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

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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\textsubscript{Sham} and PNS\textsubscript{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\textsubscript{Sham}, tDCS+PNS\textsubscript{Sham}, and PNS\textsubscript{Sham}+tDCS\textsubscript{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\textsubscript{Sham}+tDCS\textsubscript{Sham}, 15.4% relative to PNS+tDCS\textsubscript{Sham}, and 22.7% relative to tDCS+PNS\textsubscript{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,\textsuperscript{1,2} training-based customarily used neurorehabilitative treatments are insufficient to induce complete recovery of motor function in most stroke patients.\textsuperscript{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 motor\textsuperscript{4,7} and language tasks\textsuperscript{8,9} in stroke patients. Although the precise mechanisms mediating these effects are not known, it has been proposed that tDCS could influence Na\textsuperscript{+} and Ca\textsuperscript{2+} channels and NMDA-receptor activity.\textsuperscript{10,11} When applied in isolation, the beneficial effects of a single session of tDCS on motor performance appear to be modest.\textsuperscript{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,\textsuperscript{5} whereas cathodal tDCS applied over the contralesional M1 result in quantitatively similar improvements.\textsuperscript{4,7}

Peripheral nerve stimulation (PNS) has also been proposed as a possible adjuvant strategy capable of facilitating motor functions like pinch strength,\textsuperscript{12} swallowing,\textsuperscript{13} ADL-like tasks,\textsuperscript{14} and training effects in stroke patients.\textsuperscript{15-17} The mechanisms underlying the effects of PNS on motor cortical function are still under investigation but may include modulation of corticmotor excitability\textsuperscript{18} that last beyond the period of stimulation.\textsuperscript{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.\textsuperscript{21,22} PNS applied over specific body parts results in changes in motor cortical excitability that are somatotopically specific to the stimulated region.\textsuperscript{18} Mechanisms underlying PNS-induced motor effects may include modulation of GABAergic interneurons with little if any effects over NMDA receptor activity.\textsuperscript{17,18,23}
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. 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 day 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. 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 msecs). 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 interosseus (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). Application of anodal tDCS or tDCSSham (20 minutes) was overlaid the ipsilesional M1 using a frameless neuronavigation system (Brainsight, Rogue Research Inc).

PNSSham 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.

tDCSSham 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. Application of anodal tDCS or tDCSSham (20 minutes) started 100 minutes after the onset of PNS or PNSSham (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+PNSSh, and PNSSh+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 stimulation; (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 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; 1=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; 1=no attention, 10=highest level of attention), fatigue and hand tiredness (range 0 to 10; 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 (ANOVA_RM) with independent factor INTERVENTIONS (PNS+PNS, PNS+PNS, PNS+PNS, and PNS+PNS) and dependent factor TIME (Day 1, Day 2 and Day 6). Additionally, a similar ANOVA_RM 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 ANOVA_RM 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 ANOVA_RM with INTERVENTIONS as the within-subject factor and TIME (Baseline, Day 1, Day 2, and Day 6) as the repeated measure.
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\(\pm\)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\(\text{RM}\) F[3,24]=1.32, \(P=0.9\)). During the motor practice period, ANOVA\(\text{RM}\) revealed a significant effect of PRACTICE, but not INTERVENTIONS or INTERVENTIONS by PRACTICE interaction on the number of correct key presses (ANOVA\(\text{RM}\) F[4,32]=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\(\text{RM}\) 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\(\text{RM}\) INTERVENTIONS F[3,24]=3.9, \(P<0.05\); TIME F[2,16]=0.43, \(P=0.6\); INTERVENTIONS by TIME 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 PNSSham+tDCSSham at Day 1 (\(P<0.05\)). At Day 2, PNS+tDCS facilitated practice effects more than PNSSham+tDCSSham (\(P<0.01\)), PNS+tDCSSham (\(P<0.01\)), and tDCS+PNSSham (\(P<0.05\)). This Day 2 difference was evidenced by larger PNS+tDCS effects in 7 of 9 subjects relative to PNSSham+tDCSSham, in 8 of 9 relative to PNS+tDCSSham, and in 6 of 9 relative to PNS+tDCS+PNSSham, tDCS+PNSSham, and PNS+tDCS at Day 2. Values represent mean\(\pm\)SEM; *\(P<0.05\), **\(P<0.01\).

Figure 2. The graph shows the mean number of correct key presses per 30 seconds at baseline and during finger sequence practice after each stimulation condition (shaded area, mean\(\pm\)SEM). Note the comparable baseline values and the overlapping training-dependent improvements across interventions.

Figure 3. The bar graph shows the effects of the different interventions on the % change in correct key presses per 30 seconds relative to baseline (dotted line, 100%). Note that on Day 1, PNS+tDCS was significantly better than PNSSham+tDCSSham. This effect was more pronounced at Day 2 when PNS+tDCS elicited significantly more gains than PNSSham+tDCSSham, PNS+tDCSSham, or tDCS+PNSSham (black arrows) and partially present by Day 6. The inset graph shows individual patient’s change in correct key presses relative to baseline between PNSSham+tDCSSham, PNS+tDCS Sham, tDCS+PNS sham, and PNS+tDCS at Day 2. Values represent mean\(\pm\)SEM; *\(P<0.05\), **\(P<0.01\).
tDCS + PNS<sub>Sham</sub> (Figure 3, inset). At Day 6, PNS + tDCS facilitated practice effects more than PNS<sub>Sham</sub> + tDCS<sub>Sham</sub> (P<0.01) and than tDCS + PNS<sub>Sham</sub> (P<0.05; Figure 3; supplemental Table I, available online at http://stroke.ahajournals.org).

On the other hand, ANOVA<sub>RM</sub> showed a significant effect of TIME, but not INTERVENTIONS, or TIME by INTERVENTIONS interactions on the total number of key presses (ANOVA<sub>RM</sub> TIME F[3,24] = 13.92, P<0.001; INTERVENTIONS F[3,21] = 0.57, P = ns; 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<sub>RM</sub> 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, ANOVA<sub>RM</sub> for hand tiredness revealed a significant effect 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, ANOVA<sub>RM</sub> 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. 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, cortical plastic reorganization after training interventions, recovery of diaschisis, and a better understanding of the mechanisms underlying motor learning.

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 motor cortical excitability for a period of time that outlasts 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 specific increase in corticomotor excitability\textsuperscript{19} 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} 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{28,44} 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 I), 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 GABAAergic 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

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\hline
\textbf{Table 3. Sleep Data} & \multicolumn{3}{c|}{\textbf{Day1}} & \textbf{Day2} & \textbf{Day6} \\
\hline
\textbf{Sleep duration, hours} & \textbf{PNS\textsuperscript{ss} + tDCS\textsuperscript{ss}} & \textbf{PNS + tDCS} & \textbf{tDCS + PNS\textsuperscript{ss}} & \textbf{PNS + tDCS} & \\
\hline
\textbf{Sleep quality (0 to 10)} & \textbf{PNS\textsuperscript{ss} + tDCS\textsuperscript{ss}} & \textbf{PNS + tDCS} & \textbf{tDCS + PNS\textsuperscript{ss}} & \textbf{PNS + tDCS} & \\
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\end{tabular}
\end{table}

Values represent mean $\pm$ SEM of responses to sleep duration and sleep quality visual analogue scales (0 = worst possible answer, 10 = best possible response). Statistics were calculated using separate ANOVARM for each scale.
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 PNSSHAM 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 physical practice could represent a better adjuvant than application of each intervention alone in neurorehabilitation.

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Disclosures
None.

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