REVIEW ARTICLE

Non-invasive brain stimulation for fine motor improvement after stroke: a meta-analysis

A. T. O'Brien[a,*,†], F. Bertolucci[a,b,*], G. Torrealba-Acosta[c], R. Huerta[d], F. Fregni[a] and A. Thibaut[a,e,†]

[a]*Neuromodulation Center, Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA;* [b]*Department of Neuroscience and Neurorehabilitation, University Hospital of Pisa, Pisa, Italy;* [c]*Department of Neurology, Neuroscience Research Center, University of Costa Rica, San José, Costa Rica;* [d]*Department of Medicine, The National Autonomous University of Mexico, Mexico City, Mexico; and* [e]*Coma Science Group, GIGA-Consciousness, University and University Hospital of Liège, Liège, Belgium*

Keywords:
fine motor rehabilitation, motor recovery, non-invasive brain stimulation, stroke, transcranial stimulation

Received 25 September 2017
Accepted 22 March 2018

European Journal of Neurology 2018, **25:** 1017–1026

doi:10.1111/ene.13643

Abstract

The aim of this study was to determine whether non-invasive brain stimulation (NIBS) techniques improve fine motor performance in stroke. We searched PubMed, EMBASE, Web of Science, SciELO and OpenGrey for randomized clinical trials on NIBS for fine motor performance in stroke patients and healthy participants. We computed Hedges' g for active and sham groups, pooled data as random-effects models and performed sensitivity analysis on chronicity, montage, frequency of stimulation and risk of bias. Twenty-nine studies (351 patients and 152 healthy subjects) were reviewed. Effect sizes in stroke populations for transcranial direct current stimulation and repeated transcranial magnetic stimulation were 0.31 [95% confidence interval (CI), 0.08–0.55; $P = 0.010$; Tau^2, 0.09; I^2, 34%; Q, 18.23; $P = 0.110$] and 0.46 (95% CI, 0.00–0.92; $P = 0.05$; Tau^2, 0.38; I^2, 67%; Q, 30.45; $P = 0.007$). The effect size of non-dominant healthy hemisphere transcranial direct current stimulation on non-dominant hand function was 1.25 (95% CI, 0.09–2.41; $P = 0.04$; Tau^2, 1.26; I^2, 93%; Q, 40.27; $P < 0.001$). Our results show that NIBS is associated with gains in fine motor performance in chronic stroke patients and healthy subjects. This supports the effects of NIBS on motor learning and encourages investigation to optimize their effects in clinical and research settings.

Introduction

Stroke accounted for 139 874 000 disability-adjusted life years in 2015 [1]. Most stroke patients experience long-term impairment and up to 80% have persistent and incapacitating upper-limb disability [2]. Recovery occurs in about 15–33% of patients, whereas 66% of patients can have no recovery, within the first 6 months post-stroke; recovery after this is minimal [3–11]. Stroke perturbs neuromuscular recruitment, timing, coordination and execution of vital motor tasks [12]. Fine motor ability is crucial for daily activities and for a person's independence, functionality, quality of life and purpose [13]. Interventions for fine motor recovery are imperative but often limited [13,14]. Non-invasive brain stimulation (NIBS) has minimal side-effects and is proposed as a stand-alone or adjuvant treatment for improving dexterity [15,16]. However, most reviews assessing NIBS in stroke focus on gross motor skills and, thus, the therapeutic potential and magnitude of NIBS for fine motor improvement is not known [17–23]. Motivated by this gap, we performed a meta-analysis on NIBS technologies using outcomes that focus on fine motor function in stroke patients and healthy subjects.

Correspondence: A. T. O'Brien, 79/96 13th Street, Charlestown, MA 02129, USA (tel.: 612-952-6164; fax: 612-952-6060; e-mail: aobrien@neuromodulationlab.org).
*First authors.
†Senior authors.

Methods

The study's registration number is CRD42016043809 and analyzed data are available online (Appendix S1)

[24]. Private health information was not used and the study was not interventional, therefore ethical approval was not required. See protocol for full search strategy [25] and Appendix S2 for a review of outcomes. Two blinded researchers screened records from extracted abstracts with Rayyan (Qatar Computing Research Institute [Data Analytics], Doha, Qatar) and then fully reviewed eligible articles. We focused on stroke patients and healthy subjects (as a proxy of lesioned cortex) [26]. Bias was assessed with the Cochrane Collaboration tool.

Random-effects models were assumed. Means and SD before and after treatment were used for Hedges' *g*. We created forest plots with RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata 13 (StataCorp LP, College Station, TX, USA). Heterogeneity was assessed by Tau^2, Cochrane Q and I^2, meta-bias by Begg's funnel plots and sensitivity analysis studied chronicity, combined interventions, techniques and risk of bias (according to Cochrane). Authors were contacted when data were missing or unclear. We used WebPlotDigitizer 3.11 (Ankit Rohatgi, Austin, TX, USA) to extract data from graphs. We assumed baseline comparability if there were only post-treatment data, otherwise the study was excluded.

Results

The search results are summarized in Fig. 1. See Appendix S2 for excluded full texts and a summary of included studies.

We reviewed 29 studies with 351 stroke patients and 152 healthy subjects. The frequencies of outcomes used were Jebsen–Taylor Hand Function Test (38.8%), Purdue Pegboard Test (27.7%), Nine Hole Peg Test (13.9%) and Box Block Test (19.4%). Further characteristics are detailed in Tables 1 and 2.

The effect size (ES) was 0.36 in stroke patients [95% confidence interval (CI), 0.14–0.58; $P < 0.001$; Tau^2, 0.17; I^2, 50%; Q, 56.41; $P < 0.001$] and 0.74 in healthy participants (95% CI, 0.16–1.31; $P < 0.001$; Tau^2, 0.59; I^2, 82%; Q, 43.91; $P < 0.001$) (Fig. 2).

The ES in the 18 transcranial direct current stimulation (tDCS) stroke comparisons was 0.31 (95% CI, 0.08–0.55; $P = 0.01$; Tau^2, 0.09; I^2, 34%; Q, 18.23; $P = 0.110$), whereas the ES for the 11 repeated transcranial magnetic stimulation (rTMS) comparisons was 0.46 (95% CI, 0.00–0.92; $P = 0.05$; Tau^2, 0.38; I^2, 67%; Q, 30.45; $P = 0.007$). The ES of tDCS in healthy participants was 1.25 (95% CI, 0.09–2.41; $P = 0.04$; Tau^2, 1.26; I^2, 93%; Q, 40.27; $P < 0.001$), whereas that for rTMS was 0.33 (95% CI, −0.08 to 0.68; $P = 0.140$; Tau^2, 0.00; I^2, 0%; Q, 0.52; $P < 0.970$).

Sensitivity analysis in stroke

Transcranial direct current stimulation was significant in chronic stroke with an ES of 0.34 (95% CI, 0.04–0.63; $P = 0.02$; Tau^2, 0.10; I^2, 40%; Q, 18.23; $P < 0.008$). The ES of rTMS in chronic mild to moderate stroke was significant, i.e. 0.51 (95% CI, 0.12–0.91; $P = 0.01$; Tau^2, 0.00; I^2, 0%; Q, 0.30; $P = 1.00$). When tDCS was combined with an intervention the ES was 0.62 (95% CI, 0.07–1.16; $P = 0.05$; Tau^2, 0.38; I^2, 69%; Q, 22.28; $P < 0.002$). There were only two high-frequency rTMS comparisons, which limited analysis. Pooling of low-frequency rTMS studies did not reveal significant ESs. For studies with a high risk of bias the ES was 0.64 (95% CI, 0.01–1.18; $P = 0.02$; Tau^2, 0.35; I^2, 65%; Q, 19.77; $P < 0.006$), whereas for studies with a low risk of bias the ES was 0.08 (95% CI, −0.25 to 0.41; $P = 0.630$; Tau^2, 0.00; I^2, 0%; Q, 4.45; $P < 0.490$).

Sensitivity analysis in healthy participants

The ES of non-dominant hemisphere tDCS on non-dominant hand performance was 1.68 (95% CI, 0.67–2.70; $P = 0.001$; Tau^2, 0.62; I^2, 79%; Q, 9.40; $P < 0.009$). In rTMS, analysis of non-dominant hemisphere stimulation was positive but not significant. Bias was similar in healthy subjects and stroke patients (Tables 3 and 4).

Publication bias

Begg's funnel plot in stroke patients and healthy subjects was asymmetric, suggesting possible publication bias.

Discussion

There were moderate and significant improvements in dexterity after tDCS and rTMS in stroke patients, and improvements after tDCS combined with another intervention were large and significant. In healthy participants, there was a moderate ES for non-dominant hand dexterity improvement. Our positive results were mainly from chronic patients with mild to moderate impairment, aiming to increase excitability of the ipsilesional hypoactive cortex or to decrease contralesional hyperactivity [27]. Although other meta-analyses studied upper-limb movement after NIBS, they did not focus specifically on dexterity or used scales such as the Rankin Scale (which is criticized for being poorly defined and open to interpretation) [19–23,28,29]. Our review, however, focuses on outcomes that are specific to dexterity and are independent of

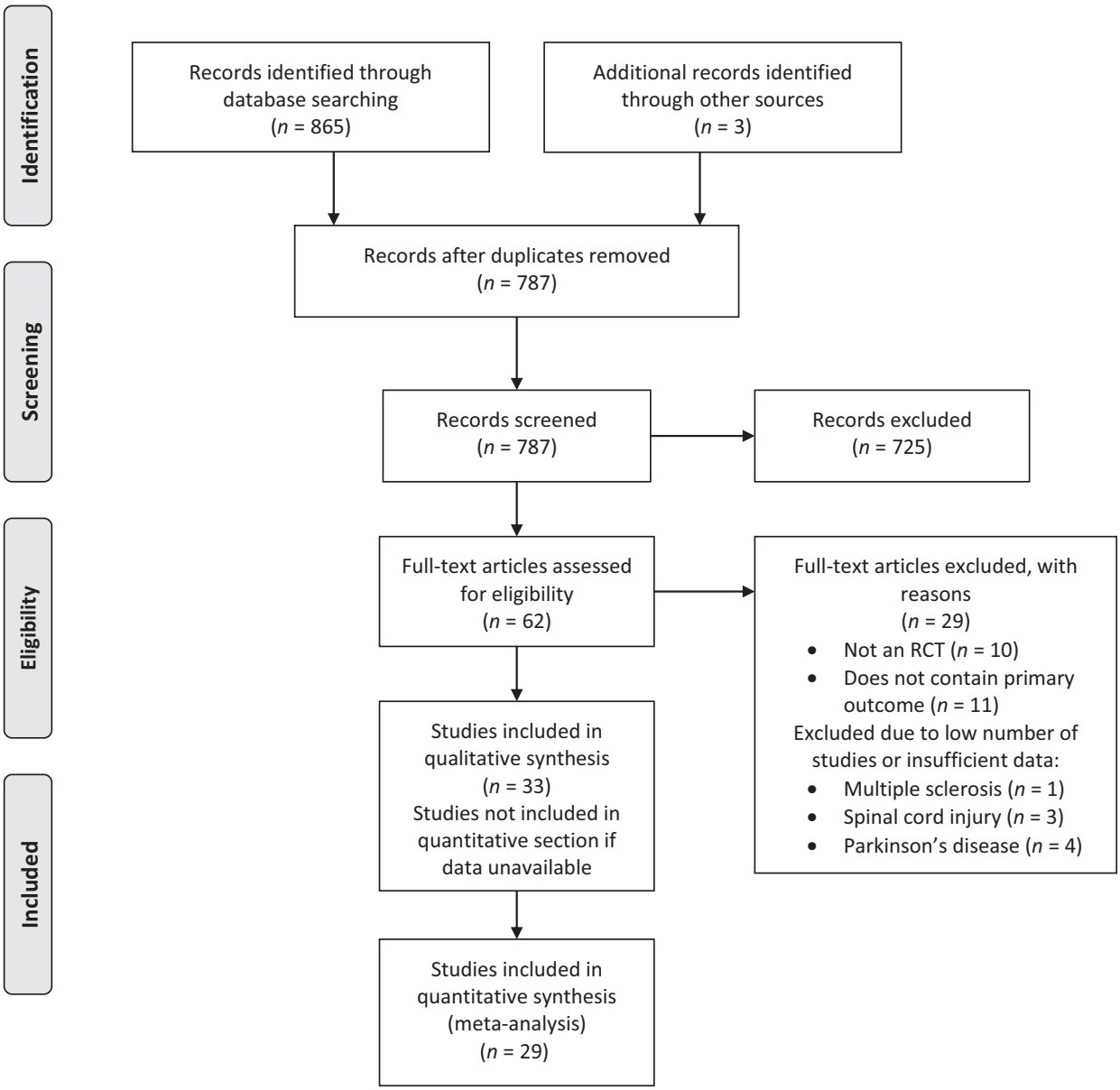

Figure 1 PRISMA 2009 flow diagram of study selection. RCT, randomized control trial.

the rater's interpretation. We discuss NIBS mechanisms that may benefit dexterity in stroke patients.

Neuronal network integrity and function are reliant on persistent sensory input and, when interrupted, the brain undergoes multiple processes to correct the disruption [30,31]. Neuroplasticity leads alterations that promote recovery of sensorimotor integration and output [32,33]. Reducing increased ipsilesional inhibitory tone may facilitate large-scale neuronal changes (e.g. release of growth factor), endogenous cell responses (e.g. neurogenesis) and neuronal remodeling (e.g. dendritic arborization) [34]. These phenomena underlie mechanisms for non-specific long-term potentiation of motor learning and sensorimotor remapping in viable brain areas [34,35]. These neuroplastic mechanisms may reflect useful therapeutic NIBS avenues.

Neuroimaging, neurophysiologic and electrophysiologic studies demonstrate increased activation and structural integrity in ipsilesional motor networks [i.e. primary motor cortex (M1), premotor cortex (PMC) and supplementary motor area (SMA)] during task-related hand motor output in well-recovered chronic stroke patients, relative to the contralesional cortex and less recovered patients [27,36–41]. For example,

in a chronic stroke case of five low-frequency rTMS sessions over the contralesional M1, functional magnetic resonance imaging showed that rTMS treatment and clinical improvements correlated with diminished contralesional M1 hyperactivity in the ipsilesional hand area [42]. A larger functional magnetic resonance imaging study demonstrated that ipsilesional M1 activation before rTMS predicted recovery of dexterity [43]. The functional integrity of the stimulated site was related to the motor network-

Table 1 General description of stroke patient studies

Study	Total	Age (years)	Gender (male)	Time since stroke (months)	Severity	NIBS parameters
Au-Yeung *et al.* (2014)	10	62.60 (±5.7)	10	8.30 (±3.2)	Mild	(1) IL a-tDCS M1, (2) CL c-tDCS M1, (3) s-tDCS. 1 session × 1 mA × 20 min, 35 cm^2 sponge
Boggio *et al.* (2007)	4	60.75 (±13.14)	4	34.50 (±27.74)	Mild	(1) s-tDCS, (2) IL a-tDCS M1, (3) CL c-tDCS M1. 4 sessions × 1 mA × 20 min × 35 cm^2 sponge
Bolognini *et al.* (2011)	14	46.71 (±14.07)	5	35.21 (±26.45)	Severe	(1) CIMT + IL a-tDCS, (2) CIMT + s-tDCS. 10 sessions × 2 mA × 40 min × 35 cm^2 sponge
Fusco *et al.* (2014)	16	60.40 (±14.90)	9	1.70 (±0.68)	Mild	(1) IL a-tDCS M1, (2) s-tDCS. Followed immediately by IDR. 10 sessions × 1.5 mA × 10 min, 35 cm^2 sponge
Fusco *et al.* (2014) (Biomed)	11	58.36 (±14.35)	5	0.50 (N.A.)	Severe	(1) CL c-tDCS M1, (2) s-tDCS. Followed by IDR. 1 session × 1.5 mA × 15 min, 35 cm^2 sponge
Hummel *et al.* (2005)	6	62.20 (±7.56)	4	43.30 (±13.1)	Mild	(1) IL a-tDCS M1, (2) s-tDCS. 1 session × 1 mA × 20 min, 25 cm^2 sponge
Kim *et al.* (2009)	10	62.80 (±13.15)	3	1.60 (±0.79)	Mild	(1) IL a-tDCS M1, (2) sham. 1 session × 1 mA × 20 min × 25 cm^2 sponge
Mahmoudi *et al.* (2011)	10	60.80 (±14.11)	31	8.30 (±5.45)	Mild to moderate	(1) BL-tDCS (IL anode and CL cathode M1), (2) IL a-tDCS M1, (3) CL c-tDCS M1, (4) IL a-tDCS M1 and cathode on contralateral deltoid, (5) s-tDCS. 1 session × 1 mA × 20 min × 35 cm^2 sponge
Mortensen *et al.* (2015)	16	63.10 (±10.15)	7	30.20 (±15.45)	Mild to moderate	(1) IL a-tDCS M1 or (2) s-tDCS. During OT. 5 sessions × 1.5 mA × 20 min × 35 cm^2 sponge
Sattler *et al.* (2015)	20	65.00 (±11.00)	9	0.18 (±0.11)	Mild	(1) IL a-tDCS + rPNS, (2) s-tDCS + rPNS. 5 sessions × 1.2 mA × 13 min, 35 cm^2 sponge. OT (3–5 times/week) started independently of the tDCS sessions at Day 4 or Day 5 (30 min/session). After discharge, OT occurred 3–5 times/week (45–90 min/session) until end of follow-up
Straudi *et al.* (2016)	23	58.20 (±14.40)	14	14.65 (±13.05)	Severe	(1) BL-tDCS (IL anode and CL cathode M1) + RAT, (2) s-tDCS + RAT. 10 sessions × 1 mA × 30 min, 35 cm^2 sponge
Wang *et al.* (2014)	9	52.90 (±7.23)	12	7.26 (±3.75)	Severe	(1) IL a-tDCS M1, (2) IL a-tDCS M1 + MP, (3) MP + s-tDCS. 1 session × 1 mA × 20 min × 35 cm^2 sponge
Avenanti *et al.* (2012)	30	62.97 (±8.80)	7	31.46 (±22.68)	Mild	(1) rTMS then PT, (2) PT then rTMS, (3) s-rTMS then PT. rTMS applied over CL M1 at 1 Hz × 10 sessions × 1500 p/s × 90% RMT
Conforto *et al.* (2011)	30	55.75 (±9.43)	16	0.92 (±0.23)	Mild	(1) 1 Hz rTMS × 1500 p/s × 10 sessions over CL M1, (2) s-rTMS
Fregni *et al.* (2006)	15	56.00 (±8.43)	18	44.94 (±31.68)	Mild to moderate	(1) 1 Hz, 1200 p/s × 100% RMT × 5 days × CL M1, (2) s-rTMS
Ji *et al.* (2014)	35	52.57 (±7.90)	11	8.89 (±2.21)	Mild to moderate	(1) rTMS + MT, (2) MT, (3) sham MT. 1 session × 10 Hz × 1500 p/s
Liepert *et al.* (2007)	12	63.00 (±11.00)	11	0.24 (±0.15)	Mild	(1) 1 Hz, 20 min, 1200 pulses, 90% RMT, CL M1, (2) s-rTMS. 1 session
Lüdemann-Podubecká *et al.* (2016)	10	71.90 (±7.90)	8	1.00 (±0.4)	Mild	(1) 1 session × 1 Hz × 900 p/s × 110% RMT, CL PMd, (2) s-rTMS
Mansur *et al.* (2005)	10	53.30 (±11.98)	6	Within 12 months (N.A.)	Mild to moderate	(1) M1 rTMS (real/sham), (2) PMd rTMS. 1 session × 1 Hz × 600 p/s × 100% RMT

(continued)

Table 1 *(Continued)*

Study	Total	Age (years)	Gender (male)	Time since stroke (months)	Severity	NIBS parameters
Matsuura *et al.* (2015)	20	73.45 (±7.02)	3	0.32 (±0.09)	Mild	(1) 5 sessions of rTMS × 1 Hz × 1200 p/s, CL M1, (2) s-rTMS
Malcolm *et al.* (2007)	19	67.00 (±4.91)	11	46.20 (±0.20)	Severe	(1) 10 sessions × 20 Hz rTMS, 2000 p/s × 90% RMT + CIMT, (2) s-rTMS + CIMT
Özkeskin *et al.* (2016)	21	60.12 (±8.81)	14	34.95 (±16.17)	Severe	(1) 10 days rTMS × 1 Hz × 1500 p/s, CL M1 + BHM, (2) s-rTMS + BHM
Total or average	351	60.45 (±2.28)	218	16.44 (±3.11)		

a-tDCS, anodal transcranial direct current stimulation; BHM, Brunnstrom hand manipulation; BL-tDCS, bilateral transcranial direct current stimulation; CIMT, constraint induced movement therapy; CL, contralesional; c-tDCS, cathodal transcranial direct current stimulation; IDR, inpatient daily rehabilitation; IL, ipsilesional; M1, primary motor cortex; MP, methylphenidate; MT, mirror therapy; N.A., not available; NIBS, non-invasive brain stimulation; OT, occupational therapy; PMd, dorsal premotor cortex; p/s, pulses/session; PT, physical therapy; RAT, robot-assisted therapy; RMT, resting motor threshold; rPNS, repeated peripheral nerve stimulation; rTMS, repeated transcranial magnetic stimulation; s-rTMS, sham repeated transcranial magnetic stimulation; s-tDCS, sham transcranial direct current stimulation; tDCS, transcranial direct current stimulation. Data are given as *n* and mean ± SD.

Table 2 General description of healthy participant studies

Study	Total	Age (years)	Gender (male)	NIBS parameters
Marquez *et al.* (2015)	34	61 (±12.20)	19	(1) 1 session a-tDCS, randomized to dominant or non-dominant hemisphere, (2) s-tDCS × 1 mA × 20 min, 35 cm^2 sponge
Park *et al.* (2014)	15	23.2 (±2.24)	7	(1) c-tDCS left M1 followed by 10 Hz rTMS right M1, (2) a-tDCS over left M1 followed by 10 Hz rTMS over right M1, (3) s-tDCS over left M1 followed by 10 Hz rTMS over right M1, (4) s-tDCS over left M1 followed by s-rTMS over right M1; rTMS parameters: 10 Hz, 1000 pulses/session at 90% RMT; tDCS parameters: 20 min × 1 mA × 35 cm^2 sponge
Boggio *et al.* (2006)	8	22.8 (range, 22–26)	0	(1) a-tDCS on non-dominant M1, (2) a-tDCS on dominant M1. 1 session × 1 mA × 20 min × 35 cm^2 sponge
Butts *et al.* (2014)	26	44 (N.A.)	N.A.	tDCS + theta burst stimulation active or sham. Anode tDCS (20 min) over non-dominant M1 and cathode over dominant M1. 10 sessions × 1 mA × 20 min, 6.25 cm^2 sponge. Prior to each tDCS session, priming with iTBS, 50 Hz over non-dominant M1, 12 000 pulses per session at 80% RMT
Kidgell *et al.* (2013)	11	29 (range, 22–36)	N.A.	(1) a-tDCS right M1, (2) BL-tDCS (anode right M1 and cathode right M1), (3) sham. 1 session × 13 min × 1 mA × 25 cm^2 sponge
Weiler *et al.* (2008)	28	21.9 (±2.29)	28	(1) 1 session of 1 Hz rTMS over non-dominant M1. 300 pulses per session at 80% RMT, (2) sham
Jelic *et al.* (2015)	30	26 (±3.00)	11	(1) 1 session, 50 Hz, 600 pulses/session, 80% RMT applied as either iTBS or cTBS
Total or average	152	33.95	65	

a-tDCS, anodal transcranial direct current stimulation; BL-tDCS bilateral transcranial direct current stimulation; c-tDCS, cathodal transcranial direct current stimulation; iTBS, intermittent theta burst stimulation; M1, primary motor cortex; N.A., not available; NIBS, non-invasive brain stimulation; RMT, resting motor threshold; rTMS, repeated transcranial magnetic stimulation; s-rTMS, sham repeated transcranial magnetic stimulation; s-tDCS, sham transcranial direct current stimulation; tDCS, transcranial direct current stimulation. Data are given as *n* and mean ± SD.

shaping potential of rTMS [43]. Non-responders showed the opposite activation, where contralesional activity increased [43]. This relates to functional magnetic resonance imaging studies where ipsilesional rTMS/tDCS increased motor performance and connectivity and task-related activity in the M1, PMC and SMA [44,45]. This highlights the role of ipsilesional M1 inhibition and contralesional M1 hyperactivity in chronic stroke and how NIBS modulates these maladaptive processes for clinical improvement. Neurophysiologic studies show that M1 anodal tDCS in chronic stroke increased mu desynchronization (a normal, physiologic attenuation of mu bands during movement) [46,47]. NIBS may facilitate recovery of normal neurophysiologic function in chronic stroke patients. These findings, in conjunction with ours, may support the neuroplastic and behavioral effects of NIBS in recovering fine hand function.

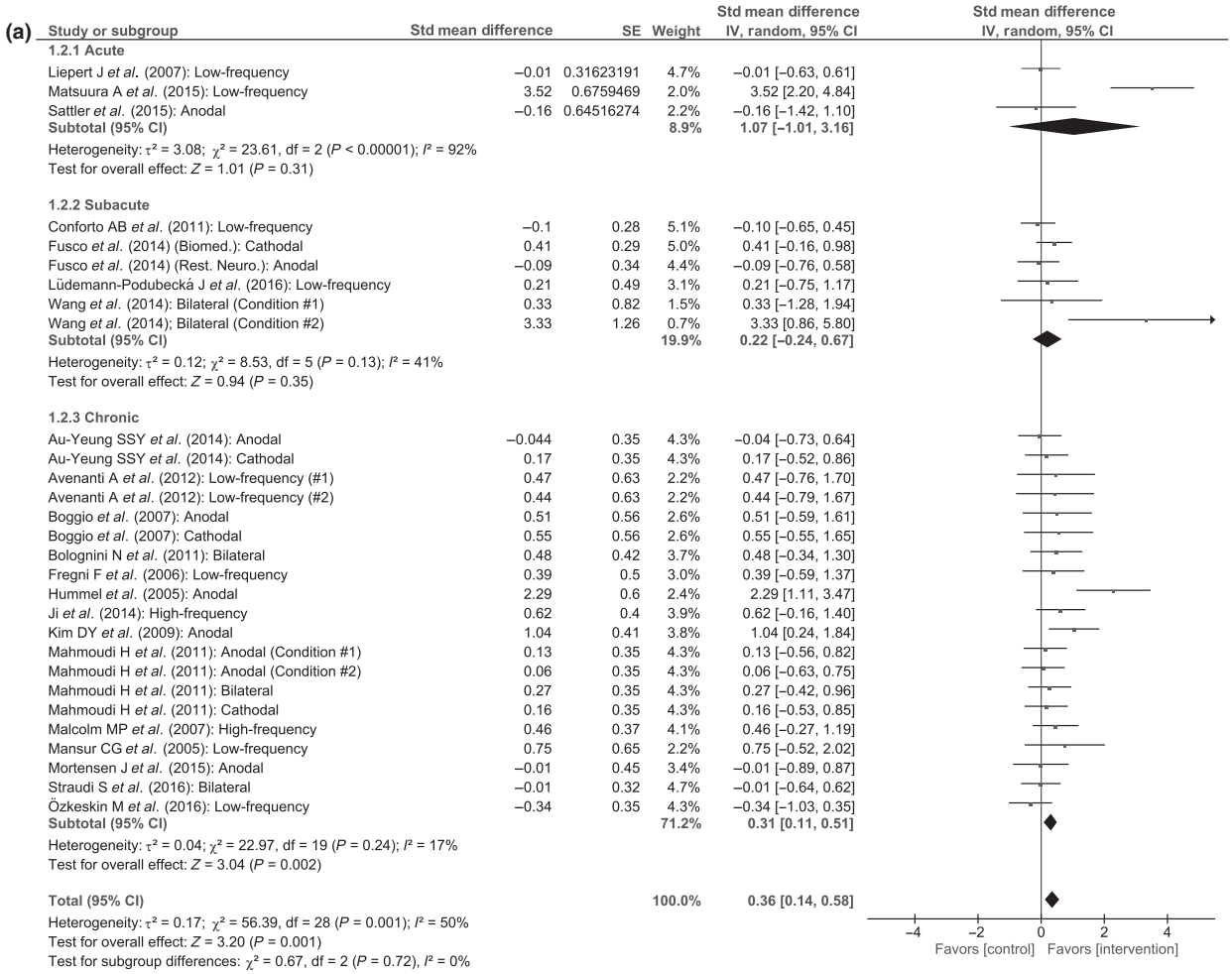

Figure 2 Forrest plot of Hedges' *g* for non-invasive brain stimulation paradigms. (a) Stroke patients; (b) healthy controls. CI, confidence interval; df, degrees of freedom; iTBS, intermittent theta burst stimulation; IV, inverse variance; rTMS, repeated transcranial magnetic stimulation; SE, standard error.

Table 3 Transcranial direct current stimulation sensitivity analysis

Description	Hedges' *g* (95% CI)	*P*	Tau^2, I^2 and Cochrane *Q* (*P*)	No. of comparisons
All stroke	0.31 (0.08 to 0.55)	0.010	0.09, 34%, 18.23 ($P = 0.110$)	18
Acute[a]				1
Subacute	0.46 (−0.33 to 1.24)	0.250	0.33, 59%, 7.25 ($P = 0.060$)	4
Chronic	0.34 (0.04 to 0.63)	0.020	0.10, 40%, 18.23 ($P = 0.080$)	13
Anodal	0.34 (−0.88 to 0.76)	0.110	0.22, 56%, 18.36 ($P = 0.020$)	9
Cathodal	0.29 (−0.05 to 0.64)	0.100	0.00, 0%, 0.65 ($P = 0.890$)	4
Bilateral	0.38 (−0.18 to 0.95)	0.180	0.16, 42%, 6.94 ($P = 0.140$)	5
Anodal + cathodal	0.33 (0.04 to 0.63)	0.030	0.11, 41%, 18.59 ($P = 0.070$)	13
Anodal + bilateral	0.38 (0.04 to 0.73)	0.030	0.19, 52%, 24.88 ($P = 0.020$)	14
Cathodal + bilateral	0.29 (0.03 to 0.55)	0.030	0.00, 0%, 7.59 ($P = 0.470$)	9
At rest	0.17 (−0.09 to 0.43)	0.190	0.00, 0%, 1.46 ($P = 0.990$)	10
Combined with an intervention	0.62 (0.07 to 1.16)	0.050	0.38, 69%, 22.28 ($P = 0.002$)	8
Low risk of bias	0.16 (−0.08 to 0.40)	0.190	0.00, 0%, 3.80 ($P = 0.920$)	10
High risk of bias	0.64 (−0.01 to 1.18)	0.020	0.35, 65%, 19.77 ($P = 0.006$)	8
All healthy (non-dominant hemisphere stimulation)[b]	1.25 (0.09 to 2.41)	0.04	1.26, 93%, 40.27 ($P < 0.001$)	4
Dominant hand[a]				1
Non-dominant hand	1.68 (0.67 to 2.70)	0.001	0.62, 79%, 9.40 ($P = 0.009$)	3
Low risk of bias	0.81 (−0.36 to 1.99)	0.170	0.98, 93%, 0.98 ($P < 0.001$)	3
High risk of bias	2.79 (1.64 to 3.95)	0.00001	Not applicable	1

Kidgel *et al.* (2013) bilateral montage was not included in calculations as the montage was contrary to the interhemispheric balance model; [a]Not enough data to calculate an effect size; [b]Not enough data to study the effects of non-invasive brain stimulation on the dominant hemisphere in healthy subjects; CI, confidence interval.

Table 4 Repeated transcranial magnetic stimulation sensitivity analysis

Description	Hedges' *g* (95% CI)	*P*	Tau^2, I^2 and Cochrane *Q* (*P*)	No. of comparisons
All stroke	0.46 (0.00 to 0.92)	0.050	0.38, 67%, 30.45 ($P < 0.001$)	11
Acute	1.7 (−1.75 to 5.16)	0.330	5.94, 96%, 18.23 ($P = 0.080$)	2
Subacute	−0.02 (−0.50 to 0.46)	0.930	0.00, 0%, 0.30 ($P = 0.59$)	2
Chronic	0.30 (−0.04 to 0.64)	0.090	0.00, 0%, 4.88 ($P = 0.580$)	7
Chronic (excluding severely impaired subjects)	0.51 (0.12 to 0.91)	0.010	0.00, 0%, 0.30 ($P = 1.000$)	6
Low frequency	0.47 (−0.30 to 1.04)	0.520	0.52, 73%, 29.25 ($P < 0.001$)	9
High frequency	0.53 (0.00 to 1.06)	0.050	0.00, 0%, 0.09 ($P < 0.001$)	2
At rest	0.67 (−0.15 to 1.48)	0.340	0.80, 81%, 26.11 ($P < 0.001$)	6
Combined with an intervention	0.24 (−0.11 to 0.59)	0.180	0.00, 0%, 4.29 ($P = 0.180$)	5
Low risk of bias	0.08 (−0.25 to 0.41)	0.630	0.00, 0%, 4.45 ($P = 0.490$)	6
High risk of bias	0.92 (−0.06 to 1.89)	0.070	0.99, 82%, 22.65 ($P < 0.001$)	5
All healthy (non-dominant hemisphere stimulation)[a]	0.30 (−0.08 to 0.68)	0.120	0.00, 0%, 0.52 ($P = 0.970$)	9
Dominant hand[b]				1
Non-dominant hand[c]	0.33 (−0.08 to 0.68)	0.140	0.00, 0%, 0.52 ($P = 0.970$)	3

[a]Not enough data to study the effects of non-invasive brain stimulation on the dominant hemisphere in healthy subjects; [b]Not enough data to calculate an effect size. [c]We only included parameters that enhance cortical excitability of the non-dominant hemisphere. CI, confidence interval.

Non-invasive brain stimulation with other interventions

We demonstrated large ESs when tDCS was combined with other interventions. Alterations to brain network connectivity on its own do not lead to motor recovery and require appropriate behavioral and contextual stimulation [48]. As tDCS induces a non-specific effect, it is critical to combine it with interventions that make it specific. For example, Bolognini *et al.* used constrained induced movement therapy with anodal, ipsilesional tDCS, whereas another study relied on tDCS to return the interhemispheric balance during robot-assisted therapy [49,50]. Simultaneous NIBS may strengthen glutamate receptor learning-dependent activity, selectively boosting training-dependent activation of specific neural networks and promoting motor learning consolidation [51]. Another study combined tDCS with methylphenidate, which has cortical excitability properties with reorganization and improvement of motor function in stroke [52]. These authors showed that tDCS with methylphenidate produced greater effects than either alone [52].

Recovery versus compensation

There is an optimal post-stroke recovery period, which is non-linear and logarithmic [53]. Upper-limb movement mostly recovers in the first 8 weeks after stroke and then plateaus [53–55]. Improvement in dexterity after this could be due to the recovery of motor patterns present before the event or compensatory patterns of remaining motor elements [56]. The outcomes reviewed do not give insight into the quality of recovery but rely on execution (e.g. time to completion). This limits our interpretation of recovery versus compensation. The large ES observed in the non-dominant hand of healthy subjects may support recovery.

The non-dominant healthy motor cortex has less cortical activity during non-dominant hand movement relative to the dominant cortex (i.e. it models a lesioned cortex) [26]. Improvement of motor performance exclusively in the non-dominant hand following non-dominant NIBS can be indicative of motor learning secondary to neuromodulation.

Limitations

Despite obtaining moderate, significant, homogenous ESs across tDCS and rTMS, multiple parameters are heterogeneous, as expected, which reduces the precision of the results [15,16,51,57,58]. Combining ESs of different NIBS techniques may be non-pragmatic as these technologies function differently and we therefore consider them separately in our analysis. We did not study quality of life, thus limiting our understanding of positive changes in patients' functionality. Also, our findings do not consider interindividual variability.

Conclusions

Our results are encouraging as they show that NIBS (eventually combined with other behavioral interventions) is able to promote improvement of dexterity in chronic stroke stages, probably through motor learning mechanisms. We also observed that a large number of studies were unclear in their reporting of multiple components on systematic error, e.g. random sequence generation and allocation concealment were hardly ever reported clearly. In addition, a substantial number of studies were deemed as being at high risk of bias for personnel blinding. As technology advances, devices/techniques to compensate for limited blinding have become available, which may be a solution for this. Finally, given the lack of consensus on best practice in clinical settings, we hope that our findings can be applied in the treatment of chronic stroke patients with mild to moderate fine motor disability and encourage future research to optimize NIBS interventions and to find reliable biomarkers to develop tailored brain stimulation for motor recovery interventions.

Acknowledgements

This work was conducted with support from Harvard Catalyst/The Harvard Clinical and Translational Science Center and financial contributions from Harvard University and its affiliated academic healthcare centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard and its affiliations. A.T. was supported by a Wallonie–Brussel scholarship, the Belgian–American Educational Foundation and Leon Fredericq Foundation. F.F. was supported by 1R01HD082302-01A1 and 1R21HD79048-01A1.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Data repository statement.
Appendix S2. Review of included and excluded studies.

References

1. World Health Organization. Global health estimates: deaths by cause, age, sex and country, 2000–2015. Geneva: World Health Organization, 2015. http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html. (accessed 26/01/2017)
2. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol* 2009; **8:** 741–754.
3. Bo Lee K, Hoon Lim S, Hoon Kim K, *et al*. Six-month functional recovery of stroke patients: a multi-time-point study. *Int J Rehabil Res* 2015; **38:** 173–180.
4. Beebe JA, Lang CE. Active range of motion predicts upper extremity function 3 months after stroke. *Stroke* 2009; **40:** 1772–1779.
5. Nijland RHM, Van Wegen E, Harmeling-Van Der Wel BC, Kwakkel G. Presence of finger extension and shoulder abduction within 72 hours after stroke predicts functional recovery: early prediction of functional outcome after stroke: the EPOS cohort study. *Stroke* 2010; **41:** 745–750.
6. Parker VM, Wade DT, Lanoton HR, Wade DT. Loss of arm function after stroke: measurement, frequency, and recovery. *Int Rehabil Med* 1986; **8:** 69–73.

7. Langton-Hewer R. The hemiplegic arm after stroke: measurement and recovery. *J Neurol Neurosurg Psychiatry* 1983; **46:** 521–524.
8. Olsen TS. Arm and leg paresis as outcome predictors in stroke rehabilitation. *Stroke* 1990; **21:** 247–251.
9. Sunderland A, Fletcher D, Bradley L, Tinson D, Hewer RL, Wade DT. Enhanced physical therapy for arm function after stroke: a one year follow up study. *J Neurol Neurosurg Psychiatry* 1994; **57:** 856–858.
10. Nakayama H, Jørgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehabil* 1994; **75:** 394–398.
11. Jørgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Støier M, Olsen TS. Outcome and time course of recovery in stroke. Part II: time course of recovery. The Copenhagen stroke study. *Arch Phys Med Rehabil* 1995; **76:** 406–412.
12. Warlow C, Van GJ, Dennis M. Stroke: practical management. *N Engl J Med* 2008; **359:** 1188–1189.
13. Wang YC, Magasi SR, Bohannon RW, *et al*. Assessing dexterity function: a comparison of two alternatives for the NIH toolbox. *J Hand Ther* 2011; **24:** 313–321.
14. Kwakkel G, Kollen BJ. Predicting activities after stroke: what is clinically relevant? *Int J Stroke* 2013; **8:** 25–32.
15. Lefaucheur J-P, Andre-Obadia N, Antal A, *et al*. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol* 2014; **125:** 2150–2206.
16. Lefaucheur J-P, Antal A, Ayache SS, *et al*. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol* 2016; **128:** 56–92.
17. Lüdemann-Podubecká J, Bösl K, Nowak DA. Repetitive transcranial magnetic stimulation for motor recovery of the upper limb after stroke. *Prog Brain Res* 2015; **218:** 281–311.
18. Le Q, Qu Y, Tao Y, Zhu S. Effects of repetitive transcranial magnetic stimulation on hand function recovery and excitability of the motor cortex after stroke: a meta-analysis. *Am J Phys Med Rehabil* 2014; **93:** 1–9.
19. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving function and activities of daily living in patients after stroke. *Cochrane Database Syst Rev* 2013; CD009645.
20. Hao Z, Wang D, Zeng Y, Liu M. Repetitive transcranial magnetic stimulation for improving function after stroke. *Cochrane Database Syst Rev* 2013; CD008862.
21. Kang N, Summers JJ, Cauraugh JH. Transcranial direct current stimulation facilitates motor learning post-stroke: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016; **87:** 345–355.
22. Pollock A, Farmer SE, Brady MC, *et al*. Interventions for improving upper limb function after stroke. *Cochrane Database Syst Rev* 2014; CD010820.
23. Tedesco Triccas L, Burridge JH, Hughes AM, *et al*. Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: a review and meta-analysis. *Clin Neurophysiol* 2016; **127:** 946–955.
24. O'Brien AT, Torrealba G, Huerta R, Thibaut A. Data from: does non-invasive brain stimulation modify hand dexterity? Protocol for a systematic review and meta-analysis. *Dryad Digit Repos* 2017; https://10.5061/dryad.hq08g.
25. O'Brien AT, Torrealba G, Huerta R, Thibaut A. Does non-invasive brain stimulation modify hand dexterity? Protocol for a systematic review and meta-analysis. *BMJ Open* 2017; **7:** e015669.
26. De Gennaro L, Cristiani R, Bertini M, *et al*. Handedness is mainly associated with an asymmetry of corticospinal excitability and not of transcallosal inhibition. *Clin Neurophysiol* 2004; **115:** 1305–1312.
27. Di Pino G, Pellegrino G, Assenza G, *et al*. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat Rev Neurol* 2014; **10:** 597–608.
28. Wilson JTL, Hareendran A, Grant M, *et al*. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. *Stroke* 2002; **33:** 2243–2246.
29. Hsu W-Y, Cheng C-H, Liao K-K, Lee I-H, Lin Y-Y. Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke: a meta-analysis. *Stroke* 2012; **43:** 1849–1857.
30. Dayan E, Cohen LG. Neuroplasticity subserving motor skill learning. *Neuron* 2011; **72:** 443–454.
31. Hosp JA, Luft AR. Cortical plasticity during motor learning and recovery after ischemic stroke. *Neural Plast* 2011; **2011:** 871296.
32. Jenkins WM, Merzenich MM. Reorganization of neocortical representations after brain injury: a neurophysiological model of the bases of recovery from stroke. *Prog Brain Res* 1987; **71:** 249–266.
33. Wall JT, Xu J, Wang X. Human brain plasticity: an emerging view of the multiple substrates and mechanisms that cause cortical changes and related sensory dysfunctions after injuries of sensory inputs from the body. *Brain Res Brain Res Rev* 2002; **39:** 181–215.
34. Dalise S, Ambrosio F, Modo M. Brain plasticity and recovery in preclinical models of stroke. *Arch Ital Biol* 2014; **152:** 190–215.
35. Chen JL, Lin WC, Cha JW, So PT, Kubota Y, Nedivi E. Structural basis for the role of inhibition in facilitating adult brain plasticity. *Nat Neurosci* 2011; **14:** 587–594.
36. Gerloff C, Bushara K, Sailer A, *et al*. Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after capsular stroke. *Brain* 2006; **129:** 791–808.
37. Thibaut A, Simis M, Battistella LR, *et al*. Using brain oscillations and corticospinal excitability to understand and predict post-stroke motor function. *Front Neurol* 2017; **8:** 1–8.
38. Schulz R, Braass H, Liuzzi G, *et al*. White matter integrity of premotor-motor connections is associated with motor output in chronic stroke patients. *Neuroimage Clin* 2015; **7:** 82–86.
39. Schaechter JD, Fricker ZP, Perdue KL, *et al*. Microstructural status of ipsilesional and contralesional corticospinal tract correlates with motor skill in chronic stroke patients. *Hum Brain Mapp* 2009; **30:** 3461–3474.
40. Milot M-H, Spencer SJ, Chan V, *et al*. Corticospinal excitability as a predictor of functional gains at the affected upper limb following robotic training in chronic stroke survivors. *Neurorehabil Neural Repair* 2014; **28:** 819–827.
41. Riley JD, Le V, Der-Yeghiaian L, *et al*. Anatomy of stroke injury predicts gains from therapy. *Stroke* 2011; **42:** 421–426.

42. Salatino A, Berra E, Troni W, *et al*. Behavioral and neuroplastic effects of low-frequency rTMS of the unaffected hemisphere in a chronic stroke patient: a concomitant TMS and fMRI study. *Neurocase* 2014; **20:** 615–626.
43. Ameli M, Grefkes C, Kemper F, *et al*. Differential effects of high-frequency repetitive transcranial magnetic stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke. *Ann Neurol* 2009; **66:** 298–309.
44. Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Subthreshold high-frequency TMS of human primary motor cortex modulates interconnected frontal motor areas as detected by interleaved fMRI-TMS. *NeuroImage* 2003; **20:** 1685–1696.
45. Stagg CJ, Bachtiar V, O'Shea J, *et al*. Cortical activation changes underlying stimulation-induced behavioural gains in chronic stroke. *Brain* 2012; **135:** 276–284.
46. Ang KK, Guan C, Phua KS, *et al*. Facilitating effects of transcranial direct current stimulation on motor imagery brain-computer interface with robotic feedback for stroke rehabilitation. *Arch Phys Med Rehabil* 2015; **96:** S79–S87.
47. Kasashima Y, Fujiwara T, Matsushika Y, *et al*. Modulation of event-related desynchronization during motor imagery with transcranial direct current stimulation (tDCS) in patients with chronic hemiparetic stroke. *Exp Brain Res* 2012; **221:** 263–268.
48. Ward NS. Restoring brain function after stroke—bridging the gap between animals and humans. *Nat Rev Neurol* 2017; **13:** 244–255.
49. 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.
50. Straudi S, Fregni F, Martinuzzi C, Pavarelli C, Salvioli S, Basaglia N. tDCS and robotics on upper limb stroke rehabilitation: effect modification by stroke duration and type of stroke. *Biomed Res Int* 2016; **2016:** 5068127.
51. Bolognini N, Pascual-Leone A, Fregni F. Using non-invasive brain stimulation to augment motor training-induced plasticity. *J Neuroeng Rehabil* 2009; **6:** 8.
52. Wang QM, Cui H, Han SJ, *et al*. Combination of transcranial direct current stimulation and methylphenidate in subacute stroke. *Neurosci Lett* 2014; **569:** 6–11.
53. Zeiler SR, Krakauer JW. The interaction between training and plasticity in the poststroke brain. *Curr Opin Neurol* 2013; **26:** 609–616.
54. van Kordelaar J, van Wegen E, Kwakkel G. Impact of time on quality of motor control of the paretic upper limb after stroke. *Arch Phys Med Rehabil* 2014; **95:** 338–344.
55. Kwakkel G, Kollen B, Twisk J. Impact of time on improvement of outcome after stroke. *Stroke* 2006; **37:** 2348–2353.
56. Levin MF, Kleim JA, Wolf SL. What do motor "recovery" and "compensation" mean in patients following stroke? *Neurorehabil Neural Repair* 2009; **23:** 313–319.
57. O'Brien AT, Amorim R, Rushmore RJ, *et al*. Motor cortex neurostimulation technologies for chronic post-stroke pain: implications of tissue damage on stimulation currents. *Front Hum Neurosci* 2016; **10:** 545.
58. Wagner T, Fregni F, Fecteau S, Grodzinsky A, Zahn M, Pascual-Leone A. Transcranial direct current stimulation: a computer-based human model study. *NeuroImage* 2007; **35:** 1113–1124.