Original Article

Somatosensory Stimulation Enhances the Effects of Training Functional Hand Tasks in Patients With Chronic Stroke

Pablo Celnik, MD, Friedhelm Hummel, MD, Michelle Harris-Love, PhD, Rebecca Wolk, BA, Leonardo G. Cohen, MD


Objective: To test the hypothesis that somatosensory stimulation would enhance the effects of training functional hand tasks immediately after practice and 1 day later in chronic subcortical stroke patients.

Design: Single-blinded and randomized, crossover study.

Setting: Human research laboratory.

Participants: Nine chronic subcortical stroke patients.

Interventions: Three separate sessions of motor training preceded by (1) synchronous peripheral nerve stimulation (PNS), (2) no stimulation, or (3) asynchronous PNS.

Main Outcome Measures: Time to complete the Jebsen-Taylor Hand Function Test (JTHFT time) and corticomotor excitability tested with transcranial magnetic stimulation.

Results: After familiarization practice, during which all patients reached a performance plateau, training under the effects of PNS reduced JTHFT time by 10% beyond the post-familiarization plateau. This behavioral gain was accompanied by a specific reduction in GABAergically mediated intracortical inhibition in the motor cortex. These findings were not observed after similar practice under the influence of no stimulation or asynchronous PNS sessions.

Conclusions: Somatosensory stimulation may enhance the training of functional hand tasks in patients with chronic stroke, possibly through modulation of intracortical GABAergic pathways.

Key Words: Electric stimulation; Motor skills; Rehabilitation; Stroke.

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Motor training is extensively used as part of rehabilitative treatments to facilitate relearning of activities of daily living (ADLs) after stroke.1,2 Despite recent advances in our understanding of more effective schedules and structure of training protocols,3,4 motor impairment represents a frequent sequela. Somatosensory input is required for accurate motor performance5,6 and for more effective motor learning.6 As predicted by these data, patients with intact somatosensory function experience more satisfactory response to rehabilitation interventions,7 and recovery of sensation in patients with sensory deficits is associated with improvement in motor control.8

In healthy subjects, relatively brief application of somatosensory stimulation in the form of peripheral nerve stimulation (PNS) results in enhanced activation of the contralateral primary sensorimotor cortex (SM1)9,10 and increased contralateral motor cortical excitability.11-15 In patients with chronic stroke, somatosensory stimulation applied to peripheral nerves innervating weak body parts transiently enhances motor performance.16-18 Although most of these studies14,16-18 measured performance immediately after the end of stimulation, little is known about the mechanisms and ability of PNS to modulate the effects of motor training in chronic subcortical stroke patients. Recently, a study19 investigated the effects of median nerve stimulation on the performance of functional hand tasks in cortical stroke patients and found improvement and better retention after PNS relative to control stimulation. This study, however, did not investigate the effects on subcortical stroke patients who may have different mechanisms of motor recovery20 and did not determine the neuroplastic changes associated to PNS.

In this study, we tested the hypothesis that PNS would enhance the effects of training functional hand tasks immediately and 1 day after practice, in a group of subcortical stroke patients. In addition, using transcranial magnetic stimulation (TMS), we investigated the underlying mechanisms associated with PNS and motor training effects.

Methods

Participants

We recruited 9 patients through the Stroke Neurorehabilitation Clinic of the National Institutes of Health (table 1). All participants had a history of single subcortical ischemic stroke, at least 1 year prior to participation in the study, leading to initial severe upper arm motor pareses (Medical Research Council scale score <2) with subsequent good recovery of function to the point of being able to complete the Jebsen-Taylor Hand Function Test (JTHFT). They all signed informed consent according to the Declaration of Helsinki and the National Institute of Neurological Disorders and Stroke Institutional Review Board approved the experimental protocol.

Experimental Design

All subjects participated in this single-blinded randomized, counterbalanced crossover study. Initially, all subjects participated in a familiarization session in which they trained with the JTHFT 30 times (3 blocks of 10 repetitions, separated by...

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30-min breaks), sufficient to reach stable performance levels in all subjects (figs 1, 2A). After this, participants returned on separate days to enter the crossover portion of the study consisting of 2 (sessions 2 and 3) counterbalanced sessions (PNS session, no-stimulation session) separated by a mean ± standard deviation of 5.6±4.4 days. Participants were randomized using a computer-generated random list with Excel. Five patients started with PNS and 4 with placebo. In these sessions, first we measured corticomotor excitability (TMS) (see fig 1B) and the time to complete the JTHFT (pretest) (see fig 1B). Subsequently, on separate sessions, PNS or no stimulation was applied for 2 hours to peripheral nerves in the paretic hand followed by practice of the JTHFT tasks 10 times (54±9min). After this practice, patients rested for 1 hour after which corticomotor excitability and JTHFT time determinations were repeated (1-hour post-test). This hour break after training, and 2 hours separation from the intervention period, were chosen to eliminate potential direct effects of PNS on the 1-hour post-test measurement, because PNS is known to increase excitability up to 60 to 90 minutes after its application.13 Additionally, this time break allowed participants to rest. After this, subjects were instructed to go home and perform their usual activities, and to

### Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Years After Stroke</th>
<th>Lesion Site</th>
<th>Motor Strength*</th>
<th>Fugl-Meyer Assessment (Upper Extremity)†</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>F</td>
<td>2</td>
<td>L subcortical</td>
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<td>92</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>M</td>
<td>2</td>
<td>R thalamus</td>
<td>4.9</td>
<td>95</td>
</tr>
<tr>
<td>3*</td>
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<td>F</td>
<td>2</td>
<td>R centrum semiovale</td>
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<td>92</td>
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<tr>
<td>4*</td>
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<td>M</td>
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<tr>
<td>5*</td>
<td>38</td>
<td>F</td>
<td>3</td>
<td>L centrum semiovale</td>
<td>4.9</td>
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<tr>
<td>6*</td>
<td>72</td>
<td>F</td>
<td>3</td>
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<td>R basal ganglia</td>
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<td>85</td>
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<tr>
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<td>F</td>
<td>6</td>
<td>R putamen</td>
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<tr>
<td>Mean ± SD</td>
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<td>3.2±1.6</td>
<td>4.6±0.4</td>
<td>93.0±1</td>
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</tr>
</tbody>
</table>

Abbreviations: F, female; L, left; M, male; R, right; SD, standard deviation.
*Measured by Medical Research Council scale.
†Percentage of total upper-extremity value.
*Subjects who participated in all sessions including asynchronous PNS session.

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30-min breaks), sufficient to reach stable performance levels in all subjects (figs 1, 2A). After this, participants returned on separate days to enter the crossover portion of the study consisting of 2 (sessions 2 and 3) counterbalanced sessions (PNS session, no-stimulation session) separated by a mean ± standard deviation of 5.6±4.4 days. Participants were randomized using a computer-generated random list with Excel. Five patients started with PNS and 4 with placebo. In these sessions, first we measured corticomotor excitability (TMS) (see fig 1B) and the time to complete the JTHFT (pretest) (see fig 1B). Subsequently, on separate sessions, PNS or no stimulation was applied for 2 hours to peripheral nerves in the paretic hand followed by practice of the JTHFT tasks 10 times (54±9min). After this practice, patients rested for 1 hour after which corticomotor excitability and JTHFT time determinations were repeated (1-hour post-test). This hour break after training, and 2 hours separation from the intervention period, were chosen to eliminate potential direct effects of PNS on the 1-hour post-test measurement, because PNS is known to increase excitability up to 60 to 90 minutes after its application.13 Additionally, this time break allowed participants to rest. After this, subjects were instructed to go home and perform their usual activities, and to

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### Fig 1. Experimental design. (A) All subjects participated in a familiarization session consistent of training the JTHFT tasks in 3 blocks of 10 repetitions each separated by 30-minute breaks. Subjective reports of fatigue, attention, and perceived difficulty to task performance were obtained at the end of this session (R). (B) Subsequently, they returned to take part in sessions 2, 3, and 4. These sessions, each performed on a different day, started with JTHFT measurements 3 times (pretest) after which subjects received 2 hours of PNS, no stimulation, or asynchronous PNS. Immediately afterward, they practiced the JTHFT tasks 10 times (mean training duration, 54±9min; see text for details). JTHFT performance was subsequently tested 1 and 24 hours later (1-hour post-test, 24-hour post-test, respectively). Subjective reports of fatigue, attention, and perceived difficulty to task performance were obtained using separate visual analog scales at different time points (R1, R2, R3, R4). Corticomotor excitability was measured immediately preceding pretest and 1-hour post-test (TMS). Abbreviation: asyn PNS, asynchronous PNS.
return the next day for retesting of the same functions (24-hour post-test). Participants described their level of attention and fatigue toward the tasks 4 times in each session (range, 1 [worst attention/fatigue] to 10 [least fatigue/best attention]), and their perceived difficulty to complete each JTHFT task at the end of each session (range 1 [extremely easy] to 10 [most difficult]) (see R1, R2, R3, in fig 1) using a visual analog scale (VAS) previously validated for mood and pain measurements, and successfully used in prior investigations.

Finally, to control for possible nonspecific effects of the sensations elicited during PNS we conducted a fourth experimental session with 4 of the 9 patients. This session was identical to the prior ones, but patients received asynchronous PNS (see below for details). This form of stimulation was chosen because, although subjects experience paresthesias as in the PNS intervention, it does not induce somatosensory receptive fields changes in rats, and does not produce changes in corticomotor excitability or tactile discrimination performance in humans.

Procedures

**Jebsen-Taylor Hand Function Test.** The JTHFT is a widely used test with standards for different age and sex groups, good validity and reliability, and capacity for detecting performance changes in tasks that resemble ADLs. It measures the time required to complete 7 different tasks (writing, turning cards, lifting objects, feeding simulation, stacking checkers, moving light and heavy cans). In previous studies, the JTHFT was able to identify performance improvements in the paretic hand elicited by brain stimulation. Similar to these studies, we excluded the writing task, due to heavy dependence on hemisphere dominance and side of stroke. Subjects were instructed to complete the tasks as rapidly and accurately as possible.

The same investigator, blinded to the intervention type, measured the JTHFT. Subjects were informed that we would test the effects of various intensities of stimulation on their performance.

**Peripheral nerve stimulation.** Using 2 electrode bars we determined the optimal positions to stimulate the ulnar and median nerves of the paretic hand following standard nerve conduction study technique. This form of stimulation was chosen because, although subjects experience paresthesias as in the PNS intervention, it does not induce somatosensory receptive fields changes in rats, and does not produce changes in corticomotor excitability or tactile discrimination performance in humans.

![Fig 2. JTHFT performance. (A) Familiarization progressively reduced JTHFT time reaching stable performance levels (shadow area). (B) Subsequently, performance at pretest was comparable with that at the end of familiarization. Training preceded by PNS elicited additional significant reductions in JTHFT time at 1-hour post-test and 24-hour post-test in the absence of changes with no stimulation. (C) Reduction in JTHFT time at 1 and 24 hours relative to pretest, were only significant in the PNS condition. *P<.01; †P<.05.](image-url)
No stimulation. The experimental setup in this session was identical to the PNS session. The only difference was that subjects were told that intensity of the nerve stimulation delivered would be below their perception threshold. Therefore, after determination of stimulation threshold for the median and ulnar nerves, the stimulus intensity was slowly tapered down. Subjects could not see the dial of the stimulator. Muscle relaxation was monitored online with electromyography, and subjects remained seated, reading or listening to music during the 2-hour period. 

Asynchronous PNS. In this session, trains of electric stimulation were delivered initially either to the median or to the ulnar nerve, alternating every 15 minutes to the other nerve, until completion of the 2-hour period. Other stimulation parameters (ie, intensity, frequency) were delivered as in the PNS session. Participants reported feeling paresthesias in their hand similarly to the PNS session.

Transcranial magnetic stimulation. Using TMS, we determined the resting motor threshold, recruitment curve, short intracortical inhibition, and intracortical facilitation before pre-test and 1-hour post-test in every session (see fig 1B). We did not measure corticomotor excitability changes prior to 24 hours post-test because we were primarily interested in understanding the mechanism underlying the modulatory effect of PNS on motor training. TMS was delivered using a Magstim 200 stimulator through a figure-of-8-shaped coil held in a 45° anteroposterior angle overlying the ipsilesional motor cortex to optimally activate the corticospinal track. This position was marked in each session for retesting after the interventions with a washable marker over the scalp of each participant. For each measurement, 10 motor evoked potentials (MEPs) were recorded with surface electrodes placed over the first dorsal interosseus muscle (FDI). Electromyographic signals were amplified and filtered (band-pass at 10 and 3000Hz), and fed into a computer for later analysis. Resting motor threshold was defined as the minimum intensity (±1%) that evoked MEP in the FDI of 50µV or more in 5 of 10 trials. Short intracortical inhibition (interstimulus interval, 2ms) and intracortical facilitation (interstimulus interval, 10ms) were measured with the paired-pulse TMS technique described by Kujojrai (conditioning stimulus intensity, 80% of resting motor threshold; test stimulus intensity, set to evoke MEPS of ~1mV). Ten trials were recorded for each stimulus intensity during recruitment curve, and for each interstimulus interval and test MEP during short intracortical inhibition and intracortical facilitation. TMS measurements lasted approximately 30 minutes and were performed always in the same order (resting motor threshold, recruitment curve, and short intracortical inhibition and intracortical facilitation randomly intermixed).

Data Analysis
An investigator blinded to the interventions recorded the VAS, JTHFT, and TMS measurements, and performed the TMS data analysis. The primary outcome measure, the mean of the total time to complete the JTHFT (JTHFT time, dependent variable) was analyzed using repeated-measures analysis of variance (ANOVA) with independent factors time (pretest, 1-hour post-test, 24-hour post-test) and intervention (PNS, no stimulation) followed by the Fisher protected least significant difference test. Separate repeated-measures ANOVA were used to evaluate the effect of the independent factors intervention and time on the dependent factors attention, fatigue, and perceived difficulty in 8 participants (for 1 participant, subjective data were lost). Errors during JTHFT performance (dependent variable), defined as any mistake that did not allow completion of the task (ie, dropping a bean), were analyzed with repeated-measures ANOVA with intervention (PNS, no stimulation) and time (pretest, 1-hour post-test, 24-hour post-test) as independent factors. To determine the stability of performance at the end of the familiarization session a paired t test was used for the dependent variable JTHFT time between blocks 2 and 3. To determine the magnitude of changes in JTHFT time, the percentage change from pretest JTHFT was calculated for 1-hour post-test JTHFT and 24-hour post-test JTHFT (dependent factor), and the results were analyzed with repeated-measures ANOVA with intervention and relative time (1-hour post-test, 24-hour post-test) as independent factors. Repeated-measures ANOVA of the relative change in JTHFT time was used in those subjects that performed asynchronous PNS session. To determine cortical excitability changes, separate repeated-measures ANOVA were used for the dependent variables resting motor threshold, recruitment curve intensities, short intracortical inhibition, and intracortical facilitation using intervention and time as independent factors. Data are expressed as mean ± standard error of the mean (SEM), and effects were considered significant if P was less than .05.

RESULTS
All participants completed the study. One patient subjective data report (attention, fatigue, perceived difficulty) was lost due to a computer error. There were no adverse events, and although subjects reported mild paresthesias in most fingers when exposed to nerve stimulation (PNS session, asynchronous PNS session) these were painless and easily tolerated by all participants.

Attention, Fatigue, and Perceived Difficulty to Complete the JTHFT Tasks
Repeated-measures ANOVA did not show significant effect of intervention, time, or intervention by time interaction on attention (F2,7=2.08; P, not significant [NS]). Time had a significant effect on fatigue and perceived difficulty (F2,7=3.55, P<.04; F1,7=13.14, P<.01; respectively). Post hoc analysis indicated that factor time was associated with decreased fatigue and perceived difficulty in 24-hour post-test time in all interventions (table 2).

Effects of PNS on JTHFT Errors
Repeated-measures ANOVA showed a significant effect of time (F2,6=6.96, P<.01), but not intervention or time by intervention interaction on the number of errors. Post hoc analysis revealed lesser errors for both PNS and no-stimulation sessions at 24-hour post-test (no-stimulation, 1.6±1.1; PNS, 1.2±0.9) relative to pretest (no-stimulation, 1.9±0.8; PNS, 2.9±1.9; P<.05) and 1-hour post-test (no-stimulation, 2.6±1.3; PNS, 3.7±1.6; P<.05).

Effects of PNS on JTHFT Time
All subjects improved in JTHFT time during familiarization reaching stable performance by blocks 2 and 3 (paired t test, t=1.2, P=.26) (see fig 2A). Performance at pretest in sessions 2 and 3 was comparable with that at the end of the familiarization period (repeated-measures ANOVA, F2,8=0.53, P=.09). Repeated-measures ANOVA revealed a significant effect of time (F2,8=4.11, P<.05) and intervention by time interaction (F2,8=4.28, P<.05) (see fig 2) on JTHFT time. Post hoc testing showed that PNS significantly reduced JTHFT time at 14-hour post-test and 24-hour post-test (from 48.59±9.34s [baseline] to 44.9±8.21s and 43.57±7.93s, re-
Tive JTHFT time changes (F1,8 = 45.02, p < .001) in the absence of changes after no stimulation (from 45.53 ± 7.63s to 45.02 ± 7.63s and 45.42 ± 7.68s, respectively; P = NS). Additionally, there was a significant effect of intervention on relative JTHFT time changes after no stimulation (F1,8 = 42.80, P < .001) (see fig 2C). One-hour post-test and 24-hour post-test improved by 6.9% ± 1.9% and 8.9% ± 1.7%, respectively, in the PNS condition and only 1.2% ± 2.3% and 0.7% ± 2.6%, respectively, in the no-stimulation intervention relative to pre-test performance level. The improvement in JTHFT time after PNS was present in 8 of 9 patients at 1-hour post-test and in every subject at 24-hour post-test.

Finally, in those subjects who participated in session 4 (asynchronous PNS session), PNS resulted in more prominent reduction in JTHFT time than did asynchronous PNS (repeated-measures ANOVA, intervention by time interaction: F2,8 = 5.76, P < .05) (see fig 2C). The relative JTHFT change associated to asynchronous PNS was similar to that found after no stimulation (see fig 2C).

Corticomotor Excitability

There were no changes in resting motor threshold (table 3) or recruitment curve (fig 3A) with either intervention. During short intracortical inhibition and intracortical facilitation measurements, test MEP amplitudes were comparable in both interventions (see table 3). Repeated-measures ANOVA revealed a significant effect of intervention (F1,8 = 9.07, P < .05) and time by intervention interaction on short intracortical inhibition (F1,8 = 5.38, P < .05). Post hoc testing showed that PNS was associated with a significant reduction in short intracortical inhibition in the absence of changes with no stimulation (see table 3, fig 3B). For intracortical facilitation, repeated-measures ANOVA evidenced a significant effect of time (F1,8 = 8.11, P < .03), but not intervention (F1,8 = 3.25, P = NS) or time by intervention interaction (F1,8 = 3.44, P = NS) (see table 3, fig 3C).

DISCUSSION

The main finding of this study is that somatosensory stimulation of the paretic hand immediately prior to physical practice enhanced the training effects of functional hand tasks involved in the JTHFT in patients with chronic stroke. This effect was documented 1 and 24 hours after the end of training and was associated with a specific reduction of intracortical inhibition in the motor cortex of the ipsilesional hemisphere.

Motor training is among the main tools of neurorehabilitation after stroke.2,3,4,38 Despite substantial advances in the development of more effective training protocols, functional recovery is usually incomplete and most stroke survivors experience long-term motor disability.39 Somatosensory input is required for learning and performance of skillful motor tasks.40 When this input is reduced or absent, as in patients with severe peripheral neuropathy, poor motor behavior ensues.41 It is not surprising then that after stroke, patients with somatosensory deficits suffer more persistent motor impairment than those without such deficits.3,8

It has been proposed that somatosensory stimulation could enhance the effects of motor training.12,14 PNS has been extensively studied in animals and humans, is easily administered, and has defined behavioral and physiologic effects on

<table>
<thead>
<tr>
<th>Time</th>
<th>Attention</th>
<th>Fatigue</th>
<th>Perceived Difficulty</th>
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<tr>
<td></td>
<td>PNS</td>
<td>No-Stim</td>
<td>PNS</td>
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<tr>
<td>R1</td>
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<td>R4</td>
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<td>5.2±0.4</td>
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</table>

NOTE. Values are mean ± SEM.
Abbreviations: NA, not assessed; No-Stim, no stimulation; R, subjective reports of fatigue, attention, and perceived difficulty to task performance (fatigue and attention: range, 1 [worst] to 10 [least fatigue or best attention]; perceived difficulty: range, 1 [extremely easy] to 10 [most difficult]); R1, baseline measurement; R2, measurement after intervention and training; R3, measurement after 1-hour post-test; R4, after 24-hour post-test.

*Post hoc R4 vs R1, R2, R3 (P < .05).
†Post hoc R4 vs R2, R4 (P < .05).
‡Post hoc R4 vs R1, R2, R3 (P < .01).

Table 3: Corticomotor Excitability

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<th>Test Intervention</th>
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<tr>
<td>Motor threshold (% of stimulator output)</td>
<td>PNS</td>
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<td>No-stim</td>
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<td>Test MEP (mV)</td>
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<td></td>
<td>No-stim</td>
<td>1.9±0.5</td>
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<tr>
<td>Short ICI (% of test MEP)</td>
<td>PNS</td>
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<td>No-stim</td>
<td>47.7±5.5</td>
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<td>ICF (% of test MEP)</td>
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<td>137.5±14.7</td>
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<tr>
<td></td>
<td>No-stim</td>
<td>112.1±11.1</td>
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</table>

NOTE. Values are mean ± SEM.
Abbreviations: ICF, intracortical facilitation; ICI, intracortical inhibition.
*Post hoc short intracortical facilitation (pre, post).
†Post hoc short intracortical inhibition (pre, post).
‡Post hoc short intracortical inhibition (pre, post).
motor cortical function that outlast the period of stimulation. It is known to activate sensory fibers originated in Ia and Ib, Golgi organs, and group II afferents from slow and rapidly adapting skin receptors, and to produce changes in receptive fields. In healthy volunteers, PNS modulates corticomotor excitability in a somatotopic specific manner beyond the period of stimulation and enhances functional magnetic resonance imaging activity in the stimulated body part representations in SM1 and dorsal premotor cortices. In stroke patients, PNS alone leads to transient improvements in swallowing, pinch force, use-dependent plasticity, and hand tasks performance. In these studies, behavioral gains have been measured shortly after PNS. A recent study reported that electric stimulation of the median nerve only might be beneficial beyond the period of peripheral stimulation in cortical stroke patients. However, it remains unknown whether somatosensory stimulation associated with training could induce longer-lasting behavioral gains in subcortical stroke patients and what are the underlying physiologic changes associated to the behavioral effect.

Effects of Somatosensory Stimulation on Learning the JTHFT Tasks

Here, we found that performance of the JTHFT motor tasks was faster 1 and 24 hours after training preceded by PNS but not after training preceded by no stimulation or asynchronous PNS. This effect was present in all participants after 24 hours. Neither no stimulation nor asynchronous PNS improved performance beyond the plateau levels reached during familiarization (see fig 2). Although subjects started the PNS session with a nonsignificant slower performance, only after PNS were they able to reduce the JTHFT time beyond the time achieved prior to any of the interventions. This was true even when the 24-hour post-test of the PNS session was compared with the pretest JTHFT time of the no-stimulation or asynchronous PNS session. These differential effects of PNS and no stimulation could not be explained by differences in attention, fatigue, or sense of effort required because patients’ reports were similar across time and interventions (see table 2). Although subjects were able to differentiate both forms of stimulation, they were not able to report which intervention they felt was more effec-

Fig 3. Corticomotor excitability. (A) Recruitment curves (RC) did not show changes in either sessions. (B) Short intracortical inhibition (ICI) expressed relative to test MEP amplitudes (dotted line) before and 1 hour after interventions. PNS plus training significantly decreased short intracortical inhibition in the absence of changes with no stimulation. (C) Intracortical facilitation (ICF) increased after both interventions, suggesting that intracortical facilitation was influenced by training rather than by somatosensory stimulation. Abbreviation: MT, motor threshold. *P<.05.
tive. Still, placebo effects cannot be completely ruled out. The number of accuracy errors showed an increase over time during the first day with both PNS and no stimulation with subsequent decrease at 24 hours. These changes probably indicate some build up in fatigue due to the duration of the intervention plus training session (see fig 1B). They also suggest that enhanced learning with PNS was not the result of a speed and accuracy trade-off, because speed improved only with PNS, whereas accuracy changed in similar ways with both interventions. These findings suggest that synchronous stimulation of median and ulnar nerve, possibly through Hebbian mechanisms, elicited more prominent beneficial effects on motor function. Advantages of our controls over others previously described in the literature include their application to the same body part as the one tested and elicitation of local perceptions in the stimulated hand comparable with those produced by PNS with asynchronous PNS.12,16,18,19

In most previous investigations, behavioral gains have been documented immediately after the end of each intervention, providing little information about the stability of the effects beyond 90 minutes.11,12,16,18,19 Recently, Conforto et al29 showed that median electric nerve stimulation could enhance performance of hand tasks even 30 days after training in a group of cortical stroke patients. Our results here extend this finding to subcortical stroke patients and indicate that the duration of behavioral gains in ADL-like activities when PNS is administered prior to motor training is more stable than previously thought, supporting its testing in real-life rehabilitation environments. The magnitude of this effect (~10%), is close to the magnitude of effects of noninvasive brain stimulation,26,32 and is consistent with other studies using somatosensory stimulation.47 These results suggest the hypothesis that PNS could enhance motor performance beyond the plateau levels reached after repetitive practice, an issue of clinical relevance that should be studied more specifically in future investigations. Of note, this relatively small improvement was the result of only a single training and stimulation session. It is possible that multiple applications could elicit more prominent effects. Somatosensory stimulation may be easier to apply than brain stimulation and may be amenable to use even in patients in whom brain stimulation may be contraindicated, as in those with poststroke seizures.

Effects of Somatosensory Stimulation on Motor Cortical Function

The main physiologic findings in this study were that intracortical facilitation increased with both interventions and intracortical inhibition decreased specifically with PNS plus training. During motor learning protocols, recruitment curve increase initially followed over time by return to normal excitability levels.24 Here, we have not seen changes in either resting motor threshold or recruitment curve, likely because the largest predicted effects on recruitment curve occurred early on during familiarization.28

Short intracortical inhibition represents predominantly a GABAergic mediated intracortical process that involves late L waves.49 PNS effects on cortical function are influenced by GABAergic neurotransmission1,4,50 and may involve long-term potentiation-like mechanisms.51 Similarly, motor learning is associated with decreased GABA concentration in SM128 and with decreased short intracortical inhibition after post-stroke rehabilitation training.52 Therefore, decreased short intracortical inhibition after PNS plus training could result from a synergistic effect of both components of this intervention, which in turn facilitated learning in the paretic hand, a proposal consistent with the known role of GABAergic function on long-term potentiation.54 Intracortical facilitation, known to increase as a result of physical training,53 was found to be more prominent after both PNS and no stimulation. This probably reflects a nonspecific effect of training present in both sessions and independent of somatosensory stimulation.

CONCLUSIONS

This study shows that PNS prior to training enhances training effects of functional hand tasks in chronic subcortical stroke patients. One possible mechanism underlying this effect may be reduction of intracortical inhibition through modulation of GABAergic interneurons in the ipsilesional sensorimotor cortex.

References


Suppliers
a. Microsoft, One Microsoft Way, Redmond, WA 98052.
b. Grass stimulator S8800; Astro-Med Industrial Park, 600 E Greenwich Ave, West Warwick, RI 02893.
c. Magstim Co, Spring Gardens, Whitland, Carmarthenshire, Wales, SA34 0HR, UK.