TMS and functionality. These results suggest that TMS can be safely and effectively used to assess brain function in subacute stroke and further suggest that CIMT may enhance cortical/subcortical motor reorganization and accelerate motor recovery when started within the first two weeks after stroke.

Introduction

Constraint-Induced Movement Therapy (CIMT) involves constraining the unaffected upper extremity of a hemiparetic stroke patient for about two weeks while the patient undergoes extensive motor training, in particular shaping of the desired improvements using successive approximations of the impaired arm and hand. CIMT has been shown to be effective in inducing central nervous system reorganization and motor recovery, but most trials of CIMT have been conducted on chronic stroke patients (Wolf *et al*., 1989; Taub *et al*., 1993; Kunkel *et al*., 1999; Miltner *et al*., 1999; Liepert *et al*., 2000; Wittenberg *et al*., 2003). Since most trials of CIMT to date excluded patients whose chronicity of stroke was less than one year, the safety and appropriateness of CIMT in subacute stroke in comparison to chronic stroke has not been very well established and the effects of CIMT on cortical/subcortical reorganization in subacute patients are unknown[1].

Previous studies suggest that CIMT in subacute stroke may be safe and effective. For example, a case report instituting CIMT within 4 months post-stroke found enhanced motor function that persisted on a three-month follow-up examination (Blanton and Wolf, 1999). Dromerick, Edwards, and Hahn (2000) randomized patients to CIMT or control groups within 14 days post-onset. A significant treatment effect was obtained for the total score and pinch score on the Action Research Arm Test (Lyle, 1981) administered immediately after completing 14 days of treatment. Limitations of this latter study, however, include the absence of follow-up assessments to determine the persistence of the treatment effect and the lack of brain mapping to evaluate lesion expansion and

Received 3 September 2004; accepted 17 January 2005.

This research was supported by a US PHS grant to Harvey Levin. We thank Magda Jungman, Eva Salmeron, Jenny Lai, and Thao Tran for assisting with patient enrollment, therapy, and assessment testing, Courtney Russell, Gurpreet Sarao, and Vibha Tare for coordinating the project, Christine Joy and Elizabeth Pienkos for assistance with collecting the TMS data, David Lane for statistical advice, and the patients for their patience and willingness to participate in this study. Scott Burgin is now at the University of Rochester.

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[1] Although Miltner *et al*. (1999) reported that response to CIMT was unrelated to the chronicity of stroke, they included only two patients who were enrolled at six months post-stroke as compared to the other 13 patients whose post-stroke interval ranged from one to 17 years.

reorganization of motor function as a result of the therapies. Thus, a further investigation is timely to investigate the cortical/subcortical neuroplasticity mechanisms of CIMT in subacute stroke and to preliminarily evaluate the safety and feasibility of CIMT and transcranial magnetic stimulation (TMS) in subacute stroke patients.

TMS is a non-invasive method for assessing cortical function (for a review, see Hallett, 2000; Jahanshahi and Rothwell, 2000; Walsh and Cowey, 2000) and has been demonstrated to reliably localize the hand area of the motor cortex (Boroojerdi *et al*., 1999; Ro *et al*., 1999), as well as changes in cortical motor representation (Pascual-Leone *et al*., 1994; Rossini *et al*., 1998; Liepert *et al*., 2000). Thus, this technique is well suited to measure effects of CIMT on motor reorganization at cortical levels in subacute stroke, although changes may also reflect differences in cortical excitability from TMS without any reorganization and/or changes at lower levels of the motor pathway. Here, we report results demonstrating the potential influences of CIMT in subacute stroke on motor function and functional reorganization as measured with TMS. Although many studies have demonstrated spontaneous reorganization of brain function after subacute stroke using TMS, no studies to our knowledge have assessed with TMS the contributions of subacute CIMT on this reorganization.

The goals of this study were therefore to: 1) determine the feasibility of using TMS to assess functional motor reorganization after CIMT in eight cases of subacute stroke; 2) determine in this preliminary sample whether CIMT in subacute stroke was feasible and safe, and might induce lasting beneficial changes in motor function (i.e., preliminary study of efficacy); 3) determine whether the brain reorganization of movement control as measured with TMS correlates with improved motor function; and 4) use the effect sizes obtained in this preliminary set of cases to compute the sample sizes for a larger group study. Based on the positive results obtained thus far, a larger group study with refined methods and procedures is now being conducted to more conclusively determine the safety and efficacy of CIMT in subacute stroke, and to replicate and extend the findings of extensive functional reorganization after the CIMT as measured with TMS in this study.[2]

Methods

Patients

Over the course of approximately 15 months[3], stroke patients from the Stroke Unit at the University of Texas/Memorial Hermann Hospital in Houston, TX, USA, were screened for this study. The screening procedure included the administration of the National Institutes of Health Stroke Scale (NIHSS) (Lyden *et al*., 1994), and review and coding of computerized tomography (CT) and/or magnetic resonance imaging (MRI) scans performed during the first two weeks after stroke. The reliability of the NIHSS has been documented (Goldstein *et al*., 1989). The NIHSS motor arm scores correspond to normal (score of 0), drift of the outstretched upper extremity (score of 1), inability to hold up the arm against gravity (score of 2–3), or no movement (score of 4). All patients who had an NIHSS motor arm score of 0 or 4 and with less than 10 degrees of movement of the digits in the affected extremity were excluded, as were patients with aphasia that prevented completion of the outcome measures. Patients with sensory loss, apraxia and/or neglect were not excluded from the study, provided they met all inclusion criteria. Stroke subtyping was carried out by a neurologist using established criteria (Adams *et al*., 1993). Although all patients started CIMT or control therapy as hospital in-patients, many of them were discharged before the end of the 14-day period. For these patients who were discharged during the course of the CIMT or control therapy, oral and written instructions were given to each patient's caregiver to ensure carryover in their home environment and each patient returned to Hermann Hospital on a daily basis, excluding Sundays, to assess the compliance of specific instructions (e.g., wearing the mitten) and for the CIMT or control treatment.

Randomization

Once a patient was enrolled, stratified sampling was used to obtain two groups (CIMT and control). To simplify the stratification process, we used two age levels (<64 vs. >64 years old) and two levels of upper extremity motor function on the NIHSS Arm Motor Function (AMF) item (score of 1 vs. score of 2–3).

Constraint-Induced Movement Therapy

Following the procedure of previous studies (Taub *et al*., 1993; 1999; Kunkel *et al*., 1999), the unaffected upper extremity of the patients assigned to the CIMT group was restrained by placing their hand in a mitten, which required the patients to carry out all activities with the affected upper extremity. These patients wore the mitten for a target of 90% of waking hours over 14 consecutive days. Exceptions to this regimen included activities in which safety would have been jeopardized by wearing the mitten. Two therapists, one occupational therapist (OT) and one physical therapist (PT), from Memorial Hermann Hospital were trained to provide CIMT at Dr. Edward Taub's laboratory at the University of Alabama at Birmingham. The CIMT included shaping of the desired improvements in movement using the technique of successive approximations, which enabled patients to achieve success without incurring failure and frustration that could suppress further use of the affected upper extremity and result in learned-nonuse (LN) (Taub *et al*., 1997, 1980). Other techniques involved in the CIMT included

[2] Preliminary results of this work have been described elsewhere (Grotta et al., 2004).

[3] For approximately five months during the course of this experiment, very few patients were screened and no patients were enrolled in this study due to the closure of Hermann Hospital as a result of the flooding from Tropical Storm Allison. This fifteen-month time frame does not include the five months when patients were not being enrolled.

repeatedly presenting the performance goal to the patient, continuous verbal feedback, and presenting trial-by-trial graphic representation of performance trends. To eliminate any therapist effect, each therapist administered the CIMT to each patient for an equal amount of time. Approximately 3 hours/day, 6 days/week of CIMT treatment was given to each patient over a period of 14 days. All CIMT treatment was administered by the participating therapists (MG and AS) in the Rehabilitation Unit of Hermann Memorial Hospital in Houston, TX.

Traditional (Control) Rehabilitation

This treatment consisted of increasing function with use of *both* hands. The sessions included active and/or active-assistive range of motion, bimanual and unilateral activities, tone modification, and activities of daily living using modified or compensatory methods. Depending on the severity of motor weakness, strengthening and coordination exercises of the impaired side were included. The focus was to increase independence in activities of daily living using compensatory techniques as needed. Similar to the CIMT group, daily treatment was conducted for approximately 3 hours/day, 6 days/week, over a period of 14 days. As with the CIMT condition, each therapist, the same ones who treated the CIMT patients, treated each patient for an equal amount of time.

Transcranial Magnetic Stimulation

For assessing the location and extent of the representation for hand movement with transcranial magnetic stimulation (TMS), a Cadwell Laboratories MES-10 stimulator (Kennewick, Washington) was used (Cadwell, 1990). A focal, figure-eight shaped coil, with each component of the figure-eight measuring 4.5 cm in its outer diameter, was used for all of the assessments. The use of this stimulator and coil to localize the hand area of the motor cortex has been validated (Ro *et al*., 1999). Electromyographic (EMG) activity from the abductor pollicis brevis (APB) of the hand contralateral to the TMS was recorded in some patients with silver-silver chloride surface electrodes connected to a Grass-Astromed (West Warwick, RI, model IP511) amplifier, which was in turn connected to a data acquisition card for digitization (CyberResearch, Inc., Branford, CT, model CYDAS 8). The EMG signal was amplified and low-pass filtered at 30 Hz and high-pass filtered at 1000 Hz and was sampled at 1 kHz. The TMS and EMG units were interfaced with an Intel (Santa Clara, CA) 486 PC with custom software. The hand area and TMS motor threshold for each hemisphere in each patient was first established at the beginning of the TMS session from the EMG recordings (Rossini *et al*., 1994) and through visual inspection when EMGs were unavailable (e.g., due to technical problems). The lowest intensity that induced an activation of the slightly contracted contralateral hand[4] was defined as threshold and the TMS intensity was set at 10% above the motor threshold for each hemisphere for the mapping. TMS to map reorganization of the hand motor representation was performed in both hemispheres of each patient at approximately (±1 day) the same time intervals as the motor performance testing: at pretreatment baseline, within 24 hours after two weeks of treatment, and at three-month follow-up.

To map the representation for hand movement, the figure-eight coil was moved systematically over the scalp in steps of 1 cm from the initial hand area localization site to identify the borders of the hand movement representation in the brain. Due to the high precision of this figure-eight coil, which sometimes induced twitches of individual digits in the contralateral hand, two investigators visually checked for movement on any area of the hand after each TMS pulse. Thus, we based the maps on the representation of the entire hand rather than just the APB muscle from which the EMGs were recorded[4]. This was done to avoid floor effects that may have been obtained had only one of the hand muscles been measured using this focal coil. Furthermore, because CIMT focuses on rehabilitating motor hand function, not just APB function, assessing excitability from the entire hand is more representative of the changes that may occur as a result of the CIMT. If there was complete consensus regarding any hand movement between the two TMS investigators regarding the induced movement on at least 3 of 5 trials, these sites were also included as being part of the hand area of the motor cortex[5]. If a consensus was not obtained between the visual inspectors, the EMGs when they were available were used for further verification and at least 3 more TMS trials were run until a consensus regarding movement was reached. Sites not activating any region of the contralateral hand were demarcated as a border of the hand area of the motor cortex. When TMS of the border regions activated some hand movements,

[4] When EMG recordings were made (in all sessions for three patients and in some of the sessions for three additional patients), sites whose stimulation produced an EMG response greater than 0.05 mV in the APB muscle on at least 3 of 5 trials were defined as part of the hand area of the motor cortex. Note that the EMG recordings from the APB muscle were in near complete correspondence with the visual inspection when TMS intensity was set at 10% above each patient's motor threshold. As there was over 99% correspondence between the visual inspection and the EMG traces representing the APB, we are confident that our visual inspection was reliable in determining motor activation following suprathreshold TMS. Nonetheless, future studies should rely upon the use of a digital goniometer or another means for more precisely measuring whole hand movements.

[5] Although there was some variability between the patients with respect to the ability to slightly contract the contralesional hand, we assumed that this variability was directly correlated with the level of upper extremity motor function, which was used as a stratification variable for randomization. Thus, there should be equal proportions of patients who had difficulties with slight contralesional extremity contractions in each of the two groups, reducing any concerns that the measured differences between the two groups was due to this variability. For patients in which slight contractions were extremely difficult or the instructions were not understood, we asked the patients to slightly contract as best as they could and to try and pretend that they were holding a baseball.

but not enough to meet the criterion of activation on at least 3 out of 5 trials, regions extending beyond this border were also tested to ensure that no more activation sites could be obtained outside the demarcated region.

Both hemispheres were mapped in each session and the order of the mapped hemispheres was counterbalanced across the subjects and sessions. Each session took approximately two hours to complete and some patients were given extensive breaks when necessary. The size of the functional motor output map in each hemisphere was defined as the number of positions whose stimulation evoked a contralateral hand movement. In this preliminary article, we report only the data reflecting changes in the size or magnitude of motor reorganization. Our extension and replication of this study with a larger sample of patients, however, will also include data on the shifts in the center of gravity. All experimenters performing the TMS (TR, RJ, as well as assistants EP and CJ) were blind to the treatment assignment of the patients.

Performance Measures

Motor performance measures were obtained at baseline, after the two weeks of CIMT, and at three months by two blinded assessors who were different occupational or physical therapists from those who carried out the treatment. Selection of these measures of motor function was guided by procedures used in previous clinical trials of CIMT in chronic stroke patients and by concern about the physical limitations of subacute stroke patients that could potentially result in floor effects at the pretreatment baseline assessment. In view of evidence that most spontaneous recovery of motor function occurs within three months after stroke (Jorgensen *et al*., 1999), it was also important to include measures that are sensitive to relatively mild residual motor dysfunction at the follow-up assessment.

The Grooved Pegboard Test (GPT) (Klove, 1963) is a timed unimanual performance test in which the patient inserts 25 pegs into small holes in a metal plate as quickly as possible. The GPT requires precise and controlled movements of the hand and digits. The score used for the analyses was the mean number of correctly placed pegs per second. This test was administered to both the intact and affected hands.

The Fugl-Meyer (FM) assessment (Fugl-Meyer *et al*., 1975) is a performance test consisting of 332 upper-extremity motor items (Fugl-Meyer *et al*., 1975). The motor items assessed movements as well as reflexes and range of motion. Items were rated on an ordinal scale. The summary score is the sum of item ratings, with higher scores representing better motor function. The FM was administered to the affected limb. The upper extremity portion (including subsection on wrist and hand) of this scale was used to measure the ability to move the affected arm outside a synergistic pattern (impairment level) on a 3-point scale (maximum score, 66 points). The reliability and validity of the FM have been well supported (Fugl-Meyer *et al*., 1975; Duncan *et al*., 1983; Sanford *et al*., 1993).

The Motor Activity Log (MAL), consisting of a 30 item semi-structured interview developed by Taub *et al*. (1999), evaluated the amount of use and quality of movement of the affected arm. Each patient rated his/her use of the affected upper limb to perform each of the 30 activities of daily living (e.g., feeding, dressing, grooming). Ratings on separate 6-point scales, from 0 to 5, were made on the amount of use and quality of movement in comparison to before the stroke. Summary scores for amount and quality were derived from the mean of the item ratings, with higher scores representing greater use of the affected limb.

Procedure

After initial screening of eligibility and consenting to participate in the study, all patients underwent baseline testing of TMS and motor performance within 2 days prior to randomization. After completion of pretreatment baseline measures patients were randomized and began either two weeks of CIMT or two weeks of control therapy. Motor cortex excitability as measured with TMS and motor performance were assessed in the same manner as in the pretreatment testing for the post-treatment assessment on the day after the final day of CIMT (or control therapy) and three months after the final treatment day (follow-up assessment). The motor performance assessors and the TMS mappers were blinded to treatment assignment and no constraints were in place on the unaffected arm during the assessments. Due to the length of each assessment (approximately four hours per session), we were restricted with respect to the number, type, and way that each assessment was performed. We therefore only included the TMS and the three performance tests rather than conducting an entire battery on motor performance.

Data Analysis

For the TMS data, an initial three-way mixed analysis of variance (ANOVA) was conducted with treatment condition (CIMT vs. control) as the between-subject factor and hemisphere (ipsilesional vs. contralesional) and time of assessment (baseline vs. three-month follow-up) as the two within-subject factors. The two-week post-treatment data were not included in this initial analysis because 3 patients did not complete this phase of the study.

For the GPT and the FM assessments, paired *t*-tests (two-tailed) rather than an ANOVA were performed on the data because no patients could perform the GPT assessment at the pretreatment baseline phase of the study. An ANOVA also was not possible because one patient (WW) was injured in a fall between the two-week and three-month assessments, which prevented her from completing the GPT and the FM,

causing an unbalanced design that could not be analyzed with ANOVA.

The remaining behavioral assessment (MAL) was analyzed with a 2 × 2 × 3 mixed ANOVA. Treatment condition (CIMT vs. control) was the between-subject factor and hemisphere (ipsilesional vs. contralesional) and time of assessment (baseline vs. two-week posttreatment vs. three-month follow-up) were the two within-subject factors.

Results

Table 1 shows 187 screened, but excluded patients and reasons for their exclusion during a representative eight-month period of this study. This table highlights the most prominent difficulties in recruiting patients for this study.

Eight patients (see Table 2) with stroke, as visualized on a pre-enrollment MRI or CT scan, qualified for the study and participated after informed consent. All were right-handed, had an ischemic stroke (handedness and hemorrhagic stroke were not exclusion criteria), and enrolled in the study on an average of 8.5 days (range: 6–10) after their stroke for the CIMT group and an average of 10 days (range: 8–12) for the control group (Table 2). All patients were ambulatory and two of the CI patients and one of the control patients had sensory loss at the time of enrollment. None of the patients had apraxia and only one patient had symptoms associated with mild hemispatial neglect (i.e., visual and tactile extinction on double simultaneous stimulation). As seen in Table 2, the average ages were slightly, but not significantly different, and the motor scores on the NIHSS were identical between the two groups (both *p*s > .10).

The TMS and performance measures for each assessment at each stage of the study are shown in Table 3 for each case in both groups. Motor performance of the affected hand improved in most patients in both treatment groups. However, the two largest and most striking differences between the two patient groups were the functional cortical/subcortical reorganizations that took place in the lesioned hemisphere, as measured with TMS, and also the motor movements in the affected limb, as measured with the GPT and the FM.

At the three-month follow-up examination, the motor representation on the lesioned side, as assessed with TMS, was systematically larger in the CIMT group as compared to the control group. The following statistics confirmed this aspect of the data. In the TMS analysis, there was thus a significant main effect of

Table 1. The type and number of excluded patients during a typical eight-month period of this study

Less than 10 degrees of movement (NIHSS AMF > 3)	30
Aphasic	8
Prior stroke interfering with interpretation of results	1
Movement insufficiently reduced (NIHSS AMF = 0)	76
Confusion	3
Pacemaker	1
Drowsy/decreased LOC	1
Spanish speaking only	3
Medical complications/unstable	9
More than one of the above exclusion criteria	55
Total	187

Note. NIHSS = National Institutes of Health Stroke Scale; AMF = Arm Motor Function; LOC = Level of consciousness.

Table 2. Details of the patients who participated in the study. All patients had an acute ischemic stroke within 14 days prior to enrollment.

Patient	Gender	Age	Handedness	Site of Lesion	NIHSS	Chron.
MA	Male	48	Right	Rt basal ganglia	1	10
MG	Female	80	Right	Rt perisylvian, FP	2	9
GK	Male	52	Right	Rt internal capsule,	3	9
JP	Male	55	Right	Lt pontine	3	6
CIMT Mean		58.8			2.25	8.5
MK	Female	72	Right	Lt corona radiata	3	8
RR	Male	58	Right	Lt CS	3	9
WW	Female	68	Right	Rt pontine	1	12
TW	Male	58	Right	Rt FPT	2	11
Control Mean		64			2.25	10

Note. The NIH Stroke Scale is a gross measure and does not specifically evaluate finger flexion or extension, particularly more than or less than 10 degrees. Lt = Left; Rt = Right; CS = Centrum semiovale; F = Frontal lobe; P = Parietal lobe; T = Temporal lobe; NIHSS = National Institutes of Health Stroke Scale score; Chron. = Chonicity of the stroke, in days, at the time of the baseline assessment.

Table 3. The number of TMS responsive sites, with TMS motor thresholds (in percent of maximum stimulator output) in parentheses, and the motor performance on each task for the CIMT (top half) and the control patients (bottom half) at each stage of the study. The numbers after each patient's initials represent the assessment number (1 = baseline, 2 = post-treatment, 3 = three-month follow-up)

	TMS (# points)		GPT (in seconds)		FM (66 max.)	MAL (0–5 rating)	
	Ipsi	Contra	Intact	Affected		Ability	Quality
CI Patient							
MA1	0 (100)	19 (60)	.180	.000	10	0.00	0.00
MA2	0 (100)	12 (58)	.210	.058	44	0.80	0.90
MA3	7 (75)	12 (72)	.180	.170	57	2.25	2.65
MG1	0 (100)	7 (48)	.087	.000	31	0.38	0.36
MG2	X	X	.130	.000	48	2.08	2.02
MG3	8 (48)	2 (48)	.210	.200	54	2.56	2.41
GK1	0 (100)	9 (70)	.195	.000	18	0.16	0.34
GK2	7 (89)	5 (77)	.230	.100	47	1.48	1.17
GK3	10 (89)	14 (77)	.210	.200	55	1.70	2.14
JP1	0 (100)	6 (65)	.160	.000	39	0.59	0.95
JP2	3 (80)	10 (65)	.190	.090	52	3.94	3.52
JP3	11 (75)	5 (60)	.210	.230	66	5.00	4.96
CI Mean1	**0.00 (100)**	**10.25(61)**	**.156**	**.000**	**24.50**	**0.28**	**0.41**
CI Mean2	**3.33 (90)**	**9.00(67)**	**.190**	**.062**	**47.75**	**2.08**	**1.90**
CI Mean3	**9.00 (72)**	**8.25(64)**	**.202**	**.200**	**58.00**	**2.89**	**3.04**
MK1	0 (100)	1 (82)	.170	.000	29	0.82	0.98
MK2	X	X	.160	.007	43	2.98	2.80
MK3	1 (67)	2 (66)	.170	.070	43	3.38	3.38
RR1	1 (59)	3 (39)	.200	.000	20	0.21	0.13
RR2	X	X	.300	.000	35	2.4	2.25
RR3	9 (52)	6 (46)	.350	.130	52	3.62	3.38
WW1	0 (100)	4 (78)	.069	.000	6	0.00	0.00
WW2	0 (100)	4 (82)	.100	.000	20	0.32	0.34
WW3[a]	0 (100)	3 (90)	X	X	X	0.44	0.44
TW1	0 (100)	6 (48)	.160	.000	21	0.32	0.43
TW2	0 (100)	4 (52)	.220	.000	21	0.32	0.43
TW3	2 (65)	8 (53)	.120	.000	32	1.10	0.96
Co Mean1	**.25 (100)**	**3.50(62)**	**.150**	**.000**	**19.00**	**0.34**	**0.38**
Co Mean2	**.00 (100)**	**4.00(67)**	**.195**	**.002**	**29.75**	**1.50**	**1.46**
Co Mean3	**3.00 (71)**	**4.75(64)**	**.213**	**.067**	**42.33**	**2.14**	**2.04**

Note. Ipsi = Ipsilesional cortical hemisphere; Contra = Contralesional cortical hemisphere; CI = Constraint-Induced patient group; Co = Control patient group; X = Data not collected.

[a]This patient fell on her affected hand, which caused swelling and decreased movement, shortly before the three-month follow-up assessment. Therefore, the FMA and the GPT assessments could not be made due to the more active nature of these tasks in comparison to the TMS, which only requires that the patients sit still, and the MAL, which is a questionnaire that the patient was able to complete.

patient group, with overall larger cortical/subcortical representations for movement in the CIMT group ($F(1,6) = 7.08$, $p < .05$). There was also a marginally significant main effect of hemisphere demonstrating a trend for larger motor representations in the contralesional, unimpaired hemisphere ($F(1,6) = 5.22$, $p < .06$). The main effect of assessment time was significant, simply showing that across patient groups and hemispheres, movement representations when stimulating cortex were larger at the three-month follow-up than at the pretreatment baseline phase of the study. The hemisphere by time of assessment interaction was significant ($F(1,6) = 27.98$, $p < .01$), demonstrating that pretreatment motor representation in the lesioned but not intact hemisphere was systematically smaller as compared to the three-month follow-up. Most importantly, the three-way interaction between patient group, hemisphere, and time of assessment was also highly significant ($F(1,6) = 16.16$, $p < .01$). None of the other interactions approached significance ($p > .10$). The three-way interaction primarily reflected greater enlargement of the cortical/subcortical motor representation of the affected hand in the CIMT group than in the control therapy patients at the three-month follow-up assessment, as revealed by the following planned comparisons.

The number of TMS activation points (i.e., the number of TMS sites that when stimulated induced movement on the contralateral hand) at baseline testing in the lesioned hemisphere did not differ between the CIMT and the control therapy groups ($p > .10$). Prior to initiation of therapy, movement was induced in only a single site for one of the patients

(see Figure 1 and Table 3). For the unimpaired hemisphere, however, there was a marginally significant difference between the two patient groups, with the CIMT patients having a larger cortical/subcortical representation for movement in the unimpaired limb ($t(6) = 2.14$, $p = .08$). This difference was primarily due to one case in the CIMT group who had a large representation for movement of the unimpaired limb (patient MA) and one control therapy case who had a very small representation for the unimpaired limb (patient MK). Immediately after CIMT or control therapy, the two groups did not differ in ipsilesional or contralesional cortical/subcortical motor representations for movement (both ps $> .10$). This, however, may have been due to limitations in sample size because two of the control patients and one of the CIMT patients did not complete the TMS assessment at this stage of the experiment. At the three-month follow-up assessment, the motor representation for the unimpaired contralesional hemisphere was not different between the two groups ($p > .10$). However, and most importantly, at three months the differences in motor representations for the affected hand between the CIMT and the control therapy groups was significant ($t(6) = 2.68$, $p < .05$). Because the data may not have been normally distributed, an additional analysis was conducted to confirm this effect. We first recalculated the number of active TMS sites at the three-month follow-up assessment by performing a log transformation on these data to reduce the skew prior to computing the t-statistic. As a result of this log transformation, the data were more normally distributed. Nonetheless, the effects for this measure still showed significance, with the CIMT patients showing an overall larger number of activation sites in the lesioned hemisphere as compared to the control patients ($t(6) = 2.58$, $p < .05$).

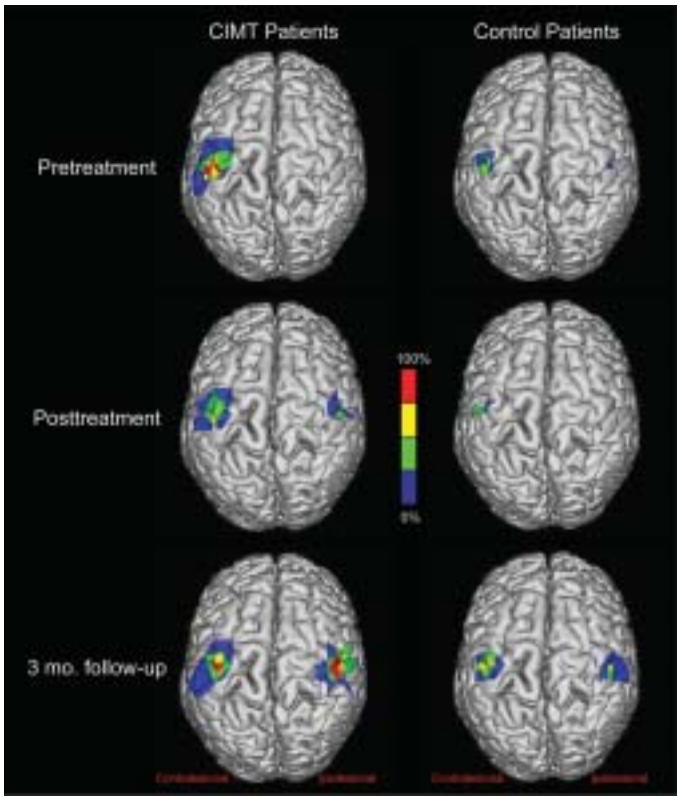

Fig. 1. Motor maps for the CIMT (left column) and control therapy (right column) groups at the baseline pretreatment stage (top row), the two-week posttreatment stage (middle row), and the three-month follow-up stage (bottom). The colors represent the percent of patients with motor activation at a given cortical site. Note that the area of the hotter colors (yellow and red), rather than the total area, is more indicative of the group's cortical motor output map since the activation points of each patient within a group are superimposed onto the same brain. Thus, the blue areas sometimes represent non-overlapping motor maps from different patients. For these figures, the normal hemisphere is on the left (left side of each rendering) and the lesioned hemisphere is on the right (right side of each rendering). These figures were generated by plotting the TMS motor activation sites of each patient onto the Montreal Neurological Institute template MRI brain using some functions of SPM99 and Matlab (Natick, MA). Note that the hand area of the motor cortex in this template brain was used as the origin and therefore this figure does not depict or accurately represent any displacement of the motor areas after a stroke and therapy. For individual patient maps, with animations of cortical motor reorganization, see http://www.ruf.rice.edu/~tro/cimt.html.

The treatment groups did not differ in their performance on the GPT or on the FM at baseline testing before any treatments were administered. However, patients in the CIMT group were significantly faster than the control patients on the GPT at both the two-week post-treatment assessment ($t(6) = 2.67$, $p < .05$) and the three-month follow-up ($t(5) = 3.85$, $p < .02$). Furthermore, patients in the CIMT group had higher FM scores than the control patients at both the two-week post-treatment assessment ($t(6) = 3.09$, $p < .05$) and the three-month follow-up ($t(5) = 2.69$, $p < .05$) (see Table 3). Note that the smaller degrees of freedom at the three-month follow-up are due to one of the control patients not completing these two tests.

At three months post-stroke, performance on the GPT was highly correlated with the motor representation of the impaired hand as measured with TMS ($r^2 = .89$, $p < .02$). Figure 2a illustrates this high correspondence between motor representation of the impaired hand and performance on the GPT using this hand. Furthermore, the performance on the FM was also highly correlated with the motor representation assessed with TMS ($r^2 = .75$, $p < .02$), as shown in Figure 2b. Note that these scatterplots were derived directly from the continuous data on these measures and that patients who received CIMT typically had a larger number of TMS activation sites, which also correlated with motor function as assessed by the GPT and the FM.

The other functional outcome measure (MAL) did not show statistically significant differences between the two patient groups at any stage of the study. Comparisons between the CIMT and control groups showed no significant differences in amount or quality of use of the impaired limb reported by the patient on the MAL (see Table 3; all ps $> .10$

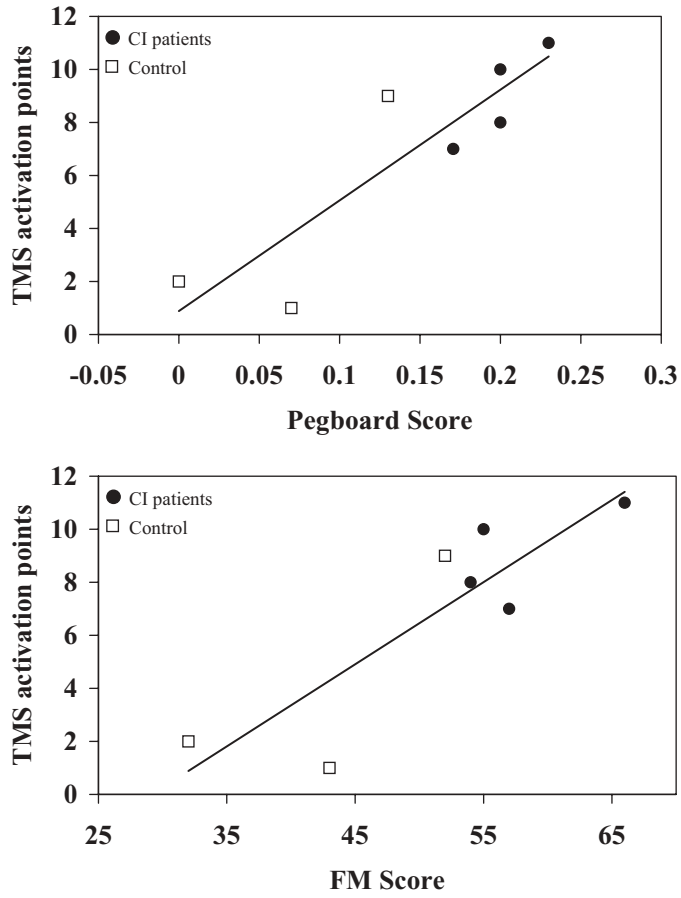

Fig. 2. The number of TMS-activated sites in the lesioned hemisphere plotted as a function of each patient's score on the a) grooved pegboard test, and b) the patient's respective score on the FM test, demonstrates a high correlation between these measures at three months after stroke. Note the high correspondence between these figures. Data from patient WW, who suffered a fall before the three-month follow-up assessment, were not included in these figures. The filled circles represent the CIMT patients and the unfilled squares the control patients.

for both amount and quality at each testing interval). The only significant effects in the ANOVAs on the MAL ratings were the main effects of assessment time for both the amount of use and quality of movement ($F(2, 6) = 28.90$, $p < .01$ and $F(2, 6) = 32.70$, $p < .01$, respectively), reflecting improved performance in both amount of use and quality of movement for both patient groups at the two-week as compared to the pretreatment phase, and at the three-month assessment in comparison to the two-week assessment ($ps < .05$ for all comparisons). No adverse events occurred throughout this study.

Discussion

Following two weeks of CIMT therapy in four cases of subacute stroke, TMS disclosed that the size of the representations for hand movement in the lesioned hemisphere had increased to a greater extent relative to findings in four cases given traditional therapy. Specifically, at three months following the therapy, the TMS output maps for the impaired hands were overall larger in patients who received CIMT as compared to the control group. Motor performance on the Grooved Pegboard Test and the Fugl Meyer assessment also improved to a greater degree in the CIMT group relative to traditional therapy in this initial study. One case in the control group (RR), however, had unusually large motor representations in both hemispheres of his brain and higher scores on the motor function tests. Interestingly, this patient's wife had spontaneously informed us that she made her husband regularly exercise and practice many of the standard rehabilitation procedures at home. Despite this one case showing enlarged bilateral representation for movement, the differences between the groups were statistically reliable even with the small sample size, which was accounted for in our statistics. To our knowledge, this is the first demonstration of induced functional plasticity following CIMT in *subacute* stroke.

We were very surprised to find that only a small percentage of acute patients qualified for CIMT. The most frequent reason for exclusion was that at one week after stroke, most patients had either no movement or had recovered movement of their affected hand. It is possible that more patients would qualify for CIMT if the time of baseline screening were later, thereby allowing for spontaneous recovery. This question is presently under evaluation. Currently, these results are suggestive of enhanced reorganization and recovery of motor function after CIMT in subacute stroke.

Because different TMS coil designs and procedures were used in another study investigating cortical/subcortical reorganization following CIMT in *chronic* stroke (Liepert *et al*., 2000), direct comparisons cannot be made regarding the magnitude of reorganization based on chronicity of stroke. Pending replication in a larger study, which we are currently conducting, this demonstration of enhanced cortical/subcortical reorganization and recovery following CIMT in subacute stroke suggests that providing this form of therapy shortly after a stroke may mitigate disability associated with LN (Taub *et al*., 1980, 1999) rather than deferring treatment until the chronic stages after a stroke. Our experience of no adverse events and the report by Dromerick *et al*. (2000) also support the safety of instituting CIMT within the first month after stroke.

It is important to note that we do not know if the TMS changes observed here reflect reorganization in cortical or subcortical structures. For example, the measured changes may be due to changes either in cortical excitability or from changes at the subcortical level. This issue could be sorted out by a detailed evaluation of changes in spinal excitability using H reflexes or F waves or by using transcranial or brainstem electrical stimulation, which was not done in this study (Ridding and Rothwell, 1995, 1997). Alternatively, serial functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) scans, which unlike TMS can probe subcortical function, might reveal contributions of

subcortical and other cortical structures to this reorganization. In fact, recent studies using functional imaging to measure neural changes after CIMT have shown, in addition to changes in ipsilateral and contralateral motor cortex, changes in cerebellum as well as supplementary motor areas (Levy *et al*., 2001; Johansen-Berg *et al*., 2002; Schaechter *et al*., 2002; Kim *et al*., 2004; Liepert *et al*., 2004), regions that are more difficult to assess with TMS and not probed in this study.

Interestingly, the cortical/subcortical reorganization and representation for movement of the impaired hand mainly evolved within the lesioned hemisphere. Although the lesion volume changes after CIMT in this study were not directly measured, the enlarged motor representation in the lesioned hemisphere after CIMT suggests that the effective cortical tissue in the lesioned hemisphere expanded. While this may also be interpreted as a decrease in lesion volume, more direct measures, such as measuring lesion volume in structural MRIs at all stages of the study, are necessary to demonstrate changes in lesion volume. Unlike in rats with acute strokes (Bland *et al*., 2000), where constraining an unimpaired limb enhanced lesion volume, CIMT in acute stroke appears to enhance motor functionality by increasing the cortical/subcortical representation for contralesional movement.

In contrast to the changes in the ipsilesional hemisphere, the motor representation in the contralesional hemisphere, representing the ipsilateral, unimpaired hand, tended to decrease in some cases after CIMT (see cases MA, MG, and JP in Table 3). Since our design was limited in measuring any ipsilaterally induced movements, however, we cannot precisely determine whether there were movement representations for the impaired limb in the ipsilateral (contralesional and unimpaired) cortex. We are now testing for bilateral representations of hand movement after CIMT in subacute patients in a replication and extension of this study. However, the tendency for decreased representation for movement of the unimpaired hand in the contralesional hemisphere suggests that the effects from the contralesional, unimpaired hemisphere on ipsilateral movements may be limited or indirect via interhemispheric interactions at best. One possibility, for example, may be that the changes in the ipsilesional hemisphere and improved motor function of the impaired limb after CIMT may have been due to a reduction in the motor representation for the unimpaired limb. This may have then resulted in reduced interhemispheric competition and/or inhibition from the contralesional hemisphere onto the lesioned one, as many studies have now been demonstrating (Kinsbourne, 1977; 1993; Seyal *et al*., 1995; Werhahn *et al*., 2002; Werhahn *et al*., 2002). This reduced inhibition from the contralesional hemisphere may be one mechanism underlying the benefits from CIMT.

Although one may argue that some of our comparisons at pretreatment were invalid due to the inability to collect GPT and TMS data from the affected hand, note that the changes at the three-month follow-up nonetheless showed differences between the treatment groups. Furthermore, since we assigned subjects to each group based on stratified sampling, using age and level of upper extremity motor function, differences at baseline are unlikely to have contributed to the measured outcomes. The lack of significant differences between the two groups on all performance measures at baseline confirms that the two groups were indeed very similar at baseline, although there did seem to be a marginally significant difference in the motor representation in the contralesional hemisphere between the two groups at baseline.

Furthermore, the lack of significant effects on the MAL may be due to insensitivity of this measure for fine motor hand function, insensitivity in subacute patients, or the limitations in our small sample size. However, since many of the MAL assessments on these patients probed for activity while the patients were hospitalized, where activity may have been extremely limited (e.g., many patients do not dress or groom themselves while in the hospital), the use and interpretation of the MAL in subacute patients should be made with caution. The overall, but nonsignificantly higher scores on the MAL for the CIMT group as compared to the control group at the three-month follow-up, however, suggest that this assessment may reveal differences with a larger sample size. Our extension of this study in a larger group of patients should address this issue, as well as issues regarding potential differences in baseline and the types of patients (e.g., higher functioning patients with higher NIHSS scores) who are most likely to benefit from CIMT.

In conclusion, our results demonstrate that there is a strong relationship between cortical/subcortical output maps for movement as determined by TMS and motor dexterity in the corresponding hand. With a high correspondence of detecting the motor hand area in normal subjects (Ro *et al*., 1999; Boroojerdi *et al*., 1999), TMS affords a non-invasive, and effective tool for measuring cortical plasticity in humans. For example, in contrast to other techniques for measuring brain reorganization, such as fMRI or PET, TMS is more economical and convenient as it can be performed at bedside. Furthermore, single-pulse TMS in subacute stroke patients appears to be reasonably safe; the lack of the occurrence of any TMS-induced seizures in our study suggests that the induction of seizures in stroke patients (Homberg and Netz, 1989; Fauth *et al*., 1992) may be an extremely rare occurrence. One outstanding question that remains is whether CI therapy in the subacute stages leads to better functional outcome as compared to delaying treatment to a more chronic phase of recovery. Nonetheless, our results extend the previous studies of CIMT in chronic patients (Wolf *et al*., 1983; Taub *et al*., 1993; Kunkel *et al*., 1999; Miltner *et al*., 1999; Liepert *et al*., 2000; Wittenberg *et al*., 2003) by suggesting that this therapy is feasible, safe, and induces more functional central nervous system reorganization and recovery as compared to traditional therapy (cf. Johansen-Berg, *et al*., 2002, but see Ward *et al*., 2003 for negative correlations between recovery and cortical

representation size). We are currently attempting to confirm these findings in a larger group of patients.

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