

# Contralaterally Controlled Functional Electrical Stimulation Improves Hand Dexterity in Chronic Hemiparesis

## A Randomized Trial

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**Background and Purpose**—It is unknown whether one method of neuromuscular electrical stimulation for poststroke upper limb rehabilitation is more effective than another. Our aim was to compare the effects of contralaterally controlled functional electrical stimulation (CCFES) with cyclic neuromuscular electrical stimulation (cNMES).

**Methods**—Stroke patients with chronic (>6 months) moderate to severe upper extremity hemiparesis (n=80) were randomized to receive 10 sessions/wk of CCFES- or cNMES-assisted hand opening exercise at home plus 20 sessions of functional task practice in the laboratory for 12 weeks. The task practice for the CCFES group was stimulation assisted. The primary outcome was change in Box and Block Test (BBT) score at 6 months post treatment. Upper extremity Fugl–Meyer and Arm Motor Abilities Test were also measured.

**Results**—At 6 months post treatment, the CCFES group had greater improvement on the BBT, 4.6 (95% confidence interval [CI], 2.2–7.0), than the cNMES group, 1.8 (95% CI, 0.6–3.0), between-group difference of 2.8 (95% CI, 0.1–5.5),  $P=0.045$ . No significant between-group difference was found for the upper extremity Fugl–Meyer ( $P=0.888$ ) or Arm Motor Abilities Test ( $P=0.096$ ). Participants who had the largest improvements on BBT were <2 years post stroke with moderate (ie, not severe) hand impairment at baseline. Among these, the 6-month post-treatment BBT gains of the CCFES group, 9.6 (95% CI, 5.6–13.6), were greater than those of the cNMES group, 4.1 (95% CI, 1.7–6.5), between-group difference of 5.5 (95% CI, 0.8–10.2),  $P=0.023$ .

**Conclusions**—CCFES improved hand dexterity more than cNMES in chronic stroke survivors.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00891319.

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**Key Words:** electrical stimulation ■ paresis ■ rehabilitation ■ therapeutics ■ upper extremity

Neuromuscular electrical stimulation (NMES) of the paretic wrist and finger extensors is routinely used in stroke rehabilitation to promote recovery of muscle strength and upper extremity function. A recent review of 31 randomized controlled trials concluded that there is strong evidence that NMES applied in the context of task practice improves upper extremity function in subacute and chronic stroke.<sup>1</sup> This is corroborated by a recent systematic review with meta-analysis that concluded that functional electrical stimulation improves activity compared with training alone.<sup>2</sup>

Cyclic NMES (cNMES) is a commonly used and widely available method of administering NMES in stroke rehabilitation.<sup>3</sup> With cNMES, stimulation is delivered according to an on–off cycle, with the cycle timing, repetitions, and intensity of stimulation set by the therapist. Thus, cNMES requires no active participation from the patient, and because the

patient does not control the timing or intensity of stimulation, cNMES is not easily used to assist functional task practice (FTP). Nevertheless, several studies have shown that cNMES can reduce upper limb motor impairment compared with control groups<sup>4,5</sup> although the longevity of effect is inconsistent across studies.<sup>6</sup>

Contralaterally controlled functional electrical stimulation (CCFES) is a new NMES modality that enables the patient to actively open their paretic hand and perform functional tasks. With CCFES, the patient controls the stimulation to their paretic hand in real-time by opening and closing their strong hand. An instrumented glove worn on the strong hand modulates the stimulation intensity to the paretic hand extensors so that both hands open synchronously (Figure I in the [online-only Data Supplement](#)).<sup>7</sup> CCFES may be more effective than cNMES because the stimulation is intention driven; the patient

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controls the stimulation intensity and therefore the degree of opening of their hand. This repetitive temporal coupling of motor intention and motor response may promote plasticity and neural reorganization that underlies recovery of function.<sup>8–10</sup> With control of the timing and intensity of CCFES, patients can participate in functional task therapy more fully than might be possible without the assistance of the stimulation. Our initial CCFES studies with patients >6 months post stroke (n=6) demonstrated that CCFES can improve finger extension strength, range of motion, and control.<sup>7,11</sup>

The goal of this study was to compare the efficacy of CCFES to cNMES on upper limb impairment and function in patients who are >6 months post stroke. We hypothesized that CCFES would improve hand function more than cNMES, and that outcomes would depend on the severity of impairment and time post stroke.

## Methods

### Participants and Treatment Assignment

This was a single-site, 2-arm parallel-group study with blinded assessment. The study was conducted at an academic medical center in Cleveland, OH, and was approved by their institutional review board. Participants were recruited from the outpatient stroke clinics and therapy services, and the study nurse obtained their informed consent. Full eligibility criteria are provided in Table I in the [online-only Data Supplement](#). An abbreviated list of selection criteria includes >6 months from hemorrhagic or ischemic stroke; unilateral finger extensor paresis indicated by a score of  $\leq 4$  of 5 on the manual muscle test (Medical Research Council scale<sup>12</sup>); sufficient active shoulder and elbow movement to volitionally position the paretic hand in the workspace for table-top task practice; hand opening elicited by electrical stimulation of the paretic finger and thumb extensors without pain; no intramuscular botulinum toxin injection of any upper limb muscle in the previous 3 months; and not receiving concomitant occupational therapy.

At enrollment, all participants were classified as having moderate or severe hand impairment by the assessing therapist. Moderate was defined as having at least 10° active wrist extension, 10° active thumb abduction/extension, and 10° active extension in at least 2 additional digits. This definition represents the least amount of movement that is required to participate in constraint-induced movement therapy.<sup>13</sup> Participants with less movement than this who met all the other selection criteria were considered to have severe hand impairment. After baseline assessment, treatment assignment to CCFES or cNMES was made using minimization, an adaptive treatment assignment procedure,<sup>14</sup> to balance the following 4 factors between the 2 treatment groups: (1) degree of impairment (ie, moderate or severe), (2) whether the paretic hand was dominant before the stroke, (3) side of paresis, and (4) sex. A computer program running the minimization algorithm<sup>14,15</sup> determined the treatment assignment that best balanced the 4 factors between the 2 treatments. The treating therapist informed the participants of their treatment assignment.

### Device Setup

For each participant, surface electrodes were positioned over the forearm finger and thumb extensors to produce hand opening.<sup>7,11,16</sup> Up to 3 electrodes were used, each delivering pulses of electric current with a pulse frequency of 35 Hz and amplitude of 40 mA. The strength of muscle contraction was modulated with pulse duration (0–250  $\mu$ s). For each electrode, a maximum pulse duration was determined, defined as that which produced a functional degree of finger and thumb extension without pain. For participants in the CCFES group, the stimulator was programmed to increase the pulse duration for each electrode in proportion to the amount of opening of an instrumented glove worn on the

contralateral nonparetic hand.<sup>7</sup> For participants in the cNMES group, the stimulator automatically and repetitively ramped the pulse durations from zero to maximum in 1 second, maintained the stimulation at maximum for several seconds, and then ramped down the pulse duration to zero, as is commonly done in clinical practice. Each participant was trained to put on the electrodes and use the stimulator at home according to their group assignment, using photographs of the electrodes on their own arm to guide electrode placement.

### Treatments

CCFES and cNMES treatments lasted 12 weeks and consisted of (1) 20 sessions of therapist-guided FTP in the laboratory (2 per week except on weeks that included an assessment session), (2) 10 sessions/wk of self-administered repetitive hand opening exercise at home.

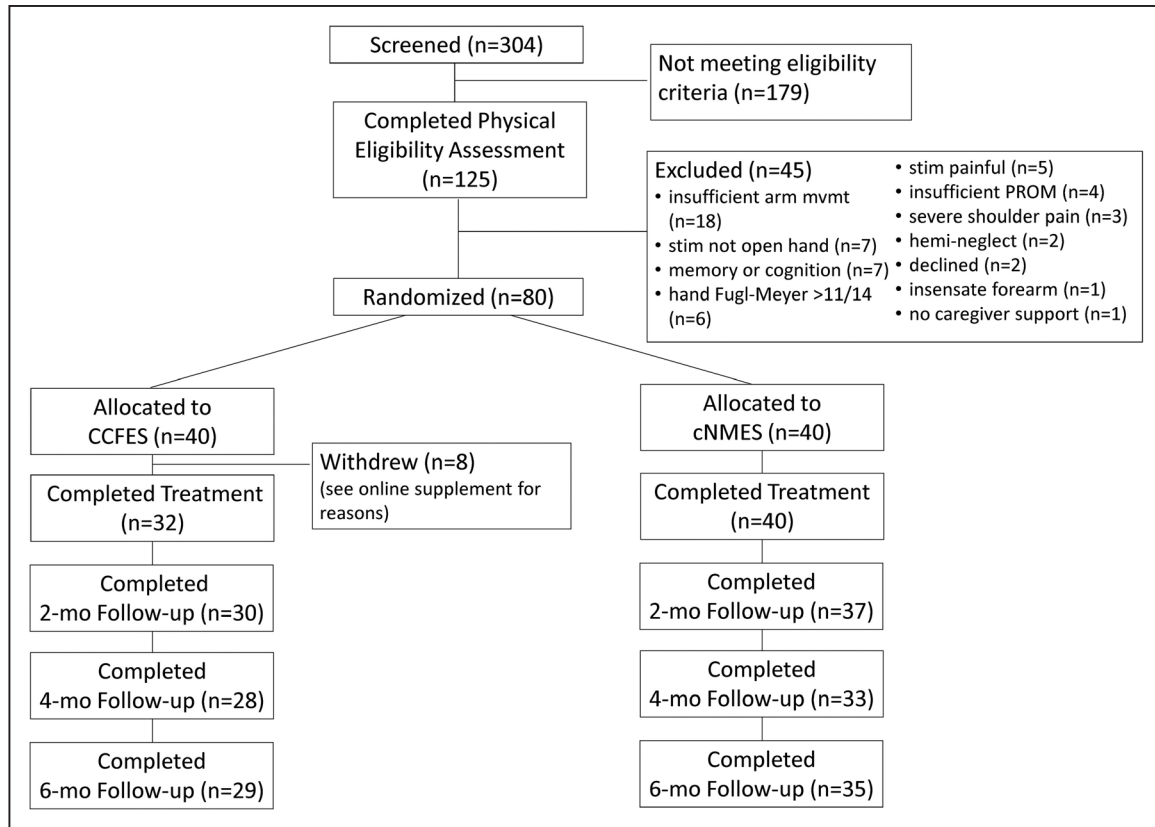
FTP was performed for 60 minutes per session. An occupational therapist instructed and guided the participants in doing tasks that required them to use their paretic hand to grasp, manipulate, and release objects commonly used in daily life.<sup>16</sup> Task difficulty was increased as the participant mastered simple hand tasks. Participants in the CCFES group used CCFES to assist the paretic hand in practicing the tasks. Participants in the cNMES group practiced tasks with no electrical stimulation because cNMES is not amenable to assisting FTP because it is not controlled by the patient. Therefore, to ensure both groups received an equivalent weekly duration of electrical stimulation, the cNMES group received longer sessions of stimulated hand opening exercise at home than the CCFES group.

The self-administered home stimulation exercise sessions were 50 minutes for the CCFES group and 60 minutes for the cNMES group, so that the total duration of stimulation received by both groups was equivalent,  $\approx 10$  hours of stimulation per week (cNMES: 60 minutes/session  $\times$  10 sessions/wk = 10 hours/wk. CCFES: 50 minutes/session  $\times$  10 sessions/wk + 60 minutes of CCFES during an FTP session  $\times$  20 FTP sessions in 12 weeks = 10 hours/wk). During an exercise session, participants with CCFES were prompted by light and sound cues from the stimulator to repeatedly open both hands for 6 seconds and then relax for 20 seconds. For participants with cNMES, the stimulator automatically turned on and off with the same timing as the cues that were produced for CCFES, and the participants were instructed to attempt to open their paretic hand when the stimulation turned on. For both groups, the open/relax durations (cues for CCFES) were progressively changed during the first 4 weeks until the open cue was 8 seconds, and the rest between contractions was 10 seconds, as in previous study.<sup>16</sup> Participants filled out diaries weekly to record when they performed their home exercise sessions. The stimulator also logged usage data, which was downloaded at each laboratory visit (twice a week), and helped identify any problems participants may have had completing the home exercises.

### Outcome Assessments

Assessments were made by a blinded assessor at baseline, every 3 weeks during the treatment period, end of treatment, and 2, 4, and 6 months after completion of treatment. Participants were asked to not use their stimulators for 24 hours before their assessments at weeks 3, 6, 9, and 12 to avoid any possible transient carry-over or fatigue effects.

The Box and Block Test (BBT) was the primary outcome measure. The BBT is a valid and reliable measure of manual dexterity,<sup>17</sup> which counts how many times the participant can pick up 1 block at a time, move it over a partition, and release it in a target area within 60 seconds. The BBT measures change in functional grasp and release, which is the focus of the treatments in this study; therefore, it was chosen as the primary outcome measure. Secondary measures included the Arm Motor Abilities Test (AMAT), an activity measure (ie, functional ability) with a maximum score of 5,<sup>18</sup> and the upper extremity Fugl–Meyer assessment, a measure of upper limb impairment with a maximum score of 66.<sup>19,20</sup>



**Figure 1.** Flow of participants through the study. Of the 45 patients who completed eligibility assessment but were not enrolled, 10 failed >1 of the eligibility criteria. CCFES indicates contralaterally controlled functional electrical stimulation; cNMES, cyclic neuromuscular electrical stimulation; and PROM, passive range of motion.

A questionnaire developed by the study team but with no independent validation was administered at the beginning of the end-of-treatment visit to assess the participants' impression of the intervention's effectiveness and ease of using the device.<sup>11</sup> Monitoring for adverse events was done at each visit by the treating therapist or study nurse (at assessment visits) who documented the occurrence or absence of adverse events in the participant notes. All adverse events were assessed by the principal investigator and referred to the study physician if necessary for follow-up.

**Statistical Analysis**

We hypothesized that participants treated with CCFES would have greater improvement in upper extremity motor function from baseline to 6 months post treatment than participants treated with cNMES, and that participants with moderate hand impairment at baseline would have greater improvements than participants with severe hand impairment at baseline. For each outcome measure, least square means, which adjusted for missing values and severity of impairment (moderate or severe), were computed for each group at each time point and were used to estimate the within-group mean changes from baseline with 95% confidence intervals (CIs) and the between-group differences in change from baseline to 6 months post treatment. These least square means were derived using a linear mixed-effects modeling approach. To detect a difference between groups of at least 6 points on the BBT at 6 months post treatment and assuming a SD of 10.5 blocks at each time point for both groups, with a 2-sided significance level of 0.05 and power of 80%, the target sample size was 80.

**Results**

From March 2009 to October 2014, 304 patients were screened, 125 underwent a formal eligibility assessment, and 80 were enrolled and assigned CCFES or cNMES (Figure 1). At

baseline, there were no significant differences between the study groups on the assessed demographic, stroke-related, and upper extremity motor characteristics (Table 1). Of the 80 participants

**Table 1. Baseline Participant Characteristics**

Characteristic	CCFES (n=40)	cNMES (n=40)
Age, y	55.4 (17.0)	56.3 (12.7)
Sex (female)	14 (35.0%)	15 (37.5%)
Race		
White	18 (45.0%)	23 (57.5%)
Black	22 (55.0%)	17 (42.5%)
No. of comorbidities	2.0 (2.0)	2.0 (2.0)
Years since stroke	1.8 (2.5)	1.6 (4.9)
Dominant side affected	19 (47.5%)	20 (50.0%)
Right side affected	20 (50.0%)	19 (47.5%)
Ischemic stroke	35 (87.5%)	32 (82.1%)*
Moderately impaired	25 (62.5%)	26 (65.0%)
Box and Blocks Test score	7.5 (15)	8.0 (17)
Upper extremity Fugl-Meyer score (max=66)	34 (14)	32 (13)
Arm Motor Abilities Test score (max=5)	2.23 (0.98)	2.33 (1.34)

Data are medians (interquartile range), or numbers (%). CCFES indicates contralaterally controlled functional electrical stimulation; and cNMES, cyclic neuromuscular electrical stimulation.

\*One participant missing data on type of stroke, n=39.

**Table 2. Changes From Baseline to 6 Months Post Treatment**

	All Participants			Participants <2 y Post Stroke With Moderate Hand Impairment at Baseline		
	CCFES (n=32)	cNMES (n=40)	Difference Between Groups (95% CI)	CCFES (n=14)	cNMES (n=14)	Difference Between Groups (95% CI)
BBT change at 6 mo post treatment	4.6 (2.2 to 7.0)*	1.8 (0.6 to 3.0)*	2.8 (0.1 to 5.5)*	9.6 (5.6 to 13.6)*	4.1 (1.7 to 6.6)*	5.5 (0.8 to 10.2)*
UEFM change at 6 mo post treatment	2.4 (0.5 to 4.3)*	2.2 (0.7 to 3.7)*	0.2 (-2.2 to 2.6)	3.5 (0.6 to 6.4)*	1.8 (-0.6 to 4.2)	1.7 (-2.0 to 5.5)
AMAT change at 6 mo post treatment	0.18 (0.06 to 0.31)*	0.04 (-0.07 to 0.15)	0.14 (-0.02 to 0.31)†	0.31 (0.13 to 0.49)*	0.07 (-0.14 to 0.28)	0.24 (-0.03 to 0.52)†

Data are expressed as mean (95% CI). AMAT indicates Arm Motor Abilities Test; BBT, Box and Block Test; CCFES, controlled functional electrical stimulation; CI, confidence interval; cNMES, cyclic neuromuscular electrical stimulation; and UEFM, upper extremity Fugl–Meyer.

\* $P < 0.05$ .

† $P < 0.10$ .

enrolled, 72 completed the treatment and were analyzed. Eight of the participants (10%) withdrew from the study within the first 3 weeks of the treatment period, all from the CCFES group. Reasons for withdrawal are provided in Table II in the [online-only Data Supplement](#). The baseline characteristics of CCFES participants who completed treatment and who withdrew are compared in Table III in the [online-only Data Supplement](#).

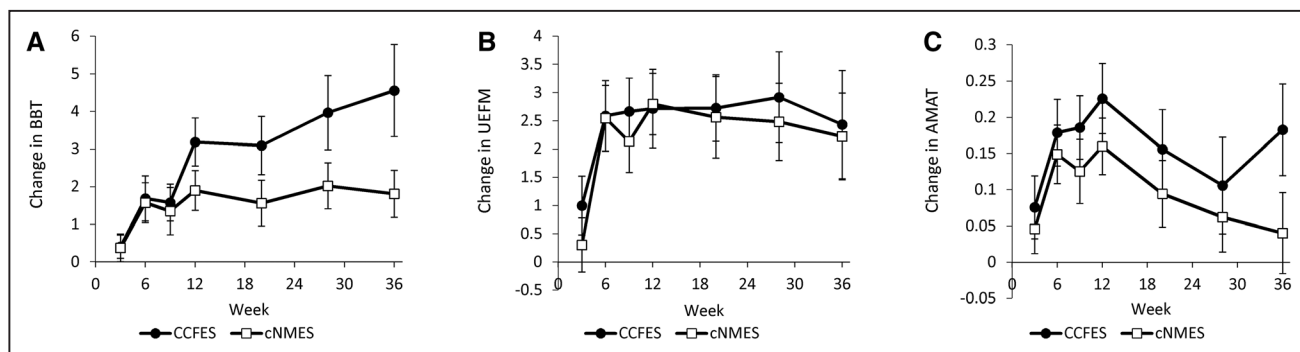
The mean (SD) percentage of prescribed hours of home stimulation exercise performed, according to the stimulators’ electronic data logger was 96% (8.7%) for the CCFES group and 94% (9.5%) for the cNMES group (Mann–Whitney  $U$  test,  $P = 0.31$ ). The mean (SD) number of FTP sessions attended, of 20 possible, was 18 (2.4) for CCFES and 18 (1.8) for cNMES (Mann–Whitney  $U$  test,  $P = 0.43$ ). In response to the questionnaire at end of treatment, all participants reported that they put on the electrodes at home independently, and all CCFES participants except one reported that they put on the glove independently.

By 6 months post treatment, both groups had significant increases in BBT score (Table 2). The gain was greater for the CCFES group than for the cNMES group, with a mean between-group difference of 2.8 (95% CI, 0.1–5.5),  $P = 0.045$  (Figure 2A; Table 2). Both groups improved on the upper extremity Fugl–Meyer (Figure 2B; Table 2), but with no significant between-group differences,  $P = 0.888$ . At 6 months post treatment, the CCFES group had a significant gain on the AMAT, but the cNMES group did not (Figure 2C; Table 2). The

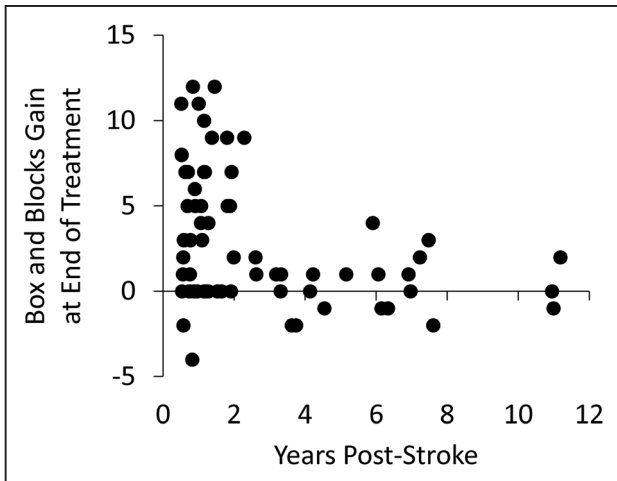
between-group difference on the AMAT was not statistically significant,  $P = 0.096$ .

Secondary analyses showed that the participants with the greatest gains on the BBT were <2 years post stroke (Figure 3) and had moderate hand impairment at baseline (Figure 4A). Among these participants, the CCFES group had 6-month post-treatment gains on the BBT of 9.6 (95% CI, 5.6–13.6) versus 4.1 (95% CI, 1.7–6.6) for the cNMES group, a between-group difference in gains of 5.5 (95% CI, 0.8–10.2),  $P = 0.023$  (Table 2). Similarly, the greatest gains on the AMAT were achieved by CCFES participants who had moderate rather than severe hand impairment at baseline (Figure 4C). But the greatest gains on the upper extremity Fugl–Meyer were achieved at midtreatment by the CCFES participants who had severe rather than moderate hand impairment (Figure 4B).

Responses to the end-of-treatment questionnaire showed that 97% of the CCFES group and 88% of the cNMES group agreed or strongly agreed with the statement, “I can use my hand better now than before the study.” Also, 91% of the CCFES group and 86% of the cNMES group agreed or strongly agreed with “I wish this treatment had been part of my initial therapy.” There were no serious, unexpected, study-related adverse events. However, 1 participant frequently had headaches after FTP sessions, 3 participants had skin irritation from the electrodes, and 1 participant found the stimulation transiently uncomfortable.



**Figure 2.** Change in (A) Box and Block Test (BBT), (B) upper extremity Fugl–Meyer (UEFM), and (C) Arm Motor Abilities Test (AMAT) scores (mean, SE). CCFES indicates contralaterally controlled functional electrical stimulation; and cNMES, cyclic neuromuscular electrical stimulation.



**Figure 3.** Box and Block Test gains at end of treatment for all participants as a function of time post stroke at baseline.

**Discussion**

Among participants with chronic moderate to severe hand impairment after stroke, 12 weeks of CCFES therapy improved manual dexterity more than an equivalent dose of cNMES. The minimum clinically important difference for the BBT has not been established, but the minimum detectable change is 5.5 blocks.<sup>21</sup> Therefore, for the main analysis, which included participants with moderate and severe hand impairment over a wide range of chronicity, the average magnitudes of change on the BBT (4.6 blocks for CCFES and 1.8 blocks for cNMES) and the average between-group difference (2.8 blocks) fall short of the minimum detectable change threshold and are not clinically relevant.

The magnitudes of improvement and between-group differences favoring CCFES were greater in participants with moderate (not severe) hand impairment at baseline whose strokes were >6 months but <2 years ago. In that subset of participants, the average change in BBT scores for the CCFES group (9.6 blocks) and the upper limit of its 95% CI (13.6 blocks; Table 2) exceeded the minimum detectable change and would likely be considered clinically important by many patients and clinicians. Also, in that subset of participants, the average between-group difference in BBT

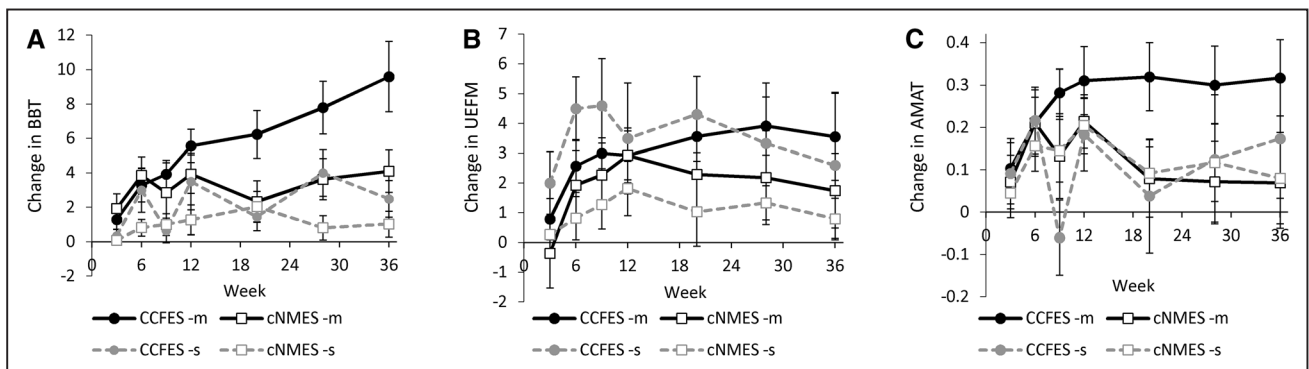
scores (5.5 blocks) and the upper limit of its 95% CI (10.2 blocks) reached or exceeded minimum detectable change.

The finding of no significant between-group difference on the upper extremity Fugl–Meyer may be because the measure is more heavily weighted toward assessing proximal upper limb movement rather than distal hand function. CCFES may have its greatest distinctive impact on distal function. The tasks rated in the AMAT require both proximal and distal function, which may explain why the CCFES group had statistically significant improvement on the AMAT but the cNMES group did not.

Few previous studies have directly compared electrical stimulation modalities. Our recently published study of 122 subacute (≤6 months) stroke survivors found no significant differences between cNMES, EMG-triggered NMES, and sensory stimulation, on their effect on upper limb function,<sup>22</sup> a finding that confirmed previous smaller studies.<sup>23,24</sup> Before the present study, our pilot randomized controlled trial with patients ≤6 months post stroke (n=21) showed that CCFES produced greater improvements than cNMES, but the small sample size limited the statistical power.<sup>16</sup> Recently, other investigators compared a variation of CCFES with cNMES in patients ≤3 months post stroke (n=60) and showed that CCFES produced significantly greater gains than cNMES.<sup>25</sup> Unlike these previous trials, the present study included only stroke survivors with chronic hemiplegia (>6 months), a population for which it is even more challenging to show positive benefits of rehabilitative therapy.

The finding of a statistically significant between-group difference on the BBT in a chronic population is encouraging and may point to a true mechanistic advantage underlying the CCFES method of electrical stimulation therapy. One or more of the elements that distinguish CCFES from cNMES may be important in facilitating motor recovery, namely, (1) real-time patient-controlled intensity of stimulation to the paretic hand (ie, intention-driven movement), (2) synchronized opening of both hands, and (3) stimulation-assisted task practice with the paretic hand. Thus, the method of NMES may matter.

This study also helps to clarify which patients with stroke may be the best candidates for NMES therapies. Patients >2 years post stroke should not be expected to achieve significant improvement with either cNMES or CCFES.



**Figure 4.** For participants <2 y post stroke (and >6 mo post stroke), change in (A) Box and Block Test (BBT), (B) upper extremity Fugl–Meyer (UEFM), and (C) Arm Motor Abilities Test (AMAT). CCFES indicates contralaterally controlled functional electrical stimulation; cNMES, cyclic neuromuscular electrical stimulation; m, moderate hand impairment at baseline; and s, severe hand impairment at baseline.

Patients <2 years post stroke with some finger, thumb, and wrist extension are the best candidates for CCFES therapy. Patients with no residual finger extension may expect to gain arm movement from CCFES, but not manual dexterity. Some patients may find it more difficult to self-administer CCFES than cNMES because it requires donning a glove on the unaffected hand and attending to cues from the stimulator, yet the reasons given by at least 6 of the 8 participants who started and discontinued CCFES did not clearly point to treatment elements that distinguish CCFES from cNMES.

Strengths of this study include high compliance rates, no concomitant therapy, extended follow-up, and careful matching of therapy dose across 2 active treatment groups. Yet, there are several limitations to this study. The subgroup analyses investigating the effects of severity of hand impairment and time post stroke were preplanned, but exploratory, and therefore the study was not powered for them.

Motor rehabilitation trials preclude double blinding, so participants were aware of their treatment assignment. All participants were informed that one group would receive stimulation that opens the weak hand, and the other group would wear a glove on the strong hand to control stimulation to the weak hand. Participants in both groups were instructed to exert effort to open their paretic hand in synchrony with stimulation during their home exercise sessions. That instruction was reinforced at each task practice session, with the expectation that similar proportions of the 2 groups would follow that instruction. There was no way to ensure that cNMES participants did not open their contralateral unaffected hand in synchrony with the stimulation. This potential crossover effect would reduce the contrast between the 2 treatments, biasing the outcome favoring cNMES.

The study was conducted at least 6 months post stroke, when rehabilitation is typically no longer prescribed; however, conducting the study with chronic patients eliminated spontaneous recovery as a possible confounder. Showing functionally relevant outcomes during the chronic phase is needed to incentivize healthcare reformers to make it possible for patients to receive such therapies even beyond 6 months.

Future trials should include validated patient reported outcomes and outcomes that are sensitive to participation and quality of life.<sup>26</sup> Also, the translatability of CCFES therapy to other research sites and to clinical practice still needs to be established. A future multisite study is needed to confirm the findings of this study and to demonstrate generalizability across different rehabilitation centers.

## Conclusions

In patients with chronic (>6 months) severe to moderate hand impairment after stroke, 12 weeks of CCFES therapy improved manual dexterity at 6 months post treatment more than an equivalent dose of cNMES. The advantage of CCFES over cNMES was greatest in participants who were <2 years post stroke and who had moderate rather than severe hand impairment.

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## Disclosures

Drs Knutson and Chae are coinventors on US Patent 8,165,685 assigned to Case Western Reserve University: System and Method for Therapeutic Neuromuscular Electrical Stimulation.

## References

1. Teasell R, Hussein N. Rehabilitation of hemiplegic upper extremity post stroke. In: Teasell R, ed. Evidence-based review of stroke rehabilitation. 16th ed. London, Ontario, Canada: EBRSR.COM; 2014.
2. Howlett OA, Lannin NA, Ada L, McKinstry C. Functional electrical stimulation improves activity after stroke: a systematic review with meta-analysis. *Arch Phys Med Rehabil*. 2015;96:934–943. doi: 10.1016/j.apmr.2015.01.013.
3. Nascimento LR, Michaelsen SM, Ada L, Polese JC, Teixeira-Salmela LF. Cyclical electrical stimulation increases strength and improves activity after stroke: a systematic review. *J Physiother*. 2014;60:22–30. doi: 10.1016/j.jphys.2013.12.002.
4. Chae J, Bethoux F, Bohine T, Dobos L, Davis T, Friedl A. Neuromuscular stimulation for upper extremity motor and functional recovery in acute hemiplegia. *Stroke*. 1998;29:975–979.
5. Hsu SS, Hu MH, Wang YH, Yip PK, Chiu JW, Hsieh CL. Dose-response relation between neuromuscular electrical stimulation and upper-extremity function in patients with stroke. *Stroke*. 2010;41:821–824. doi: 10.1161/STROKEAHA.109.574160.
6. Knutson JS, Fu MJ, Sheffler LR, Chae J. Neuromuscular electrical stimulation for motor restoration in hemiplegia. *Phys Med Rehabil Clin N Am*. 2015;26:729–745. doi: 10.1016/j.pmr.2015.06.002.
7. Knutson JS, Harley MY, Hisel TZ, Chae J. Improving hand function in stroke survivors: a pilot study of contralaterally controlled functional electric stimulation in chronic hemiplegia. *Arch Phys Med Rehabil*. 2007;88:513–520. doi: 10.1016/j.apmr.2007.01.003.
8. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science*. 1996;272:1791–1794.
9. Rushton DN. Functional electrical stimulation and rehabilitation—an hypothesis. *Med Eng Phys*. 2003;25:75–78.
10. Johansson BB. Brain plasticity and stroke rehabilitation. The Willis lecture. *Stroke*. 2000;31:223–230.
11. Knutson JS, Hisel TZ, Harley MY, Chae J. A novel functional electrical stimulation treatment for recovery of hand function in hemiplegia: 12-week pilot study. *Neurorehabil Neural Repair*. 2009;23:17–25. doi: 10.1177/1545968308317577.
12. Schwartz S, Cohen ME, Herbison GJ, Shah A. Relationship between two measures of upper extremity strength: manual muscle test compared to hand-held myometry. *Arch Phys Med Rehabil*. 1992;73:1063–1068.
13. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, et al; EXCITE Investigators. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA*. 2006;296:2095–2104. doi: 10.1001/jama.296.17.2095.
14. Taves DR. Minimization: a new method of assigning patients to treatment and control groups. *Clin Pharmacol Ther*. 1974;15:443–453.
15. Winstein CJ, Miller JP, Blanton S, Taub E, Uswatte G, Morris D, et al. Methods for a multisite randomized trial to investigate the effect of constraint-induced movement therapy in improving upper extremity function among adults recovering from a cerebrovascular stroke. *Neurorehabil Neural Repair*. 2003;17:137–152.
16. Knutson JS, Harley MY, Hisel TZ, Hogan SD, Maloney MM, Chae J. Contralaterally controlled functional electrical stimulation for upper

- extremity hemiplegia: an early-phase randomized clinical trial in subacute stroke patients. *Neurorehabil Neural Repair*. 2012;26:239–246. doi: 10.1177/1545968311419301.
17. Desrosiers J, Bravo G, Hébert R, Dutil E, Mercier L. Validation of the Box and Block Test as a measure of dexterity of elderly people: reliability, validity, and norms studies. *Arch Phys Med Rehabil*. 1994;75:751–755.
  18. Kopp B, Kunkel A, Flor H, Platz T, Rose U, Mauritz KH, et al. The Arm Motor Ability Test: reliability, validity, and sensitivity to change of an instrument for assessing disabilities in activities of daily living. *Arch Phys Med Rehabil*. 1997;78:615–620.
  19. Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. *Phys Ther*. 1983;63:1606–1610.
  20. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med*. 1975;7:13–31.
  21. Chen HM, Chen CC, Hsueh IP, Huang SL, Hsieh CL. Test-retest reproducibility and smallest real difference of 5 hand function tests in patients with stroke. *Neurorehabil Neural Repair*. 2009;23:435–440. doi: 10.1177/1545968308331146.
  22. Wilson RD, Page SJ, Delahanty M, Knutson JS, Gunzler DD, Sheffler LR, et al. Upper-limb recovery after stroke: A randomized controlled trial comparing emg-triggered, cyclic, and sensory electrical stimulation. [published online ahead of print May 24, 2016]. *Neurorehabil Neural Repair*. <http://nnr.sagepub.com/content/early/2016/05/24/1545968316650278.full.pdf>. Accessed June 10, 2016.
  23. de Kroon JR, IJzerman MJ. Electrical stimulation of the upper extremity in stroke: cyclic versus EMG-triggered stimulation. *Clin Rehabil*. 2008;22:690–697. doi: 10.1177/0269215508088984.
  24. Boyaci A, Topuz O, Alkan H, Ozgen M, Sarsan A, Yildiz N, et al. Comparison of the effectiveness of active and passive neuromuscular electrical stimulation of hemiplegic upper extremities: a randomized, controlled trial. *Int J Rehabil Res*. 2013;36:315–322. doi: 10.1097/MRR.0b013e328360e541.
  25. Shen Y, Yin Z, Fan Y, Chen CF, Dai W, Yi W, et al. Comparison of the effects of contralaterally controlled functional electrical stimulation and neuromuscular electrical stimulation on upper extremity functions in patients with stroke. *CNS Neurol Disord Drug Targets*. 2015;14:1260–1266.
  26. Katzan IL, Thompson N, Uchino K. Innovations in stroke: the use of PROMIS and NeuroQoL Scales in clinical stroke trials. *Stroke*. 2016;47:e27–e30. doi: 10.1161/STROKEAHA.115.011377.