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Limited dose response to Constraint-Induced Movement Therapy in patients with chronic stroke

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Objective: To compare outcomes in motor skill, perceived amount of use and ability of the paretic arm in daily activities between traditional Constraint-Induced Movement Therapy, consisting of 6 hours of in-clinic, therapist-guided task practice, and a shortened Constraint-Induced Movement Therapy, consisting of 1 hour of in-clinic, therapist-guided task practice coupled with 5 hours of unsupervised practice at home.
Design: A secondary analysis of two previous randomized, controlled, double-blind, parallel group studies.
Setting: A research clinic.
Participants: Thirty-nine individuals with hemiparesis from a chronic unilateral stroke who were able to extend the wrist 10° and the fingers and thumb 10° from a flexed position and were participants in one of the two studies examining the efficacy of adding neuroplasticity adjuvants to Constraint-Induced Movement Therapy.
Main outcome measures: The Wolf Motor Function Test was used to assess motor skill and the Motor Activity Log amount of use and quality of movement scales were used to assess perceived amount of use and ability respectively.
Interventions: Constraint-Induced Movement Therapy plus donepezil in the CIMT-6 study (the traditional 6 hours of in-clinic task practice) and Constraint-Induced Movement Therapy plus repetitive transcranial magnetic stimulation in the CIMT-1 study (1 hour of in-clinic task practice).
Results: Motor skill gains after two weeks of therapy were equivalent for both groups ($n = 39$; mean difference = 2.81, $P > 0.22$), but gains were not maintained six months later with either intervention protocol. Despite this, participants in the CIMT-6 group reported greater use (mean difference = 1.52, $P < 0.001$) and movement quality (mean difference = 0.95, $P < 0.004$) than those with less therapist-guided practice. Both groups had regressed somewhat in use and ability at the six-month follow-up.
Conclusion: These results suggest that 6 hours of therapist-guided practice may not be necessary to facilitate motor skill gains, but may influence patterns of use.

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Introduction

Over 700 000 people in the USA experience a stroke each year.[1] Many continue to experience decreased function of their paretic arm despite rehabilitation.[2] Thus, rehabilitation of the arm remains one of the largest challenges in stroke recovery.

Constraint-Induced Movement Therapy may enable increased motor function and use of the paretic arm.[3–6] In its traditional form, therapist-structured task practice is provided for 10 days across two weeks for 6 hours each day. In addition, the patient wears a mitt that prevents object manipulation with the non-paretic extremity for up to 90% of his or her waking hours for two weeks.

Constraint-Induced Movement Therapy is labour intensive and, therefore, expensive. Many therapists believe that their clinics do not have the resources to provide this therapy and many patients are uninterested in it because of its intensity.[7] To date, there has been little research on dosage of therapist-guided practice during Constraint-Induced Movement Therapy. Sterr *et al.*[8] and Lum and colleagues[9,10] compared the effects of 3 and 6 hours of therapist-guided practice over a two-week period, maintaining the traditional mitt-wearing schedule. In these studies, each intervention group improved in motor skill (performance speed on the Wolf Motor Function Test[11]) to the same degree. However, conflicting results were found for perceived use and ability of the paretic arm. In the studies of Lum and colleagues,[9,10] subjects who received 3 hours of therapy reported gains in arm use on the Motor Activity Log equivalent to those reported by 6-hour therapy participants, whereas in the study of Sterr et al.,[8] subjects who received 3 hours of therapy reported *less* gain in use and quality of movement than did the 6-hour group. Other studies have confounded amount of therapy per day[12] with duration or amount of mitt use,[13] precluding assessment of the impact of therapy dosage by itself.

Our team recently completed two randomized, controlled, double-blind, parallel group trials comparing the efficacy of two potential neuroplasticity adjuvants (donepezil and repetitive transcranial magnetic stimulation (rTMS)) with Constraint-Induced Movement Therapy. In neither study was the effect of the adjuvant statistically significant. However, the two trials employed different amounts of therapist-guided treatment time. Thus, in the present investigation, we have been able to combine the treatment groups within each randomized trial in order to address the following questions: Does having more therapist-guided practice lead to (1) larger short-term gains in motor skill? (2) the perception of greater use and ability of the paretic arm and hand? (3) larger retention of motor skill gains? (4) the perception of greater retention of use and ability of the paretic arm and hand?

Methods

Participants

The data from all 39 individuals with chronic stroke who were participants in one of the two studies formed our sample. There were 20 in a Constraint-Induced Movement Therapy-plus-donepezil study (hereafter referred to as the CIMT-6 group)[14] and 19 in a modified Constraint-Induced Movement Therapy-plus-rTMS study (hereafter referred to as the CIMT-1 group).[15] Both studies were randomized, controlled, double-blind, parallel group clinical trials. Figure 1 shows the flow of participants through these studies.

While most inclusion/exclusion criteria were the same in the two studies, several were unique to one of the studies. Inclusion/exclusion criteria other than the motor criteria were verified from each participant's medical records. The inclusion/exclusion criteria that were the same included: a unilateral stroke; no serious medical conditions or history of other neurological or psychiatric conditions; ability to follow simple commands and understand the requirements of the study; ability to sit unsupported; no severe limitations in passive range of motion in the arm; ability to extend the wrist 10° and the fingers and thumb 10°; and the use of no more than one medication that had the potential for inhibiting neuroplasticity (e.g. neuroleptics, α-1 noradrenergic antagonists or α-2 noradenergic agonists, benzodiazepines, anticonvulsants, or tricyclic antidepressants).

Potential candidates for CIMT-1 were excluded if they had a history of seizures, current evidence of

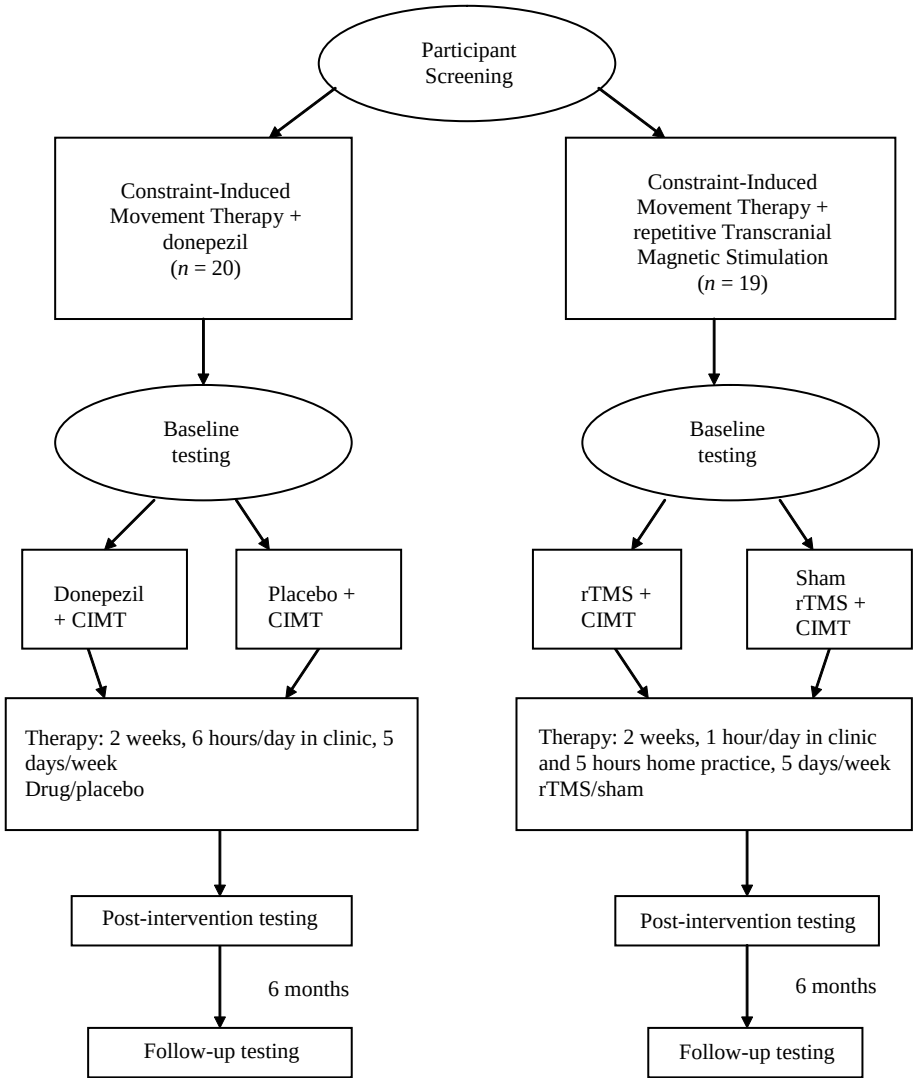

Figure 1 Flow of participants through the Constraint-Induced Movement Therapy (CIMT) plus donepezil and the Constraint-Induced Movement Therapy plus repetitive transcranial magnetic stimulation (rTMS) studies.

epileptiform activity on electroencephalograpy, or were taking medications that might lower seizure threshold; cortical haemorrhage; a pacemaker, medication pump, or implanted metal in head. Candidates for CIMT-6 were excluded if they had cardiac conditions that could be negatively impacted by a cholinomimetic drug or were taking any anticholinergic medications. Table 1 documents patient demographics and preintervention level of function. Three patients from the CIMT-1 and one from the CIMT-6 protocol were lost to six-month follow-up. Thus, we report on those 35 patients (19 in the CIMT-6, 16 in the CIMT-1 groups) for whom we had both postintervention and six-month follow-up data. The characteristics of the patients who were lost to follow-up are also given in Table 1.

The study was Institutional Review Board approved, and all subjects signed informed consent at study entry.

Table 1 Patient characteristics and preintervention scores

	CIMT-6 ($n = 19$)	CIMT-1 ($n = 16$)	*P*-value	Lost to follow-up ($n = 4$)
Age (mean years, SD)	60.12 (15.1)	66.9 (7.4)	0.099	69.50 (3.87)
Time since stroke (mean years, SD)	6.8 (10.3)	3.13 (2.5)	0.164	6.67 (6.03)
Gender (% male)	57.9	56.3	0.923	75.00
Stroke location (% left brain stroke)[a]	66.7	50.0	0.440	50.00
Hemispheric large vessel infarct	52.6	62.5		50.0
Hemisphere lacunes	5.3	31.3		50.0
Hemisphere haemorrhages	36.8	6.3		0
Brain stem haemorrhage	5.3	0		0
Dominance of paretic hand (% dominant)	63.2	43.8	0.148	75.00
Baseline Geriatric Depression Score[b]	5.7 (4.2)	9.47 (6.0)	0.050	10.25 (6.13)
Baseline Wolf Motor Function Test (seconds)	19.17 (18.8)	25.21 (27.69)	0.466	32.31 (26.54)
Baseline Motor Activity Log Amount of Use[c]	1.89 (0.58)	0.94 (0.63)	0.247	0.90 (0.57)
Baseline Motor Activity Log Quality of Movement[c]	1.11 (0.51)	1.05 (0.67)	0.791	0.85 (0.43)

[a]Greater detail on location and type of lesions are given in Nadeau *et al.*[12] and Malcolm *et al.*[13]
[b]Maximum score is 16. Scores greater than 6 are indicative of depressive symptomology.
[c]Maximum score is 5, indicating use and ability are the same as prior to stroke.

Assessment

All participants were tested prior to the start of treatment, at the end of therapy, and six months after therapy ended. Within each original study, testers and treating therapists were blind to treatment group. Motor recovery with therapy was measured with the Wolf Motor Function Test,[11] while changes in use and perceived ability of the paretic extremity were measured with the Motor Activity Log.[3] The Wolf Motor Function Test consists of 15 timed tasks ranging from simple proximal arm movements to object manipulation. The performance time score is the average time to complete these items. It is a reliable and valid measure of arm and hand motor function after stroke.[11,14,16] On the Motor Activity Log, participants rate the frequency with which the paretic arm is used in 30 common activities compared to before the stroke on a six-point scale (amount of use scale) (0 = don't use at all; 5 = as frequently as before the stroke). Participants also rate their perceived ability to complete these activities with the paretic hand (quality of movement scale) (0 = don't do activity; 5 = ability is as before stroke). Taub and colleagues[17,18] and van der Lee *et al.*[19] have recently shown that the Motor Activity Log is reliable and scores correlate with both accelerometer readings of paretic arm use and observations of paretic arm use on the Actual Amount of Use Test.

Intervention

A full description of the intervention protocols is provided in the original articles.[14,15] We will briefly describe the interventions here.

Constraint-Induced Movement Therapy

In each study, patients wore a padded mitt on their non-paretic arm for up to 90% of waking hours. The mitt allowed for performance of tasks requiring proximal arm movements (e.g. steadying self when standing or walking), but prevented object manipulation with the non-paretic arm. Patients were told to remove the mitt while sleeping and mitt removal contracts were formed to identify other specific activities for which each patient was allowed to remove the mitt, such as showering or driving. The patients documented mitt compliance in daily logs.

All patients received therapist-structured task practice with the paretic hand each weekday for two weeks. Most of this involved repetitive practice of daily activities, such as washing windows, playing card and board games, putting cans in a cupboard, and removing coins from a coin purse. The therapists (occupational and physical) selected tasks that offered a motoric challenge (in terms of

power, endurance, coordination, or range of motion), but that the patient was able to perform. Task difficulty was graded (shaped) by the amount of time or number of repetitions produced, distance or height from midline, load and size, but systematic behavioural feedback regarding daily performance was not provided.

The CIMT-6 patients received the traditional 6 hours of therapist-structured task practice each day. CIMT-1 patients received 1 hour of such practice per day with instructions to complete 5 more hours of specific activities on their own at home. Patients indicated compliance with home therapy in their daily logs. Subjects in both groups were encouraged to use their paretic arm as much as possible on the intervening weekend. The CIMT-6 patients were also given specific tasks to practise over this weekend. Patients in neither study received any intervention between completion of the two weeks of therapy and follow-up six months later.

Adjuvant interventions

CIMT-6 participants received either a non-active placebo or donepezil, starting with one 5 mg tablet per day for two weeks, followed by two 5 mg tablets per day for the subquent four weeks. Constraint-Induced Movement Therapy was provided during the last two weeks of the drug/placebo administration. Treating therapists, testers and participants were not apprised of their treatment group until after the study was completed.

The participants in the CIMT-1 group received either rTMS stimulation or sham stimulation to the motor cortex immediately prior to each therapy session. Each rTMS session consisted of 50 trains of 40 stimuli delivered at a rate of 20 Hz for 2 of every 30 seconds. Stumuli of 90% of motor threshold were administered using a 7 cm mean diameter figure-of-eight shaped coil. The coil was centred over the hand area of the ipsilesional motor cortex. Sham rTMS was provided with similar stimulus parameters from a similar coil that was specially designed to generate a greater than 90% attenuated magnetic field. This set-up resulted in noise and vibration levels comparable to the real magnetic coil. Surface electrodes under the magnet administered a train of 20 Hz electrical impulses to the scalp during each sham rTMS stimulus train to mimic the cutaneous and intramuscular neural sensory inputs experienced with real rTMS. Treating therapists, testers and participants were not apprised of their treatment group until after the study was completed.

Data analysis

First, descriptive statistics were obtained on all patient characteristics and baseline scores. Two-tailed two sample *t*-tests (for continuous variables) and chi-squared tests (for ordinal data) were performed to determine differences between the CIMT-6 group and the CIMT-1 group. Second, summary statistics were provided by study group for the three main outcome measures: the Wolf Motor Function Test[11] and the Motor Activity Log amount of use and quality of movement[3] scores.

Third, for each of the main outcome measures, a general linear model was fitted using study group as the independent variable and the baseline score on the measure as the covariate. The study group included four categories: CIMT-6 plus drug, CIMT-6 only, CIMT-1 plus rTMS, and CIMT-1 only. To test differences in therapy gains (change scores from pre-intervention to post-intervention), maintenance of therapy gains (change scores from post-intervention to 6-month follow-up), and changes from baseline to follow-up, linear contrasts were used to compare between the CIMT-6 and CIMT-1 groups. We tested three measures (Wolf Motor Function Test, Motor Activity Log-amount of use, and Motor Activity Log-quality of movement) over three intervals (pre-post, post-six months, pre-six months). Therefore, our Bonferroni-adjusted type I error level was $0.05/9 = 0.0056$.

Results

Table 2 shows the change-scores on the Wolf Motor Function Test[11] and the Motor Activity Log scales[3] across testing sessions. There were no differences between the groups in Wolf Motor Function Test change scores over any interval. Subjects receiving CIMT-6 perceived greater gains in amount of use (Motor Activity Log-amount of use) and ability to use the paretic arm (Motor

Table 2 Mean and standard deviation (SD) of the main outcome measures by study groups[a]

Outcomes	Traditional CIMT group (CIMT plus donepezil)				Shortened CIMT group (CIMT plus rTMS)				Traditional–shortened
	CIMT+drug ($N=10$) Mean (SD)	CIMT only ($N=9$) Mean (SD)	Difference Mean (SD)	Collapsed Mean (SD)	CIMT+TMS ($N=9$) Mean (SD)	CIMT only ($N=7$) Mean (SD)	Difference Mean (SD)	Collapsed Mean (SD)	Mean (SD)
WMFT									
Post–pre	−6.36 (7.67)	−3.76 (3.30)	−2.60 (3.05)	−5.13 (6.00)	−6.61 (5.54)	−9.12 (9.16)	2.51 (3.35)	−7.71 (7.18)	2.81 (2.26)
6mo–post	1.16 (6.94)	3.43 (5.93)	−2.27 (4.03)	2.24 (6.41)	5.69 (10.81)	7.73 (11.10)	−2.04 (4.42)	6.59 (10.61)	−4.42 (2.99)
6mo–pre	−5.19 (6.91)	−0.33 (5.63)	−4.86 (3.76)	−2.89 (6.65)	−0.92 (8.31)	−1.38 (11.85)	0.47 (4.13)	−1.12 (9.65)	−1.61 (2.79)
MALA									
Post–pre	3.20 (0.48)	3.08 (0.84)	0.12 (0.34)	3.14 (0.66)**	1.95 (1.01)	1.29 (0.47)	0.67 (0.38)	1.66 (0.87)	1.52 (0.25)**
6mo–post	−1.90 (0.61)	−1.25 (1.01)	−0.65 (0.40)	−1.59 (0.87)	−1.05 (1.09)	−0.23 (0.69)	−0.82 (0.44)	−0.69 (1.00)	−0.94 (0.30)**
6mo–pre	1.30 (0.59)	1.83 (1.05)	−0.53 (0.34)	1.55 (0.86)	0.90 (0.67)	1.05 (0.43)	−0.15 (0.37)	0.97 (0.57)	0.58 (0.25)*
MALW									
Post–pre	2.42 (0.72)	2.43 (0.70)	−0.01 (0.32)	2.43 (0.69)**	1.59 (0.83)	1.36 (0.49)	0.23 (0.36)	1.49 (0.69)*	0.95 (0.24)**
6mo–post	−0.98 (0.69)	−0.91 (0.58)	−0.07 (0.30)	−0.95 (0.63)	−0.62 (0.74)	−0.26 (0.57)	−0.36 (0.33)	−0.46 (0.68)	−0.51 (0.22)*
6mo–pre	1.44 (0.58)	1.52 (0.71)	0.07 (0.26)	1.48 (0.63)*	0.97 (0.49)	1.10 (0.39)	−0.13 (0.28)	1.03 (0.44)*	0.45 (0.19)*

[a]The main outcome measures are performance on the Wolf Motor Function Test (WMFT), the Motor Activity Log Amound of Use scales (MALA) and the Motor Activity Log Quality of Movement scales (MALW).
**P-value < 0.0055, the Bonferroni adjusted type I error level; *P-value between 0.0055 and 0.05.

Activity Log-quality of movement) at the conclusion of therapy. However, over the ensuing six months there was a steeper fall-off in the Motor Activity Log scores in the CIMT-6 group such that over the baseline to six months interval, there was no net difference between the two groups in change scores of perceived arm use. These findings remained the same when the non-parametric Wilcoxon test was used to compare the two dose groups on the Motor Activity Log scores.

Discussion

Several studies have found that individuals experience motor skill gains with a reduced time in Constraint-Induced Movement Therapy.[8–10,13,20,21] However, only three studies have varied time in therapist-guided motor practice without also varying number of therapy days. We found that, as in the studies of Lum and colleagues,[9,10] but in contrast to the study of Sterr *et al.*,[8] our groups made equivalent gains in motor skill on the Wolf Motor Function Test.[11]

Despite similar gains on objective performance measures, the CIMT-6 group perceived greater short-term ability and daily use of the paretic arm than did the CIMT-1 group. A weak relationship between the amount of change on performance measures of motor skill and the amount of change in Motor Activity Log[3] scores has been noted before.[19] To the extent that changes in Motor Activity Log scores reflect changes in intentional predisposition to use the paretic arm (overcoming learned non-use), rather than changes in motor skill, they may reflect neuroplasticity in a completely different domain of brain function (prefrontal rather than motor/premotor)

Clinical messages

- In people with ongoing limitation of arm function after stroke, providing 6 hours of therapist-guided task practice was equivalent to 1 hour of direct therapy with 5 hours home practice over 10 days.
- Gains after two weeks of intense practice were not sustained at six months.

In our studies, many of the gains in both motor skill and use were lost over the six months after therapy. Six-month scores on the Wolf Motor Function Test[11] in both study groups were nearly identical to baseline scores. This loss of motor skill gains is distressing because the ultimate goal of motor rehabilitation is to facilitate the development of motor skills and use patterns that are maintained after rehabilitation ends. Although some studies report maintenance of therapy gains in motor skill and use with Constraint-Induced Movement Therapy (albeit with some regression) long after therapy,[3,5,22,23] our data suggest that such maintenance is not always the case. These results point to the need for chronic interventions that will sustain or build on gains achieved during the course of concentrated therapy.

Both groups also reported less ability and amount of use of their paretic arm at six months compared with immediately after therapy, although scores remained higher than at baseline. The CIMT-6 group reported greater loss in use of the paretic hand once therapy was withdrawn than did the CIMT-1 group. Post-intervention self-reports of use by the CIMT-6 group may have been inflated and offered greater opportunity for regression to the mean. Conversely, use may actually have been increased as long as daily support from the therapist existed. In any event, these higher scores were not maintained in the absence of ongoing therapeutic support. Sterr *et al.*[8] and Taub *et al.*[10] also report regression in perceived use and ability of the paretic arm at follow-up, although the amount of regression was similar between the groups and participants continued to have higher function than at baseline.

Use of the paretic arm in daily activities will, theoretically, serve to maintain motor gains obtained in therapy. The failure to sustain the increased use (and motor skill gains) suggests either that the therapy did not facilitate a permanent change in the neural networks controlling intention or that the motor skills of our patients were not sufficient to support continued use of that extremity in daily life tasks. These observations suggest that research is strongly needed to delineate those patients who are likely to maintain

therapeutic gain from those who may need additional programming to maintain gain.

Definitive conclusions regarding the optimal session length of therapist-guided Constraint-Induced Movement Therapy will depend on completion of a suitably powered randomized controlled trial. However, the conditions underlying the treatment comparison reported here probably come as close to approximating the results of a randomized controlled trial as is possible for an uncontrolled study. The two trials were conducted nearly contemporaneously. Participants were allocated to the two trials by the same physicians according to medical attributes of subjects (e.g. presence or absence of haemorrhage that might impinge on cortical grey matter; history of seizures; or presence of cardiac disease that would contraindicate donepezil) and not on the basis of neurologic function. Treatment was delivered by the same therapists according to the same treatment principles and techniques. Table 1 reveals that, but for Geriatric Depression Scale score and stroke type, baseline characteristic of the subjects were similar in the two groups. The slightly but significantly higher Geriatric Depression Scale score of the CIMT-1 group could have produced a greater drop-off in therapeutic gains during follow-up but this was not observed. The two groups had a similar frequency of hemispheric large vessel distribution infarcts. CIMT-6 participants had a higher frequency of haemorrhages. However, by the time of study entry, these haemorrhages had been largely reduced to small haemosiderin-lined cavities deep within the brain, roughly similar in size and location with respect to motor pathways to the lacunar infarcts that were overrepresented in the CIMT-1 group.

Our data suggest that 6 hours of motor practice in the clinic *with a therapist* may not be necessary to promote motor skill gains following stroke. Our data do not speak to the relative efficacy of shortened motor practice: the participants in the CIMT-1 group also engaged in 6 hours of motor practice per day. The difference was that 5 of those hours were completed as a home programme. Thus, our data can only suggest that if individuals are motivated, home practice prescribed by a therapist may be sufficient for promoting motor skill gains after stroke. Nonetheless, additional time spent engaging in motor practice with a therapist appears to be beneficial for increasing the perceived ability and amount of use of the paretic hand.

This study has several limitations, the first being the relatively small sample size. The lack of power cannot explain, however, the greater perceived gain in paretic arm use and ability after intervention, but greater loss of this perceived use and ability at six months in the CIMT-6 patients compared with the CIMT-1 patients.

A second limitation of the study is that compliance with the home therapy and mitt-wearing schedule was not adequately documented in either study. One could argue that, perhaps, the CIMT-1 patients were less compliant and, therefore, practised less than the CIMT-6 patients.

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