

Influence of Combined Afferent Stimulation and Task-Specific Training Following Stroke: A Pilot Randomized Controlled Trial

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Background. Reorganization of the human motor cortex can be induced by specific patterns of peripheral afferent stimulation. The potential for afferent stimulation to facilitate the functional recovery associated with conventional rehabilitative techniques has not previously been investigated. **Objective.** The authors sought to determine whether combining appropriate afferent stimulation with task-specific training resulted in greater improvements than training alone in patients with impaired upper limb function in the subacute phase following stroke. **Method.** Twenty patients with hemiparesis due to stroke were allocated randomly to either a stimulation or control group. All received 9 sessions of task-specific physiotherapy training over 3 weeks. Prior to each training session, associative electrical stimulation of the motor point of 2 hand muscles was given in the stimulation group, whereas the control group received sham stimulation. Changes in dexterity were assessed using a grip-lift task, and standard measures of upper-limb function were made before and following the intervention. Corticospinal excitability was examined using transcranial magnetic stimulation. **Results.** Both groups showed comparable improvements in functional measures of upper-limb function. Of the 20 patients, only 14 could perform the grip-lift task, which is an objective measure of dexterity. Patients in the stimulation group

exhibited significantly greater improvements in this task than the control group. There was no significant change in corticospinal excitability in either group. **Conclusion.** This pilot study provides preliminary data suggesting that targeted afferent stimulation may facilitate the response to conventional rehabilitation in patients with hemiparesis due to stroke, but these results need to be confirmed in a larger scale study.

Key Words: *Plasticity—Stroke—Grip-lift task—Dexterity—Rehabilitation.*

Stroke is a leading cause of long-term disability in adults, with upper limb paresis the primary functional impairment.^{1,2} Despite intensive rehabilitative efforts, functional outcome of patients with severe hemiparesis is poor.³ Only 5% of patients with complete paralysis regain full arm function,^{4,5} and 30% to 66% never regain use of the affected arm.^{6,7} Of those who regain purposeful upper-limb movement, fine motor control or dexterity often remains impaired due to sensory loss and impairments in sensorimotor integration.⁸

It has recently been suggested that strategies that increase the excitability of corticospinal projections to paretic muscles in stroke patients may facilitate functional recovery.⁹ Corticospinal excitability can be increased in normal participants by performance of simple ballistic movements¹⁰ or more complex tasks such as the Purdue pegboard task.¹¹ Similarly, periods of peripheral,^{9,12} central,¹³ or combined peripheral and central stimulation¹⁴ have also been shown to increase motor cortical excitability. Repeated sessions of peripheral nerve stimulation over a number of days increase the cortical representation of targeted muscles, which persists beyond the final stimulation session for several days.¹⁵ The functional significance of such experimentally induced changes in cortical excitability is not well understood. However, there is recent evidence that increased motor cortical excitability

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may facilitate the performance of motor tasks by normal participants.¹⁶⁻¹⁸

In stroke rehabilitation, specific training or repetitive exercise are also known to increase corticospinal excitability^{19,20} and improve function of the paretic hand. Task-specific physiotherapy involving repetitive practice of meaningful daily activities is more effective than traditional approaches to rehabilitation of the upper limb^{21,22} and can lead to increased activation of the affected sensorimotor cortex.²³

Investigation of the potential for stimulation-induced increases in cortical excitability to improve upper limb function following stroke has recently begun. Techniques such as combined peripheral and cortical stimulation,²⁴ somatosensory stimulation,^{25,26} direct cortical stimulation,²⁷ and transcranial direct current stimulation²⁸ have been applied to small numbers of chronic stroke patients with promising results. However, despite evidence that both stimulation-induced and exercise-induced plasticity can be beneficial for recovery in hemiplegia, only one study has investigated the effect of combining these approaches. In that study, repetitive transcranial magnetic stimulation (TMS) in conjunction with rehabilitation training in acute stroke patients led to a short-term benefit in the real compared to the sham stimulation group,²⁹ but the longer-term effects of this approach have not yet been investigated.

We hypothesized that combining an afferent stimulation technique that increases motor cortical excitability with rehabilitative training would result in greater functional gains than training alone. We tested this hypothesis in a group of patients with hemiparesis due to stroke who had been discharged from formal rehabilitation due to a plateau in their motor recovery. The aim of this pilot study was to investigate the potential for repeated sessions of afferent stimulation, targeted at 2 intrinsic hand muscles and combined with task-specific training of the upper limb, to result in greater improvements in dexterity than training alone.

METHODS

Patients

Twenty patients, aged 45 to 94 years (mean \pm standard deviation [SD] = 65.6 \pm 11.8 years) with mild to moderate hemiparesis due to stroke completed the study (Table 1). All were studied between 1 and 8 months after the stroke (mean \pm SD 4.4 \pm 2.4 months). Patients were recruited according to the following criteria: (1) first-ever ischemic cerebral infarct; (2) active range of antigravity motion of the affected side of at least 60 degrees shoulder elevation and 10 degrees wrist extension; (3) passive range of

motion of the affected side of at least 75% normal in the shoulder, elbow, wrist, and hand with minimal or no pain; and (4) discharged from upper-limb rehabilitation services. Patients were excluded if they had a cardiac pacemaker, metal intracranial implants, epilepsy, complete loss of hand sensation, or language deficits that impaired cooperation in the study. All patients gave written informed consent to participate in the study, in accordance with the Declaration of Helsinki. The study was approved by the relevant Human Research Ethics Committees.

Experimental Design

Patients were randomly assigned to the stimulation or control group at the time of enrollment into the study. Allocation was determined by a computerized random-number generator performed by an independent researcher, and assignments were enclosed in sequentially numbered, opaque sealed envelopes until entry into the study, at which time baseline measures were recorded (see Figure 1). These measures were repeated 1 week later. Following this, both groups participated in a standardized training protocol designed to improve upper-limb function, which was conducted 3 times a week for 3 weeks.²¹ Patients in the stimulation group (n = 10) were given a period of electrical nerve stimulation (details below) immediately before the training period in each session, whereas patients in the control group (n = 10) were given sham stimulation (below). All patients were told that they would receive weak electrical stimulation but that the strength would vary between patients; hence, those in the sham group were unaware they were not receiving the "real" stimulation.

Intervention

Training protocol. A standardized training protocol was developed to provide upper-limb rehabilitation to all patients. Major impairments of upper-limb function were identified in the following categories: sensation, active and passive range of movement, and uni- and bimanual dexterity. Deficits in each of these areas were identified and strategies aimed to reduce the impairments were implemented. Task-specific training involving repetitive practice of everyday tasks was chosen as the training method.²¹ Tasks were standardized and repeatable and included reaching, wrist extension against resistance, and performance of fine motor tasks like placing items in a box, writing, and manipulating putty. Each patient performed only those tasks that were relevant to their impairments, but time spent on each aspect of

Table 1. Baseline Patient Characteristics

Patient No	Sex	Age (yrs)	Time Since Stroke (m)	ARAT (/57)	FMA (/66)	Sensation ^a	Site of Infarct/ Arterial Territory
Control group							
1	F	63	7	57	62	2	L ACA
2	M	55	7	54	58	2	L IC
5	M	68	7	55	55	2	R IC
10	M	66	2	51	25	2	L IC
11	F	70	2	12	25	1	R MCA and PCA
13	M	45	3	49	63	1	R MCA
14	M	54	1	53	57	2	L medial medulla
18	M	54	4	4	31	2	L frontoparietal
19	M	78	8	10	32	2	L basal ganglia and IC
20	F	48	5	47	40	1	R MCA
Mean ± SD		60.1 ± 10.5	4.6 ± 2.6	39.7 ± 20.6	47.9 ± 14.2	1.7 ± 0.5	
Stimulation group							
3	M	70	3	24	38	2	R thalamus and occiput
4	F	79	4	32	54	1	R parietal – cortical
6	F	76	6	41	46	2	L parietal – subcortical
7	M	57	3	48	56	2	L corona radiata
8	F	63	7	17	27	1	R parietal
9	F	94	3	23	43	2	R IC
12	M	77	2	41	45	1	R parietal
15	F	69	4	53	55	2	R lacunar
16	M	63	8	32	51	1	L frontoparietal
17	M	63	1	44	60	2	L IC
Mean ± SD		71.1 ± 10.8	4.1 ± 2.2	37.6 ± 11.8	47.3 ± 10.6	1.6 ± 0.5	

m = months; M = male; F = female; ARAT = Action Research Arm Test; FMA = Fugl-Meyer Assessment; R = right; L = left; IC = internal capsule; MCA = middle cerebral artery; PCA = posterior cerebral artery; ACA = anterior cerebral artery.
^aSensation to light touch: 0 = no sensation, 1 = reduced sensation, 2 = intact sensation.⁵³

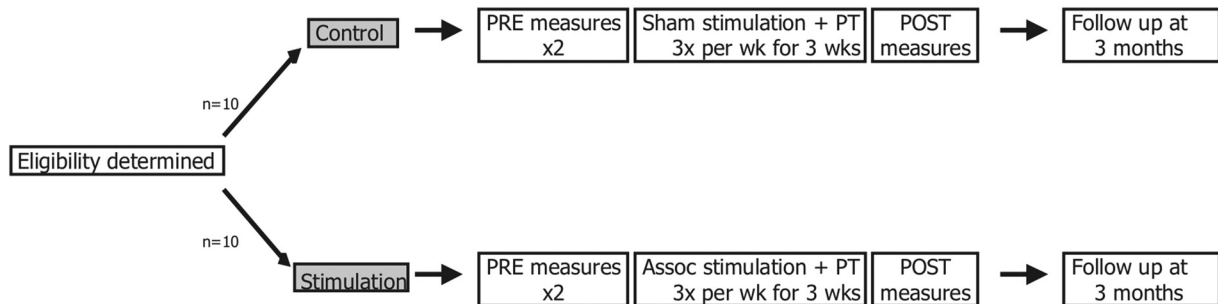


Figure 1. Experimental design. Pre- and postmeasures included functional assessment, the grip-lift task, and corticospinal excitability measures. PT refers to task-specific physiotherapy training.

impairment was comparable between patients. In accordance with the principles of motor learning,³⁰ patients were given feedback of their performance and tasks were progressed as performance improved, which helped to maintain interest and motivation. Sessions lasted for 1 hour and were conducted by an experienced physiotherapist (MMcD). All patients were prescribed appropriate

upper-limb exercises to complete at home, and they were asked to document the type and duration of exercise in a logbook.

Afferent stimulation. Patients in the stimulation group were given a period of peripheral nerve stimulation prior to each session of training. This peripheral stimulation

protocol, referred to as “associative stimulation,” induces an increase in cortical excitability in normal patients.³¹ Patients sat in a comfortable armchair with both arms supported and relaxed. Surface Ag-AgCl disposable electrodes (9 mm diameter) were placed over the motor point of the paretic first dorsal interosseous (FDI) and abductor pollicis brevis (APB) muscles with reference electrodes placed over the corresponding metacarpophalangeal joints. Stimuli were square-wave electrical pulses of 0.1 ms duration delivered simultaneously to the FDI and APB muscles by a constant-current stimulator (Digitimer DS 7, Digitimer, Hertfordshire, UK). The timing between successive stimuli was randomized in the range 0.15 to 2.85 seconds. Stimulus intensity (range 10–30 mA) was set for each muscle at a level just sufficient to evoke a visible motor response. Patients were instructed to pay attention to the relaxed, stimulated hand, and this was reinforced regularly (once every 10 minutes) during the session to assist in focusing their attention on the stimulated (paretic) hand. The stimulation paradigm was applied for 1 hour and was painless. Associative stimulation increases the excitability of the corticospinal projection to stimulated hand muscles for at least 1 hour.³¹ Therefore, it was likely that the excitability of the corticospinal projection to FDI and APB was increased during the following period of motor training in the stimulation group.

Sham stimulation. Prior to the upper limb training protocol, patients in the control group underwent the same experimental protocol as the stimulation group except that the stimulus current was zero and patients were told: “You are about to receive weak electrical pulses to your finger and thumb that you may or may not feel.” Patients were again asked to focus their attention on the paretic hand, and this instruction was repeated every 10 minutes during the 1-hour period of sham stimulation. All patients believed that they received the real stimulation.

Evaluation

Functional measures were tested on 4 occasions. Patients attended 2 sessions, 1 week apart, for baseline measures prior to commencing the intervention (Pre). Postintervention measures were made immediately following the last training session, and follow-up measures were recorded 3 months later.

Grip-Lift Task and Manual Dexterity

The ability of patients to initiate and scale grip force to load during a precision lifting task with the thumb

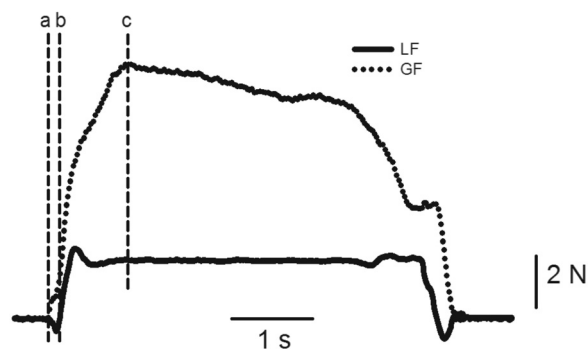


Figure 2. Typical grip-lift trace illustrating grip force (GF, dotted line) and load force (LF, solid line) as the device is lifted from the surface. Vertical lines indicate (a) onset of GF, (b) onset of positive LF, (c) GF_{max} . The time between (a) and (b) is the preload phase, and the time between (a) and (c) is the lift phase. The maximal correlation between rate of GF and LF rates during the lift phase is calculated by cross-correlating the rate of change of GF and LF during the lift phase and is an objective measure of the ability to scale the GF to the changing LF during a lift.³⁴

and index finger was investigated with a purpose-built manipulandum. The grip-lift manipulandum was similar in concept to that originally described by Westling and Johansson.³² The base held an exchangeable mass, allowing the weight of the manipulandum to be varied in 100 g increments from 240 g to 440 g. The grip force (GF), applied by the index finger and thumb onto polished brass surfaces 35 mm apart, and the load force (LF) were measured with lightweight load cells (MLP-10, Transducer Technologies, Temecula, CA).

Patients washed their hands thoroughly with soap and water and sat at a low table. They were instructed to lift the manipulandum to the height indicated (10 cm), hold it still for 3 seconds, and replace it on the table. They practised this until they were comfortable with the task. Testing consisted of 3 blocks of 5 lifts with the weight of the manipulandum changed pseudo-randomly between blocks (either 240, 340, or 440 g). The lifting task was performed first with the unaffected hand and then with the paretic hand.

For each lifting trial, data acquisition started 1 second before GF reached 1.0 N and ended when the apparatus was replaced on the table. The GF and LF signals were low-pass filtered (100 Hz), sampled at 400 Hz, digitized, and stored on a computer for off-line analysis.

We have previously reported that 2 parameters obtained from this task are sensitive objective measures of hand function in stroke patients.³³ We therefore restricted our analysis to those 2 variables (see Figure 2), namely, (1) *preload duration*: defined as the time between onset of GF and onset of positive LF as the manipulandum was lifted from the surface; (2) *maximal*

correlation: the maximal correlation coefficient obtained when the rate of change of GF (dGF/dt) and LF (dLF/dt) are cross-correlated. That is, the correlation coefficient (r) for these 2 signals was obtained at each of a series of time points to which the plot of dGF/dt was shifted in increments of 2.5 ms relative to the plot of dLF/dt. The maximal value of the correlation coefficient thus calculated is an objective measure of the ability to scale GF to the changing LF during a lift.³⁴ The average of 15 lifts on each occasion was calculated for these parameters.

Corticospinal Excitability

We measured the amplitude and latency of motor-evoked potentials (MEPs) evoked in the relaxed FDI and APB muscles by TMS. Focal TMS was performed using a flat figure-eight shaped coil (external wing diameter 9 cm) connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The optimal position for evoking responses in FDI and APB was established and marked on the scalp with a soft-tip pen to ensure reliable coil placement between trials. While the location of this point relative to the vertex was measured and recorded for future sessions, the actual stimulation site was optimized for each testing session.

Resting motor threshold and stimulus-response curves were recorded using standard techniques^{35,36} and with all muscles relaxed. The average peak-to-peak amplitude of the 8 MEPs recorded at each stimulus intensity was plotted for each patient, and the Boltzmann sigmoidal function was used to fit the data points by the Levenberg-Marquand nonlinear least-mean-squares algorithm.^{37,38} The parameters obtained from this function were (1) the maximal value or plateau of the relationship, (2) the stimulus intensity required to obtain a response of 50% of the maximum, and (3) the maximal slope.

Other Functional Outcome Measures

All performance-based functional measures were conducted by a single investigator who was blinded to group assignment. The Action Research Arm Test (ARAT) was used to assess upper-limb function.³⁹ It consists of 19 tests divided into the categories of grasp, grip, pinch, and gross arm movement. Each item is scored on a 4-point ordinal scale, with a total possible score of 57. In addition, the 66-point upper limb component of the Fugl-Meyer Assessment (FMA) was used to measure impairment. Both of these measures have been extensively used to evaluate response to intervention following stroke.^{6,40,41}

The motor activity log was used to assess the ability of patients to use their arm for daily activities.⁴⁰ This is

a semistructured interview, adapted from Taub et al,⁴² which determines the amount and quality of use of the affected arm when the patient performs 13 everyday items, scored on a 6-point scale. Its reliability and validity have been established with stroke patients.^{43,44}

Other measures of upper limb function were maximal pinch-grip strength between the thumb and the index finger, recorded with a calibrated load cell, and maximal tapping speed, determined by asking the patient to tap with the index finger as quickly as possible on a load cell for 5 seconds. Each hand was tested 3 times, with a rest period of 30 seconds between each trial. The highest value of the 3 attempts was recorded on each occasion.

Data Analysis

All baseline data from the 2 preintervention testing sessions were analyzed with paired t tests and correlated with the Spearman rank-order test to show that data obtained on the 2 occasions were well correlated ($r > .80$) and the 2 samples were not different ($P > .05$). Data were then combined to provide an average of the 2 sessions, and these averages were used as the preintervention values. Unpaired t tests were used to investigate differences between the 2 groups at baseline.

Linear mixed-effects model analysis of variance was fitted to the grip-lift, functional, and TMS data to compare results pre- and postintervention and between postintervention and follow-up. In the models, group status and time were treated as fixed effects, whereas the patient was treated as a random effect.

A Spearman rank-order correlation was used to determine the correlation between the functional measures, grip-lift parameters, and corticospinal excitability. Data are reported as mean \pm 1 SD, and results were considered significant when $P \leq .05$.

RESULTS

Patients in each group attended all sessions and were available for follow-up, and there were no adverse events. All patients participated in their home exercise program with no difference in the amount of time spent between the 2 groups (time spent on daily exercises control group 21.0 ± 6.1 minutes, stimulation group 21.5 ± 8.2 minutes; unpaired t test, $P = .88$).

Grip-Lift Task

Three patients from each group were unable to lift and hold the manipulandum with the paretic limb (patients

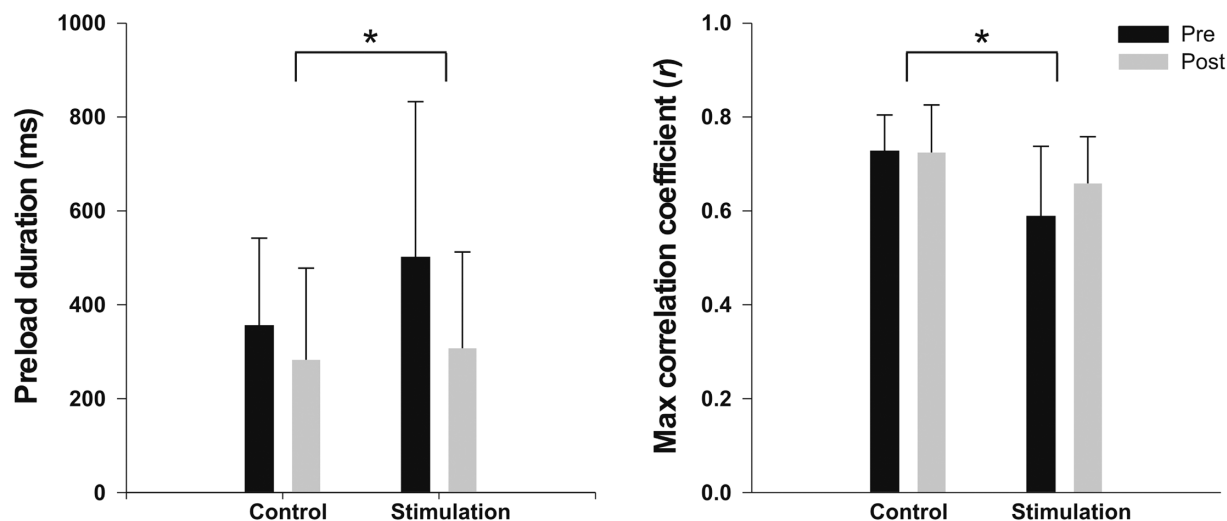


Figure 3. Changes in grip-lift characteristics over the 3-week intervention, with baseline data in black and postintervention data in gray. The decrease in preload duration was seen in both groups as patients reduced the time between establishing grip and commencing the lift. An increase in the maximal correlation coefficient indicates improved scaling of the rate of change of grip force to the load force rate during the lift and was only seen in the stimulation group. For both measures, the superiority of the stimulation group was evident as a significant “group*time” interaction for maximal correlation and preload duration ($*P \leq .05$).

11, 18, and 19 in the control group and 3, 8, and 16 in the stimulation group). Therefore the data from the remaining 7 patients in each group were used for the grip-lift analysis only.

There was a significant reduction in the time taken to establish grip prior to lifting the device from the table (the preload duration) for all patients postintervention. Analysis of variance revealed a significant effect of “time” ($F_{1,12} = 23.0$, $P < .001$) but no overall effect of “group” ($P > .05$). There was, however, a significant “group*time” interaction ($F_{1,12} = 4.75$, $P = .05$) due to greater improvement in the stimulation group (Figure 3).

The maximal correlation value changed over time in both groups (factor time $F_{1,12} = 5.2$, $P = .04$). Once again the stimulation group improved more than the control group following the intervention (group*time interaction $F_{1,12} = 6.0$, $P = .03$; Figure 3).

Corticospinal Excitability

The responses to TMS were highly variable between patients. It was possible to evoke MEPs from all patients in the stimulation group and all but 1 (patient 19) in the control group. There were no differences in resting motor threshold or MEP latency between the groups for either muscle at baseline, or over time. Similarly, there was no difference in the maximal MEP, slope, or mid-point of the stimulus-response curve for either muscle over time or between groups.

Other Functional Outcome Measures

Data from all 20 patients was obtained for functional measures. Baseline performance was not significantly different between the intervention and control groups on either the ARAT ($P = .79$) or FMA ($P = .91$). All patients demonstrated improved function on either the ARAT or the FMA, resulting in a significant effect for the factor time ($P < .001$ for ARAT and FMA). The magnitude of improvement was greater for the stimulation group for both measures: the average improvement was 6 points for the stimulation group and 4 points for the control group for both the ARAT and the FMA. However, this difference between groups did not reach a statistically significant level. Likewise, improvements were evident for both groups of patients in the motor activity log, grip strength, and tapping speed measures. Analysis of variance revealed a significant effect of time (all measures, $P < .01$), but there were no significant group*time interactions to indicate that the groups behaved differently over time.

Correlations

There were significant correlations between baseline functional scores and the grip-lift parameters. This was most evident with the preload duration, which had a significant negative correlation with the ARAT ($r = -.78$, $P = .001$). There was also a positive correlation between the maximal correlation value and the ARAT ($r = .56$,

$P = .04$). However, there was no significant correlation between the change in ARAT scores, grip-lift parameters, or corticospinal excitability measures.

Follow-up Measures

All patients returned for follow-up 3 months following the intervention. There was no significant change in the grip-lift task measures, other functional measures, or corticospinal excitability measures between groups or over time. This indicates that the improvements made during the intervention were maintained to a similar extent for both groups.

DISCUSSION

This is the first study to investigate whether combining afferent stimulation aimed to increase the excitability of the motor cortex projecting to the hand muscles with task-specific training leads to a greater gain in dexterity and upper limb function in a group of patients with hemiparesis due to stroke than training alone. All patients showed improvement in scores of upper limb function following the interventions (ie, either training alone or training plus afferent stimulation). However, the stimulation group, but not the control group, improved significantly on 2 key features of the dextrous grip-lift task.

The grip-lift task is a sensitive measure of dexterity, and several key measures obtained from this task can reliably distinguish differences in function even between the dominant and nondominant hands of normal participants,⁴⁵ as well as between affected and unaffected sides of stroke patients.³³ This capacity to detect differences in dextrous control between dominant and nondominant hands of normal participants indicates that the grip-lift task is a more sensitive measure of dexterity than other functional indices such as the ARAT and highlights the limitations of such measures for measuring functionally significant differences in hand performance.

Although the grip-lift task is a more sensitive indicator of dexterity than the ARAT, we have previously shown that a number of grip-lift parameters correlate well with the ARAT, in particular, the maximal correlation coefficient and the preload duration.³³ This was confirmed in the current study, indicating that patients who cannot coordinate their GF to conduct a smooth grip and lift of the manipulandum perform more poorly when attempting to grasp, grip, and transport objects as required by the ARAT. Factors that may contribute to poor GF control include sensory impairments that limit the ability to

signal accurately the contact between the fingers and the object, deficits in scaling motor output to the desired level, inappropriate central commands that normally anticipate the load and modulate the GF appropriately during the lift, or a combination of these factors. Sensation to light touch was intact in the majority of patients, the exceptions being 2 patients in each group who had mild sensory impairments at the commencement of the study that did not change over the intervention period. Despite this, all patients receiving associative stimulation targeting muscles of the digits involved in the grip-lift task improved their force control, suggesting that the combined intervention improved sensorimotor integration. As a whole, the stimulated group improved significantly more than the sham group on the 2 key parameters of the grip-lift dexterity assessment.

The stimulation group received a period of associative stimulation prior to each training session. Associative stimulation has previously been shown to produce an increase in cortical excitability that lasts for approximately 1 hour.^{31,46} Therefore, although not tested in the present study, it is likely that patients in the stimulation group received their training at a time during which motor cortical excitability was increased. Increased motor cortical excitability has previously been shown to facilitate motor performance both in normal participants¹⁶ and stroke patients.²⁵ Therefore, the present findings suggest that training during a period of increased motor cortical excitability may lead to additional functional gains.

The fast-conducting corticomotoneuronal pathway is critical for the independent skilled hand movements⁴⁷ that are typically lost following stroke. Cerebral infarction involving the primary motor cortex and corticospinal tract reduces cortical excitability to TMS.⁴⁸⁻⁵⁰ Changes in motor cortical excitability correlate with upper-limb strength following stroke,⁵¹ suggesting the pathway tested by TMS is involved in recovery following stroke. However, Thickbroom et al⁵¹ found no relationship between a measure of dexterity employing a subset of the McCarron test battery and MEP amplitude in a group of subcortical stroke patients. This suggests that the relationship between dexterity and MEP amplitude is complex. Furthermore, there are examples of performance changes in complex motor tasks that are not associated with modification of corticospinal excitability.¹⁶ Similarly, in the present study, improvements in the grip-lift task were not associated with significant changes in MEP measures of corticospinal excitability. This is consistent with a previous report that overlearning of a new motor skill results in consolidation and retention of that skill but no enduring change in corticospinal excitability.⁵² Therefore, the lack of change in corticospinal excitability at the end of the

3-week intervention period is not surprising and may reflect either a poor correlation between changes in dexterity and excitability or consolidation of motor skill.

In summary, this pilot study demonstrates that combining associative stimulation with task-specific training can result in improvements in several key objective measures of dexterity that are greater than those seen with training alone. Limitations of this study include the small sample size and, possibly, the limited number of treatment sessions. Future studies using similar stimulation paradigms in combination with rehabilitation, with larger sample sizes, are needed to gain further insight into the potential to induce functionally beneficial neuroplasticity in stroke patients.

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