Rehabilitation of Stroke Patients with Plegic Hands: Randomized Controlled Trial of Expanded Constraint-Induced Movement Therapy

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Abstract.

Purpose: To evaluate the efficacy of an expanded form of Constraint-Induced Movement Therapy (eCIMT) that renders CIMT, originally designed for treating mild-to-moderate upper-extremity hemiparesis, suitable for treating severe hemiparesis.

Methods: Twenty-one adults ≥1 year after stroke with severe upper-extremity hemiparesis (with little or no capacity to make movements with the more-affected hand) were randomly assigned to eCIMT (*n*=10), a placebo-control procedure (*n*=4), or usual care (*n*=7). The participants who received usual care were crossed over to eCIMT four months after enrollment. The CIMT protocol was altered to include fitting of orthotics and assistive devices, selected neurodevelopmental techniques, and electromyography-triggered functional electrical stimulation. Treatment was given for 15 consecutive weekdays with 6 hours of therapy

scheduled daily for the immediate eCIMT group and 3.5 hours daily for the cross-over eCIMT group.

Results: At post-treatment, the immediate eCIMT group showed significant gains relative to the combination of the control groups on the Grade-4/5 Motor Activity Log (MAL; mean=1.5 points, $P<0.001$, $f=4.2$) and a convergent measure, the Canadian Occupational Performance Measure (COPM; mean=2.3, $P=0.014$, $f=1.1$; f values ≥ 0.4 are considered large, on the COPM changes ≥ 2 are considered clinically meaningful). At 1-year follow-up, the MAL gains in the immediate eCIMT group were only 13% less than at post-treatment. The short and long-term outcomes of the crossover eCIMT group were similar to those of the immediate eCIMT group.

Conclusions: This small, randomized controlled trial (RCT) suggests that eCIMT produces a large, meaningful, and persistent improvement in everyday use of the more-affected arm in adults with severe upper-extremity hemiparesis long after stroke. These promising findings warrant confirmation by a large RCT.

Keywords: stroke, upper extremity, plegia, rehabilitation, randomized controlled trial

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1. Introduction

In the U.S.A., between 55-75% of stroke survivors experience residual upper-extremity hemiparesis (Lai, Studenski, Duncan, & Perera, 2002). This impairment is associated with substantial limitations in independence (Dromerick et al., 2006; K C Lin, Wu, Wei, Lee, & Liu, 2007) and quality of life (Nichols-Larsen, Clark, Zeringue, Greenspan, & Blanton, 2005). Furthermore, disuse of the arm on the more-affected side of the body after stroke is associated with a reduction in its neural representation (Gauthier, Taub, Mark, Barghi, & Uswatte, 2012; Liepert et al., 2000).

Prominent reviews of motor recovery after stroke by Luft and Hanley (2006) and Langhorne, Bernhardt, and Kwakkel (2011) conclude that evidence-based rehabilitation is available for patients ≥3 months post-stroke with mild to moderate upper-extremity hemiparesis, i.e., who meet the Grade 2 or 3 criteria in Table 1. Constraint-Induced Movement therapy (CIMT) (Taub et al., 1993; Taub, Uswatte, King, et al., 2006) is among a handful of treatments that two recent, comprehensive, review of reviews (Hatem et al., 2016; Pollock et al., 2014) recommend as efficacious for rehabilitating motor function of the more-affected arm for such patients. CIMT is a behavioral approach to physical rehabilitation that has four major components. The first is intensive training in use of the more-affected arm on functional tasks. The second is organization of this training according to shaping principles, which demand frequent, positive feedback and raising the bar required for reward in progressive, incremental steps (Skinner, 1938). Third is a group of behavioral techniques designed to transfer gains from the treatment setting to the real world, termed the "transfer package" (see **Methods,** *Interventions* for a description of the techniques). Fourth is wearing of a padded mitt to restrain

use of the less-affected hand for the portion of waking hours of the treatment period that it is safe to do so. The overall purpose of the four components is to countercondition learned nonuse (Taub, 1980; Taub, Uswatte, Mark, & Morris, 2006), i.e., a learned tendency to avoid using the more-affected arm, and to improve the quality, speed, and ease of more-affected arm movement. The treatment is provided on an outpatient basis for 3.5 hours per day for 10 consecutive weekdays. Notably, CIMT has been found to increase the neural representation of the more-affected arm (Gauthier et al., 2008; Liepert et al., 2000), in addition to producing large improvements in everyday use of that arm (Taub et al., 1993; Taub, Uswatte, King, et al., 2006; Taub, Uswatte, Mark, et al., 2013).

Inspection of the review of reviews by Hatem and colleagues (2016), which stratifies studies by whether participants had some or no movement of the more-affected hand, (Langhorne, Bernhardt, & Kwakkel, 2011; Luft & Hanley, 2006) indicates that there are no physical rehabilitation therapies with robust evidence of producing lasting gains in everyday arm function for stroke patients with greater than moderate paresis of their more-affected arm. Such patients represent between 25-50% of stroke survivors with residual upper-extremity impairment (Parker, Wade, & Langton-Hewer, 1986). Hatem and colleagues report that the only rehabilitation intervention with clear evidence of improving motor outcomes in patients with little to no movement of the more-affected hand is mirror therapy, but review of the mirror therapy studies that assess everyday use of the more-affected arm (K. C. Lin, Huang, Chen, Wu, & Huang, 2014; Michielsen et al., 2011; Thieme et al., 2013; Wu, Huang, Chen, Lin, & Yang, 2013) show that mirror therapy does not confer an advantage in this important domain of motor function. Everyday use of the more-affected arm is assessed in these studies with the Motor

Activity Log (Taub et al., 1993; Uswatte, Taub, Morris, Light, & Thompson, 2006; Uswatte, Taub, Morris, Vignolo, & McCulloch, 2005), ABILHAND (Massimo Penta, Tesio, Arnould, Zancan, & Thonnard, 2001), or Hand Function subscale of the Stroke Impact Scale (Duncan et al., 1999).

A case study (Bowman et al., 2006) and case series (Taub, Uswatte, Bowman, et al., 2013) from our laboratory, in contrast, report that patients ≥1-year after stroke with severe more-affected arm impairment, i.e., who meet the Grade-5 criteria in Table 1, show large gains in everyday use of that arm that are retained over the 6-month follow-up period. The intervention in these studies is an expanded version of CIMT that includes prescription of adaptive equipment and orthotics and elements of other rehabilitation therapies. Sterr and colleagues (2014) report similar outcomes with a 12-month follow-up period from a large trial that includes chronic stroke patients with both moderately severe and severe more-affected arm impairment and that features a no-treatment control period, i.e., provides within-subjects control with respect to the efficacy of the intervention. This paper presents evidence from a randomized controlled trial (RCT) comparing the outcomes of expanded CIMT (eCIMT) to a placebo control condition or usual care in chronic stroke survivors with plegic hands.

2. Methods

2.1 Participants

Participants were recruited from individuals who had contacted our laboratory seeking participation in previous trials but were excluded because their upper-extremity hemiparesis was too severe. Potential participants were screened using structured telephone interviews and then structured examinations by a physical or occupational therapist and a neurologist. Participants had to meet the Grade-5A or -5B criteria for active and passive range of motion (ROM) listed in Table 1. Individuals were excluded if they a) were <1 year after their most recent stroke, b) reported substantial use of the more-affected arm in daily life (Grade-4/5 Motor Activity Log [MAL] score >2.5; see *Measures*), exhibited marked spasticity in at least one more-affected arm muscle group (Modified Ashworth scale >3) (Bohannon & Smith, 1987), c) proved unable to stand for 2 minutes without assistance from another, d) reported pain in any part of the body severe enough to interfere with participation in treatment, e) scored <24 on the Folstein Mini-Mental Status Exam (Nelson, Fogel, & Faust, 1986) or were not able to follow directions for 2 out of 4 sample items from the Grade-4/5 Wolf Motor Function Test (WMFT; see below), or f) noted a Botox A injection for the upper-extremity within 3 months. Participant characteristics are described in *Results* and Table 2. The legend to Figure 1 describes the steps taken to protect the rights of participants.

2.2 Interventions

Participants were randomly assigned to eCIMT or a control condition (see Figure 1) using a computer-generated random numbers table. The first four participants assigned to the control condition received upper-extremity stretching and EMG-biofeedback from the muscles controlling movement of the more-affected arm for the same amount of time as the eCIMT

group. These four participants will be heretofore referred to as the Placebo group. The last seven participants assigned to the control condition received usual and customary care; this group will be heretofore referred to as Usual Care. The latter group was crossed over to eCIMT, which was given for a reduced number of hours daily approximately four months after enrollment. The order of assignment to one of the two control groups was sequential in their order of recruitment. However, assignment to the treatment or to a control condition was always on a random basis.

Participants in the immediate eCIMT group received 6 hours of therapy daily for 15 consecutive weekdays. Each of the elements of eCIMT is sketched in the **Appendix**, which also contains a table that breaks down the time spent on each element by participant. The protocol is described in detail in the case study (Bowman et al., 2006) and series (Taub, Uswatte, Bowman, et al., 2013) mentioned above.

Briefly, eCIMT consisted of the basic elements of CIMT noted in the Introduction: intensive practice, training by shaping movements, restraint of the less-affected arm and a "transfer package" of techniques to facilitate transfer of therapeutic gains from the laboratory to the life situation. The Transfer Package consisted of a number of components that included: 1) daily administration of the Grade 4/5 Motor Activity Log (MAL), which collects information about use of the more-affected arm in 30 important activities of daily living (see below); 2) a patient-kept daily diary, which details what a participant did when out of the laboratory overnight and the extent to which there was compliance with an agreed-upon amount of use of the more-affected arm (see next component); 3) behavioral contracts for participants and caregivers specifying agreed-upon real world activities for which the more-affected arm would

be used exclusively (1, 2, and 3 are monitoring and accountability components); 4) problem solving to help the participants overcome perceived barriers to real-world use of the more-affected arm identified during monitoring; 5) home practice of specified exercises; and 6) weekly telephone contacts with patients for the first month after the end of treatment in which the MAL is administered and problem solving is carried out. Home practice (Transfer Package component 5) was assigned both during treatment and afterwards. During treatment, participants were asked to practice up to 10 everyday, upper-extremity tasks, e.g., opening the refrigerator, carrying an object, at home. As treatment progressed, increasingly difficult tasks were assigned. Tasks were always feasible for the participants to perform. After treatment, participants were asked to practice 2 to 3 structured, repetitive tasks, e.g., reaching to a target on the wall, scooping beans with a cup, for up to 30 minutes a day. Participants were also encouraged to use their more-affected arm as much as safely possible in their daily routine. Changes to the standard CIMT protocol to adapt to therapy with severely impaired patients were lengthening from two to three weeks the duration of treatment, reducing the time that participants wore the mitt, and adding task practice with simulations of both unimanual and bimanual everyday activities. Examples of bimanual activities were using the more-affected arm to stabilize a piece of food while using the other to cut it and using both arms to carry a laundry basket.

In addition, the eCIMT protocol involved the use of orthotics and adaptive equipment, neurodevelopmental therapy (NDT) for managing tone and facilitating movement (Howle, 2004), and EMG-triggered functional electrical stimulation (FES)(Cauraugh & Kim, 2003; Chae et al., 1998). The purpose of the orthotics and splints was to maintain the fingers and wrist in better alignment to enhance the use of the more-affected arm and hand in everyday activities.

The purpose of the NDT techniques was to reduce tone and increase activation of appropriate muscles in the trunk and upper-extremity to support movement of the more-affected arm during training. EMG-FES was incorporated into selected training tasks to permit participants to train on tasks that they would not otherwise be capable of at the outset of treatment.

More-affected arm restraint was accomplished by use of a padded mitt that prevented use of the fingers of the less-affected arm. In work with higher functioning patients the requirement is set at 90% of waking hours (e.g. Taub et al., 1993; Taub, Uswatte, King et al., 2006). However, the severely impaired patients here needed to use the less-affected arm to hold an assistive device during walking and to maintain balance. Therefore, the time requirement for wearing the mitt was `relaxed to include only those times when it was safe to do so.

A typical treatment day started with approximately 25 minutes for several Transfer Package procedures (interview about use of more-affected arm at home, problem-solving to overcome perceived barriers to use of more-affected arm, review of daily dairy), 5 minutes for review of use and adjustment of any orthotics and adaptive equipment, and 30 minutes for tone management and facilitation of movement. The remainder of the 180 minute morning session was devoted to training of the more-affected arm according to shaping principles (45 minutes) and bimanual task practice with simulated everyday activities (15 minutes) interspersed with tone management and facilitation (10 minutes) and rest breaks (50 minutes) as needed. Time spent on more-affected arm training included 10 minutes in which EMG-FES was used to augment the force and excursion of participants' movements. Restraint of the less-affected arm was used for 75 out of 180 minutes. Variations from this typical schedule were based on the

therapist's judgment of the needs of the participant. Sixty minutes was provided for lunch and an extended rest break. The morning schedule was repeated in the afternoon with the exception that Transfer Package procedures (i.e., assignment of homework) and review of orthotics and adaptive equipment were done at the end rather than beginning of the session.

Participants in the Placebo condition received an equal number of hours of upper-extremity range of motion (ROM) exercises and EMG-biofeedback from the muscles controlling movement of the more-affected arm (Basmajian, Regenos, & Baker, 1977). Participants in the Usual Care control condition did not receive any treatment from study personnel but were permitted to obtain any care available on a clinical basis outside of the study. As noted, Usual Care participants were crossed over to eCIMT approximately four months after enrollment. This was done to offer Usual Care participants an inducement to agree to the two control sets of tests. In addition, the crossover procedure permitted testing of the effect of giving eCIMT for only 3.5 hours daily rather than 6. The table in the **Appendix** provides a breakdown of the time spent on each treatment component. The dose for the crossover eCIMT procedure was based on the observation of similar outcomes in CIMT studies that provided 3.5 hours of treatment daily (Taub, Uswatte, Mark et al., 2013) and 6 hours of treatment daily (Taub, Miller et al., 1993 and Taub, Uswatte et al., 2006) in stroke patients with less severe impairment than here.

Treatment of the participants in the immediate eCIMT and crossover eCIMT groups was conducted on an one-on-one basis by an occupational therapist (OT); she had approximately 12 years of experience in neurorehabilitation and 4 years of experience with CIMT, and was

certified in neurodevelopmental therapy. Treatment of the participants in the Placebo group was conducted on an one-on-one basis by a physical therapist (PT); she had approximately 20 years of experience in neurorehabilitation and 7 years of experience with CIMT, and had some training in neurodevelopmental therapy.

2.3 Measures

All of the outcome measures were administered at pre- and post-treatment or at equivalent times in the Usual Care group. In follow-up, only Grade-4/5 MAL data were collected consistently because this instrument could be administered over the telephone and several participants were from out-of-town. It was given weekly for the first month after treatment; and at the 6-month and 1-year post-treatment time points. The same schedule was followed for the subjects crossed over to eCIMT after their usual care period.

The primary endpoint was the post-treatment score on the Grade-4/5 MAL Arm Use scale. This structured interview assesses how much and how well the more-affected arm is used to complete 30 tasks in daily life. It is a version of the MAL, which is an established outcome measure (Uswatte, Taub, et al., 2006), that has been adapted for testing with severely impaired patients by changing the composition of the tasks. Twenty tasks on the MAL that require dexterity or strength outside of the range that is possible for the population studied here are omitted from the Grade-4/5 MAL and are replaced with tasks within that range (see Table 2). The scale that participants use to rate how well the tasks are performed with more-affected arm in the community, i.e., the Arm Use scale, is the same as on the MAL. The steps of the scale and

corresponding, abbreviated versions of the anchors are: 0, not used; 1, very poor use; 2, poor use; 3, fair use; 4, almost normal; and 5, normal. Analysis of the Grade-4/5 MAL pre-treatment data from the participants in the immediate eCIMT and control conditions combined suggest that the test has high internal consistency (Cronbach's $\alpha = .94$, $n = 21$). Analysis of the pre- and post-treatment data from the participants in the control conditions only suggest that the test has high test-retest reliability ($r = .95$, $n = 10$). The validity of the test is supported by (a) the finding from the eCIMT case series ($n = 6$; Taub et al., 2013) that improvement took place after treatment in both Grade-4/5 MAL scores and wrist-worn accelerometry readings, which provide an objective index of more-affected arm use in the community (Uswatte, Giuliani, et al., 2006), and (b) observation of strong correlations between changes in Grade-4/5 MAL and Canadian Occupational Performance Measure (COPM) scores here. The COPM is semi-structured interview with an established reliability and validity (McColl, Paterson, Davies, Doubt, & Law, 2000; Phipps & Richardson, 2007) that was a secondary outcome in this study in the same domain as the Grade-4/5 MAL, i.e., real-world arm use.. On the COPM, participants identify the 5 daily activities of most importance to them and, for each activity, rate their ability to carry it out (Performance scale) and satisfaction with their ability (Satisfaction scale). The correlation between pre- to post-treatment changes in Performance scale and Grade-4/5 MAL scores from participants in the immediate CIMT and Usual Care conditions combined was .78, $p < .001$, $n = 17$. (COPM data were not collected from participants in the Placebo condition.) The corresponding value for the Satisfaction scale was .76, $p < .001$, $n = 17$. The COPM differs importantly from the Grade-4/5 MAL in three way. First, participants rate their performance of and satisfaction with activities on the COPM without specific regard to use of their more-affected arm. Therefore, changes in scores on the COPM could be due to improvement in use of

the more-affected arm, the less-affected arm, other parts of the body, the social or physical environment, or some combination of these four factors. On the MAL, participants rate tasks specifically with respect to use of the more-affected arm. Second, participants select the activities to be rated, rather than rating a prescribed set of tasks as on the MAL, with the consequence that different participants are likely to evaluate activities which do not have comparable levels of difficulty. Third, the individual activities rated on the COPM may span several tasks. For example, for some participants dressing might encompass opening a drawer, removing a pair of pants and a T-shirt, carrying the clothes to the bathroom, and putting them on. On the Grade-4/5 MAL, these tasks are rated separately (see Table 2, Items 2, 3, 9, 14, and 21). As a result, improvements in function in particular components of an activity might be obscured by what takes place with the aspect of the activity that is most difficult for a participant.

Other secondary outcomes were the Performance Rate score from the Grade-4/5 WMFT and the upper-extremity motor score from the Fugl-Meyer Motor Assessment (FMA) scale (Fugl-Meyer, Jaasko, Leyman, Olson, & Steglind, 1975). The Grade-4/5 WMFT is a 10-item motor test that assesses capacity to complete actions and tasks with more-affected arm in the laboratory. This test is a version of the WMFT (Morris, Uswatte, Crago, Cook, & Taub, 2001; Wolf et al., 2001), which is an established outcome measure, that has been adapted for testing with severely impaired patients by making performance of some items less demanding. Eleven items on the WMFT that require dexterity, strength, or endurance outside of the range that is possible for the population studied here are omitted from the Grade-4/5 WMFT and are replaced with four less difficult items (see Table 3). To extend the range of the test further, each item on the Grade-4/5 WMFT has two levels of difficulty: Level A (High) and Level B (Low). Level B

are distinguished from Level A items by requiring a smaller range of motion or less complex type of grasp. Participants are instructed to attempt each item at Level A first, and to attempt an item at Level B only if they cannot perform it a Level A. As with the standard WMFT, time to complete each item is recorded and transformed into a rate, i.e., number of repetitions of the item per minute (Hodics et al., 2012). The rules for scoring Level A and B items so that times from participants performing items at different levels of difficulty can be compared are described in the footnotes to Table 3. Analysis of the Grade-4/5 WMFT pre-treatment data from the participants in the immediate eCIMT and control conditions combined suggest that the test has adequate internal consistency (Cronbach's $\alpha = .74$, $n = 21$). Analysis of the pre- and post-treatment data from the participants in the control conditions only suggest that the test has high test-retest reliability ($r = .93$, $n = 9$). The FMA is a commonly used structured physical examination that assesses capacity to execute isolated movements of the more-affected arm in the laboratory. Both the Grade-4/5 WMFT and FMA are distinguished from the Grade-4/5 MAL and COPM in that they assess motor capacity in the treatment setting rather than actual use of that capacity in the community, i.e., performance in the International Classification of Function (ICF) model of disability (Peterson, 2005). Theory, most prominently the learned nonuse formulation and the ICF model, and data support the contention that assessments of capacity can often depart from those of performance (reviewed in Uswatte & Taub, 2005), and that the two types of motor performances must be measured separately to obtain a complete picture of the effect of a physical rehabilitation intervention. The Grade-4/5 WMFT is distinguished from the FMA in that it assesses motor capacity in the context of actions and tasks, i.e., activity in the ICF model, rather than isolated movements, i.e., body structure and function in the ICF model. In

addition, Performance Rate on the Grade-4/5 WMFT is a continuous measure, which permits greater sensitivity to change than possible with the 3-step rating scale on the FMA.

Testing was conducted by the OT and PT who delivered the study interventions. Approximately equal numbers of participants in the immediate eCIMT and control conditions were tested by each: Immediate eCIMT- 4 participants tested by the OT, 6 by the PT; Control- 5 by OT, 6 by PT. The same applied to the crossover eCIMT condition: 4 by OT, 3 by PT. Pre- and post-treatment testing for a given participant was always carried out by the same tester.

2.4 Data Analysis

Two-tailed, mixed model, repeated measures analyses of variance (ANOVAs) with an α of 0.05 were used to test whether immediate eCIMT participants had better pre- to post-treatment outcomes than control participants. Repeated measures ANOVAs were used to evaluate long-term retention of gains on the MAL in the eCIMT group and Usual Care group after crossover to eCIMT. The primary analysis was by intention-to-treat with the last observation carried forward (LOCF) for missing data (Rubin & Sheiner, 1995). An additional intention-to-treat analysis substituted the group average (AVG) for any missing outcome values. A completers analysis was also conducted. Since all three analyses gave largely similar findings, only the results of the primary analysis are described below. Results from all three analyses are reported in detail in Tables 5 and 6, along with a description of missing data in the footnotes. Mean values are presented along with 95% confidence intervals (upper bound-lower bound). The *f* statistic (Cohen, 1988) was used to quantify the effect size of the pre- to post-treatment changes in the

immediate eCIMT group relative to the Control group. For this statistic, values ≥0.4 are considered large. Power was more than adequate (≥0.91) to detect a moderate effect (f =0.25) on the primary endpoint, i.e., to detect a difference in gains at post-treatment between the immediate eCIMT and control participants of at least 0.3 MAL points.

3. Results

3.1 Trial Profile and Initial Participant Characteristics

Out of 95 candidates screened by telephone, 21 were enrolled and randomized (eCIMT, n=10; Placebo, n=4; Usual Care, n=7; see Fig. 1). All assigned to immediate eCIMT completed post-treatment and 1-year follow-up testing. One participant assigned to Placebo withdrew after pre-treatment because he had not been assigned to the experimental condition. All other control participants completed post-treatment testing and 3-month follow-up (i.e., 4 months after enrollment). Usual Care participants were crossed over to eCIMT afterwards.

There were no significant differences at pre-treatment between the immediate eCIMT and control participants for any of the characteristics listed in Table 4 or study measures listed in Table 5. Participants were, on average, 54 years old (range=23-76) and 4 years after stroke (range=1-12). Eleven had paresis of the side that was dominant before stroke. Thirteen had paresis of the right side. Five had no active movement of the more-affected hand (Grade-5B), while 16 had minimal movement (Grade-5A). For the pre-treatment and subsequent analyses, the

two control conditions (Placebo and Usual Care) were combined into one Control group because their treatment outcomes were similar.

3.2 Changes after Treatment

The immediate eCIMT group had very large gains relative to the Control group on the primary endpoint. On the Grade-4/5 MAL, which measures use of the more-affected arm in daily life, the mean difference between the groups in pre- to post-treatment gains was 1.5 points (*95% CI*=1.3-1.6, *P*<0.001, *f*=4.2). Table 5 provides the mean values at pre- and post-treatment and mean changes from pre-treatment within each group. Table 6 shows that the changes in the Usual Care participants *after crossover* to eCIMT for 3.5 hours daily instead of 6 were similar to those observed in the immediate eCIMT group participants given 6 hours of treatment daily.

Examination of the outcomes on individual items of the Grade-4/5 MAL, which are depicted in Fig. 4, shows the nature of the changes observed after eCIMT. The range of scores on the instrument is from 0-5. From pre- to post-treatment, the number of items with scores of 0 or 1, reflecting no or ineffective function of the more-affected arm, fell from 83% to 30%. The number of items with scores of 2, reflecting function that was somewhat effective but very effortful or only effective with assistance from the other arm, rose from 14 to 40%. The number with scores of 3, reflecting function that was effective without assistance but required some effort, rose from 3 to 30%.

The pattern of improvements depicted in Fig. 3 suggests that both gross movements at the shoulder and elbow (e.g., reaching, pulling, pushing) and rudimentary types of grasp (e.g., raking, claw, cylindrical) improved as a result of eCIMT. None of the test items sampled tasks that require fine coordination of finger movement because we did not expect such changes. Observations by the therapy team supported this expectation. Improvements in finger movements were detected in a few patients but the changes were too small or unreliable to be measurable. Finer types of grasp (e.g., 3-jaw chuck, pincer) were not recovered, even though grosser forms of grasp improved.

The post-treatment gains made on the Grade-4/5 MAL in both eCIMT groups were retained. In the immediate eCIMT group, the mean change from pre-treatment at 1-year follow-up was 1.3 (0.8-1.7; $P<0.001$), a decrement of just 13%. In the crossover eCIMT group, the corresponding change for 5 of 7 crossovers who did 1-year follow-up was 1.5 (1.0-2.0; $P<0.001$), a decrement of 21%. On an intention-to-treat LOCF basis, this value was 1.1 (0.3-1.8; $P=0.024$).

Post-treatment results on the COPM, which also assesses real-world arm function, converged with those on the Grade 4/5 MAL. On the Performance scale, the immediate eCIMT group had very large gains relative to the Usual Care group: a difference of 2.3 points (1.6-3.0; $P=0.014$, $f=1.1$). On the Satisfaction scale, there was a trend in favor of the immediate eCIMT group: a difference of 1.5 (0.7-2.2; $P=0.106$, $f=0.7$). Changes in the crossover eCIMT group were similar to those in the immediate eCIMT group (Table 6).

On the Grade-4/5 WMFT, which assesses capacity to complete actions and tasks with the more-affected arm made on request in the laboratory, the immediate eCIMT group had large gains relative to the Control group at post-treatment: a difference of 9.6 repetitions per minute (6.0-13.2; P=0.018, f=0.8). The improvement in the crossover eCIMT group was similar (Table 6). Changes on the FMA did not differ between the eCIMT and Control groups.

3.3 Safety and Compliance

There were no adverse events related to the study procedures (see Fig. 1 legend). Moreover, there was no increase in spasticity of the more-affected arm after eCIMT, as measured by the Modified Ashworth scale. On average, the mitt was worn on the less-affected arm for 30% (24-36) of waking hours over the 3-week treatment period in the immediate eCIMT group according to a capacitive sensor embedded in the mitt. The corresponding number in the crossover eCIMT group was 43% (36-50).

4. Discussion

Prior to this study, there were no physical rehabilitation interventions for stroke survivors with severe upper-extremity hemiparesis that had evidence from a RCT of changing function of the more-affected arm in daily life (see **Introduction**). Previous CIMT studies in this population with only modest adaptations to the standard protocol, which are discussed elsewhere (Taub, Uswatte, Bowman, et al., 2013), were not successful. In this RCT, participants with severe

upper-extremity hemiparesis who received eCIMT showed, on average, a 250% gain in use of the more-affected arm in daily life immediately afterwards that was retained with little decrement at 1-year follow-up (see Fig. 2). Large gains in capacity to carry out actions and tasks with the more-affected arm were also observed immediately afterwards (Table 5 and 6). A post-hoc analysis of changes in individual items on the Grade-4/5 MAL and WMFT suggested that both gross movements at the shoulder and elbow (e.g., reaching, pulling, pushing) and rudimentary types of grasp (e.g., raking, claw) improved (see Fig. 3). eCIMT did not result in improvement in capacity to carry out movements of the more-affected arm in the laboratory when the movements were restricted to a single joint and not embedded in the context of an action or task. Participants who received one of two control procedures, Placebo or Usual Care, showed little or no change in any of the aspects of more-affected arm function evaluated.

Confidence in the pattern of changes for the primary endpoint, the Grade-4/5 MAL at post-treatment, was strengthened by four considerations. First, the changes observed in the immediate eCIMT group replicated those in a previous eCIMT case series (Taub, Uswatte, Bowman, et al., 2013), which included an objective, accelerometry-based index of upper-extremity activity in daily life (Uswatte, Giuliani, et al., 2006). Second, the changes in the immediate eCIMT group were similar to those in the crossover eCIMT group. Third, the Grade-4/5 MAL results converged with those on the COPM, which is an established measure (McColl et al., 2000; Phipps & Richardson, 2007). Fourth, the meager improvement in the Placebo group (mean Grade-4/5 MAL change = 0.2 [0.1-0.3]) was consistent with recent review of reviews that concluded that sufficient evidence is not available to support the efficacy of ROM exercises

(Hatem et al., 2016; Pollock et al., 2014) or EMG biofeedback (Pollock et al., 2014) for rehabilitating upper-extremity motor function after stroke.

The gains on the COPM, in addition to lending support to the changes observed on the Grade-4/5 MAL, addressed the question of whether the changes in real-world use of the more-affected arm were meaningful to participants. As noted, participants selected 5 activities before treatment to be rated on the COPM that were of most importance to the participants in daily life but which they had difficulty carrying out (McColl et al., 2000). After treatment, mean COPM Performance scale gains in the immediate eCIMT and crossover eCIMT groups were larger by 20% and 55%, respectively, than the threshold established for a meaningful clinical change (Phipps & Richardson, 2007).

Another noteworthy feature of the results was that the participants who received only 3.5 hours per day of treatment when crossed over to eCIMT from usual care had Grade 4/5 MAL gains that were not worse than the immediate eCIMT group, which received 6 hours of treatment per day (see Tables 5 & 6 and Fig. 2). This finding was consistent with data from stroke patients with mild-to-moderate (Grade 2) motor deficits who received CIMT: e.g., compare the similar outcomes in (Taub et al., 1993; Taub, Uswatte, King, et al., 2006), which scheduled 6 hours of treatment daily, with those in (Taub, Uswatte, Mark, et al., 2013), which scheduled 3.5 hours daily. Possible explanations of these findings regarding a sufficient dose of CIMT are that additional treatment beyond 3.5 hours daily a) does not produce additional improvement in more-affected arm function or b) does produce additional improvement but any improvement is

offset by the adverse effects of fatigue induced by additional training or by the reduction in time available to practice using the more-affected arm outside of the treatment setting.

Study limitations

A limitation of this study was the small sample size, which raises questions about the generalizability of the findings and rules out meaningful analyses of the influence of participant characteristics, such as gender or side of stroke, on treatment outcomes. A second limitation was that the assessment of outcomes was not blinded. A third was that the study design did not permit examination of which of the components of the complex intervention tested were responsible for the effects observed. These important issues might be addressed in a future study with a large sample size, a blinded tester, and several arms that evaluate various combinations of the treatment components. Such a study would also inform guidelines about how much time to commit to each component of the intervention, helping to reduce the substantial variability across participants in this aspect of the procedures present in this study (see table in **Appendix**). This study also leaves questions regarding the mechanisms responsible for the effects observed largely unanswered. However, the larger gains observed in real-world use of the more-affected arm than in its motor capacity are consistent with the hypothesis that eCIMT counterconditions learned nonuse (Taub, 1980; Taub et al., 1993; Taub, Uswatte, Mark, et al., 2006). A fourth limitation was that the amount and type of treatment received by Usual Care participants was not recorded in a systematic way. In addition, a future study that collects data on the structure and function of the brain before and after eCIMT would test whether this intervention is associated with neuroplastic changes that are similar to those observed after CIMT in chronic stroke

patients with mild to moderate upper-extremity hemiparesis (Gauthier et al., 2008; Liepert et al., 2000).

Conclusions

Notwithstanding these unanswered questions, the findings from this initial, small RCT suggest that large, meaningful, and persistent improvements can be obtained in everyday use of the more-affected arm in patients with severe upper-extremity hemiparesis long after stroke. These promising results warrant verification by a large RCT.

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Table 1

CIMT System for Classifying More-affected Arm Impairment in People with Upper-extremity Hemiparesis*

Severity of Impairment	Minimum Active Range of Motion Required				
	Shoulder	Elbow	Wrist	Fingers	Thumb
Grade 2	Flexion ≥45° and Abduction ≥45°	Extension ≥20° from a 90° flexed starting position	Extension ≥20° from a fully flexed starting position	Extension of all MCP and IP (either PIP or DIP) joints ≥10°†	Extension or abduction of thumb ≥10°
Grade 3	Flexion ≥45° and Abduction ≥45°	Extension ≥20° from a 90° flexed starting position	Extension ≥10° from a fully flexed starting position	Extension ≥10° MCP and IP (either PIP or DIP) joints of at least 2 fingers†	Extension or abduction of thumb ≥10°
Grade 4	Flexion ≥45° and Abduction ≥45°	Extension ≥20° from a 90° flexed starting position	Extension ≥10° from a fully flexed starting position	Extension of at least 2 fingers >0° and <10°‡	Extension or abduction of thumb ≥10°
Grade 5A¶	At least *one* of the following:	Initiation of extension**	Must be able to *either* initiate extension of the wrist *or* initiate extension of one digit		

	Flexion ≥30° abduction ≥30° scaption ≥30°		
Grade 5B¶	At least *one* of the following: Flexion ≥30° abduction ≥30° scaption ≥30°	Extension ≥20º from a 90º flexed starting position	No active movement required for the wrist, fingers, or thumb

*In this system, people are placed in the highest grade at which they can meet or exceed each minimum movement criterion for each joint 3 times in 1 minute. Anyone who cannot meet the minimum movement criterion for Grade 5A or 5B is placed in Grade 6. A minimum degree of passive ROM is also required. For Grades 2-4 the minimum passive ROM criteria are: shoulder flexion and abduction of at least 90° and shoulder external rotation of at least 45°, elbow extension to within 30° of the normal limit, forearm supination to at least 45°, forearm pronation to at least 45° from neutral, wrist extension to at least neutral, and MCP joint extension to within 35° of the normal limit. For Grades 5A and 5B, the passive ROM criteria are the same, except for the following relaxations of the requirements: a) forearm supination to neutral instead of to 45° and b) wrist extension to within 45° of neutral instead of to neutral. Importantly, placement in any of the Grades, in addition, requires a substantial deficit in use of the more-affected arm as documented

by a score of less than 2.5 on MAL (see **Measures**). †Informally assessed when picking up and dropping a tennis ball. ‡Informally assessed when picking up and dropping a washcloth. ¶Grade 5B is distinguished from 5A by the absence of any active extension at the wrist, fingers, or thumb on the more-affected hand; however, greater active extension of the elbow is required for Grade 5B than 5A. Without a greater degree of movement at the elbow to compensate for the lack of any movement at the hand, the movement capacity specified by Grade 5B would be too low to permit training with even rudimentary functional tasks. Please note that people who meet the Grade-5A hand and Grade-5B elbow criteria would be placed in Grade 5A. People who meet the Grade-5B hand criterion but fail to meet the Grade-5B elbow criterion, even though they exceed the Grade-5A elbow criterion, would fall into Grade 6. **Initiation is defined here as minimal movement, i.e., below the level that can be measured reliably by goniometry. Abbreviations: CIMT, Constraint-Induced Movement therapy; MCP, metacarpophalangeal; IP, interphalangeal; PIP, proximal interphalangeal; DIP, distal interphalangeal; ROM, range of motion; MAL, Motor Activity Log.

Table 2

Standard Motor Activity Log (MAL) and Grade-4/5 MAL Items

Item	Standard MAL (Grades 2/3)	Grade-4/5 MAL
1	Turn on a light with a light switch	Turn on a light with a light switch
2	Open drawer	Open drawer
3	Remove an item of clothing from a drawer	Remove an item of clothing from a drawer
4	Pick-up phone*	Wipe off a kitchen counter of other surface
5	Wipe off a kitchen counter of other surface	Get out of a car (includes only the movement needed to get body from sitting to standing outside of the car, once the door is open)
6	Get out of a car (includes only the movement needed to get body from sitting to standing outside of the car, once the door is open)	Open refrigerator
7	Open refrigerator	Open a door by turning a door knob/handle
8	Open a door by turning a door knob/handle	Wash your hands

9	Use a TV remote control*	Carry an object in your hand (draping an item over the arm is not acceptable)
10	Wash your hands	Pick up a cup by a handle
11	Turning water on/off with knob or lever on faucet*	Flush the commode†
12	Dry your hands*	Use a towel†
13	Put on your socks*	To provide support while sitting†
14	Take off your socks*	Put on pants or undergarments†
15	Put on your shoes (includes tying shoestrings and fastening straps)*	Roll over in bed†
16	Take off your shoes (includes untying shoestrings and unfastening straps)*	Apply soap to body while bathing†
17	Get up from chair*	Sit up on the side of the bed†
18	Pull chair away from table before sitting down*	Push off/pull up bed cover†
19	Pull chair toward table after sitting down*	To provide support while standing†
20	Pick up a glass, bottle, drinking cup, or can (does not need to include drinking)*	Wipe mouth†

21	Brush your teeth (does not include preparation of toothbrush or brushing dentures unless the dentures are brushed while left in the mouth)*	Put on a pullover or T-shirt†
22	Put on makeup base, lotion, or shaving cream on face*	Hold an everyday object for use (e.g., hold the phone to dial number, hold TV remote control to push button, or hold toothbrush for applying to place)†
23	Use a key to unlock a door*	Hold a jar or bottle or container for opening†
24	Write on paper (If hand used to write pre-stroke is more affected score item; if non-writing hand pre-stroke is more affected, drop item and assign N/A) *	Push or pull a door open or closed (e.g., bathroom door, cabinet door, or car door)†
25	Carry an object in your hand (draping an item over the arm is not acceptable)	Remove towel from rack†
26	Use a fork or spoon for eating (refers to action of bringing food to the mouth with fork or spoon)*	Hold paper while writing†
27	Comb your hair*	Use a fork for holding meat/food for cutting with knife†

28	Pick up a cup by a handle	Carry any object either draped over the arm or tucked under the arm†
29	Button a shirt*	Push buttons (e.g., elevator buttons, door bells, vending machines, computer, etc.)†
30	Eat half a sandwhich or finger foods*	Gather up items (e.g., clothes to hamper, newspaper, blanket, etc.) †

*Items on the MAL that do not appear on the Grade-4/5 MAL. †Items on the Grade-4/5 MAL that do not appear on the MAL.

Table 3

Standard Wolf Motor Function Test (WMFT) and Grade-4/5 WMFT Items

	Standard WMFT		Grade-4/5 WMFT	
Item	Brief Description	Brief Description	Level A: High Difficulty*	Level B: Low Difficulty*
1	Forearm to table (side)	Forearm to table (side)	Participant attempts to place forearm on table (adjacent and parallel to front edge) by abduction at the shoulder. Chair placed beside and 8.5 cm from the front table edge. Side to be tested is adjacent to the table. Back of chair is 6.5 cm beyond edge of side end of testing template placed on table.**	Same as level A except participant sits on a 7.6-cm platform topped with a 2.5-cm cushion and placed on chair seat.
2	Forearm to box (side)	Forearm to box (side)	Participant attempts to place forearm (from wrist to elbow)	Same as level A except a 5.08 cm box is used.

			on a 12.7 cm box by further abduction at the shoulder.	
			Chair position same as Item 1. The box is placed in the template area located 13.5-cm. from the front edge of the template and 13.5-cm. from midline.	
3	Extend elbow (side)†	Hand to table (front)	Participant attempts to place hand being tested on the table. Chair is facing the table and centered on the task object template. The front edges of the rear legs of the chair are	Same as level A except subject sits on a 7.6-cm platform topped with a 2.5-cm cushion and placed on the chair seat.

			60 cm. from the front table edge.	
4	Extend elbow (weight)†	Hand to box (front)	Participant attempts to place hand on a 12.7 cm box. Chair position same as Item 3. Box centered on table; front edge aligned with line 20 cm from front edge of template.	Same as level A except a 5.08 cm box is used.
5	Hand to table (front)	Extend elbow in front¶	Patient extends the elbow until any portion of the hand crosses the line 40 cm from the front edge of the testing template. Chair is facing the table and centered on the task object	Same as level A except the 28 cm line is used

			template. The front edges of the rear legs of the chair are 11 cm. from the front table edge. Elbow of arm to be tested flexed with forearm placed in a position that is comfortable for the patient.	
6	Hand to box (front)	Reach and retrieve	Participant attempts to pull 1 lb. weight across the 8 cm line. The starting position for the participant's hand is just beyond the 40 cm line. Chair position same as Item 5. 1 lb. weight on table is positioned just beyond 40 or 28 cm line.	Same as level A except the starting position is the 28 cm line.

7	Weight to box†	Hand to upper body¶	The participant flexes the shoulder and elbow lifting the hand to touch the nose. Chair position same as Item 3.	Same as level A, except that the participant flexes the shoulder and the elbow lifting the hand to touch the sternoclavicular joint.
8	Reach and retrieve	Lift washcloth¶	Participant completes the task by grasping the washcloth with any grasp they can manage, lifting it until it completely clears the table, and moving it forward over the 22 cm line. Chair position same as Item 1. Washcloth is placed flat and centered on the table with	Participant completes the task by grasping the washcloth with any grasps they can manage and lifting the wash cloth completely off the table.

			its near edge lined up with the 2 cm line.	
9	Lift can†	9. Stabilize bottle (front)¶	Participant completes task by grasping and stabilizing bottle with more-affected UE without the assistance of the less affected for placement on the bottle and removing the cap with the less-affected UE.	Participant completes task by grasping and stabilizing bottle with more-affected UE with the assistance of the less affected for placement on the bottle and removing the cap with the less-affected UE.
			Chair position same as Item 3. Bottle placed on table at subject's midline with front edge of the bottle just beyond the 20 cm line.	
10	Lift pencil†	10. Lift basket	Patient attempts to pick up basket by grasping the two lateral sides of the basket and	Same as Level A, except the subject completes the task using both hands to grasp the

			lifting it completely onto the bedside table. Subject standing and facing table. Bedside table is positioned perpendicular to the testing table with the end of the bedside table extended over the testing table and aligned with the 40 cm line.	two lateral sides of the basket and lift the basket completely up to bedside table at lowest height (i.e. touching the testing table).
11	Lift paper clip†	n/a	n/a	n/a
12	Stack checkers†	n/a	n/a	n/a
13	Flip cards†	n/a	n/a	n/a
14	Grip strength†	n/a	n/a	n/a
15	Turn key in lock†	n/a	n/a	n/a

16	Fold towel†	n/a	n/a	n/a
17	Lift basket†	n/a	n/a	n/a

Note. On the WMFT, time to complete each item is recorded. The performance time for each item is transformed into a rate by dividing the performance time by 60 s. The Performance Rate score for the entire test is the mean of the rate values for each item except for Items 4 (Extend elbow [weight]) and 7 (Weight to box) which are not timed. Instead, the amount of force that participants can exert is assessed. *On the Grade-4/5 WMFT, participants are required to attempt Level A for each item first. Level A is the more difficult version of each item. If a participant is not able to complete the item at Level A in 30 s, the participant receives a score of 60 s and is then asked to complete the item at Level B. Participants are permitted to attempt to do Level B for 60 s. If a participant is not able to do Level B, the score recorded is 60 s. Thus, the performance time for a task that a participant was not able to complete at either level is 120 s: 60 s (Level A) + 60 s (Level B) = 120 s. If a participant is not able to complete an item at Level A but was able to complete it at Level B in 20 s, for example, the performance time for that task is 80 s: 60 s (Level A) + 20 s (Level B). If a participant is able to complete an item at Level A, Level B is not attempted and the performance time is simply the number of seconds required to complete the item at Level A. After applying these rules, the Performance Rate score for the entire test is calculated in the same way as for the WMFT. Since the items on the WMFT that assess the amount of force that participants can exert, Items 4 and 7, are omitted from the Grade-4/5 WMFT, there is no need for rules handling force measurements from high and low difficultly levels of

these items. †Items on the WMFT that do not appear on the Grade-4/5 WMFT. ¶Items on the Grade-4/5 WMFT that do not appear on the WMFT. **Chair positions are listed for a person approximately 172.7 cm tall and a chair whose seat is 45 cm off the floor. The testing table is 137 cm long, 76 cm wide, and 73.5 cm high.

Table 4

Initial Characteristics of Participants in the eCIMT and Control Groups

Characteristic	eCIMT (n=10)	Control		
		Placebo (n=4)	Usual Care (n=7)	All Controls (n=11)
Demographic				
Age, y	49.0(38.3-59.7)	64.0(53.7-74.4)	52.6(45.5-59.6)	56.7(50.7-62.8)
Female	2	0	1	1
European American	5	2	7	9
African American	5	2	0	2
Stroke-related				
Time since stroke, y	3.8(1.5-6.1)	3.1(-0.7-6.9)	3.1(1.5-4.8)	3.1(1.8-4.4)
Paresis of right side	8	2	3	5
Paresis of pre-stroke dominant side	8	1	2	3
*Grade-5 subcategory**				
A (minimal hand movement)	9	2	5	7

B (no hand movement)	1	2	2	4

Note. Values are mean(95% confidence interval) for continuous data and number in class for categorical data. There were no significant differences between the eCIMT group and the combined Control group for the variables tabled. *This system for classifying the degree of more-affected arm motor impairment is described in Table 1. Abbreviations: eCIMT=expanded Constraint-Induced Movement therapy.

Table 5

Pre- to Post-treatment Changes for All in the Immediate eCIMT Group and Control Group*

	eCIMT (*n*=10)			Control (*n*=11)			Size (*f*)‡ and significance level (*P*) of between-group differences in change	
Outcome	Pre	Post	Change	Pre	Post	Change	*f*	*P value*
Measures of spontaneous use of the more-affected arm in daily life								
Grade 4/5 MAL Arm Use scale (0-5 points)								
All/Completers	0.6(0.2-0.9)	2.1(1.7-2.5)	1.5(1.3-1.8)	0.5(0.1-1.0)	0.6(0.2-1.0)	0.1(-0.1-0.2)	4.2	<0.001
LOCF†		n/a		0.5(0.2-0.9)	0.6(0.3-1.0)	0.1(-0.1-0.2)	4.2	<0.001
AVG†		n/a		0.5(0.2-0.9)	0.6(0.2-0.9)	0.0(-0.1-0.2)	4.0	<0.001
COPM Performance scale (1-10 points)								
All	1.5(1.2-1.8)	3.9(2.7-5.0)	2.4(1.2-3.5)	2.0(0.4-3.7)	2.1(0.8-3.5)	0.1(-1.4-1.7)	1.1	0.014

COPM Satisfaction scale (1-10 points)								
All	1.3(1.1-1.4)	3.8(2.5-5.1)	2.5(1.3-3.8)	1.1(0.8-1.4)	2.2(0.6-3.8)	1.1(-0.5-2.7)	0.7	0.106
Measure of capacity to complete tasks and actions with the more-affected arm in the laboratory when requested								
Grade-4/5 WMFT Performance Rate (repetitions per minute)								
All/Completers	25.1(16.2-34.1)	33.7(21.5-45.9)	8.6(1.7-15.5)	30.6(14.9-46.3)	29.3(17.1-41.6)	-1.3(-7.5-5.0)	0.8	0.030
LOCF		n/a		31.2(18.4-44.0)	30.2(19.9-40.5)	-1.0(-5.9-3.9)	0.8	0.018
AVG		n/a		31.2(18.4-44.0)	29.3(19.8-38.9)	-1.8(-7.9-4.2)	0.8	0.018
Measure of capacity to complete isolated movements with the more-affected arm in the laboratory when requested								
FMA upper-extremity motor score (0-66 points)								
All/Completers	19.4(15.4-23.3)	21.2(16.6-25.7)	1.8(-0.6-4.2)	19.0(14.8-23.2)	21.3(17.7-24.9)	2.3(-1.4-6.0)	0.1	0.800
LOCF		n/a		18.9(15.2-22.6)	21.0(17.8-24.3)	2.1(-1.3-5.4)	0.1	0.878
AVG		n/a		18.9(15.2-22.6)	21.3(18.1-24.5)	2.4(-0.9-5.7)	0.1	0.754

Note. Values are mean (95% confidence interval). *Data from the Placebo (n=4) and Usual Care (n=7) groups were combined because their outcomes were similar. †For the intention-to-treat, Last Observation Carried Forward (LOCF) analysis, missing post-treatment data were replaced with corresponding baseline values. For the intention-to-treat, group average (AVG) analysis, missing data were replaced with the group average for that testing occasion. Post-treatment data on all of the outcomes were missing from one Placebo participant. As noted, he withdrew from the study after pre-treatment testing because he was not assigned to the experimental

arm. Data were available from all the other Control participants for the Grade-4/5 MAL and FMA. Post-treatment data were missing from one additional Control participant on the Grade-4/5 WMFT. COPM data were not collected for Placebo participants; therefore, data from the eCIMT group were compared to data from the Usual Care control group only. No data were missing from any of the eCIMT participants. When no data are missing, mean values are reported just for all participants; completers and intention-to-treat analyses do not apply. ‡Cohen's *f* is a measure of effect size (large *f* = 0.4); it indexes the magnitude of the difference between the two groups in pre- to post-treatment change. For each outcome, it is the variance in the relevant outcome accounted for by the group (eCIMT, Control) x testing occasion (pre, post) interaction divided by the error variance for this factor (Cohen, 1988). ¶The effect size for the MAL Arm Use scale was 3.9 times larger than for the COPM Performance scale, even though the percent improvement on the Arm Use scale was only 1.6 times larger than on the Performance scale, principally because improvement on the Arm Use scale was 3.4 times less variable than on the Performance scale. Abbreviations: eCIMT=expanded Constraint-Induced Movement therapy, MAL=Motor Activity Log, COPM=Canadian Occupational Performance Measure, WMFT=Wolf Motor Function Test, FMA=Fugl-Meyer Motor Assessment.

Table 6

Pre- to Post-treatment Changes for All in the Crossover eCIMT Group*

Outcome	Crossover eCIMT (*n*=7)			Size (*d'*)‡ and significance level (*P*) of within-group change	
	Pre	Post	Change	*d'*	*P* value
Spontaneous use of the more-affected arm in daily life					
Grade-4/5 MAL Arm Use scale (0-5 points)					
All	0.5(0.2-0.9)	2.4(1.8-3.0)	1.9(1.3-2.4)	3.2	<0.001
COPM Performance scale (1-10 points)					
Completers	1.3(0.8-1.9)	3.3(1.5-5.1)	1.9(0.5-3.4)	1.4	0.018
LOCF†	1.3(0.8-1.9)	3.0(1.4-4.6)	1.7(0.3-3.0)	1.1	0.018
AVG†	1.3(0.8-1.9)	3.3(1.8-4.7)	1.9(0.8-3.1)	1.5	0.008
COPM Satisfaction scale (1-10 points)					
Completers	1.1(0.9-1.2)	3.4(0.8-5.9)	2.3(-0.2-4.7)	1.0	0.064
LOCF	1.1(0.9-1.2)	3.1(0.9-5.2)	2.0(-0.1-4.1)	0.9	0.062

AVG	1.1(0.9-1.2)	3.4(1.3-5.4)	2.3(0.3-4.2)	1.1	0.030
Capacity to complete tasks and actions with the more-affected arm in the laboratory					
Grade-4/5 WMFT Performance Rate (repetitions per minute)					
Completers	29.7(20.1-39.4)	41.6(25.6-57.6)	10.9(4.8-17.2)	1.9	0.012
LOCF	29.7(20.1-39.4)	39.2(25.0-53.3)	9.4(3.1-15.7)	1.4	0.010
AVG	29.7(20.1-39.4)	41.6(28.7-54.4)	11.8(6.4-17.2)	2.0	<0.001
Capacity to complete isolated movements with the more-affected arm in the laboratory					
FMA upper-extremity motor score (0-66 points)					
Completers	20.7(16.7-24.7)	23.2(8.9-37.4)	1.8(-13.2-9.6)	0.2	0.726
LOCF	20.7(16.7-24.7)	22.3(10.6-33.9)	1.6(-8.7-11.8)	0.1	0.726
AVG	20.7(16.7-24.7)	23.2(11.7-34.6)	2.5(-7.9-12.8)	0.2	0.726

NOTE. Values are mean (95% *CI*). *Participants in the Usual Care group were crossed over to eCIMT for 3.5 hours daily for 15 consecutive weekdays approximately 4 months after enrollment. †For the intention-to-treat, Last Observation Carried Forward (LOCF) analysis, missing data were replaced with the score from the testing occasion just prior to crossover to eCIMT. For the intention-to-treat, group average (AVG) analysis, missing data were replaced with the group average for that testing occasion. Post-treatment data from one participant were missing for each of the outcomes with the exception of the Grade-4/5 MAL, for which no data were missing. When no data are missing, mean values are reported just for all participants; completers and intention-to-treat

analyses do not apply. ‡Cohen's *d'* is a repeated measures index of effect size (large *d'* =.57); it is the mean pre- to post-treatment change divided by the *SD* of the change (Cohen, 1988). Abbreviations: eCIMT, expanded Constraint-Induced Movement therapy; MAL, Motor Activity Log; COPM, Canadian Occupational Performance Measure; WMFT, Wolf Motor Function Test; FMA, Fugl-Meyer Motor Assessment.

Figure Legends

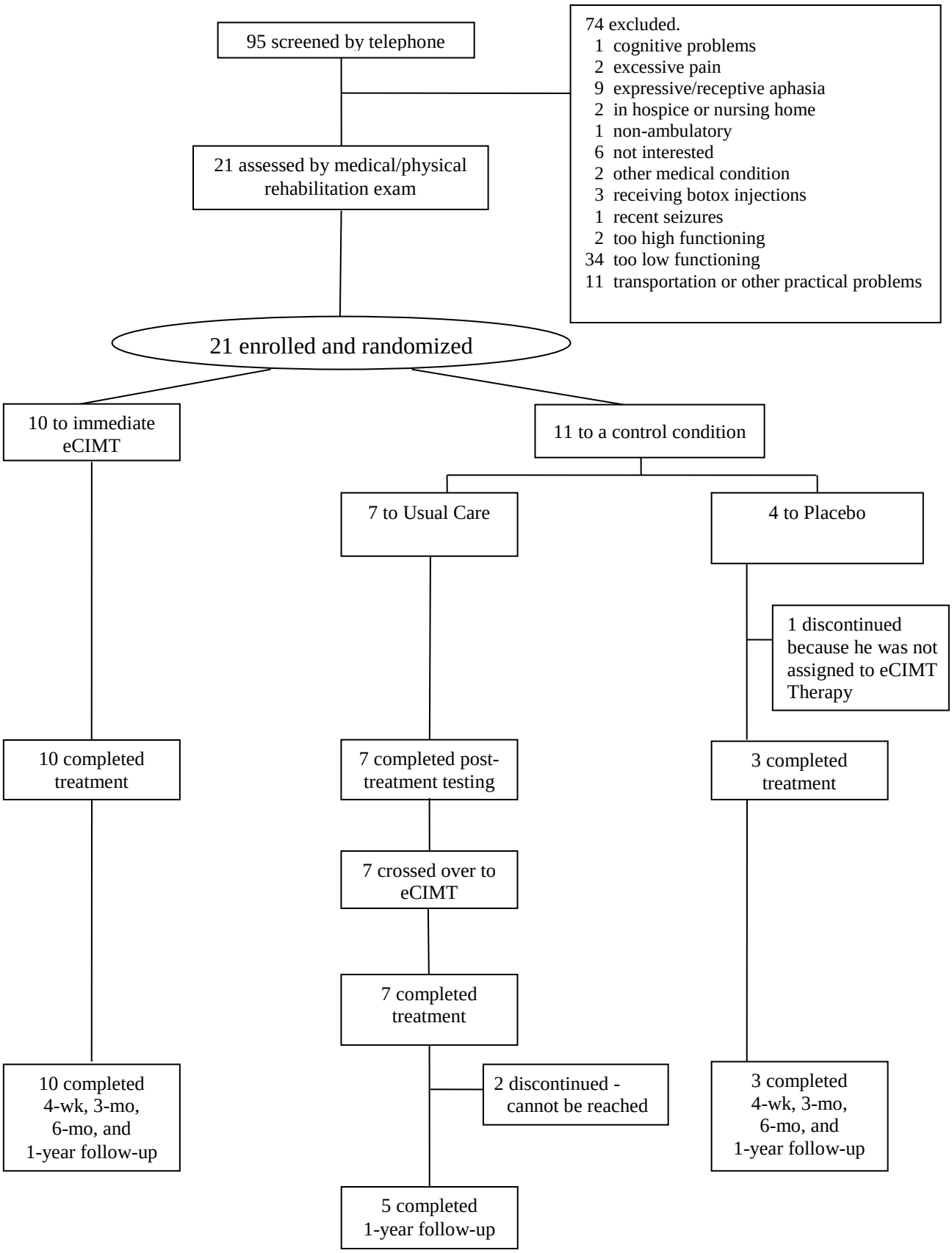
Fig 1 Trial profile. The Institutional Review Board at our university approved the study procedures. All participants gave written informed consent. The trial was registered with clinicaltrials.gov (unique identifier: NCT00366210). There were no adverse events related to the study procedures. One participant in the eCIMT group reported low-back pain at 6-month follow-up. Another had a fall on the way home from treatment but suffered no injuries. The participant was not wearing the mitt for the less-affected arm when he fell.

Fig 2 Changes in use of the more-affected arm in daily life for eCIMT and Control participants. Pre-treatment to 3-month follow-up data are plotted for all the Control participants, i.e., the Placebo and Usual Care groups combined, because the scores of the two control conditions were very similar. Crossover data are for the Usual Care group only. The Placebo group was not crossed over. Mean change from pre-treatment values are calculated on a completers basis. Error bars represent 95% confidence interval values. eCIMT=expanded Constraint-Induced Movement therapy, MAL=Motor Activity Log, Pre=pre-treatment, Post=post-treatment, Wk=week, Mo=month, Yr=year.

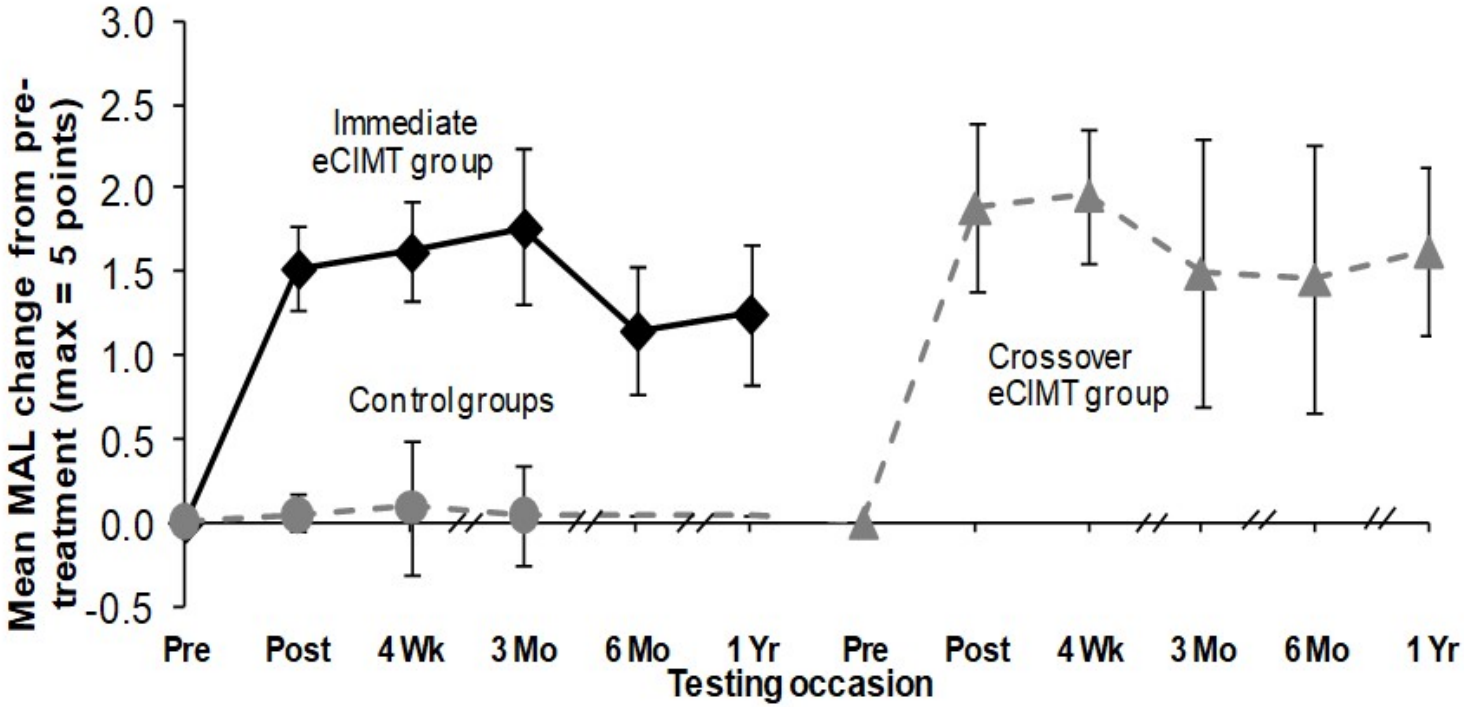
Fig 3 Type of changes observed in more-affected arm function after immediate eCIMT. *Type A* items from the Grade-4/5 MAL and WMFT required movement at the shoulder and elbow, e.g., Sit up on side of bed (Grade-4/5 MAL) and Hand to box (Grade-4/5 WMFT). *Type B* items, in addition, required rudimentary grasp, e.g., Open refrigerator (Grade-4/5 MAL) and Lift folded washcloth (Grade-4/5 WMFT). eCIMT=expanded Constraint-Induced Movement therapy, MAL=Motor Activity Log, WMFT=Wolf Motor Function Test.

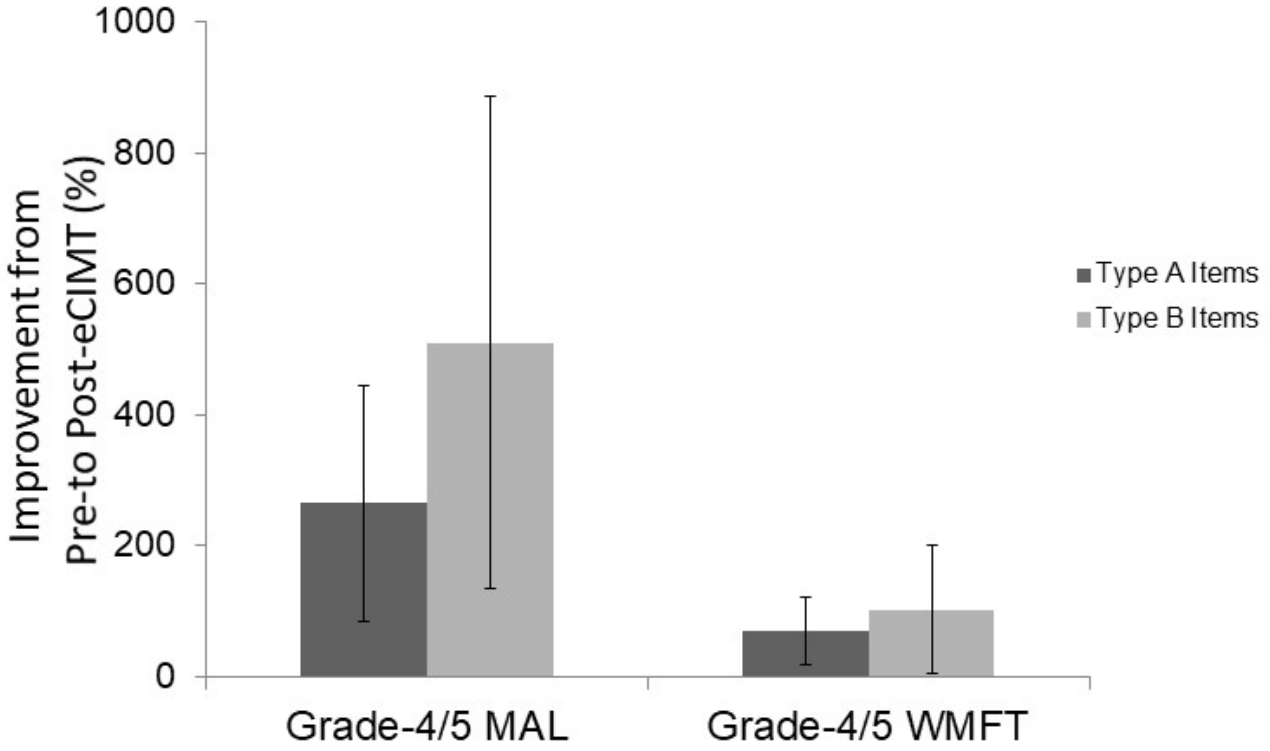
Fig 4 Number of Grade 4/5-MAL items with scores reflecting ineffective *vs* somewhat effective or better use of the more-affected in daily life before and after eCIMT. The mean number of

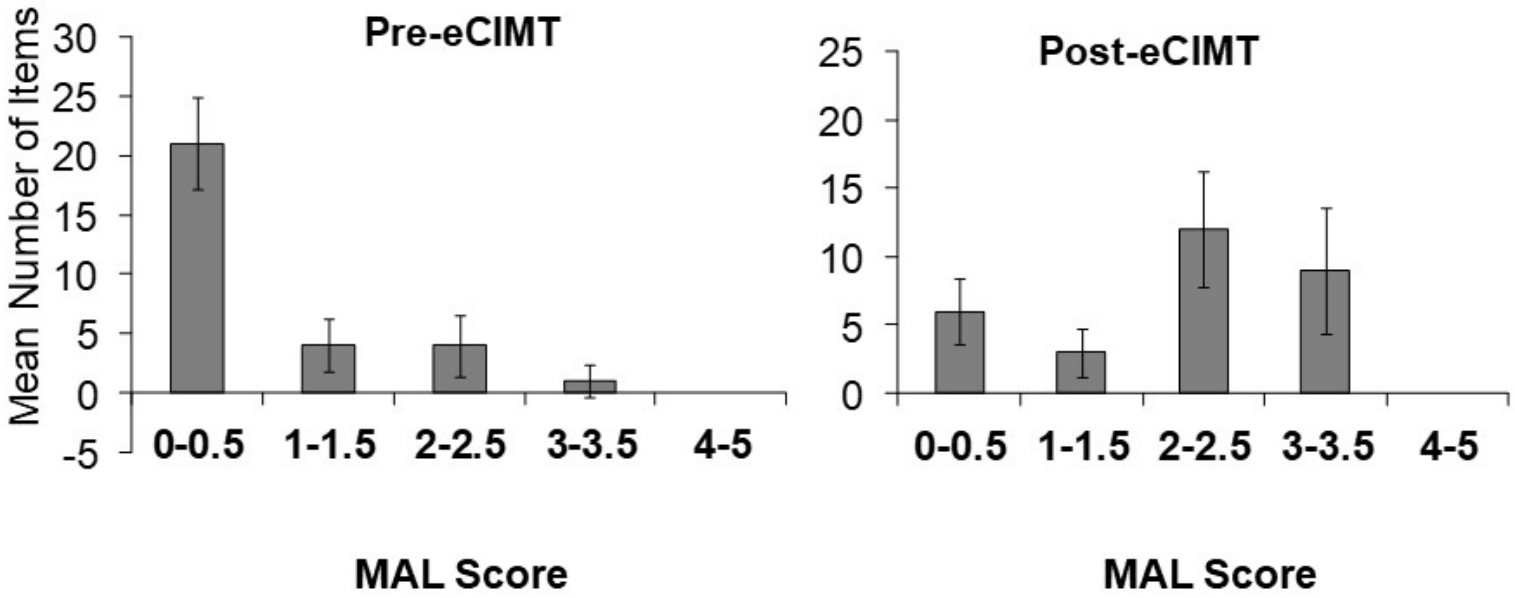
items with scores in each category is calculated on a completers basis. Errors bars represent 95% *CI* values. eCIMT=expanded Constraint-Induced Movement therapy, MAL=Motor Activity Log.


95 screened by telephone
74 excluded.
1 cognitive problems
2 excessive pain
9 expressive/receptive aphasia
2 in hospice or nursing home
1 non-ambulatory
6 not interested
2 other medical condition
3 receiving botox injections
1 recent seizures
2 too high functioning
34 too low functioning
11 transportation or other practical problems
21 assessed by medical/physical rehabilitation exam
21 enrolled and randomized
10 to immediate eCIMT
11 to a control condition
7 to Usual Care
4 to Placebo
1 discontinued because he was not assigned to eCIMT Therapy
10 completed treatment
7 completed post-treatment testing
3 completed treatment
7 crossed over to eCIMT
7 completed treatment
10 completed 4-wk, 3-mo, 6-mo, and 1-year follow-up
2 discontinued - cannot be reached
3 completed 4-wk, 3-mo, 6-mo, and 1-year follow-up
5 completed 1-year follow-up

(Intentionally left blank. Please see Figure 2 on next page.)


Mean MAL change from pre-treatment (max = 5 points)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
Immediate eCIMT group
Control groups
Crossover eCIMT group
Pre
Post
4 Wk
3 Mo
6 Mo
1 Yr
Pre
Post
4 Wk
3 Mo
6 Mo
1 Yr
Testing occasion


1000
800
600
400
200
0
Improvement from Pre-to Post-eCIMT (%)
Type A Items
Type B Items
Grade-4/5 MAL
Grade-4/5 WMFT


Pre-eCIMT
Mean Number of Items
30
25
20
15
10
5
0
-5
0-0.5
1-1.5
2-2.5
3-3.5
4-5
MAL Score
Post-eCIMT
25
20
15
10
5
0
0-0.5
1-1.5
2-2.5
3-3.5
4-5
MAL Score

(Intentionally left blank. See Appendix on next page.)

Appendix

To adapt CIMT for severely impaired patients, several changes were made in its standard components. (CIMT is described briefly in the **Introduction** and **Methods** and in detail in (Taub et al., 1993; Taub, Uswatte, King, et al., 2006). Changes to the individual components of the CIMT protocol made in eCIMT and additions to the standard protocol are described in greater detail below. In addition, Table A1 lists time spent on each component of eCIMT by individual participants in both the immediate eCIMT and crossover eCIMT groups.

Dosage

Treatment in the laboratory was scheduled for a larger number of days (15 vs. 10) and hours per day (6 vs. 3.5).

Training of More-affected Arm Use in Laboratory and Restraint of Less-affected Arm

In eCIMT, training on unimanual tasks was supplemented with training on everyday activities that require both hands, in which the more-affected arm functions as a helper. The training tasks selected for participants were less difficult than for participants with less impairment who qualify for standard CIMT. Task practice with simulated everyday activities, such as cleaning up the kitchen, was scheduled towards the end of treatment. Participants were asked to wear the padded mitt on the less-affected arm outside the treatment setting for a smaller amount of time than in standard CIMT because of safety considerations, since these participants often need to use the less-affected hand for balance and to hold a cane while walking.

Orthotics, Splints, & Adaptive Equipment

Participants were fitted with orthotics and splints for their more-affected arm and given adaptive equipment to modify household objects to match the participants' motor capabilities based on a functional analysis of their needs at the outset of treatment. The purpose of the orthotics and splints was to maintain the fingers and wrist in better alignment to enhance the use of the more-affected arm and hand in everyday activities. Examples of environmental adaptations to facilitate use of the more-affected hand were door knob turners, adaptive bath mitts, and adaptive cups. The orthotics, splints, and adaptive equipment were updated as needed throughout the treatment.

Neurodevelopmental Techniques

NDT techniques for reducing tone and facilitating movement of the trunk and upper-extremity were added to permit participants to better engage their base of support and increase activation of appropriate muscles, thereby promoting better movement of the more-affected arm during training. A participant, for example, who might not be able to open their more-affected hand wide enough to permit cylindrical grasp of a jar because of excessive tone at the outset of the treatment day would be asked to bear weight through that hand and engage in dynamic weight shifts to reduce the excessive tone. The NDT techniques included tapping, dynamic weight shifts, upper-extremity weight bearing, placing and holding, and trunk activation. Vibration, ice baths, and stretching with and without physical assistance by the therapist were also included during the NDT portions of the protocol.

In EMG-FES, electrical stimulation is used to elicit contraction of a target muscle when EMG activity in that muscle exceeds a low threshold set by the therapist. EMG-FES was incorporated into selected training tasks to permit participants to train on tasks that they would not otherwise be capable of at the outset of treatment. For example, if a participant was capable of initiating extension at the elbow but had an insufficient degree of extension to reach and then press a

simulated elevator button, sufficient electrical stimulation of the triceps was programmed to permit the patient to complete the task. The location of the EMG electrodes, EMG threshold for triggering stimulation of the target muscle (range, 3-10mv), and intensity of stimulation (range, 25-40mA) was determined individually for each participant and task by varying these parameters until the desired movement was elicited. The threshold for triggering stimulation was raised and the intensity of stimulation was lowered as participants progressed and required less assistance to complete the training tasks in question. A commercially available EMG-FES device, i.e., the MyoTrac Infiniti,[a] was used.

Table A1

Mean Time (Minutes) Spent Per Day on Each Component of eCIMT for Participants in the Immediate and Crossover eCIMT Groups

Treatment Component	Participant										
	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	**Mean**
Immediate eCIMT Group (Total treatment time per day = 360 minutes)*											
Standard CIMT Components											
More-affected arm training following shaping principles											
Mean	89	70	97	73	81	82	111	109	112	123	**95**
SD	22	36	31	29	41	30	36	46	53	51	**18**
Restraint of less-affected arm											
Mean	153	125	124	111	154	143	160	188	175	199	**153**
SD	21	44	31	42	41	43	60	48	82	41	**29**

Transfer Package†											
Mean	67	51	51	43	48	44	39	63	62	64	**53**
SD	18	33	36	21	17	27	12	30	23	27	**10**
Rest											
Mean	90	90	93	88	87	71	88	95	107	117	**93**
SD	27	38	32	34	38	38	30	35	26	32	**12**
Expanded CIMT Components											
Bimanual task practice with simulated everyday activities											
Mean	11	4	9	9	31	80	29	35	11	21	**24**
SD	12	9	14	16	23	35	46	18	21	20	**22**
Neurodevelopmental therapy (NDT)											
Mean	88	117	72	68	70	59	92	52	71	69	**76**
SD	24	151	26	43	26	32	19	22	25	32	**19**
EMG-triggered FES											
Mean	21	5	3	1	4	0	6	9	12	24	**9**
SD	27	12	7	3	10	0	14	18	17	14	**8**

Fitting of and Instructions on Orthotics and Adaptive Equipment											
Mean	7	6	14	20	1	24	7	11	12	9	**11**
SD	8	13	21	24	4	32	17	35	24	8	**7**
Crossover eCIMT Group (Total treatment time per day = 210 minutes)*											
Standard CIMT Components											
More-affected arm training following shaping principles											
Mean	75	62	63	53	74	.	.	n/a	n/a	n/a	**65**
SD	35	36	25	23	21	.	.	n/a	n/a	n/a	**9**
Restraint of less-affected arm											
Mean	125	134	105	100	128	.	.	n/a	n/a	n/a	**118**
SD	20	53	35	35	24	.	.	n/a	n/a	n/a	**16**
Transfer Package											
Mean	42	64	38	56	51	.	.	n/a	n/a	n/a	**50**
SD	18	36	22	30	22	.	.	n/a	n/a	n/a	**12**
Rest											
Mean	19	28	39	25	18	.	.	n/a	n/a	n/a	**26**

SD	17	15	21	11	11	.	.	n/a	n/a	n/a	**8**
Expanded CIMT Components											
Bimanual task practice with simulated everyday activities											
Mean	10	12	3	6	6	.	.	n/a	n/a	n/a	**7**
SD	14	19	7	12	11	.	.	n/a	n/a	n/a	**4**
Neurodevelopmental therapy (NDT)											
Mean	42	46	44	61	58	.	.	n/a	n/a	n/a	**50**
SD	10	19	18	27	10	.	.	n/a	n/a	n/a	**9**
EMG-triggered FES											
Mean	10	20	16	10	25	.	.	n/a	n/a	n/a	**16**
SD	15	25	12	11	15	.	.	n/a	n/a	n/a	**5**
Fitting of and Instruction on Orthotics and Adaptive Equipment											
Mean	6	19	0	2	2	.	.	n/a	n/a	n/a	**6**
SD	13	32	1	5	4	.	.	n/a	n/a	n/a	**9**

Note. The sum of the individual components exceeds the number of daily hours of therapy because some components overlap. For example, the restraint is worn on the less-affected arm during more-affected arm training. *Participants were randomized to Immediate eCIMT or one of two control conditions: Placebo or Usual Care. All Usual Care participants were crossed-over to eCIMT

approximately four months after enrollment. Participants in the Immediate eCIMT condition received 6 hours of therapy daily for 15 consecutive weekdays, while participants in the Crossover-eCIMT condition received 3.5 hours of therapy daily for the same number of days. Logs of the treatment sessions were available for all in the Immediate eCIMT condition. Logs of the treatment sessions were available only 5 of the 7 in the Crossover eCIMT condition, whose data are presented in the bottom half of the table. Missing data for the 2 participants for whom logs were kept but could not be located are marked by a ".". Cells in the columns headed S8, S9, and S10 are marked "n/a" to signify that these columns were not applicable to the Crossover eCIMT condition. As noted, there were only 7 in this condition. †The Transfer Package is a set of behavioral techniques, such as a keeping daily diary, completing a structured interview at the outset of each treatment day, and making follow-up telephone calls, that are designed to transfer therapeutic gains from the treatment setting into the community. Abbreviations: eCIMT = expanded Constraint-Induced Movement therapy, EMG-triggered FES = electromyography-triggered functional electrical stimulation.