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Neurorehabil Neural Repair published online 13 March 2013
DOI: 10.1177/1545968313478485

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Neurorehabilitation and
Neural Repair
XX(X) 1–11
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DOI: 10.1177/1545968313478485
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Abstract

Background. After stroke, deregulated interhemispheric interactions influence residual paretic hand function. Anodal or cathodal transcranial direct current stimulation (tDCS) can rebalance these abnormal interhemispheric interactions and improve motor function. **Objective.** We explored whether dual-hemisphere tDCS (dual-tDCS) in participants with chronic stroke can improve fine hand motor function in 2 important aspects: precision grip and dexterity. **Methods.** In all, 19 chronic hemiparetic individuals with mild to moderate impairment participated in a double-blind, randomized trial. During 2 separate cross-over sessions (real/sham), they performed 10 precision grip movements with a manipulandum and the Purdue Pegboard Test (PPT) before, during, immediately after, and 20 minutes after dual-tDCS applied simultaneously over the ipsilesional (anodal) and contralateral (cathodal) primary motor cortices. **Results.** The precision grip performed with the paretic hand improved significantly 20 minutes after dual-tDCS, with reduction of the grip force/load force ratio by 7% and in the preloading phase duration by 18% when compared with sham. The dexterity of the paretic hand started improving during dual-tDCS and culminated 20 minutes after the end of dual-tDCS (PPT score +38% vs +5% after sham). The maximal improvements in precision grip and dexterity were observed 20 minutes after dual-tDCS. These improvements correlated negatively with residual hand function quantified with ABILHAND. **Conclusions.** One bout of dual-tDCS improved the motor control of precision grip and digital dexterity beyond the time of stimulation. These results suggest that dual-tDCS should be tested in longer protocols for neurorehabilitation and with moderate to severely impaired patients. The precise timing of stimulation after stroke onset and associated training should be defined.

Keywords

transcranial direct current stimulation, precision grip, Purdue Pegboard Test, stroke rehabilitation, repetitive transcranial magnetic stimulation

Introduction

Stroke is one of the leading causes of long-term disability. According to the World Stroke Organization, only approximately 12% of stroke survivors achieve complete motor recovery after 6 months.¹ The majority of stroke patients present with hemiparesis, characterized by abnormal muscle activation and coordination in the paretic arm² and difficulties in strength control,³ digital dexterity,⁴ interjoint coordination,⁵ and precision grip.⁶ After a stroke, poor upper-limb motor recovery is coupled with a relative imbalance in interhemispheric excitability—namely, a downregulation of excitability in the ipsilesional primary motor cortex (M1) and/or an enhanced excitability in the contralesional M1.⁷ Therefore, rebalancing the deregulated interhemispheric

interactions is an appealing therapeutic option to improve motor recovery after a stroke.⁸ Indeed, noninvasive brain stimulations, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have been shown to rebalance interhemispheric

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excitability and improve motor function in stroke patients.⁹⁻¹² Anodal tDCS applied to the ipsilesional M1 or cathodal tDCS applied to the contralesional M1 improve motor performance of the paretic hand.¹³ When compared with rTMS applied to both hemispheres¹⁴ or complex combinations of rTMS and tDCS on opposite hemispheres,^{11,15} dual-hemisphere tDCS (dual-tDCS) is particularly attractive for treating stroke patients because tDCS is a simple, safe, and inexpensive method to rebalance disturbed interhemispheric interactions and improve paretic hand function. The pioneer studies that demonstrated that tDCS improves hand motor performance in stroke patients focused on relatively crude or basic measurements of speed and errors in task execution or maximal force during voluntary contraction.^{11,13,16,17} On the other hand, rTMS or theta burst stimulation (TBS) have been shown to improve the precision grip dynamics and dexterity of the paretic hand.¹⁸⁻²⁰ Currently, the potential of tDCS to improve precision grip or dexterity has not yet been explored.

The goal of the present study was to test the hypothesis that, compared with baseline, 2 important aspects of fine hand motor function relevant from an ecological point of view—the motor control of precision grip and digital dexterity—improved more after real than sham dual-tDCS in chronic stroke patients. We also explored the early time course of functional changes induced by dual-tDCS.

Methods

The study was approved by the local ethical committee and conducted according to the recommendations of the Helsinki Declaration. Written informed consent was obtained at enrollment.

Patients

A total of 19 chronic stroke patients were included in the study (Figure 1). The inclusion criteria were (1) being a chronic (>6 months) stroke patient aged 18 to 80 years, (2) with an initial motor deficit in the upper limb clinically evident during at least 1 week, and (3) having a hemispheric vascular brain lesion demonstrated by cerebral imaging. The exclusion criteria were the presence of (1) intracranial metal, (2) epilepsy, (3) alcoholism, (4) pregnancy, (5) cognitive impairment or psychiatric disorder, and (6) being unable to perform the task or understand the instructions. In all, 17 patients had an ischemic stroke. Of these, patients 12 and 16 had a secondary hemorrhagic transformation, and patients 4 and 8 had an intracerebral hemorrhage. Also, 11 patients presented with subcortical stroke (Figure 2). The degree of overall disability was quantified with the modified Rankin Scale (mRS),²¹ and manual ability was quantified with the ABILHAND Scale^{22,23} (Table 1). ABILHAND is a measure of manual

ability that has been defined as the capacity to manage daily activities requiring the use of upper limbs, whatever the strategies involved.²² During a structured interview, the patients scored the 23 ABILHAND items as “impossible,” “difficult,” or “easy.” The ABILHAND items refer to bimanual tasks such as fastening the zipper of a jacket, tearing open a pack of chips, cutting meat, or hammering a nail. Patients’ responses were classified according to the published calibration, ranging approximately from −3.5 to 6 logits, where smaller logits (−3.5) are associated with a self-perceived greatest difficulty to perform the task.²² The digital dexterity impairment was also quantified by the mean score of 3 trials with each hand on the Purdue Pegboard Test (PPT)^{24,25} (Table 1). Unfortunately, the National Institutes of Health Stroke Scale (NIHSS)²⁶ score was not available for a majority of patients. Nevertheless, all presented upper-limb motor deficits, such as hand weakness and/or disorders in fine alternating movements or dysmetria, as explicitly reported in all the medical records. At the time of inclusion, all the stroke patients were able to perform a reaching movement and a precision grip between the thumb and index finger.

Design

The patients participated in a randomized controlled trial consisting of 2 sessions (real/sham dual-tDCS) performed at least 1 week apart in a balanced order (inclusion list), with a double-blind, placebo-controlled experimental design.

During familiarization, each patient performed 10 grip-lift movements with the paretic hand to allow for fast adaptation/learning effects.²⁸ Each session was divided into 4 evaluation periods—prior to tDCS (“baseline”), during tDCS (“during”), immediately after tDCS (“after”), and 20 minutes after tDCS (“after 20 minutes”)—during which the patients performed 10 grip-lifts with the paretic hand and the PPT, 3 times with each hand.

Intervention

Dual-tDCS was delivered by an Eldith DC-Stimulator (NeuroConn, Ilmenau, Germany). The electrodes (35 cm²) were soaked in 0.9% NaCl. A Magstim 200² (Magstim Company, UK) with a figure-of-eight coil was used to determine the hot spot eliciting consistent movements in the contralateral hand. The anode was positioned over the ipsilesional M1, and the cathode was placed over the contralesional M1. During real dual-tDCS, the stimulator delivered 20 minutes of stimulation at 1 mA (fade-in/-out 8 s). During sham dual-tDCS, a short up-ramp (8 s fade-in) was followed by 40 s of direct current and 8 s of fade-out, after which ineffective current pulses (110 μ A over 15 ms, peak current 3 ms) were delivered every 550 ms. The first

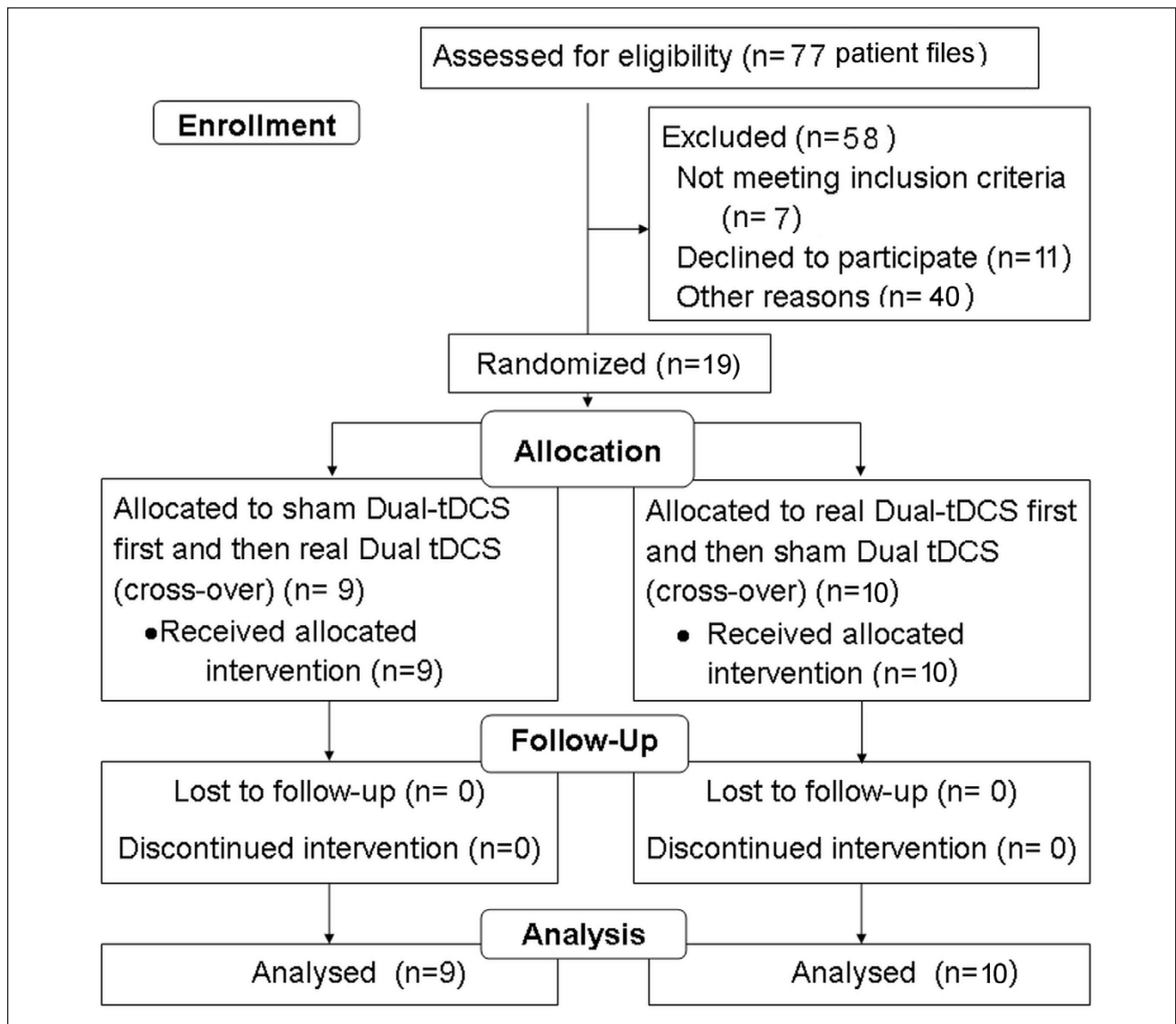


Figure 1. CONSORT flow diagram. Abbreviations: tDCS, transcranial direct current stimulation; dual tDCS, dual-hemisphere tDCS. Allocation/randomization method: a first experimenter established an inclusion list with the codes for real and sham dual-tDCS in a pseudorandomized and balanced order. These codes were used by a second experimenter to apply dual-tDCS in a double-blind fashion.

experimenter established an inclusion list with the Eldith codes (real/sham) for each session. These codes were used in a double-blind fashion by the second experimenter.

Hand Function Assessment

The primary outcome measures were the preloading phase duration (PLD) and grip force/load force ratio (GF_L/LF_L) for the precision grip—2 variables that are typically impaired in chronic stroke patients^{6,29,30}—and the PPT score for quantifying digital dexterity.^{31,32}

To measure the forces (perpendicular: left and right GFs, averaged as the global GF; and tangential: the LF) during the grip-lift task, a manufactured manipulandum fitted with 3 strain gauges (force transducers) and weighing 275 g was used (GLM Arsalis, Louvain-la-Neuve, Belgium). Analog signals were amplified, filtered with a Bessel 150-Hz cutoff low-pass fourth-order filter, and sampled at 2000 Hz. Data were analyzed offline.

During the grip-lift task, the patients were seated with their hand resting on a desk. The manipulandum was placed in front of them. The patients were asked to apply the

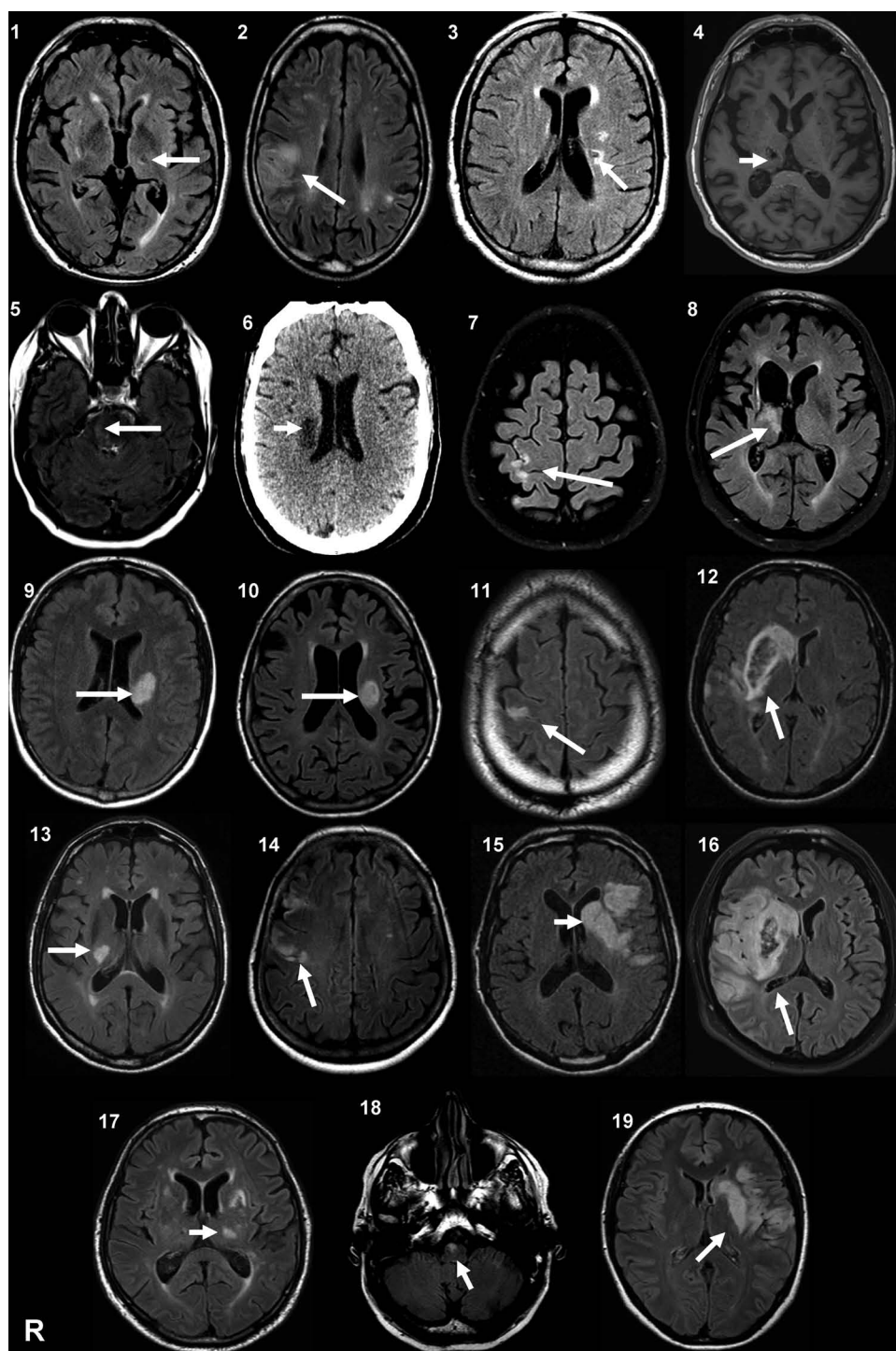


Figure 2. Brain imaging of the stroke patients. MRI or CT (patient 6) at the level of the main stroke injury; T₂-weighted FLAIR except for patient 4 (T₁). Patients 4 and 8 had an intracerebral hemorrhage. There was a slight secondary hemorrhagic transformation in patients 12 and 16. Patients 2, 14, and 19 had at least 1 other lesion compatible with a previous, minor stroke. Patients 8, 11, 13, and 17 had associated leukoaraiosis. Patients 1, 2, 11, 13, and 18 had some small chronic subcortical infarcts. Patients 3, 4, and 18 had some small chronic subcortical lacunar infarcts.

Table 1. Baseline Characteristics of the Chronic Stroke Patients.^a

Stroke Patient	Sex	Age, y	Time Since Stroke, y	Main Stroke Lesion	Additional Vascular Lesions	Dominant Hand	Paretic Hand	Paretic Hand PPT, n	Paretic Hand PPT Z-Score	Nonparetic Hand PPT, n	ABILHAND, logits	mRS
1	M	65	9	SC	SSIs	R	R	8.3	-2.93	10.7	2.5	2
2	M	54	5	C	SSIs, C	R	L	3	-2.95	10.3	0.8	2
3	M	57	8	SC	SLIs	R	R	3.3	-5.33	7	0.4	3
4	M	61	6	SC (H+)	1 SLI	L	L	2.3	-6.93	12.3	0.3	3
5	F	56	3	SC	—	L	L	7.3	-1.87	9.3	1.8	2
6	M	55	4	SC	—	R	L	7.7	-1.39	12.7	1.2	1
7	M	63	2	C	—	L	R	8.3	-2.93	12.7	2.6	1
8	M	68	1	SC (H+)	LK	R	L	8	-3.13	9.3	2.8	2
9	M	64	4	SC	—	R	R	5	-5.13	16.3	1.5	2
10	F	57	3	SC	—	R	L	0	-6.80	11.3	-1.2	3
11	M	56	3	C	LK, SSIs	R	L	8.3	-1.19	11.3	3.9	2
12	M	49	3	C	—	R	L	6	-1.96	13.7	1.7	2
13	M	70	5	SC	LK, SSIs	L	L	10.3	-0.19	12.0	1.7	2
14	F	49	2	C	C, SC	R	L	10.3	-1.96	13.7	/	1
15	M	69	4	C	—	R	R	3.7	-6.0	9.7	1.5	2
16	M	63	1	C	—	R	L	1.3	-7.6	10.3	1.9	2
17	M	76	4	SC	LK, SLIs	R	R	12	0.4	10.7	6.0	0
18	M	70	3	SC	SSIs	R	L	8	-1.23	11.3	/	2
19	F	35	3	C	SC	R	R	16.6	0.58	17.3	4.4	2
Mean \pm SD		60 \pm 1	4 \pm 2					6.9 \pm 4.0	-3.08 \pm 2.5	11.7 \pm 2.4	2.1 \pm 1.5	2 \pm 1

Abbreviations: PPT, baseline Purdue Pegboard Test score; mRS, modified Rankin Scale; M, male; F, female; SC, subcortical stroke; C, cortical stroke; H+, intracerebral hemorrhage; R, right; L, left; n, number of pegs inserted in 30 s (mean of 3 trials); SSIs, small subcortical infarctions; SLI, subcortical lacunar infarctions; LK, leukoaraiosis; SD, standard deviation.

^aIn addition to the main stroke lesion, the majority of stroke patients presented additional vascular lesions: SSIs, SLI, and LK. Z-scores were calculated on paretic hand mean PPT score compared with normative data.^{24,27} Missing ABILHAND values were reported by backslashes.

minimal forces necessary to grasp the manipulandum between the thumb and index finger, lift it 20 cm above the desk, hold it stationary for 3 s, and then replace it.

Temporal parameters of grip-lift movements were assessed by measuring the durations of 3 periods²⁸: (1) the PLD, the delay between the onset of GF and the onset of LF; (2) the loading phase duration (LD), the delay during which both GF and LF increased until LF equaled the weight of the manipulandum (2.75 N); and (3) the unloading phase duration (ULD), when LF dropped below the manipulandum's weight until the end of the movement. Dynamical parameters were assessed by measuring the maximum downward force applied during the preloading phase and the efficiency of GF scaling relative to the load induced by raising the manipulandum. The latter was computed as the ratio between GF and LF (GF_L/LF_L) at the end of the lift. The coordination between LF and GF was quantified by a cross-correlation function between the first derivative of LF and GF: dLF/dt (LF rate) and dGF/dt (GF rate).³³ This cross-correlation function was computed for the loading period. The cross-correlation was characterized by a time shift (TS1) quantifying the delay to obtain the best possible overlap between the dGF/dt and dLF/dt curves with 0.5-ms steps and a correlation coefficient (R) that reflected the strength of this correlation.

To assess digital dexterity with the PPT, the patients had to pick up as many pegs as possible one by one and insert them into the holes of a board in 30 s.^{24,31} The PPT score was the mean number of pegs placed in the holes during 3 trials for each hand²⁴ (Table 1).

Statistical Analysis

The analysis of grip-lift parameters was performed using regression of repeated measures with generalized estimating equations to consider the multiplicity of intercorrelated values in each patient.³⁴ This analysis was used to evaluate the impact of "stimulation" (real/sham) and "time" ("baseline," "during," "after," and "after 20 minutes") for each grip-lift parameter. Repeated-measures analysis of variance (RM-ANOVA) was used to explore the effects of stimulation and time on the mean PPT scores. For pairwise post hoc comparisons, t tests corrected for multiple comparisons (Bonferroni) were computed between each period and baseline and separately between sham and real dual-tDCS for the "after 20 minutes" period.

PPT score improvement at the period "after 20 minutes" with real dual-tDCS was correlated with age, mRS, and ABILHAND by Pearson coefficient. The PPT score improvement was compared according to the localization of

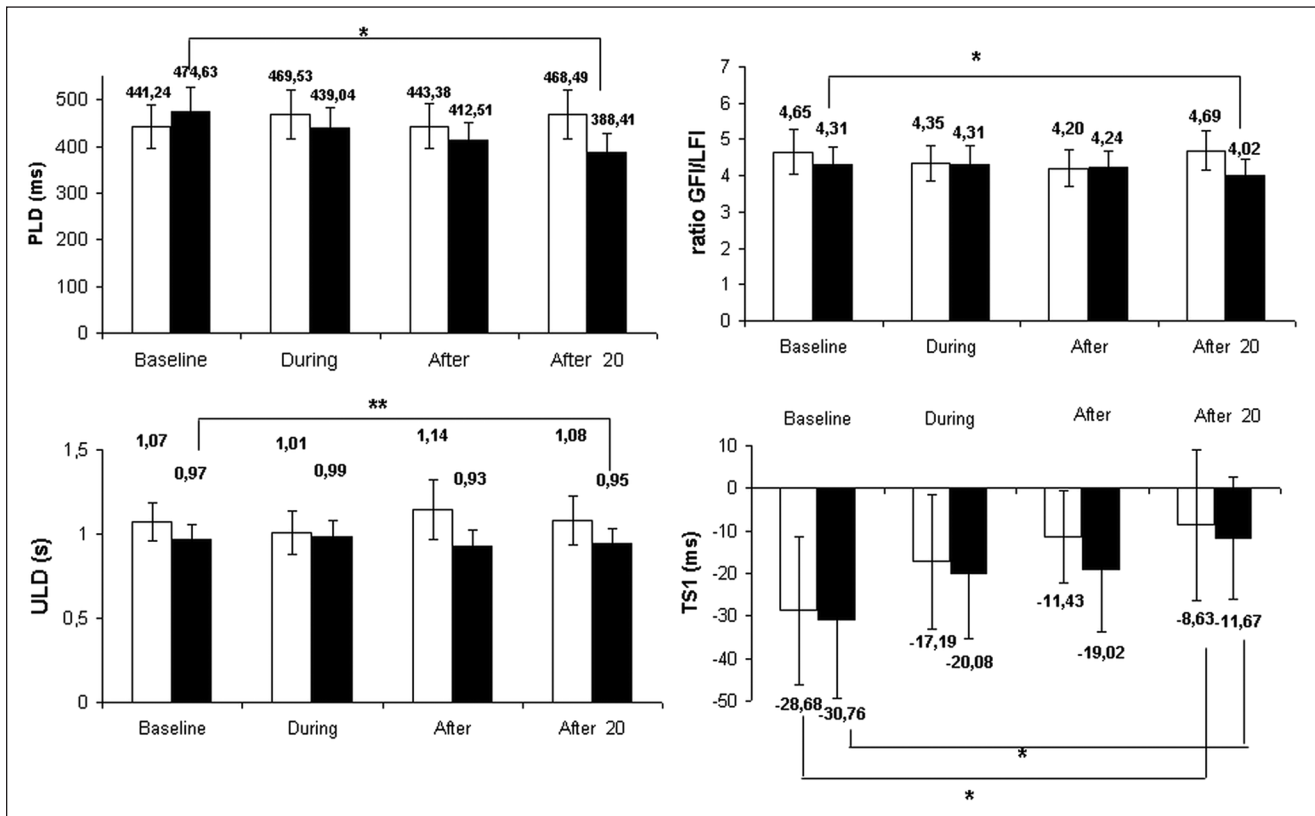


Figure 3. Precision grip parameters under sham and real dual-tDCS: changes at the group level (mean \pm SEM) under real (black bars) and sham (white bars) dual-tDCS over the 4 evaluation periods (baseline, during, after, and after 20 minutes). Abbreviations: dual-tDCS, dual-hemisphere transcranial direct current stimulation; SEM, standard error of the mean; PLD, preloading phase duration; GF, grip force; LF, load force; ULD, unloading phase duration; TS1, time shift I.

the lesion and whether the paretic hand was dominant or not, using the Student *t* test. A *P* value of .05 was considered statistically significant. All the statistical tests were two-tailed. Statistical analyses were performed using SPSS 15.0 (SPSS Inc, Chicago, Illinois).

Results

Precision Grip

A significant interaction between Time and Stimulation was observed for 3 parameters with the generalized estimating equations analysis (Figure 3): the PLD ($P < .001$), the GF_L/LF_L ($P = .009$), and the ULD ($P < .001$), suggesting that real dual-tDCS led to greater improvements than sham over time. At baseline, there were no statistically significant differences between real and sham dual-tDCS for any of the precision grip parameters. For the “after 20 minutes” period, only real dual-tDCS significantly improved the PLD from “baseline” (real: -86 ms, $P = .023$, -18% ; sham: $+27$ ms, $P = .4$, $+6\%$) as well as the GF_L/LF_L (real: -0.29 , $P = .014$, -7% ; sham: $=0.04$, $P = .9$, $+1\%$). The ULD was

significantly improved from “baseline” only with real dual-tDCS both during the “after” period (real: -37 ms, $P < .001$, -4% ; sham: $+72$ ms, $P = .5$, $+7\%$) and the “after 20 minutes” period (real: -22 ms, $P = .004$, -2% ; sham: $+10$ ms, $P = .8$, $+1\%$). In addition, there was no Time \times Stimulation interaction for TS1, but the TS1 showed significant improvement from “baseline” to “after 20 minutes” with both real ($+19$ ms, $P = .007$, $+63\%$) and sham ($+20$ ms, $P = .039$, $+70\%$) dual-tDCS. Finally, for the “after 20 minute” period, comparisons between sham and real dual-tDCS showed a significant improvement for PLD ($P = .036$; effect size = 0.4) and only a nonstatistically significant trend for ULD ($P = .1$) and GF_L/LF_L ($P = .1$).

Digital Dexterity

For the paretic hand, there was continuous improvement over time only with real dual-tDCS, and the maximal improvement was observed after 20 minutes ($+2.1$ pegs in 30 s, $+38\%$ after real dual-tDCS vs $+0.4$ pegs in 30 s, 5% after sham; Figure 4). The RM-ANOVA demonstrated a significant interaction between Time and Stimulation ($P < .001$),

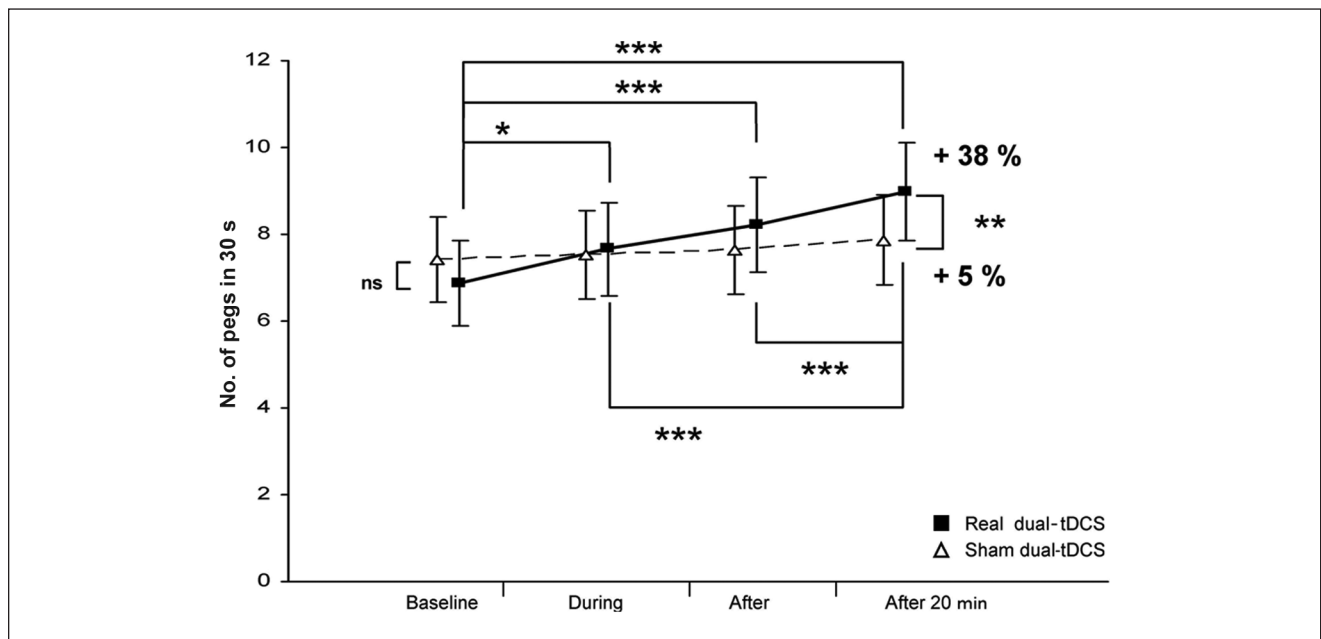


Figure 4. Purdue Pegboard Test (PPT) scores of the paretic hand under sham and real dual-tDCS: changes in the PPT score (mean \pm SEM) for the paretic hand under real (black squares) and sham (white triangles) dual-tDCS over the 4 evaluation periods (baseline, during, after, and after 20 minutes). Abbreviations: dual-tDCS, dual-hemisphere transcranial direct current stimulation; SEM, standard error of the mean; NS, not statistically significant.

* $P < .05$; ** $P < .005$; *** $P < .0005$.

suggesting that real dual-tDCS led to greater improvements than sham over time. Post hoc analyses confirmed that there was no significant performance improvement with sham dual-tDCS over time, whereas there were statistically significant performance improvements with real dual-tDCS between “baseline” and “during” ($P = .003$), “baseline” and “after” ($P < .001$), and “baseline” and “after 20 minutes” (maximal improvement: +2.1 pegs in 30 s, +38%, $P < .001$). There was a statistically significant difference between real and sham dual-tDCS exclusively for the “after 20 minutes” period ($P < .001$; effect size = 0.3).

For the nonparetic hand (Figure 5), RM-ANOVA showed that there was only a significant effect of the factor Time ($P < .001$) and no effect of Stimulation ($P = .9$) and interaction between Time and Stimulation ($P = .3$). These results suggest a progressive performance improvement regardless of the stimulation type (real/sham), with a maximal improvement after 20 minutes (real: +0.8 pegs in 30 s, +6%; sham: +1.3 pegs in 30 s, +11%).

Correlation Analyses

Correlations were performed to determine whether baseline clinical characteristics could predict the individual percentage of improvement at the period “after 20 minutes” with dual-tDCS. The patient’s age, localization of the lesion

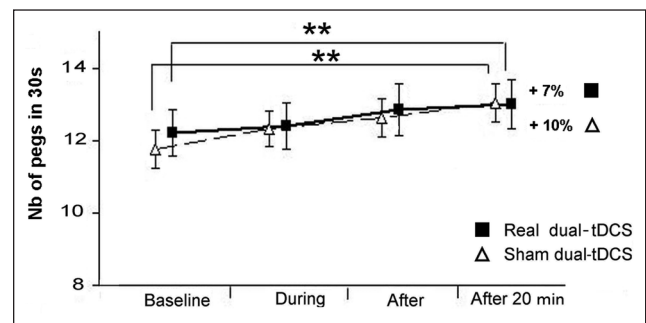


Figure 5. Purdue Pegboard Test (PPT) scores of the nonparetic hand under sham and real dual-tDCS: changes in the PPT score (mean \pm SEM) for the nonparetic hand under real (black squares) and sham (white triangles) dual-tDCS over the 4 evaluation periods (baseline, during, after, and after 20 minutes). Abbreviations: dual-tDCS, dual-hemisphere transcranial direct current stimulation; SEM, standard error of the mean.

* $P < .05$; ** $P < .005$.

(cortical/subcortical), whether the paretic hand was dominant or not, and the mRS did not significantly correlate with the PPT score improvement ($P = .87$, $P = .60$, $P = .4$, and $P = .2$, respectively). In contrast, the ABILHAND score significantly correlated with the PPT improvement under dual-tDCS ($r = -0.54$; $P = .025$).

Discussion

The main finding of this study is that in chronically and mild to moderately impaired persons after stroke, 20 minutes of dual-tDCS induced a large, rapid, and protracted improvement in performance with the paretic hand relative to baseline on a complex digital dexterity task (PPT) and a smaller, delayed improvement on the dynamics of precision grip after real dual-tDCS, compared with sham.

Dual-tDCS Improves Precision Grip and Dexterity With the Paretic Hand

Stroke has devastating effects on the precision grip ranging from eradication to typical impairments such as a prolonged PLD, an excessive GF leading to an abnormal GF/LF ratio, an abnormal time shift between the GF and LF increases, or an excessive preload force.^{4,6,35-37} The precision grip impairments that we observed in stroke patients were in line with those reported in previous articles.^{18,28,36}

Real but not sham dual-tDCS improved the GF/LF ratio of the paretic hand compared with baseline (−7%, ie, a decrement of excessive GF, versus sham dual-tDCS +1%; effect size = 0.3), which may reflect a finer control of the GFs, a better processing of the somatosensory feedback, or a more accurate planning.³⁸ By comparison, inhibitory rTMS over the contralesional M1 led to a larger improvement in the GF/LF ratio (−30%, vs sham rTMS −4%; effect size = 0.8, *n* = 12) in patients with acute subcortical stroke.¹⁸ Compared with sham, real dual-tDCS also improved the rapidity of execution of the precision grip task by diminishing the PLD (−18%, vs sham dual-tDCS +6%; effect size = 0.4) compared with baseline; inhibitory TBS over the contralesional M1 also led to a similar significant diminution of the PLD (−20%, vs sham TBS +12%; effect size = 0.5, *n* = 16).¹⁹ Whereas the unload period²⁸ has received little attention in previous studies, dual-tDCS induced a small but statistically significant shortening of the unload period duration (−2%). Finally, the improvement of the time shift relative to baseline during both real and sham dual-tDCS may suggest a nonspecific training effect. The surprising finding was that in contrast to rTMS studies^{18,19,39} and other tDCS studies,^{13,17} the improvements were not observed during or just after dual-tDCS but 20 minutes after the end of the stimulation period. This delayed improvement will be discussed below.

Dexterity is another aspect of fine sensorimotor function that may be severely impaired by stroke.^{4,6,35,36,40} In the current experiment, unlike sham, real dual-tDCS induced a strong and rapid “online” improvement in digital dexterity of the paretic hand relative to baseline.^{24,31,41} Strikingly, the maximal improvement was protracted and observed 20 minutes after the termination of dual-tDCS. The magnitude of this improvement was +38% (vs +5% after sham; effect

size = 0.3). By comparison, classical tDCS in stroke patients led to a 10% improvement on the Jebsen Taylor Test (vs 2% deterioration after sham; effect size = 1.6, *n* = 6)⁴¹ and to 6% improvement on simple reaction time (vs 5% deterioration after sham; effect size = 1.7; *n* = 11).¹⁷ In another study with stroke patients, rTMS improved the PPT score by 33% (vs 5% after sham; effect size = 0.8, *n* = 10).³²

In the current study, dual-tDCS induced various improvements in fine motor functions of the paretic hand, some improvements were equivalent (PLD) and others weaker (GF/LF ratio and PPT) compared with what was found in previous studies using classical tDCS or rTMS. It is worth noting that the differences may arise from the heterogeneity in stroke populations, stimulation paradigms, and outcome measures. To demonstrate a superiority of tDCS over rTMS for improving hand motor function in stroke patients or vice versa, a formal comparison has to be carried out with a randomized trial.

Temporal Dynamic of the Improvements Driven by Dual-tDCS

In previous studies with rTMS^{18,39} and tDCS,^{13,41} the improvements of the paretic upper limb functions were measured during or just after noninvasive brain stimulation; the temporal dynamic of these improvements after the end of stimulation has received little attention. Strikingly, in the current experiment, the dexterity of the paretic hand improved continuously over time and culminated 20 minutes after the end of dual-tDCS, coincidentally with the delayed improvement in precision grip. This may reflect a protracted/delayed effect of dual-tDCS on fine functions of the paretic hand that were previously overlooked by less-sensitive measures and tests.

Alternatively, dual-tDCS may have strongly improved a training-dependent effect, that is, motor skill learning, at least for the PPT. If this interpretation is correct, dual-tDCS could become an extremely efficient add-on therapy to boost neurorehabilitation because the amount of practice with the paretic hand, if any, was very small (50 precision grip trials, 12 PPT trials). According to the current results, the application of dual-tDCS during motor practice of complex tasks (precision grip and PPT) might place the motor system of chronic stroke patients in an optimal state for improving training-dependent performances, after a short break to avoid fatigue.

Differential Impact of Dual-tDCS on Precision Grip and Dexterity

Why did dual-tDCS induce a greater performance improvement on PPT (+38%) than on precision grip parameters (−18% at best)? The precision grip was relatively well recovered in the majority of our chronic stroke patients, and

their residual performance level may have been too high to be sensitive to a single 20-minute session of 1-mA dual-tDCS; the delayed improvement may represent a warm-up effect driven by the combination of practice and dual-tDCS. Alternatively, the precision grip's dynamics may be less sensitive to dual-tDCS-driven performance improvement, given the fact that the grasping movements may have been performed thousands of times by the stroke patients in everyday life, whereas the PPT was more novel and challenging, leaving more room for improvement. Thus, performing the PPT may lead to a broader and stronger recruitment of the cortical areas devoted to attention, motor planning and control, and feedback processing than precision grip. In turn, this would both increase the natural afferent inputs toward M1 and lead to functional improvement under dual-tDCS. Indeed, one of the hypothesized mechanisms of action of tDCS is a modulation of the neuronal resting membrane potential, which tunes the receptiveness of the target cortical area to ongoing afferent inputs.⁴² In other words, if dual-tDCS modifies the receptivity of the target areas (M1) to ongoing afferent inputs, then the large improvements in the PPT may be caused by an additive modulation through a potential increase of ongoing afferent inputs driven by the more challenging, novel PPT.

Relevance to Neurorehabilitation

The improvements in paretic hand performance were not at the expense of nonparetic hand function because the PPT scores with the nonparetic hand did not deteriorate but rather improved slightly over time. Even though the precision grip of the nonparetic hand has not been assessed, it would be surprising to observe a deterioration because inhibitory rTMS applied over the contralesional hemisphere did not induce a negative effect.¹⁸ Thus, dual-tDCS does not seem to carry a risk of impairing the fine functions of the nonparetic hand, at least in stroke patients with characteristics similar to those involved in the current study.

As suggested by the correlation between the ABILHAND scores and the improvement on the PPT, dual-tDCS had a stronger impact in the more impaired stroke patients. Despite the fact that none of them had a very severe impairment of hand function, the present cohort closely matches the characteristics of stroke patients seen in real life (ie, multiple vascular lesions, different types of vascular injuries, and older age). These results are thus encouraging in the perspective of implementing dual-tDCS as a new tool in the neurorehabilitation of a broad range of stroke patients, with different lesion locations, natures, and extents.

Limitations of the Study

The current experiment has several limitations. First, the full temporal dynamic of dual-tDCS remains to be explored

because the last measurements were performed 20 minutes after the end of stimulation. Second, the current experiment has been undertaken with the idea to modulate abnormal interhemispheric interactions in stroke patients on the basis of previous studies using unilateral noninvasive brain stimulations.^{7,8,10,11,13} Because no measure of cortical excitability with TMS has been performed in the current study, such experiments should be performed to explore the mechanisms of the improvements driven by dual-tDCS. Third, the sample of chronic stroke patients was heterogeneous. We think that this is both a weakness and strength because dual-tDCS seems to have a beneficial effect on fine motor function in patients with different forms of stroke and with an extensive lesion burden.

Conclusions

The current study is the first to demonstrate that dual-tDCS applied in chronic stroke patients improves the dynamic of precision grip and the digital dexterity of the paretic hand—2 important aspects of fine hand motor function. This improvement is independent of stroke type and does not cause deterioration of motor performance with the nonparetic hand.

Given the fact that tDCS may be easily implemented in clinical settings, is able to enhance fine motor function of the paretic hand in stroke patients, is painless, easy, and safe to use, tDCS is in the pole position for a successful bench-to-bedside translation. The full temporal dynamic of the improvements induced by dual-tDCS need to be established to ensure an optimal implementation of dual-tDCS in the neurorehabilitation of the paretic hand in stroke patients.

Acknowledgments

We thank the stroke patients who took part in this study, and we thank A. Findik for his help in screening and recruiting patients at the Cliniques Universitaires Saint-Luc (UCL, Brussels). We also thank Dr F. Evrard and J-M. Raymackers for referring patients. We are grateful to Professor E. Olivier for the use of his TMS laboratory at UCL Brussels (Institute of NeuroScience, IoNS). We also thank D. Dispa and Ph. Vincent for their help with the precision grip data analysis.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The work of YV was supported by the following grants: Fonds de la Recherche Scientifique Médicale (FRSM) 3.4.525.08.F in 2008, 2010, and 2012 and Université Catholique de Louvain (UCL) Fonds Spécial de Recherche (FSR) in 2008 and 2010. The work

of SL was supported by UCL FSR grants in 2008 and 2010. The Eldith DC-Stimulator (NeuroConn, Ilmenau, Germany) and the Magstim 200² (The Magstim Company Ltd, UK) were purchased thanks to the FRSM grants (3.4.525.08.F 2008 and 2010), the UCL FSR grants (2008 and 2010), and a grant from the Fondation Van Goethem-Brichant.

Authors' Note

Trial Registration: NCT01503073 Noninvasive Brain Stimulation for Stroke (NIBSstroke).

References

1. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke*. 2003;34:2181-2186.
2. Lang CE, Wagner JM, Bastian AJ, et al. Deficits in grasp versus reach during acute hemiparesis. *Exp Brain Res*. 2005;166:126-136.
3. Lodha N, Coombes SA, Cauraugh JH. Bimanual isometric force control: asymmetry and coordination evidence post stroke. *Clin Neurophysiol*. 2012;123:787-795.
4. Nowak DA, Grefkes C, Dafotakis M, Kust J, Karbe H, Fink GR. Dexterity is impaired at both hands following unilateral subcortical middle cerebral artery stroke. *Eur J Neurosci*. 2007;25:3173-3184.
5. Cirstea MC, Mitnitski AB, Feldman AG, Levin MF. Interjoint coordination dynamics during reaching in stroke. *Exp Brain Res*. 2003;151:289-300.
6. Hermsdorfer J, Hagl E, Nowak DA, Marquardt C. Grip force control during object manipulation in cerebral stroke. *Clin Neurophysiol*. 2003;114:915-929.
7. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol*. 2004;55:400-409.
8. Nowak DA, Grefkes C, Ameli M, Fink GR. Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. *Neurorehabil Neural Repair*. 2009;23:641-656.
9. Harvey RL, Stinear JW. Cortical stimulation as an adjuvant to upper limb rehabilitation after stroke. *PM R*. 2010;2:S269-S278.
10. Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke*. 2005;36:2681-2686.
11. Bolognini N, Vallar G, Casati C, et al. Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients. *Neurorehabil Neural Repair*. 2011;25:819-829.
12. Kakuda W, Abo M, Shimizu M, et al. A multi-center study on low-frequency rTMS combined with intensive occupational therapy for upper limb hemiparesis in post-stroke patients. *J Neuroeng Rehabil*. 2012;9:4.
13. Fregni F, Boggio PS, Mansur CG, et al. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *Neuroreport*. 2005;16:1551-1555.
14. Takeuchi N, Tada T, Toshima M, Matsuo Y, Ikoma K. Repetitive transcranial magnetic stimulation over bilateral hemispheres enhances motor function and training effect of paretic hand in patients after stroke. *J Rehabil Med*. 2009;41:1049-1054.
15. Lindenberg R, Renga V, Zhu LL, Nair D, Schlaug G. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. *Neurology*. 2010;75:2176-2184.
16. Nair DG, Renga V, Lindenberg R, Zhu L, Schlaug G. Optimizing recovery potential through simultaneous occupational therapy and non-invasive brain-stimulation using tDCS. *Restor Neurol Neurosci*. 2011;29:411-420.
17. Hummel FC, Voller B, Celnik P, et al. Effects of brain polarization on reaction times and pinch force in chronic stroke. *BMC Neurosci*. 2006;7:73.
18. Dafotakis M, Grefkes C, Eickhoff SB, Karbe H, Fink GR, Nowak DA. Effects of rTMS on grip force control following subcortical stroke. *Exp Neurol*. 2008;211:407-412.
19. Ackerley SJ, Stinear CM, Barber PA, Byblow WD. Combining theta burst stimulation with training after subcortical stroke. *Stroke*. 2010;41:1568-1572.
20. Liepert J, Zittel S, Weiller C. Improvement of dexterity by single session low-frequency repetitive transcranial magnetic stimulation over the contralesional motor cortex in acute stroke: a double-blind placebo-controlled crossover trial. *Restor Neurol Neurosci*. 2007;25:461-465.
21. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke*. 1988;19:1497-1500.
22. Penta M, Tesio L, Arnould C, Zancan A, Thonnard JL. The ABILHAND questionnaire as a measure of manual ability in chronic stroke patients: Rasch-based validation and relationship to upper limb impairment. *Stroke*. 2001;32:1627-1634.
23. Wang TN, Lin KC, Wu CY, Chung CY, Pei YC, Teng YK. Validity, responsiveness, and clinically important difference of the ABILHAND questionnaire in patients with stroke. *Arch Phys Med Rehabil*. 2011;92:1086-1091.
24. Tiffin J, Asher EJ. The Purdue pegboard; norms and studies of reliability and validity. *J Appl Psychol*. 1948;32:234-247.
25. Costa LD, Vaughan HG Jr, Levita E, Farber N. Purdue Pegboard as a predictor of the presence and laterality of cerebral lesions. *J Consult Psychol*. 1963;27:133-137.
26. Kasner SE, Chalela JA, Luciano JM, et al. Reliability and validity of estimating the NIH stroke scale score from medical records. *Stroke*. 1999;30:1534-1537.
27. Desrosiers J, Hebert R, Bravo G, Dutil E. The Purdue Pegboard Test: normative data for people aged 60 and over. *Disabil Rehabil*. 1995;17:217-224.
28. Johansson RS, Westling G. Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. *Exp Brain Res*. 1984;56:550-564.

29. Dafotakis M, Grefkes C, Wang L, Fink GR, Nowak DA. The effects of 1 Hz rTMS over the hand area of M1 on movement kinematics of the ipsilateral hand. *J Neural Transm.* 2008;115:1269-1274.
30. Nowak DA, Hermsdorfer J, Topka H. Deficits of predictive grip force control during object manipulation in acute stroke. *J Neurol.* 2003;250:850-860.
31. Gallus J, Mathiowetz V. Test-retest reliability of the Purdue Pegboard for persons with multiple sclerosis. *Am J Occup Ther.* 2003;57:108-111.
32. Mansur CG, Fregni F, Boggio PS, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. *Neurology.* 2005;64:1802-1804.
33. Duque J, Thonnard JL, Vandermeeren Y, Seire G, Cosnard G, Olivier E. Correlation between impaired dexterity and corticospinal tract dysgenesis in congenital hemiplegia. *Brain.* 2003;126:732-747.
34. Liang K-Y, Zeger S. Longitudinal data analysis using generalized linear models. *Biometrika.* 1986;73:13-22.
35. Quaney BM, Perera S, Maletsky R, Luchies CW, Nudo RJ. Impaired grip force modulation in the ipsilesional hand after unilateral middle cerebral artery stroke. *Neurorehabil Neural Repair.* 2005;19:338-349.
36. Raghavan P, Krakauer JW, Gordon AM. Impaired anticipatory control of fingertip forces in patients with a pure motor or sensorimotor lacunar syndrome. *Brain.* 2006;129:1415-1425.
37. McDonnell MN, Hillier SL, Ridding MC, Miles TS. Impairments in precision grip correlate with functional measures in adult hemiplegia. *Clin Neurophysiol.* 2006;117:1474-1480.
38. Hermsdorfer J, Elias Z, Cole JD, Quaney BM, Nowak DA. Preserved and impaired aspects of feed-forward grip force control after chronic somatosensory deafferentation. *Neurorehabil Neural Repair.* 2008;22:374-384.
39. Nowak DA, Grefkes C, Dafotakis M, et al. Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. *Arch Neurol.* 2008;65:741-747.
40. Calautti C, Jones PS, Guincestre JY, et al. The neural substrates of impaired finger tapping regularity after stroke. *Neuroimage.* 2010;50:1-6.
41. Hummel F, Celnik P, Giraux P, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain.* 2005;128(pt 3):490-499.
42. Paulus W. Transcranial electrical stimulation (tES-tDCS; tRNS, tACS) methods. *Neuropsychol Rehabil.* 2011;21:602-617.