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# Effect of Constraint-Induced Movement Therapy on Upper Extremity Function 3 to 9 Months After Stroke

## The EXCITE Randomized Clinical Trial

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**E**ACH YEAR, MORE THAN 730 000 Americans experience a new or recurrent stroke, with resulting direct and indirect health care costs totaling \$35 billion and \$21.8 billion, respectively.<sup>1</sup> Up to 85% of the approximately 566 000 stroke survivors experience hemiparesis, resulting in impairment of an upper extremity immediately after stroke, and between 55% and 75% of survivors continue to experience upper extremity functional limitations, which are associated with diminished health-related quality of life,<sup>2</sup> even 3 to 6 months later.<sup>3</sup>

Although traditional methods for rehabilitation among patients with limited upper extremity function after stroke, such as neurodevelopmental techniques,<sup>4</sup> have not been shown to be efficacious in controlled studies, more recent approaches that involve repetitive training of the paretic upper extremity on task-oriented activities give evidence of efficacy among stroke sur-

**Context** Single-site studies suggest that a 2-week program of constraint-induced movement therapy (CIMT) for patients more than 1 year after stroke who maintain some hand and wrist movement can improve upper extremity function that persists for at least 1 year.

**Objective** To compare the effects of a 2-week multisite program of CIMT vs usual and customary care on improvement in upper extremity function among patients who had a first stroke within the previous 3 to 9 months.

**Design and Setting** The Extremity Constraint Induced Therapy Evaluation (EXCITE) trial, a prospective, single-blind, randomized, multisite clinical trial conducted at 7 US academic institutions between January 2001 and January 2003.

**Participants** Two hundred twenty-two individuals with predominantly ischemic stroke.

**Interventions** Participants were assigned to receive either CIMT (n=106; wearing a restraining mitt on the less-affected hand while engaging in repetitive task practice and behavioral shaping with the hemiplegic hand) or usual and customary care (n=116; ranging from no treatment after concluding formal rehabilitation to pharmacologic or physiotherapeutic interventions); patients were stratified by sex, prestroke dominant side, side of stroke, and level of paretic arm function.

**Main Outcome Measures** The Wolf Motor Function Test (WMFT), a measure of laboratory time and strength-based ability and quality of movement (functional ability), and the Motor Activity Log (MAL), a measure of how well and how often 30 common daily activities are performed.

**Results** From baseline to 12 months, the CIMT group showed greater improvements than the control group in both the WMFT Performance Time (decrease in mean time from 19.3 seconds to 9.3 seconds [52% reduction] vs from 24.0 seconds to 17.7 seconds [26% reduction]; between-group difference, 34% [95% confidence interval {CI}, 12%-51%];  $P<.001$ ) and in the MAL Amount of Use (on a 0-5 scale, increase from 1.21 to 2.13 vs from 1.15 to 1.65; between-group difference, 0.43 [95% CI, 0.05-0.80];  $P<.001$ ) and MAL Quality of Movement (on a 0-5 scale, increase from 1.26 to 2.23 vs 1.18 to 1.66; between-group difference, 0.48 [95% CI, 0.13-0.84];  $P<.001$ ). The CIMT group achieved a decrease of 19.5 in self-perceived hand function difficulty (Stroke Impact Scale hand domain) vs a decrease of 10.1 for the control group (between-group difference, 9.42 [95% CI, 0.27-18.57];  $P=.05$ ).

**Conclusion** Among patients who had a stroke within the previous 3 to 9 months, CIMT produced statistically significant and clinically relevant improvements in arm motor function that persisted for at least 1 year.

**Trial Registration** clinicaltrials.gov Identifier: NCT00057018

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vivors who retain some ability to actively extend the fingers and wrist of their paretic upper extremity.<sup>5,6</sup>

One approach, which has substantial evidence of efficacy for individuals with long-term stroke disabilities (>1 year after event), involves intense functionally oriented task practice of the paretic upper extremity along with restraint of the less-impaired upper extremity for most waking hours. This approach encourages use of the paretic upper extremity in daily life<sup>7</sup> and is thought to help overcome what Taub<sup>8</sup> first described in a deafferented monkey model as “learned nonuse” of the paretic upper extremity. Treatment by restraining only the less-impaired upper extremity, which is typically accomplished by placing the entire arm in a sling or placing the hand in a mitt for most waking hours for 2 weeks, without supervised task practice, is referred to as “forced use” and has been applied to long-term<sup>9-11</sup> and subacute<sup>12</sup> stroke patients. Constraint-induced movement therapy (CIMT) involves ipsilesional limb restraint with training of paretic arm use conducted by a clinician following shaping and repetitive task practice principles over the same time course<sup>13,14</sup> or less intensely over several weeks.<sup>15</sup>

The Extremity Constraint Induced Therapy Evaluation (EXCITE) Trial represents the first national, randomized, single-blind study to systematically test a neurorehabilitation therapy among patients with the ability to initiate extension movements at the wrist and fingers and who had experienced a first stroke within 3 to 9 months prior to enrollment.<sup>16</sup> This time window is when most available standard rehabilitation treatment options have been completed and the opportunity for spontaneous recovery to occur is attenuated.<sup>17</sup> The trial also tests whether the previous controlled studies from a single site<sup>7</sup> can be replicated in a larger sample and extended across multiple sites. We hypothesized that patients who received CIMT up to 9 months following stroke would improve upper extremity function compared with pa-

tients with identical inclusion and exclusion criteria who received usual and customary care.

## METHODS

### Study Organization

Seven clinical sites participated in this study. Emory University, Atlanta, Ga, served as the administrative center while the University of Alabama at Birmingham served as the training center, where all evaluators and interventionists underwent a standardization process and were reviewed at 6-month intervals for adherence to protocol procedures. Washington University, St Louis, Mo, served as the data management center, where all data were transmitted electronically and analyzed. A steering committee composed of the principal investigator from each site and the data management center made all decisions concerning the conduct of the study. An independent data and safety monitoring committee reviewed recruitment, adverse events, and study progress annually.<sup>16</sup> Study procedures were approved by the respective institutional review boards of each participating site. Written informed consent, read to participants by a study member or caregiver, was obtained on site prior to enrollment.

### Study Participants

Each site attempted to recruit 40 adults who had experienced a stroke in the previous 3 to 9 months. Participants had a first-time clinical ischemic or hemorrhagic cerebrovascular accident, as ascertained from neuroimages or written medical reports during the screening procedure, and met either higher- or lower-functioning motor criteria derived from Wolf and Binder-Macleod<sup>18</sup> and Taub et al.<sup>19</sup> Higher-functioning participants demonstrated at least 20° of wrist extension and at least 10° of active extension of each metacarpophalangeal and interphalangeal joint of all digits. Lower-functioning participants had at least 10° of active wrist extension, at least 10° of thumb abduction/extension, and at least 10° of extension in at least 2 additional dig-

its. These movements had to be repeated 3 times in 1 minute.<sup>19</sup>

Participants also had to demonstrate adequate balance while wearing the restraint and transferring to and from the toilet independently, ability to stand from a sitting position, and ability to stand for at least 2 minutes with or without upper extremity support. Additional range of motion and inclusion criteria, as well as information on other neuromuscular and functional measures, including the modified Ashworth spasticity scale, Fugl-Meyer Assessment scale, and time to turn 360°, were also assessed.<sup>16</sup>

Potential participants were excluded if they scored less than 24 on the Mini-Mental State Examination<sup>20</sup> or if physician-determined major medical problems could interfere with participation. Additional exclusion criteria were previously clinically documented stroke, excessive pain in any joint of the paretic extremity, age younger than 18 years, insufficient stamina to participate, substantial use of the paretic arm in daily life as determined by a score of 2.5 or higher on the Motor Activity Log (MAL; described below), or previous participation in other pharmacologic or physical intervention studies.<sup>16</sup> Participants were permitted to undergo other forms of physical or occupational therapy, exclusive of CIMT, prior to or after receiving CIMT.

### Recruitment

Individuals were recruited from 247 facilities spanning the 7 participating sites: 40 from Emory University; 39 from University of Alabama at Birmingham; 39 from University of Florida, Gainesville; 29 from Ohio State University, Columbus; 42 from University of Southern California, Los Angeles; 18 from University of North Carolina at Chapel Hill; and 15 from Wake Forest University, Winston-Salem, NC. Participants were randomly assigned to the experimental (CIMT) or control condition using an automated, centralized system administered by the data management cen-

ter. This adaptive randomization scheme maximized the chances of an even distribution of 4 characteristics (sex, prestroke dominant side, side of stroke, and level of paretic arm function) across the study conditions.<sup>16</sup> Race was assessed by interview; the information was acquired to ensure representation indicative of regional demographics at each site.

### Study Design

The control condition was usual and customary care. Because this care might affect functional gains among participants, an attempt was made to track care received through participant reports collected during monthly phone calls by project staff and during the scheduled testing sessions. Usual and customary care ranged from no treatment to the application of mechanical interventions (orthotics) or various occupational and physical therapy approaches in the home, day treatment programs, or outpatient hospital visits. Participants in the control condition were offered the same CIMT regimen after the 12-month evaluation session.

Participants in the intervention group were taught to apply an instrumented protective safety mitt and encouraged to wear it on their less-impaired upper extremity for a goal of 90% of their waking hours over a 2-week period, including 2 weekends, for a total of 14 days. On each weekday, participants received shaping (adaptive task practice) and standard task training of the paretic limb for up to 6 hours per day. The former is based on the principles of behavioral training<sup>21,22</sup> that can also be described in terms of motor learning derived from adaptive or part-task practice.<sup>23,24</sup> Standard task practice is less structured (ie, repetition of tasks is not conducted as individual trials of discrete movements); it involves functional activities performed continuously for a period of 15 to 20 minutes (eg, eating, writing).

Adherence to mitt use while the participants were in the research laboratory was usually very high. Behavioral

techniques to enhance mitt use outside of the laboratory are described in detail elsewhere<sup>16,25</sup> and included use of a behavioral contract, caregiver contract, mitt compliance device, and daily schedule. After completing each treatment, participants were encouraged to practice 2 to 3 tasks daily at home. Adherence to the extralaboratory treatment components was monitored regularly via a physical sensor and timer placed in the mitt and by a home diary. In the few occasions when patient home diary reports did not match outputs from the mitt monitoring device, participants were informed of the discrepancy and accurate reports resulted thereafter. Malfunctions in the monitoring device rarely occurred, but such devices were replaced immediately. Participants were encouraged to perform about 30 minutes of task practice daily following completion of the intervention period.

### Outcome Measures

Primary outcomes included a laboratory-based measure of upper extremity motor function (the Wolf Motor Function Test [WMFT]<sup>9</sup>) and a structured participant interview of real-world arm use (MAL).<sup>7,26</sup> The WMFT clinometric properties have been published.<sup>27,28</sup> The test contains 15 timed and 2 strength tasks (lifting the weighted limb and grip strength), ordered from simple to complex, administered sequentially to each upper extremity and controlling for patient positioning and distance the extremity segment must traverse. Timed tasks assessing shoulder movement include moving the forearm to tabletop starting with the arm in the lap perpendicular and parallel to the table, as well as the same tasks except moving the forearm to the top of a box 26 cm in height placed on the table. Timed tasks involving the elbow include straightening the elbow while sitting parallel to the table with and without a 1-lb weight and reaching to retrieve a 1-lb weight by bringing it toward the body using elbow and wrist flexion. Timed tasks that engage the entire upper extremity and

are performed while seated and facing the table include lifting a can, pencil, and paper clip, stacking 3 checkers, turning over 3 note cards, and turning a key in a lock. One bimanual activity involves folding a towel in a specific manner, and 1 standing task requires lifting a basket containing a 3-lb weight and moving it from one table to another using trunk rotation. The 2 strength tasks include forward flexion of the shoulder in a seated position to the top of a box placed on the table using weights of up to 20 lb strapped to the forearm, as well as dynamometer grip strength for 3 seconds with the elbow bent to 90°.

Each timed task consisted of a single trial while the weight-to-box was repeated until maximum weight lift was achieved. The dynamometric task was averaged over 3 trials. Trained observers at the University of Alabama at Birmingham, who were blinded to group assignment and testing occasion, were sent a videotape of each evaluation session, from which they rated quality of movement using a 6-point functional ability scale (0=does not attempt; 5=normal movement). Strength and performance time were recorded by the test administrators; maximum time permitted to complete an item was 120 seconds.<sup>27,28</sup>

The MAL was administered to each participant and, if available, their caregiver, who independently rated how well (11-point Quality of Movement [QOM] scale) and how much (11-point Amount of Use [AOU] scale) the paretic arm was used spontaneously to accomplish 30 activities of daily living outside of the laboratory.<sup>10,26</sup> Baseline to posttreatment changes on a prior version of the MAL were highly correlated with corresponding changes on an objective, accelerometer-based measure of arm movement outside of the laboratory ( $r=0.91$ ).<sup>29</sup> Among EXCITE participants, the MAL showed excellent convergent validity ( $r>0.68$ )<sup>30</sup> with the hand function domain of the Stroke Impact Scale (SIS).<sup>31</sup> The SIS, a full-spectrum health status interview that measures changes in 8 impairment,

function, and quality-of-life subdomains following stroke, was a secondary outcome measure. Administration of the MAL to caregivers, identification of the number of MAL activities on which participants could score a 3 or higher at follow-up evaluations, and tasks that could be completed at that time and thereafter on the WMFT were also secondary outcome measures.

All testing was conducted on 5 occasions (baseline, posttreatment, and 4-, 8-, and 12-month follow-up) by trained staff blinded to group assignment.

**Data Analysis**

Consistent with the prespecified analytic plan,<sup>16</sup> a modified intention-to-treat approach was used, with all available data used for all analyses. A

repeated-measures analysis of variance model was fit with group assignment (CIMT or usual care) and paretic arm motor ability (higher or lower) as between-patient factors and visit as a within-patient factor. Least-square means, which adjust for randomly missing values, were computed for each group at each time point. Because of the skewed distribution of the WMFT Performance Time, a logarithmic transformation was used. Tabled logs were converted back to seconds to aid interpretation. For counts (eg, number of WMFT items not completed within the time limit), a corresponding generalized linear model with a Poisson link function was used.

Specific contrasts were examined to test predefined hypotheses. The over-

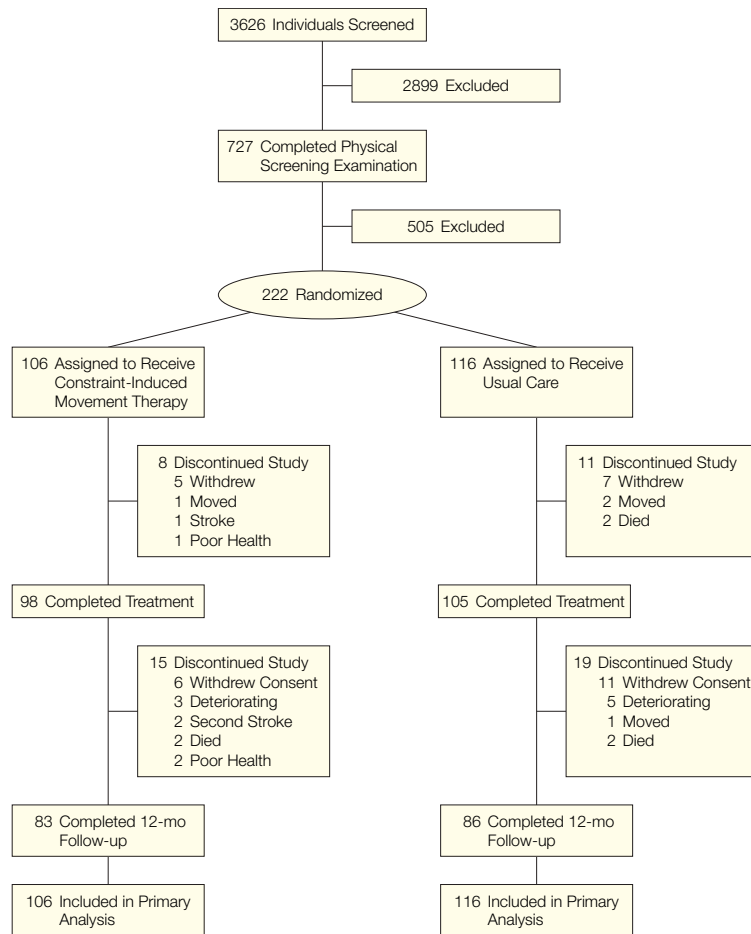
all group-by-time interaction tested whether the time course differed between the CIMT and control groups. To evaluate the effect of treatment at subsequent evaluations, comparisons between groups were tested by the interaction between group and time considering only the baseline and the testing occasion of interest. This approach effectively controlled for any differences at baseline between groups. At 12 months, the primary end point, a within-patient comparison, assessed the significance of the change from baseline within each group. Additional preplanned comparisons assessed the effects of treatment within the lower- and higher-functioning subgroups. Since the hypotheses were all prespecified, no adjustments were made to the reported *P* values.

These statistical analyses were validated by examining alternative analyses; in particular, analysis of covariance at each time point, with the corresponding baseline value used as a covariate; repeating the analyses applying an alternative definition of functional level using scores on the motor component of the Fugl-Meyer Upper Extremity Assessment<sup>32</sup> to more equally balance the sizes of the 2 functional groups; including clinic in the model and testing for interactions between clinic and treatment condition; using a last-observation-carried-forward approach for missing data; and using only observations for which the visits were in the prescribed time window. In addition, an intention-to-treat analysis was conducted in which baseline values replaced all missing values.

The sample size for the trial was determined by the most demanding hypothesis to detect the interaction between functional level and treatment. The effect size was estimated from pilot data for the MAL, using a significance level of .01, a power of 85%, and a dropout rate of 20%.

Secondary outcomes were assessed using the same set of analyses, and more complex models were fit in which a third between-group factor was added to test whether the treatment effect was

**Figure 1.** Flow of Patients Through the Trial



moderated by age (older vs younger than 65 years), sex, or side of the stroke. Survival analysis was used to examine predictors of withdrawal. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

## RESULTS

Between January 2001 and January 2003, 222 of a target number of 240 participants were assigned to the treatment (n=106) or control (n=116) groups (FIGURE 1). At baseline, there were no significant differences between the study groups on the assessed demographic, stroke-related, and cognitive characteristics (TABLE 1). Of 11 comorbidities assessed at baseline, the only significant imbalance was for diabetes (28% in the CIMT group vs 17% in the control group;  $P=.05$ ). There were no differences between groups in the number of comorbidities or in the motor characteristics assessed except for number of WMFT items not completed within 120 seconds for which the CIMT group performed better than the control group (TABLE 2 and TABLE 3). One hundred and sixty-nine participants returned for the 12-month assessment, yielding a retention rate of 76.1% (Figure 1). No demographic or baseline characteristics predicted study withdrawal.

### Effects of CIMT

There were significant changes over time that differed by group for all primary and secondary upper-extremity outcome variables, demonstrating that CIMT had a broad effect (Table 2 and Table 3). There were no between-group differences at any time point for the less-impaired arm WMFT scores (data not shown), demonstrating specificity of the intervention to the paretic arm.

The CIMT group showed larger improvements than the control group on all primary and secondary measures of paretic upper-extremity function at posttreatment ( $P<.05$  for all; Table 2 and Table 3), with the exception of the 2 WMFT strength items. The CIMT

group, however, showed larger improvement than controls on these strength items at 12-month follow-up ( $P<.001$ ). The CIMT group also showed larger improvement than the control group on WMFT Performance Time and both participant MAL scales at all follow-up testing occasions (ie, 4-, 8-, and 12-month follow-up;  $P<.01$  for all). Differences in gains between CIMT and control participants on the WMFT Functional Ability scale were not significant at 12-month follow-up. For long-term secondary outcomes, CIMT recipients displayed larger gains than controls on the caregiver MAL scales and the SIS hand function domain at 12-

month follow-up ( $P<.001$ ). No treatment effects were present for the SIS subdomains not directly related to paretic upper extremity function.

In addition, the results were assessed by alternative analyses, including analysis of covariance at each time using baseline values as covariates, using the Fugl-Meyer Motor Assessment for upper and lower functioning grouping, including clinic in the model and testing for interactions between clinic and treatment effect, using last-observation-carried-forward analysis for missing values, using only visits in prescribed time, and substituting baseline values for missing values. All analyses were concordant with

**Table 1.** Baseline Participant Characteristics\*

Characteristics	Constraint-Induced Movement Therapy (n = 106)	Usual Care (n = 116)
Age, mean (SD), y	61.0 (13.5)	63.3 (12.6)
Female	37 (34.9)	43 (37.1)
Race		
White	71 (67.0)	86 (74.1)
African American	28 (26.4)	23 (19.8)
Married	78 (73.6)	85 (73.3)
Paresis of prestroke dominant side	50 (47.2)	60 (51.7)
Ischemic stroke	97 (91.5)	98 (84.5)
No. of days since stroke, mean (SD)	179.8 (66.1)	187.7 (70.8)
Mini-Mental State Examination, mean (SD), points	28.0 (1.9)	27.5 (2.1)
No. of comorbidities, mean (SD)	1.9 (1.4)	1.8 (1.4)
Arthritis	24	25
Asthma	3	8
Cancer	11	9
Chest pain	10	14
Diabetes	30	20
Previous fracture	22	24
High blood pressure	73	73
Heart disease	10	16
Previous myocardial infarction	10	8
Osteoporosis	2	1
Seizures	6	5
Fugl-Meyer Assessment Score, mean (SD)†	42.5 (11.7)	41.1 (12.9)
360° turn, mean (SD), s	6.55 (4.9)	7.05 (4.7)
Nonuse of assistive ambulatory devices at home	53 (50.0)	59 (55.7)
Modified Ashworth Spasticity Scale, mean (SD)‡	0.88 (0.65)	0.92 (0.67)
Active range of motion, mean (SD), degrees		
Shoulder flexion	104 (45)	107 (45)
Elbow extension	66 (32)	65 (35)
Wrist extension	85 (50)	80 (48)
Finger extension	42 (31)	44 (30)

\*Data are expressed as No. (%) unless otherwise indicated.

†Maximum score, 66. Higher scores indicate better function.

‡Maximum score, 6. Higher scores indicate better function.

reported analyses. Furthermore, improvements from baseline to 12-month follow-up within each group on all paretic upper extremity outcomes also were statistically significant.

**Effects of CIMT for Subgroups of Participants**

Higher- and lower-functioning participants (based on amount of wrist and digit extension at baseline) did not have sig-

nificantly different treatment effects; none of the 3-way interactions among functional level, group assignment, and testing occasion were significant. Treatment effects by initial level of function

**Table 2.** Effect of Constraint-Induced Movement Therapy on Primary and Secondary Outcomes at Baseline Through 12-Month Follow-up and Change From Baseline to 12 Months (N = 222)

Outcome Variables	Baseline*†	Posttreatment*‡	4-mo Follow-up*‡	8-mo Follow-up*‡	12-mo Follow-up*‡	Change From Baseline to 12 mo§
<b>Constraint-Induced Movement Therapy</b>						
WMFT sample size	105	98	89	86	80	
Log performance time	2.96	2.38††	2.41**	2.35**	2.23**	-0.73††
Performance time, s¶	19.3	10.8	11.1	10.5	9.3	-52%
Functional ability (0-5 scale)	2.39	2.69††			2.75	0.36††
Weight	4.45	6.04	5.80	7.28	7.32	2.86††
Grip	7.53	9.51	10.13	11.94	12.13	4.60††
MAL sample size	105	98	89	86	80	
MAL AOU (0-5 scale)	1.21	2.24††	2.11‡	2.13‡	2.13#	0.92††
MAL QOM (0-5 scale)	1.26	2.17††	2.13‡	2.17‡	2.23**	0.97††
Caregiver MAL sample size	86	74			46	
MAL AOU (0-5 scale)	0.91	1.86††			1.97**	1.06††
MAL QOM (0-5 scale)	0.92	1.84††			2.00#	1.08††
WMFT mean No. of tasks not completed within 120 s	2.20#	0.94††	1.26*	1.17#	1.20	-1.01††
MAL AOU tasks ≥3, %	18	43††	41**	42	42	24††
MAL QOM tasks ≥3, %	22	44††	45**	46#	48	26††
SIS hand function, %	28.1		41.6#		47.6#	19.5††
SIS physical function, %	52.5		56.1		54.2	1.7
<b>Usual Care</b>						
WMFT sample size	115	104	93	92	86	
Log performance time	3.179	3.100	2.946	2.920	2.873	-0.306**
Performance time, s¶	24.0	22.2	19.0	18.5	17.7	-26%
Functional ability (0-5 scale)	2.21	2.30			2.47	0.26††
Weight	3.53	4.10	4.16	5.00	5.72	2.19††
Grip	7.23	7.91	9.29	10.30	14.47	7.24††
MAL sample size	116	103	93	92	86	
MAL AOU (0-5 scale)	1.15	1.37	1.53	1.48	1.65	0.50††
MAL QOM (0-5 scale)	1.18	1.42	1.57	1.52	1.66	0.48††
Caregiver MAL sample size	99	90			62	
MAL AOU (0-5 scale)	0.73	0.99			1.10	0.38#
MAL QOM (0-5 scale)	0.71	1.00			1.18	0.47**
WMFT mean No. of tasks not completed within 120 s	3.32	3.00	2.69	2.69	2.58	-0.74#
MAL AOU tasks ≥3, %	18	25	28	26	31	13**
MAL QOM tasks ≥3, %	21	27	33	30	34	13††
SIS hand function, %	24.3		31.1		34.4	10.1**
SIS physical function, %	52.2		51.8		52.4	0.2

Abbreviations: AOU, Amount of Use scale; MAL, Motor Activity Log; QOM, Quality of Movement scale; SIS, Stroke Impact Scale; WMFT, Wolf Motor Function Test.

\*Values are least-square means from repeated-measures analysis of variance with treatment group, functional level, and visit (time).

†P values noted in this column are for simple comparisons between the 2 treatment groups.

‡P values noted in this column are for comparisons between groups controlling for baseline at each time point by use of an appropriate set of contrasts. The primary outcome time periods are posttreatment and 12-month follow-up.

§P values noted in this column are for test for change between baseline and 12 months.

||Corresponding generalized linear models were used for WMFT number of tasks uncompleted with a Poisson link function.

¶Performance time is a conversion of the logs to original units (seconds).

#P<.05.

\*\*P<.01.

††P<.001.

are shown in FIGURE 2. Age and sex also did not moderate the treatment effect. The treatment effects were not different across clinics. Although 3-way interactions among side of stroke, pre-morbid hand dominance, group assignment, and testing occasion were significant for all of the primary outcome measures ( $P < .05$  for all), the differences in treatment gains between participants with paresis of their pre-stroke dominant side (concordant) and those with paresis of their prestroke nondominant side (discordant) were small and not clinically relevant.

### Clinically Relevant Changes

Clinically relevant improvements were ascertained by determining the number of tasks that participants completed on the WMFT. Participants receiving CIMT showed consistent increases over time in the number of tasks that could be completed. Compared with the control group, CIMT participants completed a significantly greater number of tasks at posttreat-

ment and 4- and 8-month follow-ups, although the difference between the 2 groups diminished at the 12-month follow-up. Achieving a 3 or higher on the MAL indicates at least a 50% increase in use of the impaired arm and hand than prior to the stroke (frequency; AOU scale) and without any assistance by the less impaired upper extremity (independence; QOM scale) in performing a given functional task. At 12-month follow-up, CIMT participants had increased the proportion of tasks performed to a level reported as at least 50% more use as prior to the stroke by 24% and had increased the proportion of tasks performed independently with the paretic arm relative to baseline by 65% (Table 2 and Table 3;  $P < .001$ ). The group-by-time interaction for both measures was significant. Moreover, caregiver scores on the MAL verified the perceptions of their respective participants. When stratified by functional level, lower-functioning participants improved in their AOU score after treatment and at

12 months, but there was no treatment by functional level interaction. Higher-functioning participants demonstrated AOU and QOM improvements in the proportion of tasks with scores of higher than 3 over time (data not shown).

### Adverse Events

Study participants experienced 35 serious adverse events (14 in the CIMT group and 21 in the control group) requiring hospitalization during the year following enrollment. Among patients randomized to the treatment group, only 1 event (a second stroke) occurred during the intervention period.

Among the events in the treatment group, 8 hospitalizations were related to cardiovascular events (4 strokes, 2 coronary artery bypass graft surgeries, 1 myocardial infarction, and 1 cardiac catheterization), 3 were related to orthopedic events (2 total hip replacements and 1 fractured humerus), and 3 were due to other events (1 colon infection, 1 gas-

**Table 3.** Effect of Constraint-Induced Movement Therapy on Primary and Secondary Outcomes—Difference Between Groups in 12-Month Changes (N = 222)

Outcome Variables	Difference Between Groups in 12-mo Changes (95% CI)	Difference Between Groups in 12-mo Changes (95% CI), With Baseline Values Used for Missing Data*	Within-Cell Standard Deviation†	Group × Time P Value‡
WMFT				
Log performance time	0.42 (0.13 to 0.72)	0.30 (0.04 to 0.57)	1.37	<.001
Performance time, s	34 (12 to 51)	31 (4 to 79)		
Functional ability (0-5 scale)	0.11 (-0.06 to 0.27)	0.06 (-0.08 to 0.20)	3.94	<.001
Weight	0.67 (-1.52 to 2.86)	0.89 (-1.10 to 2.88)	6.30	.32
Grip	-2.64 (-6.27 to 0.99)	-1.67 (-4.86 to 1.52)	9.70	.20
MAL				
AOU (0-5 scale)	0.43 (0.05 to 0.80)	0.33 (-0.02 to 0.68)	1.37	<.001
QOM (0-5 scale)	0.48 (0.13 to 0.84)	0.39 (0.06 to 0.72)	1.35	<.001
Caregiver MAL				
MAL AOU (0-5 scale)	0.69 (0.20 to 1.17)	0.32 (-0.06 to 0.70)	1.26	.002
MAL QOM (0-5 scale)	0.60 (0.12 to 1.08)	0.29 (-0.10 to 0.68)	1.27	.001
WMFT No. of tasks (>120 s)	-0.27 (-0.67 to 0.10)	-0.37 (-0.71 to -0.04)		<.001
MAL AOU tasks $\geq 3$ , %	11 (0 to 22)	8 (-2 to 18)	0.92	<.001
MAL QOM tasks $\geq 3$ , %	14 (3 to 24)	11 (1 to 20)	0.93	.007
SIS hand function, %	9.42 (0.27 to 18.57)	7.04 (-0.60 to 14.66)	23.8	.08
SIS physical function, %	1.48 (-5.71 to 8.66)	1.14 (-4.89 to 7.18)	15.6	.35

Abbreviations: AOU, Amount of Use scale; CI, confidence interval; MAL, Motor Activity Log; QOM, Quality of Movement scale; SIS, Stroke Impact Scale; WMFT, Wolf Motor Function Test.

\*Computed from repeated-measures analysis of variance whereby all missing values are replaced with the corresponding baseline value for that participant. This provides a conservative estimate of the treatment effect.

†Computed using the sum of the patient-to-patient variance and the residual error variance components.

‡P values are for 2-way interactions between testing occasion (eg, baseline) and group (ie, constraint-induced movement therapy or usual care). This is an overall test of whether the time course is different between groups.



trointestinal tract bleed, and 1 renal failure). Two deaths in this group resulted following congestive heart failure and abdominal obstruction.

Among the control group, 10 hospitalizations were due to cardiovascular events (6 strokes, 1 hypertension crisis, 1 coronary artery bypass graft surgery, 1 lower extremity vascular surgery, and 1 congestive heart failure), 5 were related to orthopedic events (2 hip fractures, 2 total hip replacements, and 1 open femoral reduction), and 6 hospitalizations were related to other events (2 seizures, 1 cancer, 1 respiratory infection, 1 thoracotomy, and 1 cellulitis). Four deaths in this group resulted from pancreatitis, cardiac event, sepsis, and stroke. In a generalized linear model that controlled for the repeated events within individuals, comparison of adverse even rates between groups showed no statistically significant difference ( $P=.44$ ).

**COMMENT**

The EXCITE Trial represents, to our knowledge, the first randomized multicenter trial and the largest trial of CIMT among participants who had experienced stroke 3 to 9 months prior.

These results support findings from other studies that have used CIMT for participants with long-term (>1 year) stroke disabilities.<sup>7,11,33-37</sup> In our trial, the CIMT group showed significantly larger improvements immediately after treatment than the control group in quality and speed of paretic arm movement (WMFT Functional Ability and Performance Time) and in the quality and amount of paretic arm use in daily life (MAL QOM and AOU scales). Furthermore, the advantages for the CIMT group on 3 (WMFT Performance Time and MAL QOM and AOU scales) of these 4 primary outcomes persisted for 12 months.

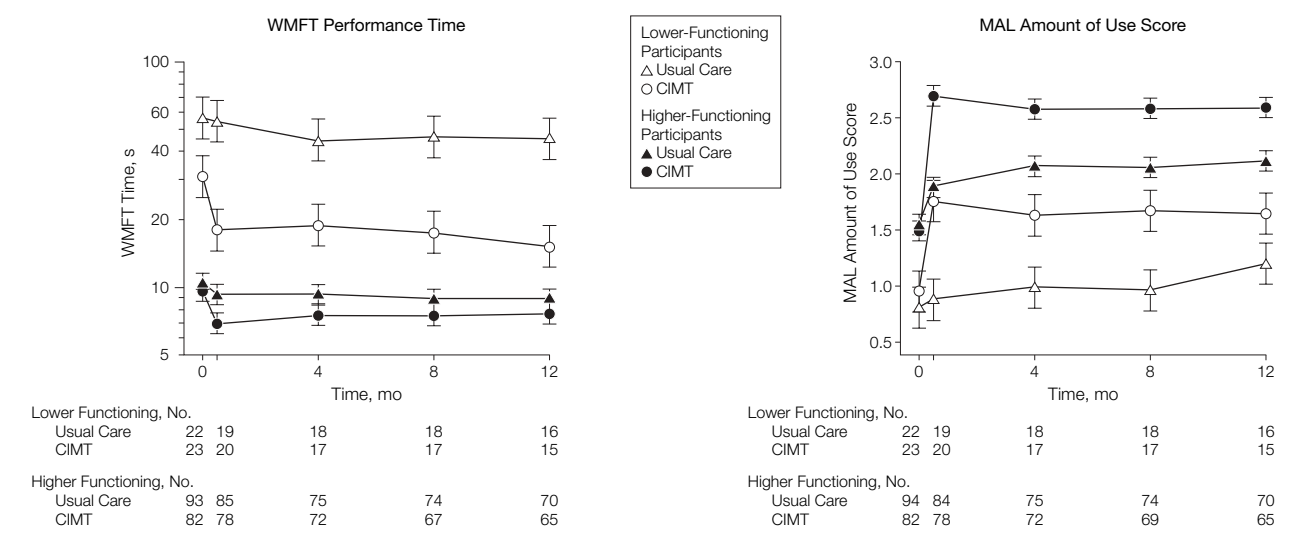
Although changes in the control group were substantially smaller than in CIMT participants, control participants also showed significant improvement in most outcomes from baseline to 12-month follow-up. Given that most EXCITE participants were within a 9-month poststroke period, some improvement due to spontaneous recovery could be expected.<sup>3</sup> Test-retest reliability studies of the WMFT<sup>27,28</sup> and MAL<sup>29</sup> in individuals with long-term stroke disabilities who are not thought to experience spontaneous recovery

have shown that WMFT and MAL scores are stable over approximately 2-week intervals, suggesting that the changes in the EXCITE control group were not due to practice effects consequent to repeated testing.

Among control participants, 48.8% received clinical care during the study, but the limited improvement in functional outcomes in this group suggests that traditional neurorehabilitation interventions have limited effectiveness in promoting motor recovery within the dosing parameters typically used.<sup>6,38</sup> Among participants in the CIMT group, 51.2% received additional therapies following the intervention. The percentage of control group and treatment group participants receiving treatment, respectively, included pharmacotherapy for spasticity (4.8% and 4.8%), other neuropharmacological treatments (3.4% and 2.9%), mechanical interventions (casting and splinting; 2.9% and 1.4%), exercise and other modes (25.4% and 24.9%), acupuncture and chiropractic (5.3% and 1.9%), and other structured interventions (personal trainers and community exercise; 7.2% and 15.3%).

Clinical relevance of the motor gains was supported by the finding that the

**Figure 2.** Back-Transformed Mean WMFT Performance Time and Mean MAL Amount of Use Scores



Data provided at baseline (0 months), 2 weeks later (posttreatment for the CIMT group), and at 4-month intervals. Bars indicate 1.0 SE of the least-square mean. First column indicates total sample available to contribute to database at baseline and subsequent columns indicate actual sample by group at each time point. CIMT indicates constraint-induced movement therapy; MAL, Motor Activity Log; WMFT, Wolf Motor Function Test.

number of items on the WMFT that could be completed by CIMT participants was substantially greater both immediately and 12 months after treatment. The finding that the paretic upper extremity was used at least half as much as before the stroke on twice as many MAL items by CIMT participants following the intervention and that this behavior persisted through the 12-month follow-up implies long-term use in daily activities. In addition, the proportion of tasks for which the paretic upper extremity could be used without the assistance of the less-impaired upper extremity had almost tripled at 1 year compared with the control group. These MAL findings were confirmed by independent reports of comparable changes from caregivers.

The only SIS domain to show improvement was use of the paretic hand. This finding is consistent with results from another large-scale, multicenter trial of a fitness intervention in acute stroke patients<sup>39</sup> that found long-term changes only on those SIS domains trained (hand function and ambulation). Those results differ from findings in a small study<sup>40</sup> of long-term stroke patients that demonstrated larger MAL changes than we observed and significant, long-term improvements in physical function, communication, and social participation on the SIS. Differences in chronicity and cultural mix among participants might have accounted for these disparate observations.

In our study, improvements on the WMFT Functional Ability scale and strength items were less robust than gains in WMFT Performance Time and MAL scores. This finding is consistent with CIMT studies in individuals with long-term stroke disabilities<sup>41,42</sup> and is not surprising considering that the emphasis during paretic arm training was on the number of repetitions of each task (ie, speed).

Kinetic data from biomechanical studies performed on a subset of participants (n=10) in our study indicate that over the course of treatment, CIMT participants gain improved control over

movements involved in complex tasks, such as turning a key in a lock.<sup>43</sup> Neurophysiological studies of cortical activity after repetitive task practice using the paretic upper extremity have also been performed. Data from a transcranial magnetic stimulation study indicate that following CIMT there is a substantial increase in the amount of cerebral cortex representation of paretic hand muscles.<sup>33</sup> A recent report using serial functional magnetic resonance imaging and a precision grip task showed a linear reduction in ipsilateral (contralesional) M1 (motor cortex) activation and that the mid-point M1 Laterality Index anticipated post-CIMT changes in time to perform the WMFT.<sup>44</sup> Determining the exact relationship between the administration of CIMT and changes in cortical activation may require examining the influence of assessment method, training intensity, stroke chronicity, and the imaging technique used.

Our study has several limitations. First, the interpretation of outcomes was limited by the smaller-than-planned number of lower-functioning individuals enrolled. While higher-functioning participants improved at all posttreatment time points and lower-functioning stroke survivors improved at posttreatment (2 weeks) and at 12 months, the sample size of the lower-functioning group reduced power to detect interactions between group assignment and functional level. Second, only 48.9% of control group participants received other treatments throughout the year. Despite the difficulty in accurately monitoring intensity of other treatments, it is unlikely that intensity of treatment was comparable between groups. Therefore, our findings do not rule out the possibility that usual and customary care provided at the same intensity as CIMT would be as efficacious. However, studies of long-term stroke patients suggest that the efficacy of CIMT is not due to nonspecific factors such as therapist attention, expectations, or time in the laboratory.<sup>7,30</sup> Differentiating the specific contributions of ipsilesional

arm immobilization from massed practice of the paretic limb to achieve improvements cannot be ascertained from this study. Third, the investigation of essential aspects of CIMT, including the extent to which the intensive CIMT schedule of delivery can be altered and is ultimately cost-effective, requires further exploration. Fourth, incomplete detailed information about the anatomical location of each stroke and lack of information regarding the extent and use of medications limit our ability to assess the influence of these relevant variables on primary outcomes.

## CONCLUSION

In summary, among patients who had experienced a first stroke between 3 and 9 months prior, administration of CIMT resulted in statistically significant and clinically relevant improvements in paretic arm motor ability and use compared with participants receiving usual and customary care. Improvements were present following the 2-week intervention, persisted for up to 1 year, and were not influenced by age, sex, or initial level of paretic arm function. These findings suggest that further research exploring central nervous system changes that accompany the observed motor gains and research on alternate models of CIMT delivery are warranted.

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**Analysis and interpretation of data:** Wolf, Winstein, Miller, Taub, Uswatte, Nichols-Larsen.

**Drafting of the manuscript:** Wolf, Winstein, Miller, Uswatte.

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