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"Effects of combined peripheral nerve stimulation and brain polarization on performance of a motor sequence task after chronic stroke"

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Abstract

Background—Recent work demonstrated that application of peripheral nerve and cortical stimulation independently can induce modest improvements in motor performance in patients with stroke.

Objective—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, cross-over designed study. In separate sessions, we investigated the effects of single applications of PNS+tDCS, PNS+$tDCS_{Sham}$, tDCS +PNS_{Sham} and PNS_{Sham}+$tDCS_{Sham}$ prior to 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.

Keywords

stroke; rehabilitation; transcranial direct current stimulation; nerve stimulation

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Conflicts on Interest Disclosures
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Introduction

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 non-invasive 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[4-7] and language tasks [8, 9] in stroke patients. While the precise mechanisms mediating these effects are not known, it has been proposed that tDCS could influence Na^{+} and Ca^{++} channels and NMDA-receptor activity[10, 11]. When applied in isolation, the beneficial effects 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 approximately 10% improvement in performance of activities of daily living (ADL)-like tasks[5], while 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 corticomotor excitability[18] 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 in stroke patients over specific body parts (often the paretic hand) results in changes in motor cortical excitability that are somatotopically specific to the stimulated region. Mechanisms underlying PNS-induced motor effects may include modulation of GABAergic interneurons with little if any effects over NMDA receptor activity[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[4, 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.

Material and methods

Patients

Nine single unilateral ischemic stroke patients (age range 40 - 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 brainstem 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 one short familiarization and four 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 four 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). 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 setup described in prior studies[17-19]. In short, trains of electrical stimulation were delivered at 1 Hz for a period of 2 hours (Grass stimulator S 8800, Grass Instrument Division, Astro-Med Inc., West Warwick, RI, USA). Each train consisted of five single pulses of 1ms duration delivered at 10 Hz (inter-pulse interval 100msec, inter-burst interval 500msecs). The stimulus intensity was adjusted to elicit small compound muscle action potentials (CMAPs) of 50-100 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 min (1mA), **as done in previous studies**[5, 7, 24]. Anodal tDCS (Iomed Phoresor® PM850, Salt Lake City, UT) was delivered through a 3"×3" sponge electrode (Amrex® part2-A103, Carson, CA) placed on the patient's scalp corresponding to the optimal spot for activation of the paretic APB muscle as determined with magnetic stimulation. In six patients, we confirmed that the anode position overlaid the ipsilesional M1 using a frameless neuronavigation system (Brainsight®, Rogue Research Inc., Montreal, Canada).

PNS_{Sham} 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.

$tDCS_{Sham}$ consisted of anodal tDCS over the ipsilesional M1 applied for only 1min after which the current was slowly tapered down to 0 for the remainder 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 $tDCS_{Sham}$ (20 min) started 100 min after the onset of PNS or PNS_{Sham} (20 minutes prior to 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 four 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+$tDCS_{Sham}$, tDCS+PNS_{Sham} and PNS_{Sham}+$tDCS_{Sham}$.

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[18 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 distractive 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 four different finger sequences that are comparable in difficulty and have minimal carry over effects between them[28] (Fig. 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 four finger sequences were used in random order across subjects for the four testing sessions: 2-5-3-4-2, 4-3-5-2-4, 3-2-4-5-3, 5-2-4-3-5. Subjects were instructed to repeat the five-elements sequence "as quickly and as accurately as possible" for a period of 3 min, which constituted one 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, San Pedro, CA). 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 (Fig 1).

Testing of motor performance—Motor performance was tested at baseline and in three different opportunities (days 1, 2 and 6) after each form of stimulation + motor training (see Fig 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 3minute block was divided in six 30sec epochs. We defined the primary outcome measure as the mean number of correct key presses per 30sec relative to baseline. We excluded the initial 30sec epoch during which patients often warmed up after each resting interval and the last 60sec epoch because some patients showed slowing and reported fatigue at that stage. Therefore, the mean number of correct key presses at baseline and post training (day 1, 2 and 6) were calculated on the bases of the 2nd, 3rd and 4th 30secs epochs (Fig 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. Post-training performance assessments were then done 30 minutes after the end of training (1hr after the completion of the stimulation period; Day 1), at 24hrs (Day 2) and 6.3 ±0.5 days later (Day 6; Fig. 1).

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

Data analysis

Normal distribution of all data was assessed by Kolmogorov-Smirnov tests. The primary outcome measure, the mean number of correct key presses per 30sec at Day 1, 2 and 6 relative to baseline was analyzed using a polynomial **repeated measure ANOVA ($ANOVA_{RM}$)** with independent factor INTERVENTIONS (PNS+tDCS, PNS+$tDCS_{Sham}$, tDCS+PNS_{Sham} and PNS_{Sham}+ $tDCS_{Sham}$) 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 30sec 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. Conditioned on significant p-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 30secs 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 ($ANOVA_{RM}$ $F[4, 32]=8.1$, $p< 0.001$; $F[3, 24]=1.1$, $p= 0.4$; and $F[12, 96]=0.5$, $p= 0.8$ respectively), indicating that all interventions resulted in comparable performance improvement (Fig. 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 30sec at Day 1, 2 and 6 relative to baseline ($ANOVA_{RM}$ INTERVENTIONS $F[3, 24]=3.9$, $p< 0.05$; TIME $F[2, 16]=0.43$, $p=0.6$; INTERVENTIONS by TIME interaction $F[6, 48]=2.6$, $p< 0.05$, Fig. 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+$tDCS_{Sham}$ ($p<0.01$), and tDCS+PNS_{Sham} ($p<0.05$). This Day 2 difference was evidenced by larger PNS+tDCS effects in 7 out of 9 subjects relative to PNS_{Sham}+$tDCS_{Sham}$, in 8 out of 9 relative to PNS+$tDCS_{Sham}$ and in 6 out of 9 relative to tDCS+PNS_{Sham} (Fig 3 inset). At Day 6, PNS+tDCS facilitated practice effects more than PNS_{Sham}+$tDCS_{Sham}$ ($p<0.01$) and than tDCS+PNS_{Sham} ($p<0.05$; Fig. 3, Table “online materials”).

On the other hand, $ANOVA_{RM}$ 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, $ANOVA_{RM}$ 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, $ANOVA_{RM}$ 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[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[31], cortical plastic reorganization after training interventions[30, 32], recovery of diaschisis[33], and a better understanding of the mechanisms underlying motor learning[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 non-invasive technique capable of modulating cortical excitability and motor behavior in stroke patients[35, 36]. It has been shown that anodal tDCS can enhance motor cortical excitability for a period of time that outlasts the stimulation window[10, 11]. In stroke patients, application of tDCS, either anodal to the ipsilesional[5] or cathodal to the contralesional[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[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[18] and results in enhanced BOLD signal in the contralateral M1 and dorsal premotor cortex[21, 22]. In animal models, it leads to changes in receptive fields in the primary somatosensory cortex[37]. In stroke patients, PNS alone has been shown to elicit transient improvements in swallowing[13], pinch force[12], use-dependent plasticity[16], performance of hand tasks[14] and ADL-like tasks[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% [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[39,40, 41]. Patients included were severely paralyzed at the time of the stroke (muscle strength of 2 or less in the neurological exam 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 four sessions were comparable, a finding consistent with previous reports[28, 41]. Interestingly, all patients learned the task over the training period to a comparable extent, regardless of the preceding stimulation type. However, **one hour after PNS+tDCS** (Day 1 measure), performance improvements relative to baseline were more prominent than after sham or after either stimulation alone (i.e. at day 1: 41.3% better than sham, 15.4% better than PNS alone and 22.7% better than tDCS alone; table "**online materials**"), 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 30sec 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, due to 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) appear to be superior to those reported before using either tDCS or PNS alone in chronic stroke patients (10 to 20 % range)[4, 5, 7, 15, 17, 27].

Our results cannot be explained by fatigue, attention or sleep differences across groups (see table 2 and 3). Not surprisingly, hand tiredness, as reported subjectively using a form of a visual analogue scale, showed worsening 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[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[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 [10, 11], and PNS modulated GABAergic interneurons activity [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 prior to physical practice could represent a better adjuvant than application of each intervention alone in neurorehabilitation.

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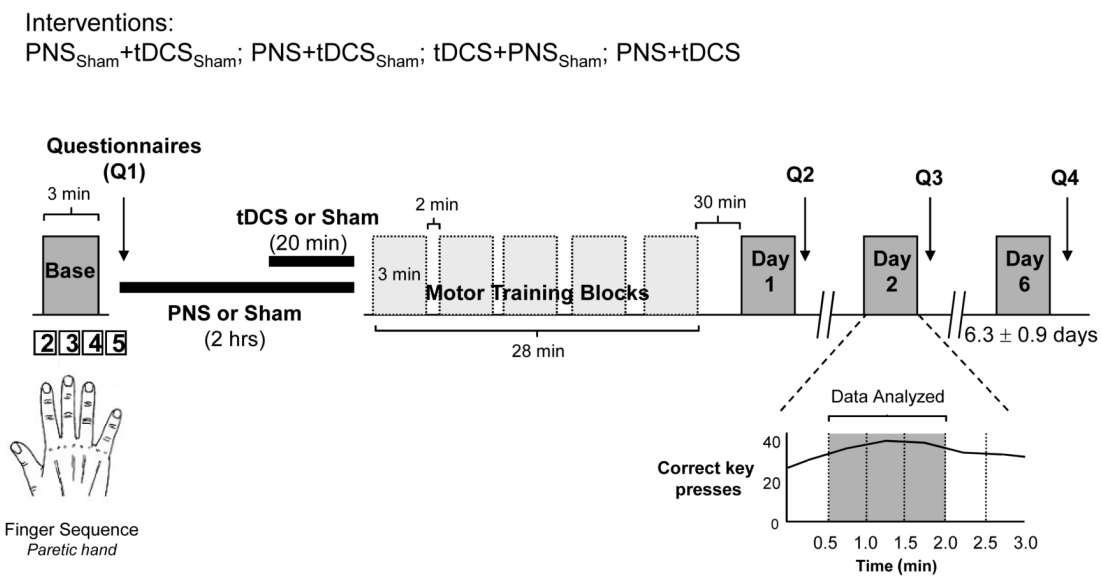

Fig. 1.

Experimental design. Patients participated in 4 sessions (order randomized across subjects): PNS_{Sham}+$tDCS_{Sham}$, PNS+$tDCS_{Sham}$, tDCS+PNS_{Sham} and PNS+tDCS (see text for details). Each session started with 3mins baseline measurement (Base) of performance of a finger sequence task followed by each form of stimulation (2hrs of PNS or Sham, combined with 20min of tDCS or Sham). Each form of stimulation preceded 5 identical blocks of 3mins motor sequence practice performed with 2mins break between blocks. Training was followed by 30mins break after which post training 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 four different time points in each session. Inset shows the number of correct key presses for one subject during each 30secs epoch. The mean number of correct key presses per 30secs during the 2^{nd}, 3^{rd} and 4^{th} 30secs epochs (dark grey area) was used to calculate the primary outcome measure (see text).

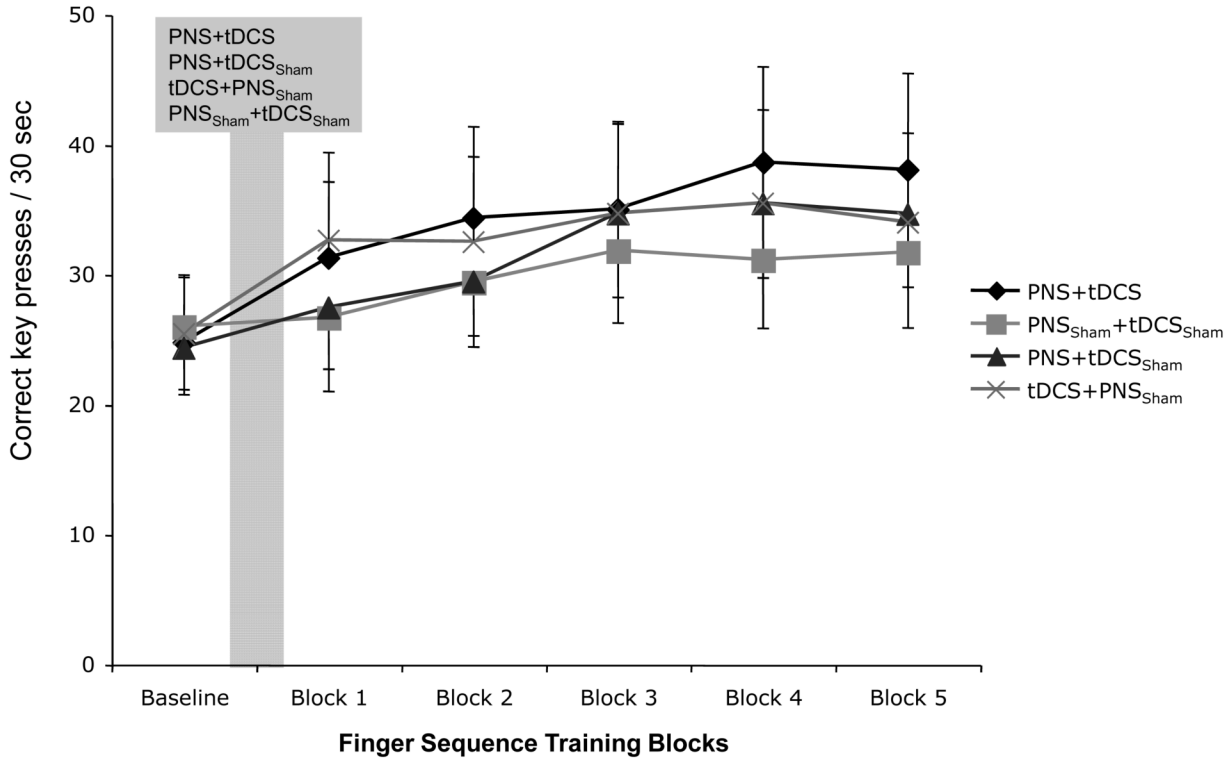

Fig. 2.

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

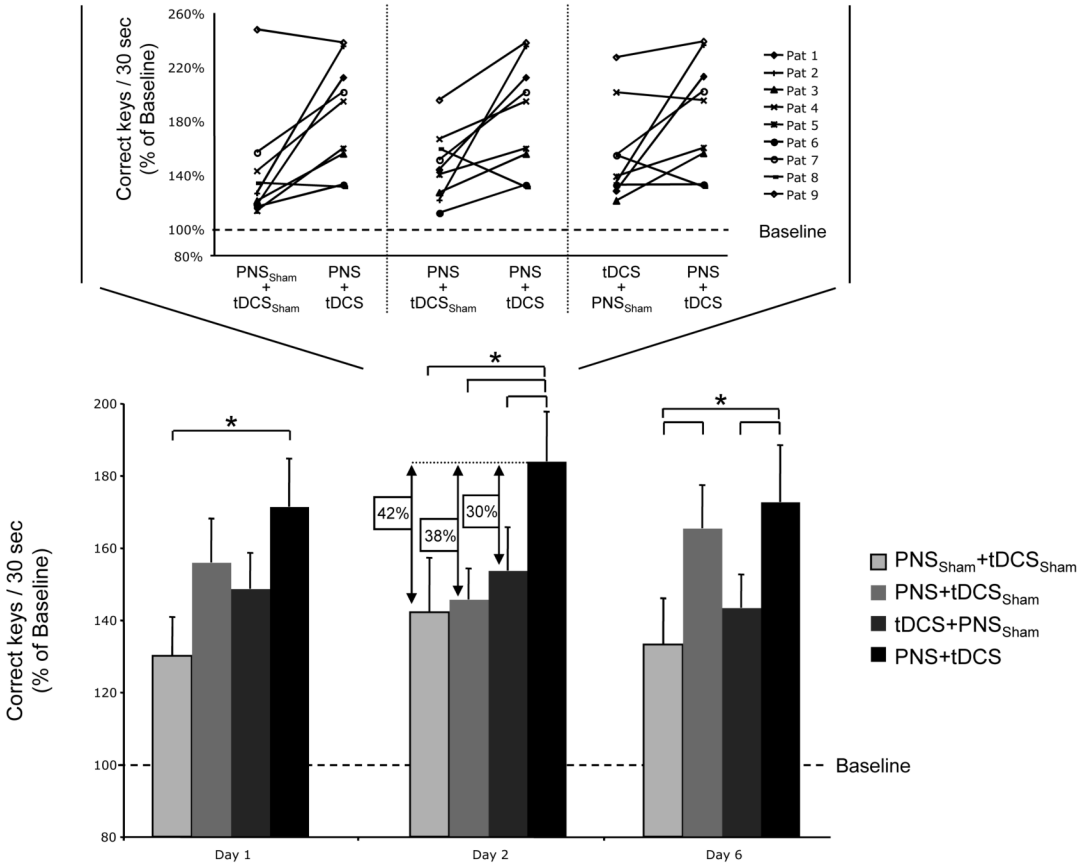

Fig. 3.

The bar graph shows the effects of the different interventions on the % change in correct key presses per 30secs relative to baseline (dotted line, 100%). Note that on Day 1, PNS+tDCS was significantly better than PNS_{Sham}+$tDCS_{Sham}$. This effect was more pronounced at Day 2 when PNS+tDCS elicited significantly more gains than PNS_{Sham}+$tDCS_{Sham}$, PNS +$tDCS_{Sham}$ or tDCS+PNS_{Sham} (black arrows) and partially present by Day 6. The inset graph shows individual patients' change in correct key presses relative to baseline between PNS_{Sham}+$tDCS_{Sham}$, PNS+$tDCS_{Sham}$, tDCS+PNS_{Sham} and PNS+tDCS at Day 2. Values represent mean±SEM; *$p < 0.05$, **$p < 0.01$.

Table 1

Patient Data Table

	Age (years)	Sex	Time after stroke (months)	Lesion site	Handedness (EDS)	MMSE	FMS (%)	MAS
Patient1	65	F	43	R Cortical and subcortical (ant. temporal, insula and corona radiata)	Right (50/50)	29/30	97	0
Patient2	41	M	31	L Cortical (post. Frontal and sup. temporal)	Right (50/50)	29/30	87	1+
Patient3	61	F	65	L Cortical (fronto-parietal and insula)	Right (47/50)	28/30	89	2
Patient4	62	M	52	R Cortical (fronto-parieto-temporal)	Left (10/50)	25/30	91	0
Patient5	73	M	41	L Cortical and subcortical (fronto-parieto-occipital and basal ganglia)	Right (44/50)	28/30	94	0
Patient6	53	M	68	R Cortical and subcortical (parietal operculum, post-insula and corona radiata)	Right (47/50)	30/30	94	1+
Patient7	46	F	55	L Cortical (parieto-occipital junction)	Right (50/50)	29/30	98	0
Patient8	40	F	59	L Cortical (deep frontal)	Right (43/50)	27/30	98	0
Patient9	57	M	87	R Subcortical (globus pallidus, corona radiata, putamen)	Right (46/50)	30/30	99	0
Mean±SE	55.3±3.76		55.7±5.57			28.3±0.53	94±1.4	

F=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

Table 2

Questionnaire Data

		Q1	Q2	Q3	Q4	Statistics $ANOVA_{RM}$		
						Intervention effect	Time effect	Intervention X Time
Attention (0 - 10)	PNS_{Sham}+$tDCS_{Sham}$	9.1±0.6	8.5±0.9	9.4±0.4	9.0±0.6	ns	ns	ns
	PNS+$tDCS_{Sham}$	8.6±0.5	9.0±0.6	9.3±0.4	9.1±0.5			
	tDCS+PNS_{Sham}	8.9±0.6	8.5±0.8	9.3±0.5	8.5±0.8			
	PNS+tDCS	8.5±0.8	8.4±1.1	9.0±0.6	9.3±0.5			
Fatigue (0-10)	PNS_{Sham}+$tDCS_{Sham}$	9.0±0.7	8.3±0.9	9.0±0.6	8.8±0.8	ns	ns	ns
	PNS+$tDCS_{Sham}$	8.6±0.5	9.0±0.6	9.1±0.5	8.9±0.6			
	tDCS+PNS_{Sham}	8.6±0.7	8.4±0.7	8.9±0.7	8.4±0.7			
	PNS+tDCS	8.4±0.8	8.4±1.1	8.8±0.7	8.9±0.6			
Hand Tiredness (0-10)	PNS_{Sham}+$tDCS_{Sham}$	8.3±1.1	7.6±1.2	9.0±0.9	8.9±0.9	ns	<0.05	ns
	PNS+$tDCS_{Sham}$	8.5±0.9	8.4±1.0	8.6±1.0	8.8±0.7			
	tDCS+PNS_{Sham}	8.6±0.8	7.4±0.9	8.1±0.9	8.6±1.0			
	PNS+tDCS	8.2±1.1	8.0±1.2	8.4±1.1	8.6±0.8			
Subjective Sequence Difficulty (0-10)	PNS_{Sham}+$tDCS_{Sham}$	4.4±1.1	4.4±1.1	3.0±0.9	3.0±1.0	ns	<0.01	ns
	PNS+$tDCS_{Sham}$	4.5±0.8	3.5±0.9	3.1±1.1	2.6±0.7			
	tDCS+PNS_{Sham}	4.6±0.9	4.5±1.0	3.0±1.2	3.1±1.1			
	PNS+tDCS	4.0±1.0	3.3±1.1	2.8±1.2	3.1±1.0			

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 $ANOVA_{RM}$ for each scale.

Table 3

Sleep Data

		Day1	Day2	Day6	Statistics $ANOVA_{RM}$		
					Intervention effect	Time effect	Intervention X Time
Sleep Duration (hours)	PNS_{Sham}+$tDCS_{Sham}$	7.3±0.5	7.6±0.6	7.4±0.5	ns	ns	ns
	PNS+$tDCS_{Sham}$	6.4±0.6	7.7±0.3	7.5±0.5			
	tDCS+PNS_{Sham}	7.2±0.6	6.9±0.8	7.5±0.6			
	PNS+tDCS	7.6±0.5	7.4±0.5	6.9±0.5			
Sleep Quality (0-10)	PNS_{Sham}+$tDCS_{Sham}$	8.9±0.4	9.1±0.3	9.1±0.5	ns	ns	ns
	PNS+$tDCS_{Sham}$	7.8±0.8	9.4±0.2	8.9±0.4			
	tDCS+PNS_{Sham}	9.0±0.5	8.9±0.5	8.3±0.7			
	PNS+tDCS	8.6±0.6	8.9±0.5	8.3±0.6			

Values represent mean±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 $ANOVA_{RM}$ for each scale.

Online Materials Only

Percent differences across interventions and sessions on relative improvement of correct key presses

	Day 1	Day 2	Day 3
PNS+tDCS vs. PNS_{Sham}+$tDCS_{Sham}$	41.3	41.8	39.5
PNS+tDCS vs. PNS+$tDCS_{Sham}$	15.4	38.2	7.3
PNS+tDCS vs. tDCS+PNS_{Sham}	22.7	30.2	29.4

Values represent the percentage difference of correct key presses between interventions for the different days. Note that combined PNS+tDCS resulted in clear gains relative to all other interventions at all time point measurements.