Effect of Combined Peripheral Nerve Stimulation and Brain Polarization on Performance of a Motor Sequence Task After Chronic Stroke

Pablo Celnik, MD; Nam-Jong Paik, MD, PhD; Yves Vandermeeren, MD, PhD; Michael Dimyan, MD; Leonardo G. Cohen, MD

Background and Purpose—Recent work demonstrated that application of peripheral nerve and cortical stimulation independently can induce modest improvements in motor performance in patients with stroke. The purpose of this study was to test the hypothesis that combining peripheral nerve stimulation (PNS) to the paretic hand with anodal direct current stimulation (tDCS) to the ipsilesional primary motor cortex (M1) would facilitate beneficial effects of motor training more than each intervention alone or sham (tDCS_sham and PNS_sham).

Methods—Nine chronic stroke patients completed a blinded crossover designed study. In separate sessions, we investigated the effects of single applications of PNS + tDCS, PNS + tDCS_sham, tDCS + PNS_sham, and PNS_sham + tDCS_sham before motor training on the ability to perform finger motor sequences with the paretic hand.

Results—PNS + tDCS resulted in a 41.3% improvement in the number of correct key presses relative to PNS_sham + tDCS_sham, 15.4% relative to PNS + tDCS_sham, and 22.7% relative to tDCS + PNS_sham. These performance differences were maintained 1 and 6 days after the end of the training.

Conclusions—These results indicate that combining PNS with tDCS can facilitate the beneficial effects of training on motor performance beyond levels reached with each intervention alone, a finding of relevance for the neurorehabilitation of motor impairments after stroke. (Stroke. 2009;40:1764-1771.)

Key Words: stroke • rehabilitation • transcranial direct current stimulation • nerve stimulation

Despite recent advances,1,2 training-based customarily used neurorehabilitative treatments are insufficient to induce complete recovery of motor function in most stroke patients.3 Thus, developing safe and more effective interventions to enhance training effects after stroke is a crucial need.

In recent years, different forms of noninvasive brain stimulation techniques have been explored. One of these interventions, transcranial direct current stimulation (tDCS), has generated excitement as a potential neurorehabilitative adjuvant strategy to facilitate performance of motor1–7 and language tasks8,9 in stroke patients. Although the precise mechanisms mediating these effects are not known, it has been proposed that tDCS could influence Na+ and Ca2+ channels and NMDA-receptor activity.10,11 When applied in isolation, the beneficial effects of a single session of tDCS on motor performance appear to be modest.6 For instance, anodal tDCS applied over the ipsilesional primary motor cortex (M1) results in an approximate 10% improvement in performance of activities of daily living (ADL)-like tasks,3 whereas cathodal tDCS applied over the contralesional M1 result in quantitatively similar improvements.4,7

Peripheral nerve stimulation (PNS) has also been proposed as a possible adjuvant strategy capable of facilitating motor functions like pinch strength,12 swallowing,13 ADL-like tasks,14 and training effects in stroke patients.15–17 The mechanisms underlying the effects of PNS on motor cortical function are still under investigation but may include modulation of corticmotor excitability18 that last beyond the period of stimulation.18–20 Additionally, PNS applied to one body part can modulate BOLD activity in its motor cortical representation in M1 and possibly in the dorsal premotor cortices.21,22 PNS applied over specific body parts results in changes in motor cortical excitability that are somatotopically specific to the stimulated region.18 Mechanisms underlying PNS-induced motor effects may include modulation of GABAergic interneurons with little or any effects over NMDA receptor activity.17,18,23

Received October 20, 2008; final revision received November 7, 2008; accepted November 12, 2008.

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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.108.540500
The magnitude of facilitatory effects induced by a single session of PNS or tDCS on performance of motor tasks in stroke patients appear to be moderate and quantitatively comparable.5,7,15,17 Here, we tested the hypothesis that combination of both tDCS and PNS would enhance the beneficial effects of motor training beyond levels reached by application of either intervention alone in patients with chronic stroke.

Materials and Methods

Patients

Nine single unilateral ischemic stroke patients (age range 40 to 73 year; 4 female) participated in the study (Table 1). All participants had severe motor deficits at stroke onset, as reflected by muscle strength score of 2 or less, and subsequent good recovery to the point of being able to perform the finger sequence task. The experimental protocol was approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke, and written informed consent was obtained from all patients. We excluded patients who had professionally practiced playing a keyboard musical instrument or trained as typists, patients with cerebellar or brain stem lesions, and those with severe depression, language disturbances, or serious cognitive deficits (MMSE <23/30 points).

Experimental Design

All subjects participated in 5 sessions including 1 short familiarization and 4 experimental sessions. The first session was always the familiarization day, in which all patients practiced for 3 minutes a 4-finger key press sequence on a keyboard and got acquainted with the laboratory equipment. Subsequently, they participated in 4 experimental sessions separated by 6.3±0.9 days (mean±SD). Different forms of stimulation and sham were applied in different sessions. The sessions’ order was randomized across subjects using a computer-generated randomization list.

Stimulation Types

Peripheral nerve stimulation of the median and ulnar nerve of the paretic hand. PNS was applied simultaneously over the median and ulnar nerve at the wrist using 2 electrode bars with the cathode in a proximal position following a set-up described in prior studies.15,19 In short, trains of electric stimulation were delivered at 1 Hz for a period of 2 hours (Grass stimulator S 8800, Grass Instrument Division, Astro-Med Inc). Each train consisted of 5 single pulses of 1-ms duration delivered at 10 Hz (interpulse interval 100 msec, interburst interval 500 msec). The stimulus intensity was adjusted to elicit small compound muscle action potentials (CMAPs) of 50 to 100 µV from the abductor pollicis brevis (APB) and first dorsal interosseous (FDI) in the absence of visible muscle twitches. During the stimulation period, patients remained relaxed and were allowed to read or listen to quiet music. Electromyography activity was monitored throughout the 2-hour stimulation period to ensure relaxation. All subjects perceived mild paraesthesias under the PNS stimulation electrodes associated to the stimulation.

Transcranial direct current stimulation (tDCS) was applied with the anode positioned over the ipsilesional M1 and the cathode over the contralateral supraorbital region for 20 minutes (1 mA), as done in previous studies.5,7,24 Anodal tDCS (Iomed Phoresor; PM850) was delivered through a 3”x3” sponge electrode (Amrex; part-A103) placed on the patient’s scalp corresponding to the optimal spot for activation of the paretic APB muscle as determined with magnetic measurement of the M1. Application of anodal tDCS or tDCSSh (20 minutes) started 100 minutes after the onset of PNS or PNSSh (20 minutes) and was followed by simultaneous practice. tDCSSh was sham tDCS with the anode positioned over the contralateral M1 and the cathode over the ipsilesional M1, and patients were not aware of which form of stimulation was applied.

Table 1. Patient Data

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Time After Stroke (months)</th>
<th>Lesion Site</th>
<th>Handedness (EDS)</th>
<th>MMSE</th>
<th>FMS (%)</th>
<th>MAS</th>
</tr>
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<tbody>
<tr>
<td>Patient 1</td>
<td>65</td>
<td>F</td>
<td>43</td>
<td>R Cortical and subcortical (ant. temporal, insula and corona radiata)</td>
<td>Right (50/50)</td>
<td>29/30</td>
<td>97</td>
</tr>
<tr>
<td>Patient 2</td>
<td>41</td>
<td>M</td>
<td>31</td>
<td>L Cortical (post. Frontal and sup. temporal)</td>
<td>Right (50/50)</td>
<td>29/30</td>
<td>87</td>
</tr>
<tr>
<td>Patient 3</td>
<td>61</td>
<td>F</td>
<td>65</td>
<td>L Cortical (fronto-parietal and insula)</td>
<td>Right (47/50)</td>
<td>28/30</td>
<td>89</td>
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<tr>
<td>Patient 4</td>
<td>62</td>
<td>M</td>
<td>52</td>
<td>R Cortical (fronto-parieto-temporal)</td>
<td>Left (10/50)</td>
<td>25/30</td>
<td>91</td>
</tr>
<tr>
<td>Patient 5</td>
<td>73</td>
<td>M</td>
<td>41</td>
<td>L Cortical and subcortical (fronto-parieto-occipital and basal ganglia)</td>
<td>Right (44/50)</td>
<td>28/30</td>
<td>94</td>
</tr>
<tr>
<td>Patient 6</td>
<td>53</td>
<td>M</td>
<td>68</td>
<td>R Cortical and subcortical (parietal operculum, post-insula and corona radiata)</td>
<td>Right (47/50)</td>
<td>30/30</td>
<td>94</td>
</tr>
<tr>
<td>Patient 7</td>
<td>46</td>
<td>F</td>
<td>55</td>
<td>L Cortical (parieto-occipital junction)</td>
<td>Right (50/50)</td>
<td>29/30</td>
<td>98</td>
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<tr>
<td>Patient 8</td>
<td>40</td>
<td>F</td>
<td>59</td>
<td>L Cortical (deep frontal)</td>
<td>Right (43/50)</td>
<td>27/30</td>
<td>98</td>
</tr>
<tr>
<td>Patient 9</td>
<td>57</td>
<td>M</td>
<td>87</td>
<td>R Subcortical (globus pallidus, corona radiata, putamen)</td>
<td>Right (46/50)</td>
<td>30/30</td>
<td>99</td>
</tr>
</tbody>
</table>

F indicates female; M, male; R, right; L, left; MAS, Modified Ashworth Scale; EDS, Edinburgh Handedness Scale; FMS, Fugl-Meyer Scale, percent scores for the paretic upper extremity are given; MMSE, Mini-Mental State Examination.

Mean±SE 55.3±3.76 55.7±5.57 28.3±0.53 94±1.4

Division, Astro-Med Inc). Each train consisted of 5 single pulses of 1-ms duration delivered at 10 Hz (interpulse interval 100 msec, interburst interval 500 msec). The stimulus intensity was adjusted to elicit small compound muscle action potentials (CMAPs) of 50 to 100 µV from the abductor pollicis brevis (APB) and first dorsal interosseous (FDI) in the absence of visible muscle twitches. During the stimulation period, patients remained relaxed and were allowed to read or listen to quiet music. Electromyography activity was monitored throughout the 2-hour stimulation period to ensure relaxation. All subjects perceived mild paraesthesias under the PNS stimulation electrodes associated to the stimulation.

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PNSSh consisted of PNS delivered to the deep peroneal and posterior tibial nerves of the paretic leg for 120 minutes with the same parameters as previously described for PNS of the median and ulnar nerves stimulation.

tDCSSh consisted of anodal tDCS over the ipsilesional M1 applied for only 1 minute, after which the current was slowly tapered down to 0 for the remaining 19 minutes. This procedure, implemented out of the field of view of the patients, has been shown to blind effectively cutaneous sensations elicited by a longer anodal tDCS stimulation period in both stroke patients and healthy volunteers.5,25 Application of anodal tDCS or tDCSSh (20 minutes) started 100 minutes after the onset of PNS or PNSSh (20 minutes) before completion of the peripheral nerve stimulation. In this manner, both forms of stimulation or sham (PNS and tDCS) were completed at the same time.

The order of the 4 sessions was randomized across patients, and both patients and investigators carrying out testing of behavioral measurements were blind to the particular types of intervention combination: PNS+tDCS, PNS+tDCSSh, tDCS+tPNSsh, and tDCSSh+tDCSSh.

Motor training was carried out immediately after the end of each stimulation type because: (1) both forms of stimulation (tDCS and PNS) induce changes in motor cortical excitability that outlasts the period of stimulation18,26; (2) simultaneous performance of practice...
with stimulation could have influenced practice quality, particularly during PNS; and (3) by practicing after stimulation we eliminated potentially distracting effects of each stimulation type as a factor in the interpretation of the results, a strategy used in previous PNS studies.15–17,27

Motor Practice
Participants practiced 4 different finger sequences that are comparable in difficulty and have minimal carry over effects between them28 (Figure 1). The practiced sequences were different in each session and were chosen in a counterbalanced order. Subjects were instructed to press each key on a special keyboard containing only 5 keys using the 2nd, 3rd, 4th, or 5th digit of the paretic hand. The following 4 finger sequences were used in random order across subjects for the 4 testing sessions: 2 to 5 to 3 to 4 to 2, 4 to 3 to 5 to 2 to 4, 3 to 2 to 4 to 5 to 3, 5 to 2 to 4 to 3 to 5. Subjects were instructed to repeat the 5 elements sequence “as quickly and as accurately as possible” for a period of 3 minutes, which constituted 1 block. A computer was used to display the sequences to the patient and to record the time and accuracy of each key press (Superlab; Cedrus). In each session, participants read the sequence corresponding to that day 5 times and memorized it. Subsequently, they practiced 5 blocks of 3 minutes each, separated by 2 minutes rest periods for a total of 28 minutes (Figure 1).

Testing of Motor Performance
Motor performance was tested at baseline and in 3 different opportunities (days 1, 2, and 6) after each form of stimulation + motor training (see Figure 1). In each of these tests, patients performed 1 block of 3 minutes, similar to those implemented in the practice period. For analysis purposes, each 3-minute block was divided in 6 30-second epochs. We defined the primary outcome measure as the mean number of correct key presses per 30 seconds relative to baseline. We excluded the initial 30-second epoch during which patients often warmed up after each resting interval, and the last 60-second epoch because some patients showed slowing and reported fatigue at that stage. Therefore, the mean number of correct key presses at baseline and after training (day 1, 2, and 6) were calculated on the bases of the 2nd, 3rd and 4th 30-second epochs (Figure 1).

Experimental Sessions
Each experimental session started with baseline determination of motor performance followed by the type of stimulation corresponding to that day, and motor practice. Posttraining performance assessments were then done 30 minutes after the end of training (1 hour after the completion of the stimulation period (Day 1), at 24 hours (Day 2), and 6.3±0.5 days later (Day 6; Figure 1).

In each session, participants completed questionnaires about the duration and quality of the previous night sleep (range 0 to 10; 0=very poor, 10=very good). In addition, we recorded 4 times in each session the subject’s perceived level of attention (range 0 to 10; 0=no attention, 10=highest level of attention), fatigue and hand tiredness (range 0 to 10; 0=highest level of fatigue or tiredness, 10=no fatigue or tiredness), and sense of difficulty in carrying out the training task (range 0 to 10; 0=very simple, 10=very difficult; see Q1 to Q4 in Figure 1).17

Data Analysis
Normal distribution of all data were assessed by Kolmogorov–Smirnov tests. The primary outcome measure, the mean number of correct key presses per 30 seconds at Day 1, 2, and 6 relative to baseline was analyzed using a polynomial repeated measure ANOVA (ANOVARM) with independent factor INTERVENTIONS (PNS, tDCS, PNS+tDCSSham, tDCS+PNSSham and PNS+Sham) and dependent factor TIME (Day 1, Day 2 and Day 6). Additionally, a similar ANOVARM was implemented to evaluate intervention-dependent changes in the total number of key presses using the same TIME and INTERVENTIONS factors. To determine changes in mean number of correct key presses per 30 seconds during the 5 practice blocks we performed ANOVARM with factors PRACTICE (Training Blocks 1, 2, 3, 4, and 5) and INTERVENTIONS.

To compare the effects of INTERVENTIONS and TIME on attention, fatigue, hand tiredness, perceived difficulty, quality of sleep, and the amount of sleep, we used separate ANOVARM with INTERVENTIONS as the within-subject factor and TIME (Baseline, Day 1, Day 2, and Day 6) as the repeated measure. Conditioned on

Figure 1. Experimental design. Patients participated in 4 sessions (order randomized across subjects): PNS(Sham+tDCS(Sham), tDCS+PNS(Sham), and PNS+tDCS (see text for details). Each session started with 3-minute baseline measurement (Base) of performance of a finger sequence task followed by each form of stimulation (2 hours of PNS or Sham, combined with 20 minutes of tDCS or Sham). Each form of stimulation preceded 5 identical blocks of 3-minute motor sequence practice performed within a 2-minute break between blocks. Training was followed by a 30-minute break after which posttraining measurements were obtained on Day 1, Day 2, and Day 6 (6.3±0.5 days). Questionnaires (Q) where patients reported the level of attention, fatigue, hand tiredness, and perceived difficulty to each sequence were obtained using separate visual analogue scales at 4 different time points in each session. Inset shows the number of correct key presses for one subject during each 30 seconds epoch. The mean number of correct key presses per 30 seconds during the 2nd, 3rd, and 4th 30 seconds epochs (dark gray area) was used to calculate the primary outcome measure (see text).
significant probability values \( (P<0.05) \), post hoc analyses were conducted and corrected for multiple comparisons with LSD tests. All data are expressed as mean±SEM.

**Results**

All participants completed the study and did not experience complications.

At baseline, the mean number of correct key presses per 30 seconds was comparable in the 4 sessions (ANOVA\(RM\) \( F[3,24]=1.32, P=0.9 \)). During the motor practice period, ANOVA\(RM\) revealed a significant effect of PRACTICE, but not INTERVENTIONS or INTERVENTIONS by PRACTICE interaction on the number of correct key presses (ANOVA\(RM\) \( F[3,24]=8.1, P<0.001; F[3,24]=1.1, P=0.4 \); and \( F[12,96]=0.5, P=0.8 \) respectively), indicating that all interventions resulted in comparable performance improvement (Figure 2).

After practice was completed, ANOVA\(RM\) showed a significant effect of INTERVENTIONS and more importantly INTERVENTIONS by TIME interaction, but not TIME on the percent change of the mean number of correct key presses per 30 seconds at Day 1, 2, and 6 relative to baseline (ANOVA\(RM\) \( \text{INTERVENTIONS} F[3,24]=3.9, P<0.05; \text{TIME} F[2,16]=0.43, P=0.6; \text{INTERVENTIONS by TIME} \text{interaction} F[6,48]=2.6, P<0.05, \) Figure 3). Post hoc testing revealed that, relative to baseline, PNS+tDCS facilitated practice effects to a larger extent than PNS\(_{Sham}+tDCS\_{Sham}\) at Day 1 \( (P<0.05) \). At Day 2, PNS+tDCS facilitated practice effects more than PNS\(_{Sham}+tDCS\_{Sham}\) \( (P<0.01) \), PNS\(_{Sham}+tDCS\_{Sham}\) \( (P<0.01) \), and tDCS+tDCS\(_{Sham}\) \( (P<0.05) \). This Day 2 difference was evidenced by larger PNS+tDCS effects in 7 of 9 subjects relative to PNS\(_{Sham}+tDCS\_{Sham}\), in 8 of 9 relative to PNS+tDCS\(_{Sham}\), and in 6 of 9 relative to
Table 2. Questionnaire Data

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
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<tbody>
<tr>
<td><strong>Attention (0 to 10)</strong></td>
<td></td>
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<tr>
<td>PNS_Sham + tDCS_Sham</td>
<td>9.1 ± 0.6</td>
<td>8.5 ± 0.9</td>
<td>9.4 ± 0.4</td>
<td>9.0 ± 0.6</td>
</tr>
<tr>
<td>PNS + tDCS_Sham</td>
<td>8.6 ± 0.5</td>
<td>9.0 ± 0.6</td>
<td>9.3 ± 0.4</td>
<td>9.1 ± 0.5</td>
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<tr>
<td>tDCS + PNS_Sham</td>
<td>8.9 ± 0.6</td>
<td>8.5 ± 0.8</td>
<td>9.3 ± 0.5</td>
<td>8.5 ± 0.8</td>
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<tr>
<td>PNS + tDCS</td>
<td>8.5 ± 0.8</td>
<td>8.4 ± 1.1</td>
<td>9.0 ± 0.6</td>
<td>9.3 ± 0.5</td>
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<tr>
<td><strong>Fatigue (0 to 10)</strong></td>
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<tr>
<td>PNS_Sham + tDCS_Sham</td>
<td>9.0 ± 0.7</td>
<td>8.3 ± 0.9</td>
<td>9.0 ± 0.6</td>
<td>8.8 ± 0.8</td>
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<tr>
<td>PNS + tDCS_Sham</td>
<td>8.6 ± 0.5</td>
<td>9.0 ± 0.6</td>
<td>9.1 ± 0.5</td>
<td>8.9 ± 0.6</td>
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<tr>
<td>tDCS + PNS_Sham</td>
<td>8.6 ± 0.7</td>
<td>8.4 ± 0.7</td>
<td>8.9 ± 0.7</td>
<td>8.4 ± 0.7</td>
</tr>
<tr>
<td>PNS + tDCS</td>
<td>8.4 ± 0.8</td>
<td>8.4 ± 1.1</td>
<td>8.8 ± 0.7</td>
<td>8.9 ± 0.6</td>
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<tr>
<td><strong>Subjective sequence difficulty (0 to 10)</strong></td>
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<tr>
<td>PNS_Sham + tDCS_Sham</td>
<td>4.4 ± 1.1</td>
<td>4.4 ± 1.1</td>
<td>3.0 ± 0.9</td>
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<tr>
<td>PNS + tDCS_Sham</td>
<td>4.5 ± 0.8</td>
<td>3.5 ± 0.9</td>
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<td>2.6 ± 0.7</td>
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<tr>
<td>tDCS + PNS_Sham</td>
<td>4.6 ± 0.9</td>
<td>4.5 ± 1.0</td>
<td>3.0 ± 1.2</td>
<td>3.1 ± 1.1</td>
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<tr>
<td>PNS + tDCS</td>
<td>4.0 ± 1.0</td>
<td>3.3 ± 1.1</td>
<td>2.8 ± 1.2</td>
<td>3.1 ± 1.0</td>
</tr>
</tbody>
</table>

Values represent mean ± SEM of responses to attention, fatigue, hand tiredness, and subjective sequence difficulty visual analogue scales (0=worst possible answer, 10=best possible response). Statistics were calculated using separate ANOVArm for each scale. NS indicates nonsignificant P value.

On the other hand, ANOVArm showed a significant effect of TIME, but not INTERVENTIONS, or TIME by INTERVENTIONS interactions on the total number of key presses (ANOVA \_rm TIME F[3,24]=13.92, P<0.001; INTERVENTIONS F[3,8]=0.57, P=0.63; and TIME by INTERVENTIONS interactions F[9,72]=1.09, P=0.14), indicating that the interventions did not influence the total number of key presses as they did on the percent of correct key presses relative to baseline.

ANOVA \_rm for attention and fatigue did not show effects of INTERVENTIONS (F[3,21]=1.09, P=ns, and F[3,21]=1.42, P=ns; respectively), TIME (F[3,21]=2.45, P=ns, and F[3,21]=1.75, P=ns; respectively), or INTERVENTIONS by TIME interaction (F[9,63]=1.61, P=ns, and F[9,63]=0.93, P=ns; respectively). In contrast, ANOVArm for hand-tiredness showed significant effects of TIME (F[3,21]=4.11, P<0.05), but not INTERVENTIONS (F[3,21]=0.96, P=ns) or INTERVENTIONS by TIME interaction (F[9,63]=0.92, P=ns), reflecting a comparable increment in hand tiredness over time across conditions (Table 2). Similarly, ANOVArm revealed a significant effect of TIME (F[3,21]=10.35, P<0.01), but not INTERVENTIONS (F[3,21]=0.81, P=ns) or INTERVENTIONS by TIME interaction (F[9,63]=0.62, P=ns) on the patients’ sense of sequence difficulty, reflecting a comparable decrease of sequence performance difficulty over time but not across interventions (Table 2). Finally, duration and quality of sleep were comparable across INTERVENTIONS (F[3,21]=0.22, P=ns, and (F[3,21]=1.62, P=ns; respectively) and TIME (F[2,14]=0.75, P=ns, and F[2,14]=2.79, P=ns; respectively) with no INTERVENTIONS by TIME interaction (F[6,42]=1.94, P=ns, and F[6,42]=1.13, P=ns; respectively, Table 3).

**Discussion**

The main finding of this study was that the combination of PNS of the paretic hand with anodal tDCS of the ipsilesional M1 enhanced the beneficial effects of training on motor sequence performance beyond levels reached by solely motor practice or by practice combined with either intervention alone, an effect that outlasted the stimulation and training periods by at least 6 days.

Customarily used neurorehabilitative treatments often result in incomplete recovery of motor function after stroke.\(^\text{29,30}\) Recent work has led to improved understanding of some mechanisms underlying the beneficial effects of rehabilitative interventions and recovery of function after stroke, including restitution of blood flow to different cortical areas,\(^\text{31}\) cortical plastic reorganization after training interventions,\(^\text{30,32}\) recovery of diaschisis,\(^\text{33}\) and a better understanding of the mechanisms underlying motor learning.\(^\text{34}\)

It would be important to develop effective adjuvant strategies that could enhance training effects beyond those...
reached by these interventions. In recent years, tDCS has shown promise as a noninvasive technique capable of modulating cortical excitability and motor behavior in stroke patients.\textsuperscript{35,36} It has been shown that anodal tDCS can enhance motor cortical excitability for a period of time that outlasts the stimulation window.\textsuperscript{10,11} In stroke patients, application of tDCS, either anodal to the ipsilesional\textsuperscript{5} or cathodal to the contralesional\textsuperscript{4,7} primary motor cortex, facilitates transiently and to a similar magnitude performance of tasks resembling activities of daily living. The proportion of these changes is also comparable to those induced in pinch force when anodal tDCS is applied over ipsilesional M1.\textsuperscript{24} Another recently explored intervention to modulate the effects of training is PNS, which applied to a body part leads to a somatotopically preserved increase in corticomotor excitability\textsuperscript{18} and results in enhanced BOLD signal in the contralateral M1 and dorsal premotor cortex.\textsuperscript{21,22} In animal models, it leads to changes in receptive fields in the primary somatosensory cortex.\textsuperscript{37} In stroke patients, PNS alone has been shown to elicit transient improvements in swallowing.\textsuperscript{13} In pinch force,\textsuperscript{12} use-dependent plasticity,\textsuperscript{16} performance of hand tasks,\textsuperscript{14} and ADL-like tasks.\textsuperscript{15,17,38} Interestingly, these studies applying a single session of either tDCS or PNS alone showed only transient discrete behavioral changes in the order of 10% to 20%.\textsuperscript{4,5,7,15,17,27} In this study, we hypothesized that the synchronous application of both forms of stimulation could potentially facilitate motor behavior further.

We studied performance of finger motor sequences that engage activity in a distributed network including M1.\textsuperscript{39,40,41} Patients included were severely paralyzed at the time of the stroke (muscle strength of 2 or less in the neurological examination at stroke onset), but recovered to the extent that they could perform the task required in this experiment (Table 1). At baseline, performance levels across the 4 sessions were comparable, a finding consistent with previous reports.\textsuperscript{28,41} Interestingly, all patients learned the task over the training period to a comparable extent, regardless of the preceding stimulation type. However, 1 hour after PNS+tDCS (Day 1 measure), performance improvements relative to baseline were more prominent than after sham or after either stimulation alone (ie, at day 1: 41.3% better than sham, 15.4% better than PNS alone and 22.7% better than tDCS alone; supplemental Table 1), an effect that was more pronounced on Day 2 and that remained present, albeit to a lesser extent, on Day 6. This intervention-dependent improvement was evident in the mean number of correct key presses per 30 seconds relative to baseline, whereas the total number of key presses improved to similar extent with all interventions, suggesting that PNS+tDCS mediated its effect through improvement in accuracy rather than speed. The lack of a significantly different effect of PNS+tDCS relative to the other interventions on speed might be explained by a ceiling effect on motor performance in patients that were otherwise well recovered, or alternatively, because of saturation of the mechanisms of action of the combined intervention. Interestingly, the magnitude of performance improvements measured in this investigation with a single session of PNS+tDCS (approximately 42% better than Sham in Day 2) appears to be superior to that reported before using either tDCS or PNS alone in chronic stroke patients (10 to 20% range).\textsuperscript{4,5,7,15,17,27}

Our results cannot be explained by fatigue, attention, or sleep differences across groups (see Tables 2 and 3). Not surprisingly, hand tiredness, as reported subjectively using a form of a visual analogue scale, increased over time during the training day, but this was the case for all interventional groups. These results are consistent with those of previous investigations that evaluated corticomotor excitability effects of application of paired associative stimulation protocols (PAS), a form of combined peripheral and central nervous system stimulation, in patients with stroke.\textsuperscript{42,43} However, this is the first report showing that a combined application of both forms of stimulation may bear behavioral benefits relative to the use of each intervention alone.\textsuperscript{44}

It is possible that the additive effect of PNS+tDCS was mediated through modulation of different pathways where tDCS affected sodium and calcium voltage dependent channels and NMDA receptor activity,\textsuperscript{10,11} and PNS modulated GABAergic interneurons activity.\textsuperscript{18} However, the exact mechanisms underlying this effect remain to be determined. Caveats to keep in mind for future studies include whether
application of this combined intervention could facilitate training effects in patients with more profound impairment than those reported here and whether multiple sessions can have longer lasting effects. Additionally, it could not be fully ruled out that PNS_{SHAM} intervention could have influenced the hand cortical representation or induced differential regional effects on attention.

In summary, the present study presents evidence that combining peripheral nerve stimulation to a paretic hand with anodal tDCS to the ipsilesional M1 in association with motor training induces superior improvements in performance of a motor task relative to the use of each stimulation type alone in combination with sham and training. Superiority of behavioral gains with the proposed combined intervention was 4-fold larger than after sham, and 1 to 2 times more robust than using either stimulation alone. Importantly, these effects were maintained 1 and 6 days after the completion of the training. These findings suggest that combining peripheral nerve stimulation with anodal brain polarization before physiological practice could represent a better adjuvant than application of each intervention alone in neurorehabilitation.

Acknowledgments
The authors thank D. Einstein, J. Samuels, and E.R. Buch for data acquisition, P. Gandiga for technical assistance, S. Ravindran and M. Brooks for helping with patient recruitment.

Sources of Funding
This research was supported by the intramural research program of NINDS, NIH, USA. P. Celnik was supported by the American Heart Association (0665347U), NCRR, NICHD, NIH (R01HD053793) and the Rehabilitation Medicine Scientist Training Program (RM-STP; 5K12HD001097).

Disclosures
None.

References


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Stroke. 2009;40:1764-1771; originally published online March 12, 2009;
doi: 10.1161/STROKEAHA.108.540500
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
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