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Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke

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Summary

Stroke is a leading cause of adult motor disability. Despite recent progress, recovery of motor function after stroke is usually incomplete. This double blind, Sham-controlled, crossover study was designed to test the hypothesis that non-invasive stimulation of the motor cortex could improve motor function in the paretic hand of patients with chronic stroke. Hand function was measured using the Jebsen–Taylor Hand Function Test (JTT), a widely used, well validated test for functional motor assessment that reflects activities of daily living. JTT measured in the paretic hand improved significantly with non-invasive transcranial direct current stimulation (tDCS), but not with Sham, an effect that outlasted the stimulation period, was present in every single patient tested and that correlated with an increment in motor cortical excitability within the affected hemisphere, expressed as increased recruitment curves (RC) and reduced short-interval intracortical inhibition. These results document a beneficial effect of non-invasive cortical stimulation on a set of hand functions that mimic activities of daily living in the paretic hand of patients with chronic stroke, and suggest that this interventional strategy in combination with customary rehabilitative treatments may play an adjuvant role in neurorehabilitation.

Keywords: cortical stimulation; motor control; rehabilitation; stroke

Abbreviations: CS = conditioning stimulus; ICF = intracortical facilitation; JTT = Jebsen–Taylor Hand Function Test; MT = motor thresholds; RC = recruitment curves to TMS; SICI = short-interval intracortical inhibition; tDCS = transcranial direct current stimulation; TMS = transcranial magnetic stimulation; TS = test stimulus

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Introduction

Stroke is the leading cause of long-term disability among adults in industrialized countries, and is responsible for 2–4% of total health-care expenses (Turney *et al*., 1984; Whisnant, 1984; Jongbloed, 1986; Broderick *et al*., 1989; Dobkin, 1995; Taylor *et al*., 1996). More than 60% of stroke survivors suffer from persistent neurological deficits (Gresham *et al*., 1975) that impair activities of daily living (i.e. dressing, eating, self-care and personal hygiene) (Gresham *et al*., 1975; Carod-Artal *et al*., 2000; Clarke *et al*., 2002), underlining the need for development of new neurorehabilitative treatments (Nudo *et al*., 1996; Nudo, 2003).

Recent studies have demonstrated that non-invasive brain stimulation enhances the beneficial effects of motor training on cortical plasticity (Butefisch *et al*., 2004), visuo-motor coordination (Antal *et al*., 2004*a*, *b*), implicit motor learning (Nitsche *et al*., 2003*c*), probabilistic classification learning (Kincses *et al*., 2004) and analogic reasoning (Boroojerdi *et al*., 2001*b*) in healthy volunteers. In animal models, preliminary reports suggested that cortical stimulation could facilitate motor function in animals with focal brain lesions involving the primary motor cortex (Adkins-Muir and Jones, 2003; Kleim *et al*., 2003; Plautz *et al*., 2003; Teskey *et al*., 2003). Thus, it is possible that cortical stimulation could

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facilitate performance of skilled motor tasks in human stroke patients (Brown *et al*., 2003; Hummel and Cohen, 2005).

Transcranial direct current stimulation (tDCS) (Nitsche *et al*., 2003*a*; Paulus, 2003) is a non-invasive, painless cortical stimulation technique (Nitsche and Paulus, 2000, 2001) that is well tolerated, does not elicit auditory or somatosensory perceptions beyond the initial minute of application (thereby facilitating the design of Sham interventions) (Priori *et al*., 1998; Nitsche and Paulus, 2000; Nitsche *et al*., 2003*b*, *c*; Hummel *et al*., 2004) and exerts facilitatory effects on learning processes in healthy volunteers (Nitsche *et al*., 2003*c*; Kincses *et al*., 2004). In this study, we investigated the hypothesis that non-invasive, painless cortical stimulation (tDCS) delivered to the motor cortex of the affected hemisphere could improve performance of motor tasks that mimic activities of daily living in patients with chronic stroke.

Material and methods

Patients

Six patients with a history of a single ischaemic cerebral infarct (Table 1) aged 38–84 years (mean ± SE, 62.2 ± 7.56 years; two of them females, all but one right-handed) participated in the study. All gave written informed consent to each experiment according to the Declaration of Helsinki [http://www.wma.net/e/policy/b3.htm (1997)] and the NINDS Institutional Review Board approved the study protocol. Patients were tested at least 1 year after the stroke (3.7 ± 1.1 years, range 1.9–8.9; Table 1). All patients had single ischaemic subcortical strokes leading to initial severe upper arm motor paresis (MRC grade <2) that over time recovered to the point of being able to perform the required motor tasks. Modified Ashworth Scale for Grading Spasticity (Bohannon and Smith, 1987) ranged from 0–2 and upper arm Fugl-Meyer scale ranged from 91% to 99% (Fugl-Meyer *et al*., 1975). Mini-Mental State Examination (MMSE) ranged between 28 and 30 (Folstein *et al*., 1975) in both groups. Patients with severe depression, history of severe alcohol or drug abuse, severe language disturbances, particularly of a receptive nature, or serious cognitive deficits (MMSE <23/30 points) were not enrolled in the protocol.

Experimental design

tDCS and behavioural testing

Initially, all patients participated in a familiarization session (Session 1) in which they practised the Jebsen–Taylor Hand Function Test (JTT) (the endpoint measure of the study) 10 times, sufficient to reach stable motor performance in all individuals. Subsequently, they moved on to the double-blind crossover portion of the study consisting of two (Sessions 2 and 3) counterbalanced sessions (tDCS and Sham) separated by 10.3 ± 2.06 days (mean ± SE). Half of the patients did tDCS first and half did Sham first. All of the patients participated in Sessions 1–3, during which the behavioural measurement (JTT) was determined. Finally, five out of six patients participated in an additional session that tested the effects of tDCS, as administered in the crossover section of the study, on motor cortical excitability to transcranial magnetic stimulation (TMS) (Session 4). Each session started with a questionnaire (see below) followed by the three measurements of baseline JTT (JTT1–3), intervention (tDCS or Sham) and follow-up JTT measurements, with one JTT measurement during (JTT4) and two more after (JTT5–6) the intervention (Fig. 1). On average, JTT6 was tested 26.5 ± 3.4 min (mean ± SE) after the end of each intervention. Additionally, JTT was tested ∼10 days after each intervention (JTT7).

All patients described their level of attention toward the task (range 1–7; 1 = no attention, 7 = highest level of attention) and their perception of fatigue (range 1–7; 1 = highest level of fatigue, 7 = no fatigue; see Q1–4 in Fig. 1) four times in each session, and their sense of discomfort/pain after each session ended (range 1–10; 1 = no discomfort/pain, 10 = maximal discomfort/pain) using visual analogue scales that have good internal consistency, reliability and objectivity (Folstein and Luria, 1973; Gracely, 1999; Chibnall and

Table 1 *Patient data*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Mean ± SE
Age (years)	41	72	38	72	66	84	62.2 ± 7.56
Sex	M	F	F	M	M	M	
Time after stroke (months)	48	34	31	23	23	107	44.3 ± 13.1
Lesion site	R frontal operculum, putamen, corona radiata and insula	R basal ganglia	L subcortical frontal lobe	L subcortical centrum semiovale, basal ganglia	R thalamus	L basal ganglia	
Handedness (EDS)	Left (12/50)	Right (46/50)	Right (49/50)	Right (46/50)	Right (49/50)	Right (47/50)	
MMSE	30/30	29/30	29/30	30/30	28/30	29/30	29.2 ± 0.31
Motor function:							
MRC	4.8	4.8	4.9	4.7	4.9	4.8	4.8 ± 0.03
FMS (%)	95	96	99	91	95	96	95 ± 1.0
Abil-Hand	0.86	0.88	1	0.84	0.94	0.97	0.92 ± 0.03
ASS	2	0	0	1+	0	0	

F = female; M = male; R = right; L = left; ASS = Ashworth Spasticity Score; EDS = Edinburgh Handedness Scale; FMS = Fugl-Meyer Scale; MMSE = Mini-Mental State Examination; MRC = scale to determine strength by the Medical Research Council (mean MRC value of the tested muscles).

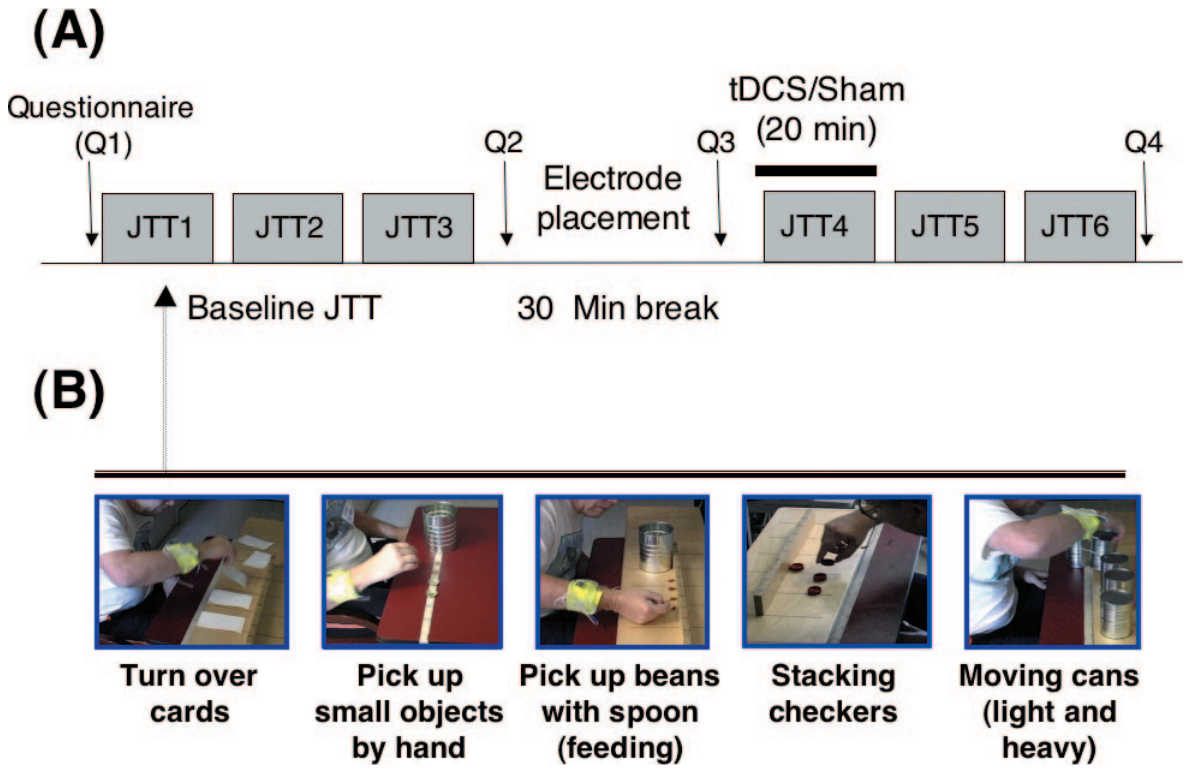

Fig. 1 (**A**) Experimental design. Patients participated in three sessions. In the first session, they familiarized themselves with the JTT and reached a stable level of performance. The second and third sessions started with questionnaires followed by baseline determinations of JTT (JTT1–3), cortical stimulation (tDCS) or Sham in a counterbalanced double-blind design and later by post-intervention JTT (JTT4–6), with JTT4 determined during stimulation and JTT5–6 after stimulation. Questionnaires (Q) in which patients characterized (self-report on visual analogue scales) level of attention and fatigue during the experiment were given at four different times in each session. A fourth session was included later to test the effects of tDCS on motor cortical function tested with TMS. (**B**) Subtests of the JTT (Jebsen *et al*., 1969) included: turning over cards, picking up small objects and placing them in a can, pick up beans with a tea spoon, placing them in a can (mimicking a feeding function), stacking chequers, moving large light cans, and moving heavy cans.

Tait, 2001; Reisine *et al*., 2003; Floel *et al*., 2004). Additionally, after the completion of the study, patients were asked to identify in which session they received 'real' cortical stimulation (tDCS). Instructions to the patients were identical for Sessions 2 and 3 (tDCS and Sham).

Jebsen-Taylor Hand Function Test

The JTT is a widely used assessment of functional hand motor skills (Jebsen *et al*., 1969). It has good validity and reliability, and normative data are available for different ages and both genders (Jebsen *et al*., 1969; Hackel *et al*., 1992). We included in this study six of the seven JTT subtests: turning over cards, picking up small objects and placing them in a can, picking up small objects with a teaspoon and placing them in a can (mimicking a feeding function), stacking chequers, moving large light cans, and moving heavy cans (Fig. 1B). Since some patients were unable to perform writing tasks (the seventh JTT subtest) due to dominant hemisphere strokes, we excluded this particular subtest from the study. Patients were instructed to perform the tasks as rapidly and accurately as possible according to written standardized instructions in the testing set (Jebsen *et al*., 1969; Stern, 1992). Total JTT time and partial subtest JTT times (except for the writing task, which was not included) were recorded for analysis. Feedback on task performance was not provided. Dropping of an object (cards, 'small objects', cans) was counted as an accuracy error and analysed off-line.

Non-invasive cortical stimulation

tDCS was delivered through two gel-sponge electrodes (TransQE; IOMED®, Salt Lake City, UT, USA; surface area 25 cm^2) embedded in a saline-soaked solution. The anode was positioned on the projection of the hand knob area (Yousry *et al*., 1997) of the primary motor cortex of the affected hemisphere on the patient's scalp, and the cathode on the skin overlying the contralateral supraorbital region. The hand knob area of the motor cortex was first identified on each patient's MRI and then co-registered to the scalp using a frameless neuronavigation system (Brainsight®; Rogue Research Inc., Montreal, Canada). Stimulating electrodes were centred on the projection of this anatomical site on each patient's scalp. Anodal tDCS was delivered for 20 min in the tDCS session and for up to 30 s in the Sham session using a Phoresor® II Auto (Model No. PM850; IOMED®). At the onset of both interventions (tDCS and Sham), current was increased in a ramp-like fashion (Nitsche *et al*., 2003*a*) eliciting a transient tingling sensation on the scalp that faded over seconds, consistent with previous reports (Nitsche *et al*., 2003*c*). Current (1 mA) remained on for 20 min in the tDCS session and for up to 30 s in the Sham session. In both sessions, currents were turned off slowly over a few seconds, a procedure that does not elicit perceptions (Nitsche *et al*., 2003*c*) and that was implemented out of the field of view of the patients. The investigator testing motor function (JTT) and the patients were blind to the intervention (tDCS or Sham), which was administered by a separate

Table 2A *Fatigue and attention*

	tDCS				Sham				Statistics $ANOVA_{RM}$
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
Fatigue (1–7) (mean ± SE)	5.2 ± 0.3	4.9 ± 0.5	5.2 ± 0.8	5.0 ± 0.3	5.1 ± 0.4	4.7 ± 0.4	5.1 ± 0.4	4.8 ± 0.5	ns
Attention (1–7) (mean ± SE)	5.0 ± 0.3	4.6 ± 0.3	4.7 ± 0.3	5.0 ± 0.4	4.9 ± 0.3	4.8 ± 0.4	4.4 ± 0.5	4.7 ± 0.5	ns

See timing of questionnaires (Q) in Fig. 1. Fatigue scale (1–7; 1 = highest level of fatigue; 7 = no fatigue). Attention scale (1–7; 1 = no attention; 7 = highest level of attention to the task). ns = not significant.

investigator who did not participate in motor testing or data analysis.

tDCS and corticomotor excitability

In session 4, we evaluated the effects of application of tDCS on measures of corticomotor excitability including motor thresholds (MT), recruitment curves to TMS (RC), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) (Kujirai *et al*., 1993; Cohen *et al*., 1998; Chen, 2000). Measures of corticomotor excitability were obtained immediately before (baseline), immediately after (TMS_1) and 25 min following the end (TMS_2) of tDCS (post). TMS was delivered from a Magstim 200 (Magstim Co., Whitland, UK) through a figure-of-eight shaped 70-mm coil. Motor evoked potentials (MEP's) were recorded from the first digital interosseus muscle (FDI) of the paretic hand. The optimal coil position for stimulation was determined by moving the coil in 1-cm steps on the scalp to identify the optimal spot for activation of the FDI in the paretic hand. The magnetic coil was held tangentially to the scalp at an angle of 45° to the midline with the handle backwards. Resting MT was defined as the lowest stimulus intensity evoking a MEP of 50 μV in five of 10 trials in the relaxed FDI (Rossini *et al*., 1994). SICI and ICF were measured using the paired-pulse technique (Kujirai *et al*., 1993). In brief, a suprathreshold test stimulus adjusted to a MEP amplitude of ∼1 mV (TS; mean 129% ± 3.3 MT) was preceded by a subthreshold conditioning stimulus (CS; 80% MT) at interstimulus intervals of 3 and 10 ms, sampling inhibitory (3 ms, SICI) and excitatory (10 ms, ICF) windows, respectively. Ten stimuli were applied at each interval in a randomized order. MTs were determined separately before and after tDCS; as they did not change, it was not necessary to adjust stimulus intensities. For RC, the stimulation intensity was changed systematically in steps of 10% of the individual's motor threshold, between 100% and 150% MT. For analysis of the RC, MEP amplitudes obtained at different stimulus intensities (100–150% MT) were expressed relative to the MEP amplitude at 100% MT (e.g. RC at 150% MT = $\text{MEP amplitude}_{150\%MT}/\text{MEP amplitude}_{100\%MT} \times 100$).

Data analysis

Data were normally distributed as evaluated by Kolmogorov–Smirnov test. Repeated measures $ANOVA_{(RM)}$ was used to evaluate the effects of $TIME_{Baseline,post}$ and $INTERVENTION_{tDCS,Sham}$ on total JTT time and the effects of $TIME_{baseline,post}$, $INTERVENTION_{tDCS,Sham}$ and $SUBTEST_{cards,objects,feeding,chequers,lightcans,heavycans}$ on subtest JTT time. Additionally, we evaluated the effects of $TIME_{baseline,post}$ and $INTERVENTION_{tDCS,Sham}$ on JTT tasks grouped according to predominant reliance on fine distal or more proximal arm function $MOTOR\ CONTROL_{fine\ distal,proximal}$ and the effects of $INTERVENTION_{tDCS,Sham}$ on attention ($TIME\text{-}QUEST_{attention(Q1,Q2,Q3,Q4)}$) and fatigue ($TIME\text{-}QUEST_{fatigue(Q1,Q2,Q3,Q4)}$). Paired *t*-tests were used to evaluate the effect of $INTERVENTION_{tDCS,Sham}$ on discomfort/pain. To evaluate the effects of tDCS on motor cortical excitability, $ANOVA_{RM}$ with factors $TIME_{baseline,post}$ and TMS $INTENSITY_{110\%,120\%,130\%,140\%,150\%\ MT}$ was used to compare RC. Paired *t*-tests were used to evaluate the effect of tDCS on SICI and ICF. Conditioned on significant *F*-values ($P < 0.05$), *post hoc* testing was performed and corrected for multiple comparisons (Bonferroni). JTT changes in percentage and net changes in percentage were calculated according to the following equations (see Table 3):

$$\text{Change in } \% = \text{JTT4}-6/\text{JTT1}-3 \times 100 - 100$$

$$\text{Net changes in} \% = \text{change in } \%_{tDCS} - \text{change in } \%_{\text{Sham stimulation}}$$

All data are expressed as mean ± SE.

Table 2B *Pain/discomfort*

	tDCS	Sham
Patient 1	1	1
Patient 2	1	1
Patient 3	1	1
Patient 4	1	1
Patient 5	2	1.5
Patient 6	1	1
Mean ± SE	1.17 ± 0.1	1.08 ± 0.5

Pain/discomfort scale (1–10; 1 = no pain; 10 = strongest imaginable pain).

Results

Psychophysical data

$ANOVA_{RM}$ did not show significant differences of factors TIME-QUEST, $INTERVENTION_{tDCS,Sham}$ or $TIME\text{-}QUEST \times INTERVENTION_{tDCS,Sham}$ interaction on either attention [$F(3,16) = 1.11$; not significant (ns)] or fatigue [$F(3,16) = 1.25$; ns] (Table 2A). Discomfort/pain was negligible ranging between 1 and 2 out of 10, and it was comparable in the tDCS and Sham sessions (paired *t*-test, ns) (Table 2B). All patients were unable to distinguish the tDCS from the Sham session.

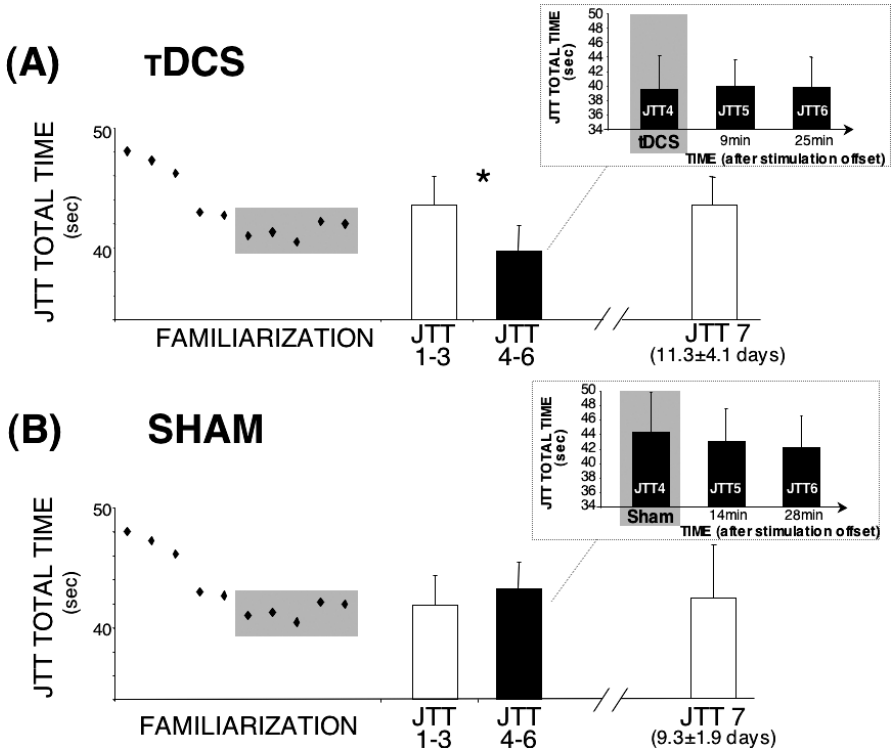

Fig. 2 Effects of tDCS/Sham on motor performance. JTT total time in the familiarization session (displayed in both **A** and **B** for comparison), at baseline (JTT1–3), during and following (JTT4–6) and >9 days after tDCS (**A**) and Sham (**B**). Note that patients reached stable JTT performance during the initial familiarization session that was comparable to JTT1–3 baseline levels in Sessions 2 and 3. Additionally, half of the patients did tDCS first and half did Sham first. tDCS (**A**, asterisk) but not Sham (**B**) resulted in shorter total times (JTT4–6) relative to baseline (JTT1–3). Performance improvements that appeared during tDCS, persisted beyond the stimulation period for at least 25 min (**A**, inset) and returned to baseline levels days later (JTT7).

Effects of non-invasive cortical stimulation on JTT time

Total JTT time improved initially, reaching stable levels in all patients and subtests during the initial familiarization session (Fig. 2). After the familiarization session, baseline total JTT time was comparable immediately preceding both the tDCS and the Sham sessions (Fig. 2A and B). Error rates were comparable (paired *t*-test, ns) during Sham (2.78 ± 1.90%) and tDCS (4.63 ± 1.71%). $ANOVA_{RM}$ revealed a significant interaction $TIME_{baseline,Post} \times INTERVENTION_{tDCS,Sham}$ on total JTT time [$F(1,10) = 10.87$; $P < 0.01$]. *Post hoc* testing showed that tDCS significantly reduced total JTT time (from 43.57 ± 2.36 s at baseline to 39.72 ± 2.15 s post-stimulation; $P < 0.05$; Fig. 2A, asterisk) in the absence of changes with Sham (from 41.87 ± 2.5 s baseline to 43.27 ± 2.19 s post-stimulation; ns; Fig. 2B). Additionally, tDCS led to more prominent reductions in JTT time relative to baseline than Sham (–6.19 ± 7.81 s, −4.78 ± 5.05 s and −4.03 ± 6.11 s for JTT4, JTT5 and JTT6, respectively; mean ± SD). Therefore, performance improvements were already evident at the measurement of JTT4 (during tDCS) and outlasted the stimulation period by at least 25 ± 2.9 min (Fig. 2A, inset). Retesting 11.3 ± 4.1 days later showed values comparable to those identified at the end of the familiarization session and at the beginning of the tDCS session (Fig. 2A). Improvements in total JTT time with tDCS were identified in every single patient (Fig. 3).

The interaction $TIME_{baseline,post} \times INTERVENTION_{tDCS,Sham} \times SUBTEST_{cards,objects,feeding,checkers,light\ cans,heavy\ cans}$ was not significant [$F(5,60) = 1.28$, ns), indicating that there was no detectable differential effect of tDCS on the different individual subtests (Table 3). However, tests that require finer motor control (turn over cards, pick up small objects by hand and spoon: fine distal tasks) tended to improve more than those requiring more proximal arm motions (stacking chequers, moving light and heavy cans: proximal tasks). $ANOVA_{RM}$ showed a significant interaction $TIME_{baseline,post} \times INTERVENTION_{tDCS,Sham}$ [$F(1,68) = 9.79$; $P < 0.01$] and a trend for a interaction $TIME_{baseline,post} \times INTERVENTION_{tDCS,Sham} \times MOTOR\ CONTROL_{fine\ distal,proximal}$ [$F(1,68) = 2.91$; $P = 0.09$; Table 3]. *Post hoc* testing showed a significant difference between tDCS-induced improvements in JTT for fine distal tasks versus proximal tasks ($P < 0.05$). tDCS-induced performance improvement in fine distal tasks/proximal tasks ratio correlated well with MRC scores ($r^2 = 0.70$; $P = 0.039$) and showed a correlation trend with Fugl-Meyer scores ($r^2 = 0.61$; $P = 0.068$).

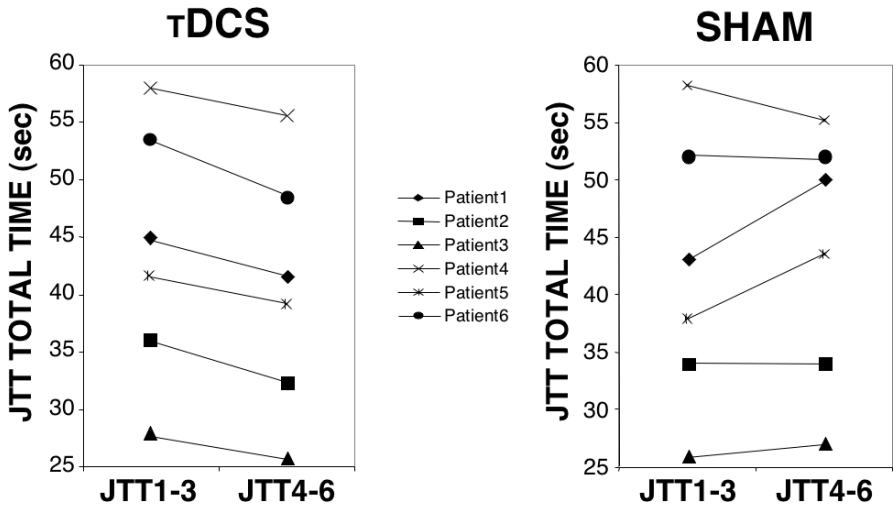

Fig. 3 Effects of (**A**) tDCS and (**B**) Sham on total JTT time in individual patients. Note shortening of total JTT time with tDCS in all patients.

Table 3 *Effects of tDCS and Sham on JTT subtests*

	tDCS			Sham			Net changes in %
	Baseline (JTT1–3)	JTT4–6	Change in %	Baseline (JTT1–3)	JTT4–6	Change in %	
Cards	5.65 ± 0.47	4.78 ± 0.35	−15.4	5.4 ± 0.41	5.23 ± 0.35	−3.15	−12.25
Objects	10.63 ± 0.87	9.86 ± 0.77	−7.24	10.31 ± 0.83	10.32 ± 0.64	0.1	−7.34
Feed	12.08 ± 0.69	11.43 ± 0.68	−5.38	11.86 ± 0.7	13.31 ± 1.12	12.23	−17.61
Chequers	5.69 ± 0.38	5.12 ± 0.32	−10.02	5.35 ± 0.35	5.18 ± 0.29	−3.18	−6.82
Light cans	4.77 ± 0.18	4.38 ± 0.2	−8.18	4.61 ± 0.27	4.61 ± 0.2	0	−8.18
Heavy cans	4.75 ± 0.19	4.41 ± 0.2	−6.17	4.65 ± 0.26	4.62 ± 0.2	−1.08	−5.09

All values are mean ± SE. Change in % = (JTT4–6/JTT1–3 × 100–100). Net changes in % = change in $\%_{tDCS}$ – change in $\%_{Sham\ stimulation}$. Negative values indicate a reduction in total JTT time and consequently performance improvement.

Effects of non-invasive cortical stimulation on motor cortical excitability

In Session 4 MT did not change with tDCS (from 46 ± 2.6% to 45 ± 1.9%, ns). On the other hand, $ANOVA_{RM}$ showed a significant effect of $TIME_{baseline,post}$ [$F(1) = 13.69$; $P < 0.001$] and a trend for a significant effect of TMS $INTENSITY_{110\%,120\%,130\%,140\%,150\%\ MT}$ [$F(4) = 2.39$; $P = 0.08$], in the absence of a significant interaction $TIME_{baseline,post}$ × TMS $INTENSITY_{110\%,120\%,130\%,140\%,150\%\ MT}$ [$F(1,4) = 0.22$; $P = 0.92$], indicating an overall increase of RC with tDCS (Fig. 4A). The tDCS-induced enhancement in RC slope correlated well with tDCS-induced improvements in JTT ($r^2 = 0.78$; $P < 0.05$; Fig. 4B). tDCS led to a change of SICI (from 57.17 ± 7.97% to 68.13 ± 6.36% of the test unconditioned MEP) reflecting reduced inhibition, which was more prominent immediately after the end of tDCS ($P < 0.05$; Fig. 4C, TMS_1), and to a non-significant increase in ICF (from 145.11 ± 4.12% to 175.12 ± 15.99% of the test unconditioned MEP; $P = 0.19$). TS MEP amplitude was 1.1 ± 0.11 mV at baseline and 1.33 ± 0.12 mV at post.

Discussion

The main finding of this double-blind, crossover study was that non-invasive cortical stimulation in the form of tDCS applied to the motor cortex of the affected hemisphere resulted in functional improvement in the paretic hand of chronic stroke patients that outlasted the stimulation period and was present in every patient tested.

The JTT assesses functional hand motor skills (Jebsen *et al*., 1969), has good validity and reliability (Jebsen *et al*., 1969; Hackel *et al*., 1992), and has been extensively studied in rehabilitative settings (Spaulding *et al*., 1988; Kraft *et al*., 1992; Neistadt, 1994; Alon *et al*., 2003). Subcomponents of the JTT mimic activities of daily living that require skilled hand and arm motor function. Performance of these motor tasks is conducted through fast cortico spinal projections (Muller and Homberg, 1992) originated in the primary motor cortex (Jancke *et al*., 2004). While some of these subtests rely predominantly on skillful control of distal hand function, as, for example, picking up small objects, others rely predominantly on more proximal arm control like moving light or heavy cans (Jebsen *et al*., 1969). In previous studies,

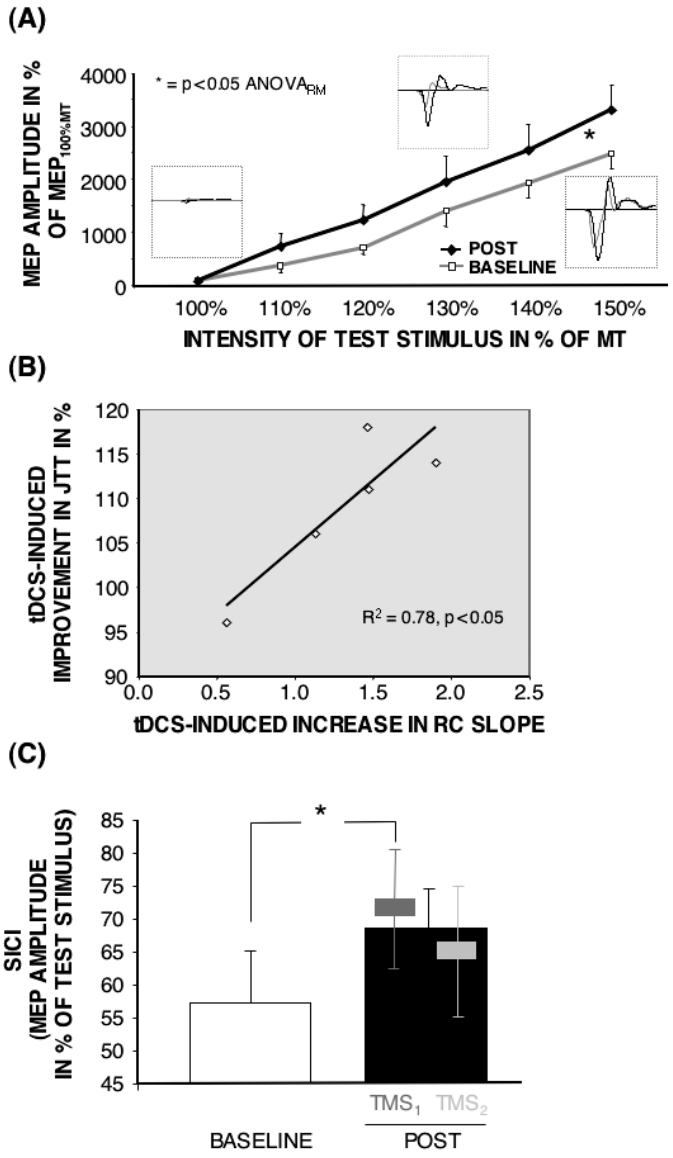

Fig. 4 Effects of tDCS on corticomotor and intracortical excitability. (**A**) Recruitment curve (RC). Data for different stimulus intensities (100% to 150% MT) were calculated and displayed in percentage of the MEP amplitude elicited by the test stimulus at 100% MT (e.g. RC at 150% MT = MEP amplitude 150% MT/MEP amplitude 100% MT $\times$ 100; *y*-axis) before (baseline, grey lines) and after (post, black lines) tDCS. Insets display raw data in one individual. (**B**) The abcissa displays the tDCS-induced increase in RC slope calculated as the ratio of the RC slope before (RC-slope$_{baseline}$) and after tDCS (RC-slope$_{post}$), corresponding to the equation RC-slope$_{post}$/RC-slope$_{baseline}$ (values >1 indicate larger RC with tDCS, while values <1 reflect decreases in RC with tDCS). The ordinate displays tDCS-induced improvement in JTT measured as the average percentage improvement for all subtests in each individual. Note the significant correlation between tDCS-induced increase in RC slope and tDCS-induced improvement in JTT. (**C**) Intracortical inhibition (SICI). Magnitude of SICI expressed as percentage of test MEP amplitude before (black bar) and after (white bar) tDCS. TMS_1 and TMS_2 display measurements obtained immediately and ~25 min after the end of tDCS, respectively. Note the decrease of SICI that was more prominent immediately after the end of tDCS (*$P < 0.05$).

improvement in JTT correlated well with functional gains during rehabilitative training after stroke (Kraft *et al*., 1992; Alon *et al*., 2003; Wu *et al*., 2004). Therefore, JTT is a valid measure of hand function in the recovery process following a brain lesion such as stroke.

Our results document that non-invasive stimulation of motor regions of the affected hemisphere in patients with chronic stroke results in functional gains in motor function of the paretic hand. This finding is consistent with previous studies showing that direct stimulation of a motor cortical representation in rodents elicits cortical reorganization (Nudo *et al*., 1990), while non-invasive cortical stimulation in humans influences motor cortical excitability (Chen *et al*., 1997; Pascual-Leone *et al*., 1998; Nitsche and Paulus, 2000, 2001). Additionally, non-invasive cortical stimulation can facilitate cortical plasticity elicited by motor training (Butefisch *et al*., 2004) and ischaemic nerve block (Ziemann *et al*., 1998*b*), and induce behavioural gains in the form of enhancement of implicit motor learning (Nitsche *et al*., 2003*c*), visuo-motor processing (Antal *et al*., 2004*a*, *b*), probabilistic learning (Kincses *et al*., 2004) and analogic reasoning (Boroojerdi *et al*., 2001*b*) in healthy human volunteers. These findings raised the hypothesis that non-invasive cortical stimulation could contribute to recovery of motor function in stroke patients, a proposal that gained support from preliminary reports of improvements in motor function in brain-lesioned rodents and primates (Adkins-Muir and Jones, 2003; Kleim *et al*., 2003; Plautz *et al*., 2003; Teskey *et al*., 2003) and in one patient with stroke (Brown *et al*., 2003) with stimulation delivered through epidural electrodes.

In our experimental design geared to test this hypothesis, patients initially familiarized themselves with the task and reached a stable performance level in the first session. Baseline levels (JTT1–3) measured days apart in the following two counterbalanced sessions (tDCS and Sham) were comparable to those determined at the end of the familiarization session, demonstrating test reproducibility over time (Fig. 2). JTT improvements in the tDCS condition (see inset in Fig. 2A) persisted for more than 25 min after the stimulation ended and returned to baseline levels when retested ~10 days later, but we do not know the precise duration of the effect. The fact that discomfort/pain (at minimum levels of 1–2 out of 10), attention and fatigue were comparable in tDCS and Sham sessions, together with the finding that patients were unable to distinguish the tDCS from the Sham session, as well as the lack of side-effects and the stratified design by which intervention and testing were performed by different investigators are consistent with success of an experimental design geared to blind both patients and investigators. The finding that error rates were comparable in both sessions supports the view that improvements in JTT did not originate in a change of speed accuracy trade-off. The magnitude of tDCS-induced improvement in JTT, while modest (~12%), was robust since it was documented in every single subject tested (Fig. 3), supporting the proposal

that cortical stimulation combined with motor training could enhance functional gains in stroke patients beyond levels reported in this investigation with tDCS alone. Consistent with this proposal are recent reports showing that cortical stimulation applied in synchrony with motor training enhanced training-dependent plasticity in healthy human volunteers (Butefisch *et al*., 2004) and increased functional recovery in animals with focal motor cortical lesions (Adkins-Muir and Jones, 2003; Teskey *et al*., 2003). The finding of slightly longer JTT in three patients after Sham (Fig. 3) could reflect mild fatigue in these individuals, insufficient to reach overt perception in analogue scales. This result underlines the beneficial effect detected in the tDCS session, leading to clear improvements in every single subject.

While our results are suggestive of differential effects of tDCS on different JTT subtests, it remains to be determined whether functional improvements elicited by this form of stimulation are more prominent for tasks that involve fine distal hand movements than for those involving more proximal functions. In our patients with chronic subcortical stroke, severe weakness right after the ictal event, and relatively good motor function at the time of testing, the magnitude of tDCS-induced improvement in JTT (11.75 + 3.61%) was similar to that elicited by the same intervention in age-matched healthy volunteers (10.96 + 2.75%) (Hummel *et al*., 2004), suggesting a comparable ability for neuroplastic changes in the motor system, possibly contributing to successful recovery. It remains to be determined whether the beneficial effects of tDCS of the affected hemisphere on JTT performance are mediated through stimulation of primary motor cortex alone (Nudo *et al*., 1990; Werhahn *et al*., 2003; Murase *et al*., 2004) or in combination with ipsilesional dorsal premotor cortex (Liu and Rouiller, 1999; Fridman *et al*., 2004), both regions closely located and actively involved in recovery of motor function after stroke. The dimension of tDCS electrodes does not allow at this time more focal stimulation, an issue that could be addressed specifically using focal TMS (Siebner *et al*., 2001; Johansen-Berg *et al*., 2002; Fridman *et al*., 2004).

Interventional tDCS is easy to apply, painless, presents advantages for the design of Sham controls and can influence motor cortical function for up to 90 min (Nitsche and Paulus, 2001). tDCS effects on motor cortical function appear to rely to some extent on increased efficacy of NMDA receptor activity (Liebetanz *et al*., 2002; Nitsche *et al*., 2004*a*, *b*), a mechanism that also influences recruitment curves and intracortical inhibition (Ziemann *et al*., 1998*a*; Schwenkreis *et al*., 1999; Stefan *et al*., 2002). Therefore, our finding of enhanced recruitment curves that correlate with tDCS-induced performance improvements and of reduced short-interval intracortical inhibition suggest the involvement of NMDA (Liebetanz *et al*., 2002; Nitsche *et al*., 2004*a*, *b*) and possibly GABA (Boroojerdi *et al*., 2001*a*; Chen, 2004) receptor-dependent mechanisms on JTT improvements identified in this study. tDCS did not affect motor thresholds in our patients (which were comparable to MT reported in healthy volunteers; Peinemann *et al*., 2001; Jancke *et al*., 2004), but elicited a non-significant trend for increase in intracortical facilitation, both consistent with previous studies in healthy volunteers (Nitsche *et al*., 2004*b*, *c*). Overall, association between increases in motor cortical excitability and performance improvements in motor function or motor learning have been also described in healthy subjects (Muellbacher *et al*., 2001; Garry *et al*., 2004) and patients with brain lesions (Traversa *et al*., 1997; Liepert *et al*., 1998), but cause-effect links between both remain to be demonstrated. Finally, it is conceivable that factors such as lesion site, size, location, time after the ictal event or impairment levels (Fridman *et al*., 2004; Wu *et al*., 2004) influence functional results of cortical stimulation.

In summary, this study demonstrates that non-invasive cortical stimulation of motor regions of the affected hemisphere can beneficially influence skilled motor functions of the paretic hand in patients suffering from chronic stroke. This finding supports the hypothesis that non-invasive cortical stimulation combined with motor training could represent a useful adjuvant to traditional interventions in neurorehabilitation.

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References

Adkins-Muir DL, Jones TA. Cortical electrical stimulation combined with rehabilitative training: enhanced functional recovery and dendritic plasticity following focal cortical ischemia in rats. Neurol Res 2003; 25: 780–8.

Alon G, Sunnerhagen KS, Geurts AC, Ohry A. A home-based, self-administered stimulation program to improve selected hand functions of chronic stroke. Neurorehabilitation 2003; 18: 215–25.

Antal A, Nitsche MA, Kincses TZ, Kruse W, Hoffmann KP, Paulus W. Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extrastriate visual areas in humans. Eur J Neurosci 2004a; 19: 2888–92.

Antal A, Nitsche MA, Kruse W, Kincses TZ, Hoffmann KP, Paulus W. Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. J Cogn Neurosci 2004b; 16: 521–7.

Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987; 67: 206–7.

Boroojerdi B, Battaglia F, Muellbacher W, Cohen LG. Mechanisms influencing stimulus–response properties of the human corticospinal system. Clin Neurophysiol 2001a; 112: 931–7.

Boroojerdi B, Phipps M, Kopylev L, Wharton CM, Cohen LG, Grafman J. Enhancing analogic reasoning with rTMS over the left prefrontal cortex. Neurology 2001b; 56: 526–8.

Broderick JP, Phillips SJ, Whisnant JP, O'Fallon WM, Bergstralh EJ. Incidence rates of stroke in the eighties: the end of the decline in stroke? Stroke 1989; 20: 577–82.

Brown JA, Lutsep H, Cramer SC, Weinand M. Motor cortex stimulation for enhancement of recovery after stroke: case report. Neurol Res 2003; 25: 815–8.

Butefisch CM, Khurana V, Kopylev L, Cohen LG. Enhancing encoding of a motor memory in the primary motor cortex by cortical stimulation. J Neurophysiol 2004; 91: 2110–6.

Carod-Artal J, Egido JA, Gonzalez JL, Varela de Seijas E. Quality of life among stroke survivors evaluated 1 year after stroke: experience of a stroke unit. Stroke 2000; 31: 2995–3000.

Chen R. Studies of human motor physiology with transcranial magnetic stimulation. Muscle Nerve Suppl 2000; 9: S26–32.

Chen R. Interactions between inhibitory and excitatory circuits in the human motor cortex. Exp Brain Res 2004; 154: 1–10.

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997; 48: 1398–403.

Chibnall JT, Tait RC. Pain assessment in cognitively impaired and unimpaired older adults: a comparison of four scales. Pain 2001; 92: 173–86.

Clarke P, Marshall V, Black SE, Colantonio A. Well-being after stroke in Canadian seniors: findings from the Canadian Study of Health and Aging. Stroke 2002; 33: 1016–21.

Cohen LG, Ziemann U, Chen R, Classen J, Hallett M, Gerloff C, et al. Studies of neuroplasticity with transcranial magnetic stimulation. J Clin Neurophysiol 1998; 15: 305–24.

Dobkin B. The economic impact of stroke. Neurology 1995; 45: S6–9.

Floel A, Nagorsen U, Werhahn KJ, Ravindran S, Birbaumer N, Knecht S, et al. Influence of somatosensory input on motor function in patients with chronic stroke. Ann Neurol 2004; 56: 206–12.

Folstein MF, Luria R. Reliability, validity, and clinical application of the Visual Analogue Mood Scale. Psychol Med 1973; 3: 479–86.

Folstein MF, Folstein SE, McHugh PR. ''Mini-mental state''. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Fridman EA, Hanakawa T, Chung M, Hummel F, Leiguarda RC, Cohen LG. Reorganization of the human ipsilesional premotor cortex after stroke. Brain 2004; 127: 747–58.

Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med 1975; 7: 13–31.

Garry MI, Kamen G, Nordstrom MA. Hemispheric differences in the relationship between corticomotor excitability changes following a fine-motor task and motor learning. J Neurophysiol 2004; 91: 1570–8.

Gracely RH. Pain measurement. Acta Anaesthesiol Scand 1999; 43: 897–908.

Gresham GE, Fitzpatrick TE, Wolf PA, McNamara PM, Kannel WB, Dawber TR. Residual disability in survivors of stroke—the Framingham study. N Engl J Med 1975; 293: 954–6.

Hackel ME, Wolfe GA, Bang SM, Canfield JS. Changes in hand function in the aging adult as determined by the Jebsen Test of Hand Function. Phys Ther 1992; 72: 373–7.

Hummel F, Cohen LG. Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke. Neurorehabil Neural Repair 2004; In press.

Hummel F, Wu CW, Floel A, Gerloff C, Cohen LG. Improvement of skilled motor functions in elderly healthy volunteers by cortical stimulation. Neuroimage 2004; 22: S29.

Jancke L, Steinmetz H, Benilow S, Ziemann U. Slowing fastest finger movements of the dominant hand with low-frequency rTMS of the hand area of the primary motor cortex. Exp Brain Res 2004; 155: 196–203.

Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. Arch Phys Med Rehabil 1969; 50: 311–9.

Johansen-Berg H, Rushworth MF, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. The role of ipsilateral premotor cortex in hand movement after stroke. Proc Natl Acad Sci USA 2002; 99: 14518–23.

Jongbloed L. Prediction of function after stroke: a critical review. Stroke 1986; 17: 765–76.

Kincses TZ, Antal A, Nitsche MA, Bartfai O, Paulus W. Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. Neuropsychologia 2004; 42: 113–7.

Kleim JA, Bruneau R, VandenBerg P, MacDonald E, Mulrooney R, Pocock D. Motor cortex stimulation enhances motor recovery and reduces peri-infarct dysfunction following ischemic insult. Neurol Res 2003; 25: 789–93.

Kraft GH, Fitts SS, Hammond MC. Techniques to improve function of the arm and hand in chronic hemiplegia. Arch Phys Med Rehabil 1992; 73: 220–7.

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. J Physiol (Lond) 1993; 471: 501–19.

Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain 2002; 125: 2238–47.

Liepert J, Miltner WH, Bauder H, Sommer M, Dettmers C, Taub E, et al. Motor cortex plasticity during constraint-induced movement therapy in stroke patients. Neurosci Lett 1998; 250: 5–8.

Liu Y, Rouiller EM. Mechanisms of recovery of dexterity following unilateral lesion of the sensorimotor cortex in adult monkeys. Exp Brain Res 1999; 128: 149–159.

Muellbacher W, Ziemann U, Boroojerdi B, Cohen L, Hallett M. Role of the human motor cortex in rapid motor learning. Exp Brain Res 2001; 136: 431–8.

Muller K, Homberg V. Development of speed of repetitive movements in children is determined by structural changes in corticospinal efferents. Neurosci Lett 1992; 144: 57–60.

Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. Ann Neurol 2004; 55: 400–9.

Neistadt ME. The effects of different treatment activities on functional fine motor coordination in adults with brain injury. Am J Occup Ther 1994; 48: 877–82.

Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000; 527: 633–9.

Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001; 57: 1899–901.

Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation—technical, safety and functional aspects. Suppl Clin Neurophysiol 2003a; 56: 255–76.

Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol 2003b; 114: 2220–2; reply 2222–3.

Nitsche MA, Schauenburg A, Lang N, Liebetanz D, Exner C, Paulus W, et al. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. J Cogn Neurosci 2003c; 15: 619–26.

Nitsche MA, Grundey J, Liebetanz D, Lang N, Tergau F, Paulus W. Catecholaminergic consolidation of motor cortical neuroplasticity in humans. Cereb Cortex 2004a; 14: 1240–5.

Nitsche MA, Jaussi W, Liebetanz D, Lang N, Tergau F, Paulus W. Consolidation of human motor cortical neuroplasticity by D-cycloserine. Neuropsychopharmacology 2004b; 29: 1573–8.

Nitsche MA, Liebetanz D, Schlitterlau A, Henschke U, Fricke K, Frommann K, et al. GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. Eur J Neurosci 2004c; 19: 2720–6.

Nudo RJ. Adaptive plasticity in motor cortex: implications for rehabilitation after brain injury. J Rehabil Med 2003: 7–10.

Nudo RJ, Jenkins WM, Merzenich MM. Repetitive microstimulation alters the cortical representation of movements in adult rats. Somatosens Mot Res 1990; 7: 463–83.

Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct [see comments]. Science 1996; 272: 1791–4.

Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. J Clin Neurophysiol 1998; 15: 333–43.

Paulus W. Transcranial direct current stimulation (tDCS). Suppl Clin Neurophysiol 2003; 56: 249–54.

Peinemann A, Lehner C, Conrad B, Siebner HR. Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. Neurosci Lett 2001; 313: 33–6.

Plautz EJ, Barbay S, Frost SB, Friel KM, Dancause N, Zoubina EV, et al. Post-infarct cortical plasticity and behavioral recovery using concurrent cortical stimulation and rehabilitative training: a feasibility study in primates. Neurol Res 2003; 25: 801–10.

Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport 1998; 9: 2257–60.

Reisine S, Fifield J, Walsh SJ, Feinn R. Do employment and family work affect the health status of women with fibromyalgia? J Rheumatol 2003; 30: 2045–53.

Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 1994; 91: 79–92.

Schwenkreis P, Witscher K, Janssen F, Addo A, Dertwinkel R, Zenz M, et al. Influence of the N-methyl-D-aspartate antagonist memantine on human motor cortex excitability. Neurosci Lett 1999; 270: 137–40.

Siebner H, Peller M, Bartenstein P, Willoch F, Rossmeier C, Schwaiger M, et al. Activation of frontal premotor areas during suprathreshold transcranial magnetic stimulation of the left primary sensorimotor cortex: a glucose metabolic PET study. Hum Brain Mapp 2001; 12: 157–67.

Spaulding SJ, McPherson JJ, Strachota E, Kuphal M, Ramponi M. Jebsen Hand Function Test: performance of the uninvolved hand in hemiplegia and of right-handed, right and left hemiplegic persons. Arch Phys Med Rehabil 1988; 69: 419–22.

Stefan K, Kunesch E, Benecke R, Cohen LG, Classen J. Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. J Physiol 2002; 543: 699–708.

Stern EB. Stability of the Jebsen–Taylor Hand Function Test across three test sessions. Am J Occup Ther 1992; 46: 647–9.

Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF. Lifetime cost of stroke in the United States. Stroke 1996; 27: 1459–66.

Teskey GC, Flynn C, Goertzen CD, Monfils MH, Young NA. Cortical stimulation improves skilled forelimb use following a focal ischemic infarct in the rat. Neurol Res 2003; 25: 794–800.

Traversa R, Cicinelli P, Bassi A, Rossini PM, Bernardi G. Mapping of motor cortical reorganization after stroke. A brain stimulation study with focal magnetic pulses. Stroke 1997; 28: 110–7.

Turney TM, Garraway WM, Whisnant JP. The natural history of hemispheric and brainstem infarction in Rochester, Minnesota. Stroke 1984; 15: 790–4.

Werhahn KJ, Conforto AB, Kadom N, Hallett M, Cohen LG. Contribution of the ipsilateral motor cortex to recovery after chronic stroke. Ann Neurol 2003; 54: 464–72.

Whisnant JP. The decline of stroke. Stroke 1984; 15: 160–8.

Wu CW-H, Seo HJ, Cohen LG. Improvement of paretic hand function by somatosensory stimulation in chronic stroke. Fifth World Stroke Congress, Vancouver, 2004; 262.

Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, et al. Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. Brain 1997; 120: 141–57.

Ziemann U, Chen R, Cohen LG, Hallett M. Dextromethorphan decreases the excitability of the human motor cortex. Neurology 1998a; 51: 1320–4.

Ziemann U, Corwell B, Cohen LG. Modulation of plasticity in human motor cortex after forearm ischemic nerve block. J Neurosci 1998b; 18: 1115–23.